Title
Characterization of Headache Following Endoscopic Foreheadplasty Surgery in Women: Evidence for a Peripheral Trigger for Migraine

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Characterization of Headache Following Endoscopic Foreheadplasty Surgery in Women: Evidence for a Peripheral Trigger for Migraine

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Nursing

by

Julia Lassegard

2014

ABSTRACT OF THE DISSERTATION

Characterization of Headache Following Endoscopic Foreheadplasty Surgery in Women:

Evidence for a Peripheral Trigger for Migraine

by

Julia Lassegard

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2014

Professor Paul Macey, Chair

Background: Endoscopic Foreheadplasty Surgery (EFS) is a surgery addressing facial aging. Frequent consumers of EFS are females (91%) between ages 35-64. Case reports reveal commonly experienced moderate to severe incapacitating postoperative headache lasting 2-7 days. Headache characteristics, medication management, and impact on emotional and functional status are not well understood. The specific aims for this study were to explore in women following EFS: 1) the intensity, location, quality, and duration of headache; 2) compare EFS headache with migraine; 3) examine medication use and efficacy following EFS; 4) evaluate headache and a) emotional and b) functional outcomes; and 5) evaluate the effect of estrogen levels on headache for patients undergoing EFS.

Methods: Forty-two women (mean age 59.0 ± 7.9 years) undergoing EFS were recruited from twelve private cosmetic practices in three California counties. Four interviews with the Acute Short-Form 12v2, and the Headache Questionnaire were conducted on postoperative days (POD) 1, 3, 7, and 30.

Results: Most women experienced headache (93%) which was moderate to severe in intensity (64%). Headache was associated with migraine-like symptoms, including light sensitivity and nausea. Current acute therapy provided inconsistent relief. Most EFS triggered headaches (79

%) met International Classification of Headache Disorders (ICHD) criteria for migraine (with the exception of the requirement for previous episodes and limited duration), even in women with no previous history of migraine. Functional and emotional status deteriorated below baseline level postoperatively. Emotional status returned to baseline levels by POD 7 and functional status by POD 30. Those on hormone replacement therapies (HRT) had lower pain intensity, shorter headache duration, and less associated symptoms than those not on HRT.

Conclusion: The findings confirm women experience significant headache following EFS, which improves by POD 7. EFS headache was consistent with ICHD migraine criteria, providing evidence migraine may have an extracranial trigger. With current management inconsistent in relieving EFS headache migraine therapies may be of benefit. This study also offers evidence that HRT and a history of migraine both influence headache episodes and characteristics. Future investigations applying effective migraine strategies for those with EFS migraine–like headache may lead to improved patient outcomes.

Committee

The dissertation of Julia Lassegard is approved.

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2014

DEDICATIONS

In the first quarter of returning to school, this quote by Bernard Edmonds struck a profound chord with me. It remains on the door of our refrigerator today. “To dream anything you want to dream. That is the beauty of the human mind. To do anything you want to do. That is the strength of the human will. To trust yourself to test your limits. That is the courage to succeed.” I challenged myself to dream big and test my limits. I am proud to say, I did it!

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Lassegard, J. (2010). Peripheral Sensitization of Trigeminal Nerve Results in Acute Cephalalgia Poster Presentation, 29th Annual Scientific American Pain Society, Baltimore, MD.

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CHAPTER 1: INTRODUCTION

Endoscopic foreheadplasty surgery (EFS) is a minimally invasive surgical procedure, most commonly performed on women (ASAPS, 2010). The procedure is primarily performed to eliminate or ease signs of aging in the upper one third of the face by correcting eyelid ptosis and minimizing glabella and forehead wrinkles (Honig, Frank, & de La Fuente, 2008; Marchac, Ascherman, & Arnaud, 1997b; Puig & LaFerriere, 2002b). EFS may also be performed to correct physical genetic abnormalities from disease or traumas (plastic surgery), as well as to alter the body for enhancement of physical beauty (cosmetic surgery) (Atiyeh, Rubeiz, & Hayek, 2008).

Individuals undergoing EFS commonly complain of acute severe headache pain following surgery. The etiology of headache pain following EFS is not entirely understood, but is believed to be due to inadvertent nerve and muscle trauma that occurs during dissection (Hwang, Suh, Lee, & Chung, 2004; Puig & LaFerriere, 2002b; Werner & Andary, 2002). With the EFS surgical approach, superior branches of the trigeminal nerve can be injured. Activating the trigeminal nerve releases potent inflammatory mediators and nociceptive messengers, resulting in headache pain (Costigan, Scholz, & Woolf, 2009; Goadsby, 2002).

Described in postoperative interviews with EFS patients and mentioned in the surgical literature research (Jones & Grover, 2004; Nassif, 2007), EFS headache pain is as severe and debilitating as another common headache that is believed to be involve the trigeminal nerve, i.e. migraine. Migraine is a disorder that results from neuronal hyperexcitability, activation and sensitization of the trigeminal nerve. Structural and chemical changes in the peripheral nervous system may be responsible for incapacitating headache pain lasting hours to days (Burstein, 2001; Lipton, Bigal, et al., 2007a; Peterlin, Rosso, Nair, Young, & Schwartzman, 2010; Saxena & Tfelt-Hansen, 2006). EFS headache pain is described as similar to migraine in severity and

etiology, suggesting that they share a neurogenic mechanism (Borsook, Burstein, Moulton, & Becerra, 2006; Jakubowski et al., 2006).

Emotional and functional outcomes are negatively impacted in individuals experiencing headache pain (Lipton, Hamelsky, Kolodner, Steiner, & Stewart, 2000; Terwindt et al., 2000; Trask, Iezzi, & Kreeft, 2001). The World Health Organization identifies emotional and functional consequences as two important components to evaluate the impact of any disorder (Skevington, Lotfy, & O'connell, 2004). Emotional status reflects a disruption in normal emotional state and may be measured by anxiety, irritability, worry, fear, frustration, and depression (Lipton et al., 2000; Terwindt et al., 2000). Functional status reflects the ability to maintain usual daily activities defined as a disruption in the ability to maintain normal daily routine including work, home and social activities, that may require bed rest (Brandes, 2009; Dueland, Leira, Burke, Hillyer, & Bolge, 2004; Lipton, Stewart, Diamond, Diamond, & Reed, 2001). For example, in migraine, uncontrolled headache pain is one of the migraine symptoms that results in emotional distress, anxiety, irritability (emotional status), and decreased ability to perform routine activities in daily living and work productivity resulting in bed rest (functional status) (Aegidius, Zwart, Hagen, Schei, & Stovner, 2007; Peterlin et al., 2010). Although the functional status of EFS headache is unknown, we do know the functional status regarding migraine, which is similar to EFS headache.

Estrogen modulates pain, a phenomenon likely related to gender differences in pain perception and responses. Women have higher rates of headache (Lipton, Bigal, et al., 2007c), neuropathic (Alstadhaug, 2009), and musculoskeletal (Picavet & Hazes, 2003; Wijnhoven, De Vet, & Picavet, 2006) pain than men. Compared to men, women have lower pain thresholds and tolerance, greater propensity for pain disorders, greater sensitivity to pain, and report higher pain

intensity scores and functional impairment (Fillingim & Maixner, 1996; Macfarlane et al., 2002; Shinal & Fillingim, 2007). Hormonal changes, specifically estrogen, have been attributed to differences in pain experiences. Estrogen fluctuations (i.e., increases and decreases both occur during the menstrual cycle and sudden decreases are seen following surgical hysterectomy) induce neuronal excitability, leading to increases in pain intensity and in use of analgesic medication consumption for trigeminal headache pain in general, and migraine specifically (Brandes, 2006c; Lichten, Lichten, Whitty, & Pieper, 1996; Puri et al., 2006). Similar to migraine, fluctuating estrogen levels may also contribute to headache pain experiences for women undergoing EFS.

The purpose of the proposal is to empirically examine headache pain experienced by women following EFS. Specifically, this study will describe 1) intensity, location, quality, and duration of headache pain; 2) medication use and perceived relief; and 3) the relationship between headache pain and a) emotional status and b) functional status. In addition, the relationship of EFS headache to estrogen level will be explored because EFS headache may be analogous to hormone-induced migraine.

Background & Significance

Aspiring for physical beauty or attractiveness dates back to 1600 BC during times of the Pharaohs (Koblenzer). Creams produced from sugar cane and fruits, and pine oils and flower scents were used as aromatherapy to attain the much-desired toned, soft skin. Cleopatra, in 51 BC, bathed in goat's milk, honey, and almonds to acquire highly regarded soft skin (Oumeish). In the Renaissance period, cosmetic surgery was used to reconstruct stigmatizing syphilis nasal deformities and later, the wounds of war soldiers, allowing both to return to society (American Society of Plastic Surgeons ASPS, 2007; Gilman, 1999).

Cosmetic surgery has flourished as the fastest growing area of plastic surgery (Ching, Thoma, McCabe, & Antony, 2003). The total number of cosmetic surgeries performed increased from 412,901 in 1992 to almost 1.6 million in 2010, resulting in $10.1 billion total expenditure (American Society of Plastic Surgeons ASPS, 2010). Facelift and foreheadplasty surgeries are the two most common for women 35 to 64 years of age (American Society of Plastic Surgeons ASPS, 2010). In 2009, although men undergoing cosmetic surgeries increased by 8%, 9 million or 90% of the total cosmetic procedures were performed in women, 71% of them 35-74 years old. Even in these difficult economic times, EFS is ranked ninth in popularity for cosmetic surgeries performed in the USA (American Society of Plastic Surgeons ASPS, 2010). The increasing popularity of cosmetic surgery may be attributed to the improvement in equipment and technology, less invasive surgical procedures, and safer anesthetics. Endoscopic technique for foreheadplasty surgery, introduced in 1991 as a less invasive procedure, contributed to the increase in foreheadlift surgeries from 13,501 in 1991 to 120,971 in 2000. The EFS technique minimizes lengthy scars and alopecia with overall aesthetic outcomes equal to the traditional coronal incision approach (Foustanos & Zavrides, 2007; Isse, 1994; Marchac, Ascherman, & Arnaud, 1997a; Puig & LaFerriere, 2002a; Ramirez, 1997). (Figure 1)

In cultures that value attractiveness and youth, cosmetic surgery offers surgical procedures to improve function, appearance, and ease wrinkles and lines, or to eliminate the physical characteristics of aging (Cano, Klassen, & Pusic, 2009; Gimlin, 2000). Attractiveness and beauty have been shown to improve one's social and financial value (Gimlin, 2000; Koblenzer, 2003). Today, elective cosmetic surgery has been conceptualized as an opportunity for surgical enhancement for persons who feel that their physical bodies are not in alignment with “self.” Cosmetic surgical patients explain their decisions with statements such as, “I just did

not like the way I looked," "it's a natural instinct to want to look better" or "I wanted to restore my body to the way it looked" (Darisi, Thorne, & Iacobelli, 2005). Post-cosmetic surgical patients report improved self-image, self-esteem, personal self-assuredness, feelings of personal empowerment, and quality of life (Atiyeh et al., 2008; Gimlin, 2000; Grossbart & Sarwer, 2003; Rankin, Borah, Perry, & Wey, 1998). Commonly thought to be only for wealthy individuals, (Atiyeh et al., 2008) cosmetic surgery such as EFS is increasingly affordable, common, and acceptable as a means to improve body imperfections, and even described as a "life-enhancement" technique (Marchac, 2007; Mavroforou, 2004; Swami et al., 2008).

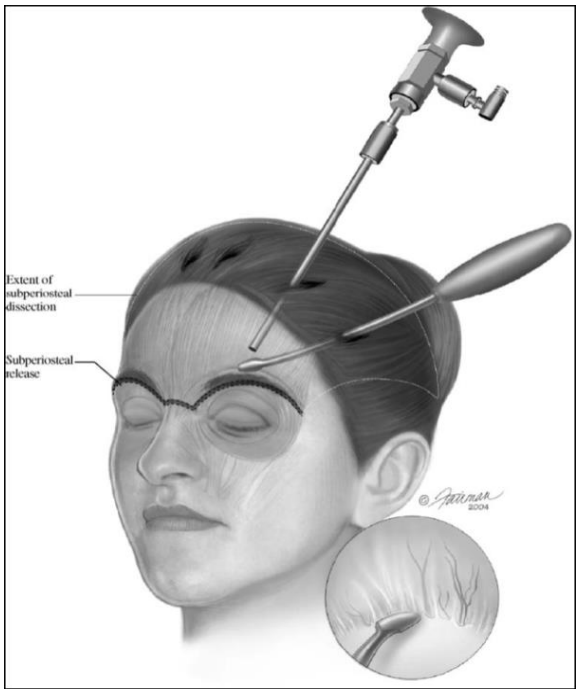


Figure 1.

Endoscopic Foreheadplasty Surgery Reprinted with Permission. Romo, Thomas III & Yalamanchili, Haresh, Endoscopic Forehead lifting, Dermatology Clinics, Saunders Company, 2005.

The EFS Procedure and Postoperative Headache

The EFS procedure is an outpatient surgery designed to reverse the signs of aging (Foustanos & Zavrides, 2006; Isse, 1994; Keller & Mashkevich, 2009; Nassif, 2007). As we age, gravity and loss of elasticity in facial tissue lead to permanent skin creases and sagging of the forehead and eyebrows. Deep permanent lines and wrinkles develop in the glabella and forehead from hypertonicity and downward pull of the depressor muscles, orbicularis occuli, procerus and corrugator supercilii (Knize, 2009). (Figure 2) To reverse this normal aging process, surgeons perform EFS to eliminate and minimize furrows and wrinkles and to lift the forehead and eyebrows. To perform EFS, an endoscope and dissecting instruments are inserted through small incisions to dissect scalp tissues in order to lift the forehead and eyebrows. Scalp fixations are sutured or implanted superficially or drilled into the skull to support elevated forehead tissue and muscle following dissection (Patel, 2006a).

Through experience in clinical practice and anecdotal reports, postoperative headache pain following EFS has been identified as a challenging problem in nursing care. It is commonly expected that women will experience moderate to severe headache pain, even with current prescribed medications, following EFS. In the first postoperative days, EFS headache pain interferes with eating, sleeping and normal daily functioning. These women and their caretakers express frustration and exasperation with prescribed analgesics, which offer insufficient pain relief. Currently, there are no established guidelines available for nurses to assess and manage EFS headache and outcomes.

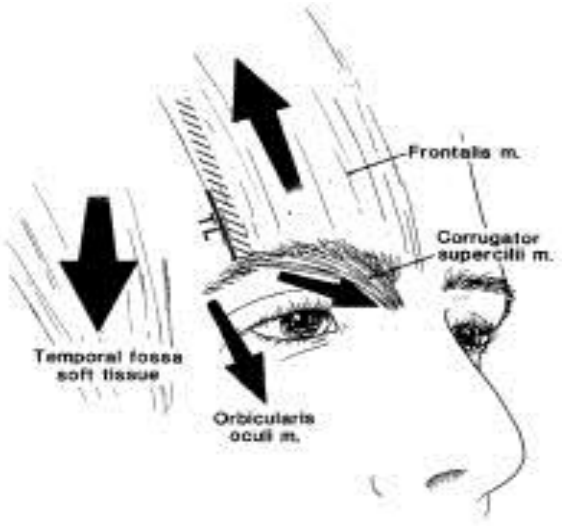


Figure 2.

Mechanism of Eyebrow Ptosis. Reprinted with permission. Knize, David. Plastic And Reconstructive Surgery, Wolters Kluwer Health, 1996.

Trigeminally Mediated Pain and Migraine

EFS surgical dissection includes manipulation of soft tissue and nerves (mechanical crushing and compression), leading to normal regional inflammation, ecchymosis and edema, which result in both nociceptive and neuropathic pain (IASP, 2008; Sorkin & Yaksh, 2009; Vadivelu & Sinatra, 2005). While nociceptive pain is a normal occurrence following surgical dissection, neuropathic pain usually does not occur and is therefore the focus of exploration in this study. As noted, EFS headache appears to be mediated by trauma to the trigeminal nerve. Specifically, the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve offer sensory innervations to the face and head and are distributed in areas involved in EFS dissection. (Figure 3A) Neurons in the trigeminal nerve regulate neuropeptides responsible for blood flow and inflammation to peripheral neural tissues, including meninges and dura mater (Puri et al., 2006). Calcitonin gene-related peptide (CGRP) and substance P released from activation of the

trigeminovascular system, promote vasodilation and an inflammatory environment resulting in intracranial hypersensitivity and pain (Burstein, Jakubowski, & Rauch, 2011; Goadsby, 2009).

Trigeminally mediated pain is often reported as severe and excruciating (Bennett, 2004), and this nerve may be considered a source in migraine pain (Burstein, 2001; Campbell & Meyer, 2006; Goadsby, 2009; Lipton, Bigal, Steiner, Silberstein, & Olesen, 2004; Xu, Aita, & Chavkin, 2008). Classified as trigeminally mediated pain, there is evidence that migraine follows brain excitability due to trigeminal activation and neurological dysfunction involving both peripheral and central sensitization (Burstein, 2001; Burstein, Yarnitsky, Goor-Aryeh, Ransil, & Bajwa, 2000; Goadsby, 2009; Lipton et al., 2008; Penfield & Mc, 1940). (Figure 3B)

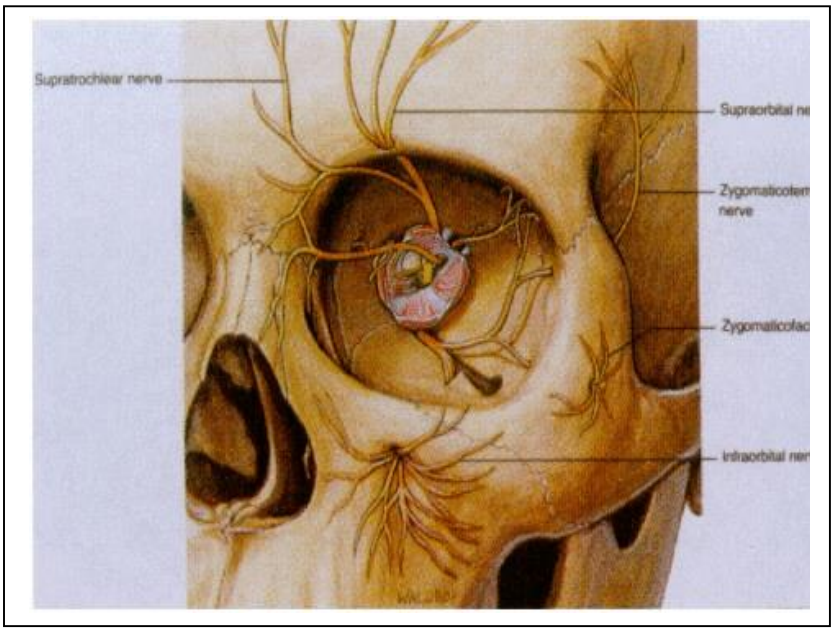


Figure 3A.

Supratrochlear, supraorbital, zygomaticotemporal nerves. Reprinted with Permission. Slade, Clifton, Cohen, Steven, Elicitation of the Oculocardia Reflex during Endoscopic Forehead Lift Surgery, Wolters Kluwer Health, 1999.

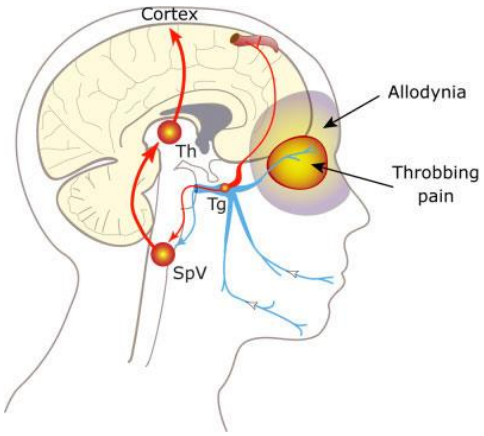


Figure 3B.

The trigeminovascular pathway subserving migraine pain. Neurons in the trigeminal ganglion (Tg) that innervate the meninges (i.e., meningeal nociceptors) carry pain signals to trigeminovascular neurons in the spinal trigeminal nucleus (SpV). From there the pain signals are conveyed to several thalamic nuclei (Th) en route to the somatosensory cortex, where the perception of pain is formed. REPRINTED with permission from John Wiley and Sons.

Trigeminally mediated pain in general, and migraine pain specifically, is described as incapacitating, moderate to severe pain (Lipton, Bigal, Diamond, Freitag, Reed, Stewart, et al., 2007). The World Health Organization (WHO) reported migraine to be as disabling as quadriplegia and dementia, ranking migraine the 19th overall cause of "years lived with disability" (Olesen et al., 2006). The symptoms, characteristics, and effects of migraine on emotional and functional status are well described in the literature and include depression, mood changes, emotional distress, anxiety, and irritability (Lipton, Liberman, et al., 2003; Magnusson & Becker, 2003; Peterlin et al., 2010); as well as more serious effects that cause physical limitations resulting in severe impairment and total incapacitation (Burstein, Yarnitsky, et al., 2000; Cady, Schreiber, & Farmer, 2004; Goadsby, 2005; Lipton, Liberman, et al., 2003; Lipton, Bigal, et al., 2007c; Stovner & Hagen, 2006). Migraine often disrupts social, home, and work activities, resulting in personal loss of social involvement, work absenteeism affecting

productivity, and increased medical costs (Holroyd, Drew, Cottrell, Romanek, & Heh, 2007a; Jensen & Stovner, 2008; Lipton, Liberman, et al., 2003; Peterlin et al., 2010). Pain management for migraine often includes a multimodal pharmacologic and supplemental nonpharmacologic approach (Attal et al., 2006; Davis, 1999; Dworkin, O'Connor, Audette, Baron, Gourlay, Haanpää, et al., 2010; Jakubowski, Levy, et al., 2005; Schiapparelli et al., 2010). Current pharmacologic migraine treatments include non-steroidal anti-inflammatory medications (NSAIDs), inhibitors of cyclooxygenas-1 and cyclooxygenase-2, antiepileptic, ergot alkaloids, derivatives, and triptans (Alstadhaug, 2009; Burstein, Collins, & Jakubowski, 2004; Goadsby, 2002; Matchar et al., 2002; Tfelt-Hansen et al., 2000). Speculated to stabilize estrogen induced inflammation and neuronal excitability, magnesium has been found to be beneficial for migraine (Goadsby, 2009; Mauskop, Altura, & Altura, 2002; Sun-Edelstein & Mauskop, 2009; Taylor, 2011). Nonpharmacologic protocols are often considered when pharmacologic management is ineffective or not cost effective, or when the desire to lower the use of potent pharmacologic use is warranted (Dobos & Tao, 2011; Linde et al., 2009; Nestoriuc & Martin, 2007; Wachholtz & Pargament, 2008).

Role of Estrogen

Tolerance to pain evoked by thermal, mechanical, and chemical noxious stimuli is lower for women compared to men (Craft, 2007). Estrogen, an ovarian female hormone that modulates multiple body systems responses, including pain, appears to influence pain perception for women (Brandes, 2006c; Hall, 2001; Martin & Behbehani, 2006b).

Estrogen regulates genes critical in the development of inflammation, excitability and nociception, which directly affects trigeminal neurons that mediate migraine pain (Granella et al., 2004; Puri et al., 2006; Silberstein, Elkind, Schreiber, & Keywood, 2004). In animal models

afferent trigeminal stimulation increases neuronal activity and more pain exists in females than males suggesting estrogen has pronociceptive effects (Dong et al., 2007; Puri et al., 2006).

Women experience a higher incidence of migraine with sudden decreases in estrogen during the luteal phase in menstrual cycle and surgical removal of ovaries. There are less frequent incidents of migraine with more stable higher estrogen levels during pregnancy and lower levels in menopause (Brandes, 2006b; Granella et al., 2004; Silberstein et al., 2004). Migraine incidents notably decrease during natural occurring menopause, versus surgical menopause, when hormone levels are stabilized with hormonal supplements (Brandes, 2006c; Lichten et al., 1996). In summary, overall these data suggest that women report higher pain levels than men. In addition, specifically women often experience more severe trigeminally mediated headache pain responses than do men, possibly due the pronociceptive action of estrogen leading to brain hyperexcitability. Finally, it also suggests that women on HRT may experience less pain due to neuronal stabilization.

Estrogen stability has been shown to diminish a neurological cascade of events that result in migraine, adding supporting evidence regarding the role of estrogen in trigeminally mediated neuronal hyperexcitability (Loder, Rizzoli, & Golub, 2007; Welch, Brandes, & Berman, 2006). Estrogen variabilities due to the menstrual cycle, perimenopause or the use of oral birth control contraceptives (which includes a 7 day period of no estrogen leading to sudden drop in estrogen) increase the likelihood of sensitivity to neuronal excitability (Craft, 2007; Loder et al., 2007). In migraine, women report higher pain scores compared to men and experience more intense accompanying symptoms such as nausea and vomiting, phonophobia, photophobia (Penzien, Rains, & Andrasik, 2002).

Due to shared etiology and phenomenology, it is hypothesized that the headache following EFS is likely to be similar in nature to migraine with respect to headache pain characteristics, analgesic response, and emotional and functional outcomes. Further, because estrogen affects trigeminally mediated pain, estrogen may play a role in EFS headache pain. However, it is unknown how hormone fluctuations contribute to headache pain characteristics, pain medication consumption, and outcomes for women following EFS.

Statement of the Problem

Although described as severe and debilitating, similar to migraine, the overall experience and consequences of EFS headache are unknown. To improve treatment, characterization of headache requires exploration and description of symptoms in women following EFS.

Specific Aims

In an effort to describe EFS headache characteristics, analgesic responses, and emotional and functional consequences; this study will use a descriptive design to follow a convenience sample of women undergoing EFS during their first postoperative week. Further, appearing to be a headache similar to migraine, the influence of estrogen (HRT) on EFS headache and outcomes will be explored. The specific aims of this study are as follows:

1) To describe the headache experience following EFS, specifically, intensity, location, quality, and duration.

2) Compare EFS headache characteristics with migraine.

3) To examine medication use and efficacy for headache following EFS.

4) To evaluate the relationships between headache characteristics, medication response, and a) emotional and b) functional outcomes following EFS.

5) To evaluate the effect of estrogen (HRT) on headache for patients undergoing EFS.

Nursing Implications

Cosmetic surgery to enhance external body attractiveness has been shown to improve mood, self-esteem, and self-confidence (Gimlin, 2000; Koblenzer, 2003). Even though nurses' primary function is to work with patients with illnesses or injuries, the nursing philosophy is to promote and support subjective and self-determined quality of life characteristics for all patients (Cano et al., 2009; Gimlin, 2000).

Surgical procedures to improve quality of life often result in postoperative pain. Nurse researchers, clinicians, and theorists strive to understand subjective pain experiences, with the general consensus being that pain "is whatever the experiencing person says it is, and exists whenever he [sic] says it does" (Ferrell & Coyle, 2008; McCaffery, 1972). The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 2008). Pain includes physical discomfort and mental distress and is the primary symptom for which medical care is sought (Mularski et al., 2006). Thus, pain includes both physiological and psychological components expressed uniquely by the individual experiencing pain.

Nurses have the critical thinking skills, interpersonal relationship capabilities, access, and compassion to make a difference with patients experiencing pain (Ferrell & Coyle, 2008). The American Nurses Association (ANA) and American Association of Nurse Anesthetists (AANA) state that pain relief is a professional obligation and ethical duty of nurses (Anesthetists, 2011; Brennan, Carr, & Cousins, 2007). Certified Registered Nurse Anesthetists (CRNAs) practice includes pain management as a "critical component in the delivery of anesthesia care"(Anesthetists, 2011). Physicians tend to rely on nurses to provide patient pain management

(Larson, 1994), and patients rely on nurses to not only provide pain management but to educate patients on symptom recognition and home management (Larson, 1994; Larson et al., 1999). In addition, the world's health care system considers managing patient pain the nurse's responsibility (Larson et al., 1999).

New nursing knowledge will be derived from these study findings. The proposed work will provide data upon which to base interventions for EFS headache. This new knowledge will raise awareness and provide nurses and other health care professionals with a fuller understanding of the clinical significance of EFS headache.

Summary

EFS is a common surgical procedure performed primarily on women to reverse signs of upper facial aging. A poorly described moderate to severe throbbing headache pain often follows EFS. Current medication protocols appear to be ineffective in relieving this headache pain, and emotional and functional status consequences have not been reported.

EFS dissection is performed in areas of the trigeminal nerve, which are associated with migraine. Migraine research provides strong evidence that in women, estrogen may be an important mediator of headache pain. Although seminal to the practice of nursing, currently no guidelines exist to assist nurses to assess and evaluate EFS headache and plan for effective pain management strategies. This study will provide preliminary characterization of EFS headache pain, provding direction for attempts to decrease discomfort, improve outcomes, and identify patients at risk for poorer response due to hormone activity.

CHAPTER 2: THEORETICAL FRAMEWORK

Introduction

An established nursing theoretical framework with pertinent constructs will be used to explore the EFS headache pain experience and outcomes. Philosophical assumptions and tenets provide the supportive foundation for research methods that maintain scientific rigor. For this study, an empiricist approach will be used to test the relationships among study concepts.

Philosophy

Empiricism supports this proposed study's goal to better understand EFS headache pain. Empiricism is a philosophical position that values measureable sense experiences as the basis of all knowledge (Rodgers, 2005). Sir Francis Bacon (1561-1626), the so called "father of modern science," utilized his political influence to advance science and knowledge through experimentation and observation and to challenge Medieval scripture-based thinking (Horner & Westacott, 2000; Magee, 2001). Bacon believed that the pursuit of information, facts, and data was fraught with errors, including researcher bias, and thus he was instrumental in the development of systematic scientific processes to promote consistent methods in seeking new knowledge. Further, he suggested that an empirical approach contributes to science the experimenta fructifera or fruitful products, or knowledge that benefits society (Bacon, 1620). British philosopher John Locke (1632-1704) further developed empiricist thinking with the belief that humans are born with a "blank slate," and with each sensory experience, thinking and ideas develop. Knowledge, according to Locke, originates only from measureable sensory experiences and observations (raw data) and is not innate (Locke, 1690). To maintain scientific standards and advance science empirically, Locke believed that acquired data must be verified (Rodgers, 2005).

Building upon this perspective, in the early 1900s, Hans Hahn, Otto Neurath, and Philipp Frank, philosophers in the Vienna Circle, developed the ideas of logical positivism. Logical positivists, or empirical positivists, believe scientific standards are maintained with the accruement of meaningful sense data that is value free and objectively obtained. This paradigm supports utilizing standardized instruments, records, charts, questionnaires, and statistical analysis, which results in new knowledge (Harding, 1995). Logical positivists consider verified empirical data an imperative component for developing theories that explain, predict, and control phenomena, thus advancing science (Rodgers, 2005). This perspective is often adopted by nurse researchers and is the basis for quantitative research methods (Polit, 2004).

Contemporary empiricism upholds the basic foundation that sense experiences are important sources of knowledge. Weiss (1995) describes three major assumptions held by contemporary nurse empiricists: 1) "some degree of predictability exists," implying there may be no absolutes in human behaviors or experiences, but reasonable predictions or estimates can be surmised; 2) "the purpose of nursing science is to develop the basis for nursing care," suggesting the accruement of knowledge should either explain human phenomena or predict intervention effectiveness; and 3) "human responses to health and illness can be identified, measured, and understood," suggesting that “individual parts and whole” are important to understand and explain phenomena contributing to nursing knowledge (Weiss, 1995, pages 14-16) (Weiss, 1995). Empirical underpinnings support the use of sense evidence grounded in reality, without researcher interpretation, as objective data to explain and predict outcomes (Rutty, 1998).

Two major tenets of empiricism are 1) deductive reasoning, which minimizes bias, maximizes objectivity, and withstands repeated testing; and 2) substantiation of theoretical claims, which establishes possible explanations for a phenomenon (Weiss, 1995). Empiricist

tenets support the proposed study's goal to gather objective data directly and indirectly on EFS headache pain so that reasonable predictions can be made, thus advancing nursing science. Empirical indicators have been strategically chosen for this study to acquire quantitative data on EFS headache pain symptoms experiences, symptoms management, and outcomes.

In summary, objective data on EFS headache collected with empirical measures will be quantitatively analyzed. Empirical philosophical underpinnings support this proposed study goal to examine headache following EFS in women, including predictors and responses. Through deductive reasoning and theoretical support, this study's findings will add new knowledge to nursing science in an effort to maximize healthy outcomes in this population.

Definition of Key Terms

For clarification and consistency of study concepts and variables, the following definitions will be used:

1. Headache Pain: Pain is an undesirable psychological (i.e., anxiety, depression, and irritability) and unpleasant physiological sensory (i.e., throbbing, stabbing, exploding, imploding) experience inside and around the head or forehead by women following EFS. Specific for this study, trigeminally mediated pain is defined as undesirable discomfort as a result of injury to the trigeminal nerve from surgical dissection that maybe unilateral or bilateral, constant or intermittent, and throbbing/pulsing, sharp, aching, pain lasting hours to days (Cheshire, 2007; Eller, Raslan, & Burchiel, 2005; Ngeow & Nair, 2010).

2. Endoscopic Foreheadplasty Surgery (EFS): A cosmetic surgery procedure using an endoscope and dissecting instruments to reverse signs of facial aging by eliminating furrows and wrinkles, and lift the forehead and eyebrows.

3. Emotional status: Psychological or mood state that allows for the continuation of normal routine activities or work.

4. Functional Status: The ability to maintain normal daily routine activities including work, home and social activities.

5. Estrogen: Global term for the family of estrogens or female steroid sex hormones that are synthesized in response to pituitary hormones in the ovary and participate in modulating multiple body systems.

6. Pain medication: Prescribed opioid, nonopioid, or other analgesic medications for the treatment of postoperative headache pain following EFS.

Theoretical Framework

Theoretical frameworks offer structure to assist and guide nursing research. Theories of pain range from the focus on a single sensory symptom of pain to more complex multidimensional experience of a pain, including correlates and outcomes. Based on experiments and clinical observations, early physiologists developed theories of pain focused on identification and descriptions of nerves, fibers, and pathways. From these, pathophysiological pain theories were derived, and psychological contributors to the pain experience were integrated to better predict, explain, and control pain experiences. The theoretical framework used to examine this study's constructs of interest was identified after a review of existing pain theories, ranging from historical perspectives to more complex current theories.

Early Pain Theories

Understanding the symptoms of pain has challenged scientists, healers, and philosophers since antiquity. Aristotle (384-322 BC) viewed pain as an emotion originating from the heart and leading to a sensory experience (Dallenbach, 1939; Perl, 2007). Descartes (1644) suggested a

direct transmission of pain information from the peripheral source of injury to the brain (Gedaly-Duff & Burns, 1988; Kim, 1980). Psychologists, including Henry Marshall and Mark Baldwin, philosophers such as Herbert Spencer and John Dewey, as well as physicians William James and Wilhelm Wundt who were both psychologists and philosophers, believed pain was an affective experience, contrary to pleasure, unrelated to a specific sense organ but could affect all body parts (Dallenbach, 1939; Perl, 2007).

Neurologic Physiological Pain Theories

The 1800s brought pain theories that focused on the physiological mechanisms and transmission of nociceptive signals in the nervous system (Melzack & Wall, 1965). Pattern pain theory suggests that all nerve fibers are similar and capable of transmitting cold, warmth, pressure, and pain information following activation (Adams & Bromley, 1998). Johannes Muller (1801-1858) theorized the body had five sensory nerves, and that the fifth nerve class, "feelings," was responsible for transmitting pain sensations, depending on the energy status of the body (Muller, 1840). Sturge (1883) was the first to suggest central nervous system involvement in pain, proposing that pain occurring in a set of spinal nerves could activate afferent nerves in close proximity, altering sensations in another dermatome and resulting in so called referred pain (Sturge, 1883). Ross (1888) and Mackenzie (1909) supported this theory further, stating that infraspinal cord activation affected not only altered pain trafficking but also motor and sensory neurons (Mackenzie, 1918; Ross, 1888). In the late 1890s, Max Von Frey and Henry Head advanced sensory pain theory, proposing that the skin was composed of four specialized sensory bulbs: temperature, pressure, chemical, and pain nerve endings or receptors (Head, 1893; von Frey, 1894). These conceptualizations of pain are consistent with specificity pain theory, which suggests that specific tissue pain receptors (such as nociceptors), were responsible for

transmitting pain information (Gedaly-Duff & Burns, 1988; Kim, 1980) directly to the pain center in the brain (Adams & Bromley, 1998). Both specificity and pattern theories propose that pain severity is dependent on the extent of tissue and nerve damage (Brannon & Feist, 2000; McCance & Huether, 1990).

Neuropathic Pain Theory

Neuropathic pain theory moves beyond understanding neurophysiologic mechanisms of pain and provides a pathophysiological theory of pain. More than two decades ago, pain of pathophysiological origin was described and subsequently categorized as neuropathic pain. This theory suggests neuropathic pain, which offers no protective purpose, originates from nerve dysfunction or disruption within the peripheral nervous system (PNS) or central nervous system (CNS) (Dworkin, Backonja, Rowbotham, Allen, Argoff, Bennett, Bushnell, Farrar, Galer, & Haythornthwaite, 2003; Kehlet, Jensen, & Woolf, 2006; Treede et al., 2007; Woolf, 1989; Woolf & Mannion, 1999). Chronic neuropathic pain states occur when nerve injury or dysfunction leads to neuroplastic changes and extends beyond the point of the original injury (Costigan et al., 2009; Devor, 2001; Dworkin, Backonja, et al., 2003b; Woolf & Mannion, 1999). Related to nerve destruction, phantom pain following amputation is an example of chronic neuropathic pain (Gedaly-Duff & Burns, 1988; Melzack & Wall, 1965).

Neuropathic pain theory has been supported using pharmacological strategies. Assuming that neuropathic activity at afferent nerves results in muscle spasm and headache pain, Jakubowski and colleagues (2006) investigated whether onabotulinum toxin A (BTX-A), a paralytic neurotoxin, would eliminate headache pain. BTX-A enters motor neurons and disrupts acetylcholine release, thereby inhibiting afferent nerve impulse transmission and muscle tone (Lalli, Bohnert, Deinhardt, Verastegui, & Schiavo, 2003; Volknandt, 1995). They found that

BTX-A muscle paralysis was effective in relieving tension-type headache pain caused by neuropathic nerve firing and subsequent muscle spasm (Jakubowski et al., 2006). (5 or 6 double blind, placebo controlled studies investigated botox for tension type headache, and all found no benefit).

Neuropathic pain has been shown to be related to activity at voltage-gated sodium and calcium channels, which activate specific nociceptors involved in pain (Bell, Thaler, Castiglioni, Helton, & Lipscombe, 2004; Bowersox et al., 1996; Matzner & Devor, 1994). Thus, it is hypothesized that antagonists to these channels would decreased pain. The ability of Lidocaine and carbamazepine to antagonize selective sodium channels and diminish neuropathic pain has been established (Kastrup, Petersen, Dejgard, Angelo, & Hilsted, 1987; Treede et al., 2008). Recently, Sheets and colleagues (2008) investigated the effects of lacosamide for managing neuropathic pain compared to active controls carbamazepine and lidocaine. Lacosamide, an agent shown to have specificity on three peripheral nociceptive neurons, targets three therapeutic sodium channels: $Na_v1.3$, $Na_v1.7$, and $Na_v1.8$. The investigators found that although all three drugs effectively antagonize sodium channels, lacosamide exhibited greater specificity. Lacosamide was superior in selectively antagonizing neuronal activity resulting from chronic depolarization associated with nerve injury and neuropathic pain, suggesting its potential analgesic superiority compared to lidocaine or carbamazepine (Sheets, Heers, Stoehr, & Cummins, 2008).

Pain processing and transmission involves peripheral and central neurological components (Charles & Baca, 2013; Dodick & Silberstein, 2006a). With peripheral nerve injury, neuronal excitation is transmitted to the spinal cord and higher pain centers. Abnormal pain processing, such as that seen in neuropathic pain, can result in allodynia, which is painful

responses to normally innocuous stimulation. In a third study, assuming neuropathic pain occurs from central neuronal dysfunction, Burstein and colleagues investigated in rats the posterior thalamic involvement in modulating hypersensitivity and allodynia. Allodynia is pain experienced in response to normally non-noxious stimuli and in areas other than the point of stimulation (Burstein et al., 2010). Following stimulation of the posterior thalamus to mimic central sensitization from nerve injury or dysfunction, investigators found hypersensitivity and allodynia was present, supporting their hypothesis. This study supports neuropathic pain theory, finding that stimulation of brain pain centers, including posterior thalamus and resultant aberrant nerve dysfunction, appear to be involved in neuropathic pain development.

Pain Theories with both Psychological and Physiological Components

As early as 1890, the scientific literature recognized pain as containing both psychological and physiological aspects (Naunyn, 1889). Specificity and pattern pain theories were critical steps in interpreting and understanding pain, although neither could explain why pain was experienced so differently across individuals.

Melzack (1965), building on these theories, developed the Gate-Control Theory (GCT), the best-known theory of pain, in which both physiological and psychological aspects are appreciated (Melzack & Wall, 1965). The physiologic component of GCT considers sensory discriminative aspects of pain with respect to intensity, quality, and location. Psychological dimensions of pain in GCT are 1) evaluative; and 2) affective – motivational. These two dimensions together provide subjective meaning to the experience of pain (Melzack & Wall, 1965; Sparks, 2001; Summers, 2000). Thus, GCT explains pain transmission and modulation from periphery to spinal cord pain systems, with affective contributions occurring in the central nervous system (Kim, 1980; Melzack, 1973; Melzack & Wall, 1965; Perl, 2007). In this theory,

fast-firing (A-delta) conduction overrides the slow-firing (C-fiber) conduction unless there is destruction in this nerve conduction system, in which case the slow dominates the fast. GCT explains how nerve dysfunction that specifically involves peripheral and central pain processing components contributes to a slow, diffuse, burning pain and/or hyperalgesia. Melzack and Wall (1965) proposed in GCT that pain information transmitted via specific fibers can be interrupted by closing "pain gates" at the spinal cord level prior to reaching higher processing centers. For example, peripheral tactile stimulation such as rubbing or touching activates larger primary afferent A-fibers, thereby blocking smaller unmyelinated C-fibers transmitting ascending pain information. Similarly, cognitive distraction interventions transmit descending pain information, inhibiting pain pathway transmission. Both successfully close pain gates, thus modifying pain perception (McEwen, 2007; Melzack & Wall, 1965).

Providing evidence that cognitive distraction decreases pain experience because of descending pain “gates,” Good and colleagues (2005) found that music and relaxation significantly reduced pain, facilitating ambulation following intestinal surgery (Good, Anderson, Ahn, Cong, & Stanton Hicks, 2005). Tse and colleagues, guided by GCT, in an interventional crossover design study with forty healthy control individuals, found that cognitive distraction with visual video display successfully improved pain tolerance and increased pain thresholds with tourniquet pain (Tse, Ng, Chung, & Wong, 2002).

The success of electrical stimulation for pain relief (electroanalgesia), first described by Wall and Sweet (1967) (Wall & Sweet, 1967), supports the theory that counter-stimulation can relieve pain by closing gates for ascending nerve transmission. Electrical stimulation, also known as transcutaneous electrical nerve stimulation (TENS), blocks large afferent peripheral nerve transmission, interrupting pain information. It has been shown to successfully improve walking,

gait distance, and vital capacity following abdominal surgery (Rakel & Frantz, 2003; Sharma, Aggarwal, Bahadur, & Gupta, 2011; Walsh, Howe, Johnson, & Sluka, 2009); and to reduce knee joint pain in animals at 4 and 24 hours, and 2 weeks following intra-articular injection with chemical agents known to induce inflammatory pain (Vance, Radhakrishnan, Skyba, & Sluka, 2007). These studies provide empirical evidence supporting the adequacy of GCT to implement interventions by successfully closing ascending and descending "pain gates" to improve both affective and physiological aspects of pain experiences, thus improving outcomes.

The Theory of Unpleasant Symptoms (TOUS) builds on Melzack and Wall's conceptionalization of pain as a psycho-physiological sensory experience by evaluating both psychological and physiological aspects of pain. Proposed by Lenz, Pugh, Milligan, Gift, and Suppe in 1995 (and updated in 1997), the goal of the TOUS was to assist nurses in identifying, predicting, and managing multiple unpleasant symptoms in varying patient populations and settings. The 1997 theory revision included the basic model content but added bidirectional arrows between antecedents, appreciating the relationships among baseline factors. The fundamental premise of TOUS is that previous physiological (e.g., comorbidities and/or disease stage), psychological (e.g., mood, anxiety, uncertainty, depression), and situational (e.g., support, environment, resources) factors can influence the characteristics of an unpleasant symptom or symptoms, which further affects functional and cognitive performance (including physical activity, activities of daily living, and social and role performance). Thus, the TOUS has the capacity to guide multi-symptom nursing research in many situations (Lenz, Suppe, Gift, Pugh, & Miligan, 1995; McEwen, 2007).

In a study by Kless (2010), results indicate that advanced age and poorer physical status levels are predictive factors for moderate to severe postoperative pain following abdominal

surgery. These results support the TOUS framework and Kleiss's understanding that pain experiences are physiological and psychological and influenced by antecedent factors (Kless, 2010). In a similar study to evaluate outcome, a concept represented in TOUS, Tofthagen (2010) found that nurses' were able to identify and predict neuropathic symptoms and their effect on functioning following chemotherapy treatment (Tofthagen, 2010).

Similarly, the TOUS supported Kurian and Hemalatha's (2011) study to identify any correlation between children's self-report with FACES and nurses' pain assessment with FLACC (faces, legs, activity, cry, console ability) of medical, surgical, and procedural pain. Even though this study included TOUS concepts, it was primarily a test of validity for FLACC and FACES. Findings included a strong correlation ($p=0.771$) between children's self-report scores with FACES and nurses' assessment scores with FLACC, indicating the two scales are comparable. These findings will help improve pain assessment and promote pain management for children, regardless of age, communication skills, development stage, and previous antecedents (Kurian & Hemalatha, 2011).

Spector and colleagues' study (2002) examined timing of two concepts, symptom (pain) and outcomes (performance, quality of life), following two different types of surgical procedures performed for gastrointestinal cancer. The mere presence of symptoms lowered quality of life (QOL) scores, and scores lowered further as symptoms frequency increased. Psychological aspects such as distress further lowered QOL, and socialization was affected by symptoms, although family and friend connections were maintained. Although TOUS concepts were supported by this study, the primary aim was a comparison of outcomes and symptoms between two gastrointestinal cancer surgical procedures. Researchers concluded that these findings will

assist nurses to individualize patient symptom management, based on the surgical procedure (Spector, Hicks, & Pickleman, 2002).

Summary of Pain Theories

As reviewed above, theories of pain provide important constructs and relationships to understand pain and pain experiences. Both specificity and pattern theories were important first steps in the identifying specific pain receptors and the role of the nervous system in pain (Dallenbach, 1939; Melzack, 1973). Physiological pain theories identified specific nerve receptors and transmission pathways as useful constructs for exploring pain and pain relationships. Neuropathic pain theory suggests pain constructs in which pain may result from nerve dysfunction, trauma, or disease, and clarifies nerve involvement and dysfunction in the relationship between specific pain disorders and involved pathways. This theory critically influences this proposed study because it describes pain resulting from dysfunctioning nerve activity resulting in neuropathic syndromes, including trigeminally mediated pain disorders. Together, these theories provide the conceptual basis of this proposed study. Physiological pain theories suggest that EFS headache most likely has a neurological source, while neuropathic pain theory supports the theory that EFS headache pain follows nerve trauma that occurs during surgical dissection and results in pain due to nerve dysfunction and aberrant neuronal activity.

Advancing from more rudimentary pain theories, the GCT offers specific ideas about pain gates that mediate ascending and descending pain transmission. In addition to the physiological aspects of pain, GCT includes psychological components such as mood, anxiety, and uncertainty, recognizing these potential contributors as influential features in pain experiences and outcome. Like TOUS, this important perspective appreciates pain as a multidimensional complex experiences, requiring pain management strategies and predicting

outcomes based on individual experiences and not specific pain disorders alone. Informing the proposed study, these theories support an understanding of both physiological and psychological features that contribute to a more holistic understanding of pain experiences. The GCT, which encourages consideration of psychological and functional responses to pain, and the TOUS, which identifies antecedents and their potential effect on pain experiences, will together provide the theoretical foundation for this study.

Symptoms Management Theory

For this proposed study, a theoretical framework which includes the constructs of symptoms experience, management, and outcomes, the University of California San Francisco Symptoms Management Theory (UCSF-SM) will be used to investigate postsurgical EFS headache pain. (Figure 4) The theory was developed by faculty at the University of California, San Francisco in 1994 to improve upon previous theories of self-care (i.e., Orem, 1983 and Sorofman, et al., 1990) by including the patient's experience, management strategies, and desired outcomes (Larson, 1994; Orem, 1983; Sorofman, 1990) to health status. The model comprises three major constructs in a multidimensional process emphasizing the relationships among 1) perceived symptom (experience, response and evaluation), 2) management approach, and 3) outcome, with the basic assumption that for effective symptom management, all three must be considered (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, & Rankin, 2001; Larson, 1994; Larson et al., 1999). The theory constructs are embedded in the nursing science metaparadigm of person, including the following: 1) demographics (sex, age, ethnicity, marital status, and financial status); 2)psychological (personality traits, cognitive, and motivation), sociological (family unit, culture and religion), physiological (activity patterns and physical capacity), and developmental variables; 3) health and illness, which includes risk factors

(behavioral hereditary and/or behavioral), health status (physiological rhythm, bodily structure and function), and disease or injury (acute or chronic deviations due to pathology); and 4) environment, which includes physical, social, ethnic and cultural variables (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, Rankin, et al., 2001; Fawcett, Watson, Neuman, Walker, & Fitzpatrick, 2001). Being consistent with the nursing metaparadigm, the UCSF-SM theory supports research that focuses on the complexity of the whole patient with a multitude of influencing factors affecting health outcomes.

In 2008, the UCSF-SM was revised and renamed the Symptoms Management Theory (SMT) so that the model better considered symptom *clusters* (e.g., inability to eat, nausea and vomiting, depression, inability to sleep, breathing difficulties such as wheezing, and coughing) (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, & Rankin, 2001; Humphreys, Houston, et al., 2008). Pain is specifically identified in the SMT as a sensory emotional symptom cluster that can be self-perceived, responded to, and evaluated.

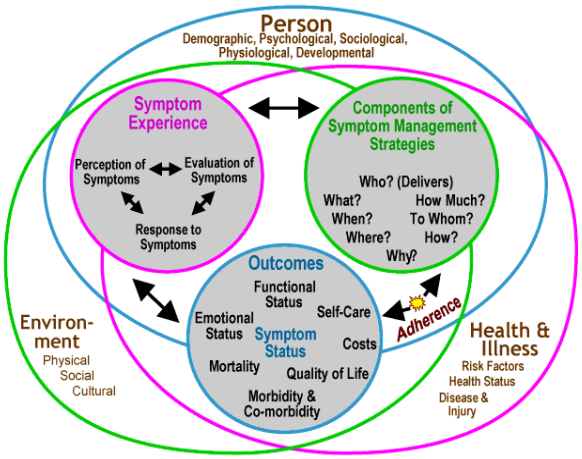


Figure 4.

University of California San Francisco Symptoms Management Theory. Reprinted with permission from Dodd M, Janson S, Facione N, Faucett J, Froelicher ES, Humphreys J, Lee K, Miaskowski C, Puntillo K, Rankin S,

Taylor D. (2001). Advancing the Science of Symptom Management. Journal of Advanced Nursing, 33(5), 668-676.

Assumptions underlying SMT are consistent with those of the proposed study, including: 1) The gold standard for the study of symptoms is based on the perception of the individual experiencing the symptom and his or her self-report; 2) management strategies may be targeted to the individual, a group, a family, or the work environment; 3) symptom management is a dynamic process – that is, it is modified by individual outcomes and the influences of the nursing domains of person, health/illness, or environment (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, & Rankin, 2001).

Strengths of the SMT model are its flexibility and ability to offer valuable information regarding the relationship between self-reported patient symptoms, management, and outcomes (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, & Rankin, 2001; Larson, 1994; Smith & Liehr, 2008). The framework organizes concepts (pain experience, pain management, and outcomes) broadly and therefore is useful across different populations experiencing a symptom. Weaknesses include limited appreciation of the relationships between adherence and the three conceptual components; the complex multifactorial nature of the model; and lack of consideration of the effect of time, limiting its longitudinal applications (Smith & Liehr, 2008). The framework has been supported in studies of symptoms of dyspnea, fatigue, and depression with breast cancer and HIV (Van Onselen et al., 2010; Voss, Portillo, Holzemer, & Dodd, 2007), pain in children with sickle cell (Jacob et al., 2003), and pain in infants with brain injury (Bay & Bergman, 2006)

The theory that guides the proposed study is deduced from the SMT. (Figure 5) With respect to headache pain symptom following EFS, theory concepts include self-reported EFS headache pain (**symptom experience**), analgesic management strategies (**symptom**

management), and the impact of these on emotional and functional status (**outcome**). In addition, appreciating the role estrogen may play in EFS, estrogen status (HRT vs. no HRT) is included as a moderating variable, reflecting the SMT construct of health status (physiological rhythm).

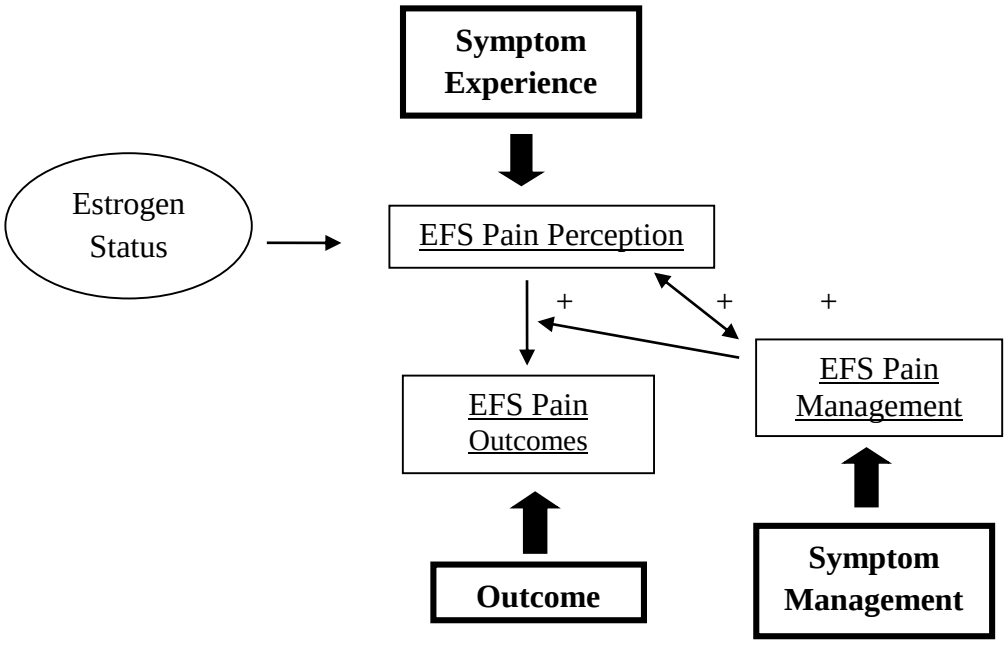


Figure 5.

EFS Headache Theory

Bold Boxes = SMT Constructs

EFS Headache Pain Experience

For this proposed study, the experience of headache pain following EFS will be first construct examined. Symptoms experienced rely entirely on the personal perceptions, feelings, and sensations of the individual undergoing EFS; thus sensory information must be confirmed by the experiencing person (Rhodes & McDaniel, 1999). Based on the SMT model, symptom experience is defined as a dynamic process involving the patient's self-interpretation of the pain's severity and treatability, as well as the effects of EFS headache. Derived from the SMT framework, the subconcept, perception of EFS headache pain, will be examined (Humphreys,

Lee, et al., 2008). Perception of EFS headache pain is based on the individual's interpretation of his or her personal sensory information (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, & Rankin, 2001; Larson, 1994). For this proposed study, the concept of EFS pain evaluation is the independent variable.

EFS Headache Pain Management

The second construct in the SMT, symptom management, is defined as the biomedical, professional and self-care strategies used to offer easing, elimination, or reduction of undesirable symptoms. According to the SMT, there are three means of accomplishing symptom control: minimizing or preventing symptom occurrence, reducing symptom intensity, and alleviating response to the symptom or outcome. Management specifics are defined as follows: "who or to whom" refers to the individual providing symptom management or to the patient, who is often responsible for and active in his or her own symptom management; "what" refers to the name of the pharmacologic or nonpharmacologic management strategy used; "where" refers to home or laboratory; "when" refers to timing of strategy or dose; and "how and how much" refers to actual delivery of management or may be compared to environmental variations in an intervention (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, Lee, Miaskowski, Puntillo, & Rankin, 2001).

Based on this construct, the EFS model conceptualizes symptom management as analgesic use patterns. This construct will guide this study to evaluate pain management medication patterns and efficacy. Symptom management will be examined and operationalized as the type and amount of analgesics used by individuals for headache pain following EFS, and will include name and efficacy. For this study, EFS pain management is a mediating variable because it mediates the relationship between two concepts, EFS pain perception and EFS pain

outcomes, such that when management is successful, pain perception and outcome will improve, and when pain management is unsuccessful, pain perception and outcome will be unchanged or further deteriorate.

EFS Headache Pain Outcomes

The third major construct of the SMT, symptom outcome, is defined by theorists as the costs or negative impact of the symptom in eight domains: symptom status, self-care, financial costs, quality of life (QOL), emotional status, functional status, morbidity and comorbidity, and mortality (Smith & Liehr, 2008; The University of California San Francisco. Larson, 1994). Based on the SMT, the EFS model will examine two symptom outcomes of EFS headache pain in women following EFS: emotional status and functional status.

Emotional status has been operationalized in the headache literature to include disruption in normal emotional status by symptoms such as anxiety, irritability, worry, fear, frustration, and depression (Lipton, Liberman, et al., 2003; Peterlin et al., 2010; Stovner & Hagen, 2006). For this study, the definition of emotional status includes general health, vitality, social functioning and role, and emotional and mental health following EFS. Functional status reflects participants' ability to maintain normal daily activities and has been operationalized as a disruption in the ability to maintain normal social activities and daily routine at work and at home, that may require bed rest (Brandes, 2009; Dueland et al., 2004; Lipton et al., 2001). For this study, the construct *outcomes* is a dependent variable.

Estrogen

As noted, contextual variables in the SMT are organized by the nursing metaparadigm of Person, Environment, and Health and Illness. Contextual variables affecting an individual's pain perception include person, health, and illness (Larson, 1994).

The Health and illness construct of the SMT includes risk factors, health status, and disease or injury, all of which determine an individual's symptom response. Included in health status are inherent physiological variables that influence symptom perception, which in this study is the relationship between EFS headache pain and estrogen levels.

It has been established that estrogen directly contributes to neuronal activity in the peripheral and central nervous systems, which in turn contributes to varying excitability and nociception (Bereiter, 2001). For women, there are two distinct phases during the menstrual cycle, luteal phase when estrogen levels are highest and follicular phase when estrogen levels are lowest. (Table 1) These phases contribute to different pain perceptions, with evoked ischemic muscle and pressure pain reported to be lower during the follicular phase compared to luteal phase (Riley III, Robinson, Wise, & Price, 1999). It has been concluded that estrogen is a contributing factor in why women experience more neuropathic pain disorders, including migraine and trigeminally mediated pain than men (LeResche, 1997; Lipton, Bigal, et al., 2007a; Lipton, Bigal, et al., 2007c).

Table 1

Monthly hormonal fluctuation (Martin & Behbehani, 2006a)

Follicular Phase	Early estradiol-25-50 pg/ml progesterone <1ng/ml	Mid estradiol-25-50pg/ml progesterone <1ng/ml	Late estradiol-100-400 pg/ml progesterone >1ng/ml
Luteal Phase	Early estradiol-100-400 pg/ml progesterone <1ng/ml	Mid estradiol-200-300 pg/ml	Late estradiol-25-50 pg/ml progesterone <2ng/ml

The migraine community has identified and classified one type of headache, menstrual migraine, based on the fact that it coincides monthly with cyclical estrogen fluctuations (Granella et al., 2004). Specifically, pain in migraine and trigeminally mediated disorders are reduced

when estrogen levels are sustained, whether due to estrogen being low during menopause with menstrual cycle cessation, or high during the second and third trimester of pregnancy (Brandes, 2006c; Craft, 2007; LeResche et al., 2005; Mueller, 2000). However, sudden abrupt drops in estrogen, such as occurs following ovulation or childbirth or with surgical hysterectomy, lowers pain thresholds leading to greater pain intensity and perception (Brandes, 2006a). Such sudden drops in estrogen may negatively influence pain perception following EFS. In migraine, oral hormone replacement therapy (HRT) for menopausal vasomotor symptoms contributes to higher pain perception than transdermal applications (Li et al., 2002; Nappi et al., 2001). For this study, estrogen health status by self-report will be operationalized by menstrual cycle phase, use of hormone replacement therapies (oral or transdermal), and history of hysterectomy with or without removal of ovaries.

The following relationships or propositions amongst study concepts are hypothesized. EFS headache pain perception (symptom experience, defined as intensity, duration, location and quality) is affected both directly and indirectly through symptom management. The EFS individual experiencing headache pain will manage EFS pain with prescribed medications. There is a positive correlation between pain management and pain perception if symptom perception continues when medications prescribed are ineffective and more medications are consumed in an attempt to manage headache pain. If medications are effective, there will be a negative correlation between pain management and pain perception because when pain perception is reduced, less medication will be consumed. Symptom management is a mediator of the relationship between pain perception and outcome (emotional and functional status). In the event that pain management is not effective in controlling pain, pain perception scores will increase and outcomes will decrease, and there is a negative correlation between symptom perception and

outcome. If pain is adequately managed, the relationship between pain perception and outcome will have a negative correlation, pain perception will decrease, and outcomes will increase. If effective pain medication improves pain perception, then outcomes improve, pain perception scores will decrease, and outcome scores will increase. Symptom perception can negatively or positively influences both symptom management and outcome. As pain perception increases, there is a positive correlation between symptom management and outcomes, medication consumption will increase and emotional and functional status will deteriorate. If symptom perception is decreased, pain medication consumption decreases and outcomes improve, which is a negative correlation. Estrogen as a moderator can only influence one variable. In this study estrogen (HRT) will be considered a moderator EFS headache pain perception experience only. A strong negative correlation is suggested if estrogen levels drop suddenly, worsening headache pain and elevating pain perception scores.

Chapter Summary

To contribute to nursing knowledge in a meaningful way, it is critical to engage in research that is both philosophically sound and theory-based. Empiricism values measureable sense data as contributing to the advancement of scientific knowledge and empirical methodology, thus providing the foundation for this proposed study. Specifically, the empiricist methodology supports this study's goal of using validated measures to objectively gathering data on EFS headache pain, as experienced by women following EFS.

In search of theoretical support for this study, a review and evaluation of extant pain theories was conducted. While several theories reviewed provide fundamental understanding upon which this work is based, the SMT was found most suitable to explore and describe headache pain following EFS. Deduced from the SMT, the EFS theory incorporates pain

symptom perception, symptom management, and outcomes and the relationships among them. Included in the EFS theory is the effect of estrogen on the EFS headache pain experience. With the guidance of the EFS theoretical framework, these study findings will reveal postoperative EFS headache pain characteristics, efficacy of current symptom management, and the effects of headache pain on emotional and functional status outcome. This theory predicts that medication use acts as a mediating variable affecting the relationship between headache pain perception and outcome such that if medications are not effective, EFS headache pain will not be alleviated and outcome ratings will decrease. If medications are effective in managing EFS headache, pain perceptions will decrease pain scores, and outcomes ratings will improve. Estrogen is predicted to act as a moderator to EFS headache pain perception.

CHAPTER 3: LITERATURE REVIEW

Introduction

This chapter provides a summary of past research that has examined concepts relevant to this study. In the previous literature on headache pain experiences following EFS, EFS pain appears to be a trigeminally mediated pain.

Literature on neuropathic pain disorders with trigeminal origin with similar effects were reviewed, as were study constructs of headache pain perception that included intensity, quality, duration, and location, management strategies and their effectiveness, emotional and functional status, and outcomes. In that migraine is the most common and extensively research trigeminally mediated headache pain, migraine literature was reviewed and used as an analogous model for EFS headache pain. Finally, the role of estrogen in trigeminal headache was reviewed. Together, these reviews provide the basis for an evaluation of the relevant literature and of the state of the science in understanding EFS headache pain.

Endoscopic Foreheadplasty Surgery and Endoscopic Foreheadplasty Headache

The EFS procedure is an outpatient surgery designed to reverse the signs of aging in the face (Foustanos & Zavrides, 2006; Isse, 1994; Keller & Mashkevich, 2009; Nassif, 2007) (Figure 3). As we age, gravity and loss of elasticity in facial tissue leads to permanent skin creases and sagging of the forehead and eyebrows. Deep permanent lines and wrinkles develop in the glabella and forehead from hypertonicity and downward pull of the depressor muscles, orbicularis occuli, procerus and corrugator supercilii (Knize, 2009) (Figure 4).

To soften forehead lines and wrinkles, surgeons performing EFS, make 3-5 small scalp incisions in the hairline for instrumentation and endoscope insertion. EFS dissection includes the separation of forehead tissues from the skull by lifting, stretching and detaching tissues in areas

of trigeminal nerve distribution. Once forehead to skull attachments are released, tissues underlying previous wrinkled areas are weakened by cutting, debulking, or cauterization (Daniel & Tirkanits, 1996; Foustanos & Zavrides, 2006; Jones & Grover, 2004; Puig & LaFerriere, 2002b; Tower & Dailey, 2004). External devices, such as glues, screws, or sutures, are used to permanently fasten newly aligned tissues to a more youthful anatomical position (Patel, 2006a).

Endoscopic brow lift, forehead lift, browplasty, and foreheadplasty are all synonymous terms for this minimally invasive surgical procedure first described in the early 1990s by Keller and Vasconez (Keller, 1991; Romo, Jacono, & Sclafani, 2001; Vasconez, 1992; Vasconez et al., 1994). The innovative procedure quickly grew in popularity and provides rejuvenation outcomes similar to the gold standard coronal forehead lift. EFS advantages include shorter incisions, translating to shorter scars, shorter surgical time, less edema and bleeding, less alopecia, decreased scar widening, and shorter recovery time compared to the gold standard coronal browlift (Dayan, Perkins, Vartanian, & Wiesman, 2001; Isse, 1994).

An exhaustive search in Pubmed and Cinahl Plus using key terms "foreheadlift," "foreheadplasty," "endoscopic foreheadlift," "endoscopic foreheadplasty," "endoscope," "browlift," and "headache" or "pain" was conducted. Surprisingly, no EFS research was found that mentions postoperative headache pain. Since its introduction, the majority of research on the EFS procedure focuses primarily on anatomical dissection, surgical techniques, and aesthetic outcomes, most often comparing results to the gold standard open coronal forehead lift (Keller, Gregory 2009; Knize, David, 2009; Kim, Brian, 2009; Dayan, Steve, 2001). In an effort to maximize aesthetics and longevity of these outcomes, surgeons have tested various tissue fixations following forehead dissection, elevation, and repositioning, including bioabsorbable devices, wires and plates, temporary and permanent screws, sutures, and adhesives (glues)

(Chasen, 1999; Foustanos & Zavrides, 2006; Holzapfel & Mangat, 2004; Jones & Grover, 2004; Landecker, Buck, & Grotting, 2003; Sidle, Loos, Ramirez, Kabaker, & Maas, 2005; Smith, 1996).

This review revealed only 3 studies on EFS surgical procedures, none of which directly examine EFS headache, and what is described regarding EFS headache is conflicting. In the classic surgical review paper, Patel describes EFS anatomy, forehead dissection, and fixation, speculating that postoperative issues associated with EFS are attributed to injury to the trigeminal nerve (Patel, 2006b). Albeit without supporting data, he suggests that trigeminal nerve manipulation contributes to postoperative nausea and pain following EFS. Suggesting a moderating role for estrogen, he continues, stating postoperative nausea and vomiting is three times more likely in women who are menstruating premenopausal (Patel, 2006a). In a second review paper, Nassif (2007) describes patient selection for EFS, anatomical dissection, and the use of absorbable suture fixation. With respect to postoperative sequelae, Nassif mentions that patients may experience minimal pain and headache (Nassif, 2007).

With respect to research, only 2 articles could be found that referred to EFS headache, and neither focused on headache pain as a primary outcome. In the first, Jones and Grover (2004) evaluated EFS aesthetic outcome, comparing two fixations, fibrin glue (N=189) versus suture fixation (N=349), for 538 women with a mean age of 50.3. Results and outcomes between the 2 groups were similar at one month evaluation. However, with fibrin glue fixation, pupil to brow distance (aesthetic outcome) was significantly less and lacking in sustainability (5.93 to 3.79 mm; $p< 0.01$), compared to suture outcome (6.21 to 6.16 mm; $p=0.34$), from one month to 9 months (Jones & Grover, 2004). No specific data were reported regarding postoperative experiences, although the authors stated that "short-term postoperative headache was common,

and one patient in the suture group experienced severe neurologic pain in the right frontal area that persisted for more than a year and was refractory to treatment" (Jones, 2004, p.1245). Specific data on headache pain were not provided.

In a similar study, Foustanos and Zavrides (2006) compared EFS outcomes using a convenience sample of patients (N=300); researchers compared patients with an absorbable suture fixation versus other previously used alternative fixation methods. Following subperiosteal dissection, results were evaluated at 1 week, 2 weeks, 1 month, 3 months, 6 months, and yearly. They found postoperative complications, including swelling, ecchymosis, apraxia (inability to perform motor functions due to nervous system disorder or damage), and forehead and scalp sensation changes. Facial nerve stretching during surgical dissection was reported to contribute to postoperative frontal apraxia (N=4), which resolved in 3-4 months. Incision site alopecia was also observed (N=7) and later excised for aesthetic purposes (Foustanos & Zavrides, 2006). Contradicting Jones & Grover, Foustanos reported that "short-term postoperative headache or severe neuralgic pain was not seen" (Foustanos, 2006, p.603).

Thus, literature on EFS headache pain is sparse and contradictory, and lacks empirical evidence. While there is evidence that EFS headache occurs (Nassif, 2007, Jones & Grover, 2004) and is likely due to manipulation of the trigeminal nerve during dissection (Patel 2006a), empirical evidence for its severity, management, and outcome is lacking. Clinical observation and anecdotal reports have revealed that postoperative EFS headache is moderate to severe, bilateral, throbbing, and unrelieved with currently prescribed medications, affecting emotional and functional status. No literature was found that offered any postoperative management recommendations following EFS or consideration of effects of headache on emotional and functional status.

Trigeminally Mediated Pain

It has been suggested that, due to involvement of trigeminal nerve in EFS dissection, headache pain following EFS is a trigeminally mediated pain (Patel, 2006b). While postoperative pain typically has a strong nociceptive pain component as a result of tissue damage, EFS headache pain appears to involve inflammatory and neuropathic pain resulting from tissue and trigeminal nerve trauma occurring during surgical dissections (Patel, 2006b).

The trigeminal nerve, the largest cranial nerve, is responsible for sensory and motor innervation to extracranial (skin, muscle, periosteum, and arteries) and intracranial (dural and cerebral arteries and veins) structures of the face and head (Dubner, Sessle, & Storey, 1978; Ray & Wolff, 1940; Zhang, Strassman, Burstein, & Levy, 2007). The most superior branch, ophthalmic (V1), carries sensory information for the upper face, including scalp, forehead, upper eyelids, conjunctiva and cornea, frontal sinus, and nose. The middle maxillary (V2) branch carries sensory innervation for the midface to the maxillary, sphenoid, and ethmoid sinuses, lower eyelids, cheek, upper lip, upper teeth and gums, soft palate, and part of the meninges and pharynx. The lowest mandibular (V3) branch carries both sensory and motor information to the lower lip, external ear, lower teeth and gums, jaw, chin, and mouth (Gray, 2003; Zhang et al., 2007) (see Figure 5). As EFS surgical dissection involves only the V1 and V2 trigeminal nerve branches, V3 is not believed to be involved in the subsequent headache pain. Dural and cerebral arteries, including veins and middle meningeal and external carotid arteries, are surrounded by sensory fibers originating from neurons in the trigeminal ganglion.

Injury to the trigeminal nerve initiates a cascade of neurological and inflammatory events, including activation of meningeal pain fibers A-δ and C-fibers (Goadsby, Edvinsson, & Ekman, 1988; Olesen, Burstein, Ashina, & Tfelt-Hansen, 2009). Potent neuropeptide

vasodilators, including calcitonin gene-related peptide (CGRP) and substance P (SP), and hormones such as histamine, serotonin, bradykinins, and prostaglandins are released producing neurogenic inflammation, dura inflammation, vasodilation, excitability, dura mast cell degranulation, and intracranial hyperalgesia, resulting in trigeminally mediated pain disorders such as trigeminal neuralgias and migraine headache pain (Burstein, 2001; Dworkin, Backonja, Rowbotham, Allen, Argoff, Bennett, Bushnell, Farrar, Galer, & Haythornthwaite, 2003; Goadsby, 2009; IASP, 2008; Moskowitz, 2008; Moskowitz, Brody, & Liu-Chen, 1983; Sorkin & Yaksh, 2009; Vadivelu & Sinatra, 2005). In that the headache pain of migraine is qualitatively similar to that of EFS and appears to share neurogenic mechanisms, the examination of the latter is guided by understanding of the former. The International Association for the Study of Pain (IASP) defines trigeminally mediated pain disorders as craniofacial neuropathic pain syndromes associated with trauma, tumors, aneurysms, and surgery, and which occur in sensory distribution areas of the trigeminal nerve (Svensson, Jadidi, Arima, BAAD HANSEN, & Sessle, 2008). Painful trigeminally mediated dysfunctions and disorders include trigeminal neuralgia, postherpetic neuralgia, posttraumatic painful peripheral neuropathy, periodontal pain, temporomandibular joint disease, orofacial pain, and the relatively common migraine (Bennett, 2004; Burstein, 2001; Campbell & Meyer, 2006; Goadsby, 2009; Lipton et al., 2004; Messlinger, 2009; Xu et al., 2008). (Table 2)

Table 2

Trigeminal nerve mediated pain disorders

Pain Disorders	**Intensity**	**Quality**	**Duration**	**Medications Prescribed**
1) Migraine	Moderate to Severe	continuous pulsing or throbbing, unilateral or bilateral	4 ≥72 hours	Triptans, tricyclic antidepressants, anticonvulsants, and potent opioids (Jakubowski, Levy, et al., 2005)
2) Trigeminal Neuralgia	Severe to Excruciating	severe sudden sharp, stabbing, or electric, unilateral	minutes hours	carbamazepine, oxcarbazepine, baclofen, gabapentin, lamotrigine, phenytoin and BOTOX; and microvascular decompression or balloon compression surgeries, radiofrequency thermocoagulation, rhizotomies, alcohol branch blockade and stereotactic gamma knife radiosurgery (Cheshire, 2007; Eller et al., 2005; Ngeow & Nair, 2010)
3) Postherpetic Neuropathy	Moderate to Severe	burning, stabbing, aching, unilateral or bilateral	weeks to decades	Gabapentin, topical lidocaine, and opioids (Dworkin, Backonja, Rowbotham, Allen, Argoff, Bennett, Bushnell, Farrar, Galer, & Haythornthwaite, 2003)
4) Posttraumatic painful peripheral neuropathy, atypical odontalgia, & temporal mandibular joint disorder	Moderate to Severe	unilateral, pulsating, constant/persistent, headache pain	variable (days to > 6 months)	NSAIDs, tricyclic antidepressants, anticonvulsants, and potent opioids (Baad-Hansen, Leijon, Svensson, & List, 2008; Finnerup, Sindrup, & Jensen, 2010; Kanai, Segawa, Okamoto, Koto, & Okamoto, 2009; List et al., 2007)

Probably the best known example of these types of trigeminally mediated headache pain is migraine. Migraine is classified as a neurological dysfunction resulting in peripheral and central sensitization (Burstein, 2001; Burstein, Cutrer, & Yarnitsky, 2000; Goadsby, 2009; Lipton et al., 2008). Experienced several times a month by over 30 million people in the United

States (Bigal, Rapoport, Lipton, Tepper, & Sheftell, 2003; Brandes, 2006c; Burstein, 2001; Goadsby, 2009; Lipton et al., 2004; Messlinger, 2009), this episodic headache pain is described as moderate to severe with continuous pulsing or throbbing lasting hours to days (Burstein, 2001). The 'drivers' of migraine headache are believed to be meningeal nociceptors, which are modulated by the inhibitory facilitator neurons in the periaqueductal gray (PAG) and in the ventromedial medulla (Burstein & Jakubowski, 2005). Dysfunction in the trigeminothalamic tract neurons and modulation via the brainstem are thought to be integral in development of migraine headache pain (Burstein, 2001; Burstein & Jakubowski, 2005; Dodick & Silberstein, 2006b; Jensen, 2000; Schreiber, 2006). Triggers leading to migraine include changes in sleep and eating patterns, stress, and hormonal influences (Qu et al., 1996; Sakurai et al., 1998). These triggers are believe to change brain excitability and may indirectly activate trigeminovascular pathways, which include first-order nociceptors (trigeminal ganglion, which innervates the meninges), second-order nociceptors (trigeminothalamic tract neurons receiving sensory information from the meninges, periorbital skin, and neck muscles), and third-order thalamocortical neurons, which process sensory information from the meninges and neurons in the somatosensory cortex (Burstein & Jakubowski, 2005).

Supporting a trigeminal origin for migraine pain, reduced headache episodes and intensity were reported in a retrospective descriptive study of patients with diagnosed migraine (N=18) who underwent surgical decompression of V1 and V2 trigeminal nerve branches. Nine patients experienced 75% reduction in frequency, duration, and intensity, and three patients experienced complete relief of headache pain. In follow-up, 39% had discontinued all migraine medications (Poggi, Grizzell, & Helmer, 2008). Similar results were found for another migraine patient sample (N=46) undergoing a similar V1 and V2 release and surgical decompression.

Greater than 50% relief was experienced for 83.7% of patients, and 57.7% experienced complete elimination of migraine (Guyuron et al., 2009; Poggi et al., 2008). While these studies are believed to be controversial, they do suggest there may be trigeminal involvement and migraine.

Trigeminally Mediated Pain Characteristics

Pain intensity levels are commonly reported to be moderate to excruciating in trigeminally mediated nerve disorders. Depending on the nerve involved, pain may be either unilateral or bilateral, and descriptions of pain include sudden, sharp, pulsating, electric, burning, constant, and aching. The pain is described as lasting minutes to months, and in extremely severe cases, resulting in incapacitation (Gnann Jr & Whitley, 2002; Pappagallo, Oaklander, Quatrano-Piacentini, Clark, & Raja, 2000; Ragozzino, Melton 3rd, Kurland, Chu, & Perry, 1982).

Other symptoms such as photophobia, phonophobia, nausea, vomiting, fatigue, and other sensory changes may exist simultaneously with migraine pain. (BAAD HANSEN, 2008; Bennett, 2004; Burstein, 2001; Cheshire, 2005, 2007; Kehlet et al., 2006; Marciani, 2007; Ngeow & Nair, 2010; Noseda et al., 2010a; Zahn, Pogatzki, & Brennan, 2002). Normal daily functional activities such as smiling, chewing, talking, swallowing, brushing teeth, head movement, and any activity involving pressure to the head and face can evoke pain for individuals with established trigeminally mediated pain disorders (Cheshire, 2005; Goadsby, 2009; Gray, 2003; Olesen et al., 2009; Sadosky, McDermott, Brandenburg, & Strauss, 2008). Treatments with demonstrated efficacy include nonsteroidals, antiepileptics, ergot alkaloids, opioids, muscle paralytics, and the triptans (Brandes et al., 2006; Burstein et al., 2004; Dworkin, Backonja, et al., 2003a; Goadsby et al., 2008; Jakubowski, Levy, et al., 2005; Jakubowski et al., 2006; Ngeow & Nair, 2010). Sex hormones, including estrogen, have a critical influence in nerve excitability and nociceptive experiences. Specifically, estrogen has a direct effect on trigeminal

neuron signaling in female rats, suggesting sex hormones have a role in pain transmission and processing (Barsky, Peekna, & Borus, 2001; Puri et al., 2006).

Intensity

Regardless of etiology, pain intensity is often described as moderate to excruciating for individuals experiencing trigeminally mediated nerve disorders (BAAD HANSEN, 2008; Bennett, 2004; Burstein, 2001; Cheshire, 2005, 2007; Kehlet et al., 2006; Marciani, 2007; Ngeow & Nair, 2010; Zahn et al., 2002). In general, McDermott and colleagues (2006) found that most individuals with neuropathic pain disorders (N=602), including trigeminal neuralgia, postherpetic neuropathy, and posttraumatic painful neuropathy, reported moderate (54%) to severe (25%) pain (McDermott, Toelle, Rowbotham, Schaefer, & Dukes, 2006a).

In individuals with established trigeminal neuralgia (TN), a trigeminally mediated pain disorder also known as tic douloureux, pain is often described as severe neuropathic pain in the maxillary and mandibular sensory innervated areas of the face (Cheshire, 2005, 2007; De Simone, Ranieri, Bilo, Fiorillo, & Bonavita, 2008). Vascular compression on trigeminal nerve roots results in neuronal discharge, which provokes pain in the intraoral or nasolabial regions by touching or movement (e.g., chewing, talking, brushing teeth, and smiling) (Cheshire, 2002; Zakrzewska, 2002).

Aging and abnormal immune system dysfunction may reactivate a normally dormant varicella virus (chicken pox), resulting in postherpetic neuralgia. This syndrome is the result of peripheral sensory neuron invasion in one dermatome's ganglion, resulting in extremely painful skin lesions (shingles) (Freynhagen & Bennett, 2009; Gnann Jr & Whitley, 2002; Pappagallo et al., 2000; Ragozzino et al., 1982)**.** While literature on trigeminally mediated involvement in postherpetic neuralgia is limited, significant findings regarding pain intensity were reported. In a

study comparing trigeminally mediated (N=20) versus thoracic (N=29) postherpetic neuralgia, pain intensity was found to be 6.35 ± 2.01 versus 7.5 ± 2.02, respectively, on a visual analogue scale (VAS), where 0 is no pain and 10 represents the worse pain ever (Pappagallo et al., 2000). In a retrospective descriptive longitudinal review of postherpetic neuralgia (N=500), of which head and neck represents 54% of the sample, pain intensity was reported as 8% mild (N=84 or 9%), 22% moderate (N=359 or 39%), and 69% severe (N=481 or 52%), using the Medical Outcomes Short Form 36. While this sample included postherpetic neuralgia in three other distributions, thorax (21% or 240), sacrum (10% or 89) and low back (8% or 75), the head and neck represent over half of the sample, suggesting these findings may have some significance for trigeminally mediated postherpetic pain (Chidiac et al., 2001). It would have been more precise and valuable to have pain descriptions identified by distributions.

Posttraumatic trigeminal pain may be the result of oral procedures and surgeries such as tooth extractions, root canal procedures, oral local analgesic injections zygomatico-orbital fractures, atypical odontalgia, and odontalgia (toothache) and often result in acute moderate to severe pain. Trauma to the trigeminal nerve often leads to moderate to severe facial and head neuropathic pain (Marciani, 2007; Sandstedt & Sörensen, 1995; Sessle, 2006). In a study of patients with trigeminally mediated pain following surgical management of impacted third molars (N=630), investigators reported 54% experienced pain intensity on postoperative day 1 (POD 1). No specific data were available even though a 7-point Likert scale was used to assess pain intensity (Marciani, 2007). Baad Hansen and colleagues (2008) found study subjects reported similar pain intensity ratings (5.0 ± 0.3 and 5.3 ± 0.4 respectively) for atypical odontalgia (N=46) and for temporomandibular disorders, using the 10-point visual analogue scale (BAAD HANSEN, 2008). In a cross-sectional observational study of neuropathic pain

disorders (N=602), pain intensity was rated as mild (21.4%), moderate (54%), or severe (24.7%) in a population with trigeminally mediated disorders, including postherpeutic neuralgia (14%), trigeminal neuralgia (12%), and posttraumatic neuropathy (12%). Data were collected via self-report using the Brief Pain Severity Inventory 10-point scale (McDermott et al., 2006a). In a prospective study, following third molar extraction (N= 630), 54% of subjects experienced severe trigeminally mediated pain at postoperative day 1, 31% on postoperative day 4, and 15% on postoperative day 7 (White et al., 2003).

Across and within these trigeminally mediated disorders reviewed above, pain resulting from activation of the trigeminal nerve is most often described as moderate to severe (Baad Hansen, Leijon, Svensson, & List, 2008; Marciani, 2007; McDermott et al., 2006a). In a classic prospective study of trigeminally mediated migraine, subjects reported pain as severe (85%), moderate (14%), and mild (1%) (N=975), using self-administered questionnaires. (Rasmussen, Jensen, Schroll, & Olesen, 1991). Lipton and colleagues compared symptom experiences for subjects with migraine (N=200) to a control group (N=200), utilizing the Medical Outcomes Study Short Form 36-Item Health Survey (SF-36). Migraine pain was reported as ranging 5-10 on a 10-point numerical rating scale (NRS), with no pain reported in control individuals (Lipton, Liberman, et al., 2003). Researchers explored pain intensity experienced by individuals with nonallodynic migraine (N=12) to those with central sensitization migraine pain, as assessed by the presence of allodynia (N=19), which is pain resulting from a non-noxious stimulus to normal skin. Pain intensity levels in the allodynic and nonallodynic groups were reported as moderate to severe (6.9 + 0.5 and 5.6 + 0.5, $p<0.1$, respectively) on the visual analogue scale (VAS) (Burstein et al., 2004). In an unmatched cross-sectional longitudinal study, pain intensity in two types of migraines, episodic (N=58) and chronic (N=6), were explored. Pain intensity was rated

primarily as severe (65.5, 100%) compared to moderate (22.4%, 0%), regardless of migraine type (Ashina, Lyngberg, & Jensen, 2010). Trigeminally mediated migraine headache pain is consistently reported as moderate to severe, irrespective of whether allodynia coexists or headache pain is episodic or chronic.

Quality

Trigeminally mediated pain disorders have characteristic pain qualities. For those diagnosed with trigeminal neuralgia, pain is described as sudden sharp, stabbing, paroxysmal (spastic bursts), electric, and shock-like; postherpetic neuropathy is more likely to be described as constant, burning, and aching; and in posttraumatic painful peripheral neuropathy, pain is reported as pulsating and constant (BAAD HANSEN, 2008; Bennett, 2004; De Simone et al., 2008; Marciani, 2007; Noseda et al., 2010b; Sandstedt & Sörensen, 1995; Sessle, 2006). In a prospective longitudinal 18-year study, pain qualities were described, including several trigeminally mediated pain etiologies (N=1052) such as facial trauma, oral surgery, sinusitis, odontalgia, and herpes pain. Trigeminal pain qualities included shooting (38%), boring (28%), squeezing-pressing (18%), dull (20%), smarting-burning (14%), pricking-sticking (7%), paraesthetic (3%), and throbbing (5%) (Rasmussen, 1990). Normal activities such as talking, brushing teeth, smiling, continuous skin contact, yawning, touching, or moving intraoral or nasolabial areas by chewing was described as inciting excruciating pain (Cheshire, 2002; Schmader, Gnann Jr, & Watson, 2008). Baad Hansen (2008) and List (2007) reported atypical odontalgia was described as persistent pain. In another study on the impact of postherpetic neuralgia on quality of life, such pain was often described as causing unpleasant sensations and included severe pruritus and allodynia (Schmader et al., 2007).

In migraine, pain qualities were described as unilateral (59%), bilateral (40%), pulsating (78.7%), pressing (17%), and stabbing (0.3%) (Rasmussen & Olesen, 1992). Burstein (2004) found that 60-75% migraine patients with or without allodynia described headache pain as throbbing. Ashina (2010) reported headache pain quality for episodic migraine and chronic headache as pressure-like (34.5%, 33.3%) and more often as pulsating (65.5%, 66.7%). Regardless of the way in which different etiologies of trigeminally mediated pain quality are described, characteristics are similarly abnormal, uncomfortable and undesireable.

Duration

The duration of pain experienced in trigeminally mediated disorders varies depending on the individual disorder. For example, trigeminal neuralgia pain lasts minutes to hours (Cheshire, 2007; Eller et al., 2005; Ngeow & Nair, 2010). In a prevalence prospective longitudinal study, Rasmussen (1990) found duration of pain for several types of trigeminally mediated pain varied depending on etiology (N=1052). Duration of pain for TN (N=229) lasted less than year for 15%, 1-5 years for 43%, 5-10 years for 23%, 10-20 years for 13% and greater than 20 years for 6%. Pain episodes for posttraumatic facial pain (N=578) was reported to last minutes for 3%, hours for 32%, days for 9%, or was constant for 56%. Chidiac and colleagues (2001) found that postherpetic neuralgia pain (N=935) was intermittent for 45% and permanent for 55%. In another postherpetic neuralgia sample (N= 385), pain lasted 3.3 $\pm$ 4 years (Oster, Harding, Dukes, Edelsberg, & Cleary, 2005). For trigeminally mediated posttraumatic pain, incidents lasted less than 1 year for 21%, 1-5 years for 40%, 5-10 years for 19%, 10-20 years for 22%, and greater than 20 years for 5%. Pain duration in a cross sectional study for TN (N=82) was reported to be experienced 3-5 months for 19.5%, 7-12 months for14.6%, 13-35 months for 12.2%, and over 36 months for 53.7% (Tölle, Dukes, & Sadosky, 2006). Baad Hansen and colleagues (2008) found

that individuals with atypical odontalgia experienced longer duration of pain compared with pain from temporomandibular disorders (7.7 ± 1.1 years and 4.5 ± 0.1 years, respectively) (Baad-Hansen et al., 2008). Similarly, pain duration for atypical odontalgia was 7.7 =/- 7.8 years (List et al., 2007).

Migraine headache pain commonly lasts hours to days (Burstein, 2001; Burstein, Yarnitsky, et al., 2000; Goadsby, 2009; Lipton et al., 2008; Olesen et al., 2009). Rasmussen and Olesen (1992) reported pain duration in patients to be less than 30 minutes for 3%, 30 minutes to 4 hours for 22%, 4 to 24 hours for 74.1%; 24 to 72 hours for 26%, and greater than 72 hours for 3.0%. Burstein and colleagues (2004) found pain duration in migraine was reported to be 22.5 ± 3.7 hours. Lipton and colleagues (2003) reported that pain duration lasted less than 5 hours (N=34), 5-24 hours (N=82), and 25+ hours (N=80). Ashina and colleagues (2010) reported duration of pain in episodic and chronic headache pain was less than 4 hours (27.6%, 16.7%), 4 hours to 1 day (55.2%, 66.6%), and longer than one day (17.2%, 16.7%), respectively. Both trigeminally mediated pain disorders and migraine headache are pain conditions found in large populations and occurring daily, episodically, or chronically, lasting minutes to days or even continuing several years.

Location

Trigeminally mediated disorders such as trigeminal neuralgia and posttraumatic peripheral neuropathy are most likely to occur unilaterally due to one-sided trigeminal nerve involvement (Finnerup et al., 2010; Kanai et al., 2009). However, postherpetic neuropathy may be unilateral or bilateral depending on the extent of trigeminal nerve involvement (Dworkin, Backonja, et al., 2003a). In trigeminal neuralgia (N=50), pain distribution was found to be located in the mandibular region for 60%, maxillary region for 34% and ophthalmic region for

6%, and on the right of the face for 64% compared to the left for 35%, with no bilateral incidents noted (Shah, Murad, Salaar, & Iqbal, 2008). In migraine, Rasmussen and Olesen (1992) reported that headache pain was experienced both unilaterally (59%) and bilaterally (40%). In Ashina's 2010 study comparing headache characteristic for two types of headache, episodic migraine and chronic headache, they found that, regardless of headache type, pain was experienced similarly, as either unilateral (65.5%, 66.7% and bilateral (34.5%, 33.3%), respectively. For both trigeminally mediated disorders and migraine, pain is primarily experienced unilaterally, although bilateral pain can occur, depending on nerve involvement.

In summary, regardless of the etiology of trigeminally mediated pain, it is commonly described as severe. The qualities of the pain have been reported as paroxysmal or constant, unilateral or bilateral, sharp, throbbing/pulsating, stabbing, aching, and electric shock-like pain. The location of pain is more commonly described as unilateral but has also been reported as bilateral. The duration of pain ranges from minutes to hours to ongoing for days or even decades.

Estrogen and Trigeminally Mediated Pain

That females experience pain differently from men has been established in multiple fronts. Pain is a subjective complex phenomenon, and women reportedly express themselves using more descriptors than men, even though there are no physical neurological structural differences (Berkley, 1997). In the immediate postoperative period, it has been reported that women verbalize more incidents of pain at higher pain intensity than men and require as much as 30% more morphine (opioid). Sarton and colleagues (2000) compared opioid analgesia for women (N=10) and men (N=10). In women, morphine had a slower uptake and offset and a greater potency in an experimental study with electrically induced pain, than it did in men (Sarton et al., 2000). Anticipation of opioid analgesics having slower onset, longer offset, and

greater potency in women means administering immediate careful treatment with due vigilance to not overtreat, which could potentially result in life-threatening events such as respiratory depression (Aubrun, Salvi, Coriat, & Riou, 2005; Cepeda & Carr, 2003; Pleym, Spigset, Kharasch, & Dale, 2003; Rollman, 2003; Sarton et al., 2000).

Research studies consistently report that women have a higher prevalence of trigeminal neuralgia, postherpetic neuropathy, posttraumatic peripheral neuropathy, and migraine, compared to men (Bennett, 2004; Lipton, Bigal, et al., 2007c; McDermott, Toelle, Rowbotham, Schaefer, & Dukes, 2006b; Noseda et al., 2010b; Schmader et al., 2008; Tölle et al., 2006). Women with migraine also report higher pain scores and experience more intense accompanying symptoms, such as nausea and vomiting, phonophobia, and photophobia, than do men (Penzien et al., 2002). The overall consensus is that, compared to women with stable estrogen levels and to men, women with elevated or suddenly decreased estrogen levels are more likely to verbalize pain and to perceive intensity levels that require immediate larger doses of pain medications for effective pain relief .

Estrogen

Sex hormones regulate neurotransmitters essential in the perception and inhibition of pain. Pain inhibitor neurotransmitters, such as gamma aminobutyric acid (GABA) and the body's endogenous opioid system, are dependent on estrogen and other hormones to process nociceptive information for both peripheral and central nervous system pain pathways (Barsky et al., 2001; Fillingim & Ness, 2000; Puri et al., 2006). Estrogen fluctuation influences pain processing, including responses to opioids and nonopioids, neuroactive agents, and the sympathetic nervous system (Berkley, 1997).

Menstrual cycles have two phases, follicular (first day of menstrual bleeding to first day of ovulation) and luteal (time period from ovulation to end of cycle), both with early, mid, and late time intervals. During the early to mid follicular phase, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which binds to anterior pituitary receptors, stimulating the release of follicle-stimulating hormones (FSH) and luteinizing hormones (LH). In the late follicular phase, FSH and LH stimulate ovarian follicle formation, which produces estrogen from cholesterol in the ovary. Serum estradiol is the most potent estrogen, compared to estrone and estriol, and is most frequently measured when assessing ovarian estrogen hormone activity (Brandes, 2006c; Watson, Jeng, & Kochukov, 2008). When estrogen reaches its highest levels, a surge of LH through positive feedback from the pituitary promotes ovulation within 48-72 hours. After ovulation, in which release of the ovarian follicle occurs, residual ovarian tissue forms the corpus luteum, which produces estradiol and progesterone during the early and mid-luteal phase of the menstrual cycle. When no fertilized implantation occurs, the corpus luteum degenerates, resulting in decreased levels of estrogen and progesterone in the late luteal phase. Endometrial lining sloughing and bleeding occurs as a result of decreased progesterone levels in the late luteal phase (Martin & Behbehani, 2006b). Sufficient levels of estrogen and progesterone (maintained by corpus luteum) and estradiol (secreted by placenta and ovary) are necessary to support pregnancy (Zacur, 2006). Variability in estrogen levels with pregnancy, childbirth, premenopause, spontaneous menopause, and surgical menopause, as well as with the use of oral or transdermal HRT appear related to migraine incidents and severity, further supporting an estrogen to CNS dysfunction connection (Loder et al., 2007).

Women in their childbearing years, particularly during the luteal phase, consume more pain medication due to increased pain sensitivity, decreased pain tolerance, and lower pain

threshold (Fillingim, 2000; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley Iii, 2009). It has been found that when estrogen levels are heighten during the proestrous phase of the female cycle, female rats had increased response rate to stimuli and larger reactive fields compared to males and to female rats who had lower estrogen levels or were in the diestrous phase (Bereiter, 2001). This suggests pain thresholds will be lower during female cycles when estrogen is higher, and higher when estrogen is lower; and that males have even higher pain thresholds, as they have very low estrogen levels. It has been established that, compared to women with lower estrogen levels and to men, women with higher estrogen levels are more sensitive to pain, as measured by time of pain recognition, pain intensity, and unpleasantness. (Fillingim & Maixner, 1996; Riley III, Robinson, Wise, Myers, & Fillingim, 1998).

Women experience 50-200% more trigeminally mediated nerve disorders, including primary, tension-type, and migraine headaches, and temporomandibular disorders (TMDs) (LeResche, 1997; Lipton, Bigal, et al., 2007a) than do men (Holroyd & Lipchik, 2000; Lipton, Bigal, et al., 2007c). The high prevalence of migraine in women compared to men (3:1, respectively) suggests that estrogen may contribute to migraine (Brandes, 2006b). Hormones have a complex effect on headache. With the onset of menstruation, women experience higher rates of migraine (18%), compared to men (6%), suggesting a hormone link (Lipton et al., 2001). Headache reportedly is a side effect of OC, however, there is little evidence that oral contraceptives (OC) worsen or promote migraine. OC consumption often improves migraine during the 21 active days 21 which includes estradiol and progestin consumption. However, migraine is more likely during the hormone-free or placebo week (Granella et al., 2000; Loder, Buse, & Golub, 2005).Those with a history of migraine with aura often experience worsening of migraine with OC. Mueller (2009) found most women with a history of migraine on OC

(n=299) experienced improvement or no change (n=225) versus worsening (n=74).She further reported those n HRT (n=120) more often had no change or improvement of migraine (n=93) compared those reporting worsening (n=27) (Mueller, 2000). HRT are often prescribed for uncomfortable vasomotor symptoms such as night sweats, memory loss, irritability, and hot flashes, which occur when estradiol levels drop due to follicle depleted ovaries. In women using HRT for such purposes, migraines were unchanged (39.8-64.1%), improved (13.3-24.4%), or worse (22-35.7%) (Cupini et al., 1995; Granella et al., 1993; Mueller, 2000). The stable maintenance of hormone level provided with transdermal (local) HRT resulted in less migraine frequency and lower pain intensity, compared to use of oral (systemic) HRT (Li et al., 2002; Nappi et al., 2001). Brandes (2006) summarized women's unique paradoxical sensitivity to estrogen and its role in neuronal stabilization and excitation in migraine. Sudden decreases in estrogen (surgical hysterectomy or following childbirth) may provoke the onset of migraine, while maintenance of either higher estrogen levels (pregnancy or HRT) or complete estrogen depletion (natural menopause) greatly diminishes the occurrence of migraine (Brandes, 2006b; Brandes, 2006c). That migraine incidents vary with age, oral contraceptives, and HRT further suggests a connection between hormones and migraine (Granella et al., 2004; Victor, Hu, Campbell, Buse, & Lipton, 2010)**.**

Findings in studies by Bereiter (2001) and Flake (2005) suggest the role of estrogen in trigeminally mediated disorders. In their study of trigeminally mediated temporomandibular joint disorder (TMJ), Bereiter and colleagues found significantly more ($p<0.001$) gene Fos-positive neurons in proestrous female rats compared to male and diestrous female rats, indicating a more pronounced trigeminal neuronal activation with higher estrogen levels (Bereiter, 2001). Similarly, Flake and colleagues (2005) found that high estrogen levels contributed to neuronal

excitability in the trigeminally mediated disorder, temporomandibular joint (TMJ) in female rats compared to males (Flake, Bonebreak, & Gold, 2005). The release of neuropeptide transmitters that excite trigeminal afferent A δ and C-fibers is higher in female rats compared to males, a finding that further supporting estrogen's influence on pain (Cairns, 2007, 2005; Moskowitz, 2008). These animal studies suggests estrogen contributes to trigeminal neuronal excitability, further supporting estrogen's role as a contributor to trigeminally mediated pain in females.

Menstrual migraines are defined as headaches that occur when estrogen and progesterone levels precipitously plummet 1-2 days prior to menstruation (Brandes, 2006a). Menstrual migraines are most often reported to be severe in pain intensity and to increase in recurrence, last longer, resist treatment therapies, lead to greater amount of days of disability and work weeks missed, and result in greater consumption of medications, compared to nonmenstrual migraines (Brandes, 2006a; Granella et al., 2004). Because follicular and luteal ovarian hormone fluctuations were similar for both menstrual and nonmenstrual migraine patients, researchers concluded that women with menstrual migraine appear to have CNS dysfunction with normal ovarian hormone fluctuations, illustrating a connection between estrogen and migraine (Brandes, 2006b; Davies, Eccles, Steiner, Leathard, & Rose, 1989; Loder et al., 2007; Martin & Behbehani, 2006a). During pregnancy, women often experience significant improvement in and even total remission of migraines. Due to plummeting estradiol levels an hour after childbirth and placenta birth, migraines often return for women in one week (34%) and one month (55%) (Sances et al., 2003; Tulchinsky & Korenman, 1971)**.** Medical oophorectomy by depo-leuprolide injections resulted in >50-74% migraine improvement, substantiating the contribution of fluctuating hormones to migraine (Lichten, Lichten, Whitty, & Pieper, 1995; Martin & Behbehani, 2006b).

When women with migraine experience spontaneous menopause (natural cessation of menstruation), they report an increase in migraines premenopause, during which dramatic swings in estrogen may occur, followed by decreased incidents of migraine after menopause, when hormone levels decrease and stabilize. Reportedly, women with preexisting migraine experienced new onset (13%), improvement (8-36%), or worsening (9-42%) of migraine after menopause (Cupini et al., 1995; Granella et al., 1993; Mueller, 2000). Women with migraine who experience surgical menopause (hysterectomy with removal of ovaries) often report increased migraine incidents from the sudden estrogen reduction (Nappi et al., 2001; Victor et al., 2010; Wang, Fuh, Lu, Juang, & Wang, 2003).

In conclusion, because estrogen instigates neuronal excitability contributing to pain experiences for women, it can also be surmised that estrogen may act as a priming mechanism, increasing the likelihood that women may experience more severe pain and have a higher prevalence of pain disorders. Trigeminal nerve excitability appears to be susceptible to estrogen's influences, as illustrated in studies of trigeminally mediated pain disorders such as TMD, TMJ, and migraine. The effect of estrogen on headache pain has been extensively examined in studies of trigeminally mediated migraine. The stabilization of estrogen levels has been shown to prevent migraine neurological cascade by offering neuronal stability and diminishing potential excitation. This may suggest headache pain for women undergoing EFS may experience greater pain in the days prior to ovulation or during premenopause when the pain threshold is lower, thus increasing sensitivity and susceptibility to pain.

Summary

In conclusion, very little evidence in the literature is currently available that describes headache pain following EFS. While headache pain has been mentioned in surgical articles,

specific pain characteristics, management and outcomes have not been explored. Trigeminally mediated pain disorders such as TMJ and TMD, as well as the extensive research on migraine, describe pain as devastating, disabling, and difficult to manage. When undermanaged, trigeminally mediated pain often forces individuals to endure pain that alters their emotional and functional status. Women appear to be more susceptible to pain disorders, as illustrated by higher prevalence when compared to men. Women with unstable estrogen levels have an increased propensity to experience pain compared to women with stable estrogen levels. With the higher prevalence of migraine in women compared to men, it has been suggested that estrogen most likely is an underlying factor in trigeminally mediated migraine. Currently, there are no guidelines to assist nurses in evaluating, assessing, and managing headache pain following EFS. The purpose of this proposed study is to examine headache pain experienced by women following EFS to improve outcomes for our patients in pain.

Trigeminally Mediated Pain Management

The severity of trigeminally mediated neuropathic pain emphasizes the need to implement immediate effective management. Pain management protocols for trigeminally mediated pain include traditional multimodal pharmacologic, nonpharmacologic, and nonprescription mineral supplementation (Attal et al., 2006; Davis, 1999; Jakubowski, Levy, et al., 2005; Schiapparelli et al., 2010). Despite these, effective treatment for trigeminally mediated pain is incomplete (Dworkin, O'Connor, Audette, Baron, Gourlay, Haanpää, et al., 2010; Johnson et al., 2010). Currently, evidence-based pharmacologic and nonpharmacologic management approaches have been described for trigeminally mediated disorders.

Pharmacologic Strategies

Several classes of drug types have been shown to control pain for trigeminally mediated pain disorders. Anticonvulsants such as gabapentin mimic the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which blocks calcium channel excitatory neuronal transmission, have been shown to be effective for treating trigeminally mediated pain. In addition to GABA inhibitors, some anticonvulsants affect voltage-gated sodium channels, which inhibit excitatory neurotransmitters such as glutamate, thereby decreasing ectopic neuronal discharge. These anticonvulsants are also known evidence-based pain management for trigeminally mediated pain, and include carbamazepine, oxcarbazepine, and lamotrigine (Hendrich et al., 2008; Mao & Chen, 2000; Meldrum & Rogawski, 2007). Treatment for trigeminal neuralgia and migraine also includes the antiepileptic sodium voltage channel stabilizer phenytoin and afferent nerve impulse transmission antagonist BOTOX (Cheshire, 2007; Ngeow & Nair, 2010). Another sodium channel stabilizer, topical lidocaine, and opioids that bind to opioid receptors resulting in analgesia, are also used in conjunction with anticonvulsants for postherpetic neuropathy (Dworkin, O'Connor, Audette, Baron, Gourlay, Haanpaa, et al., 2010). Nonsteroidal anti-inflammatory (NSAID) medications such as acetaminophen, ibuprofen, diclofenac, and naproxen are additional medications used for posttraumatic painful peripheral neuropathy (Finnerup, Otto, McQuay, Jensen, & Sindrup, 2005; Kanai et al., 2009) (see Table 2). While Schmader et al. (2007) did not specifically name medications used to manage postherpetic neuralgia pain management in their patient sample, they did report treatment was primarily antiviral agents (85%), analgesics (70%), and tricyclics antidepressants (8%) (Schmader et al., 2007). In a neuropathic pain sample with trigeminal neuralgia, postherpetic neuropathy and posttraumatic painful neuropathy, 93% of participants'

pain was successfully managed with analgesics (71%), antiepileptics (51%), antidepressants (29%), and sedatives/hypnotics (15%) (McDermott et al., 2006a). For postherpetic neuralgia, treatment included level I (30%) and II (42%) analgesics, and antidepressants (19%) (Chidiac et al., 2001). Specific analgesics prescribed following third molar extraction were not reported. However, it was reported that analgesic consumption for postoperative days 1, 7, and 14 were 96%, 55%, and 13%, respectively (White et al., 2003).

The pharmacologic treatment of trigeminally mediated pain has been best evaluated in the case of migraine. The American Headache Society United States Headache Consortium Guidelines (2006), and current migraine research findings recommend NSAIDs, inhibitors of cyclooxygenas-1 and cyclooxygenase-2, both key in the inflammatory process; ergot alkaloids and derivatives and triptans, all of which have agonist effect on serotonin 5-HT_{1D} receptors; and both serotonin 5-HT_{1D} and 5-HT_{1B} respectively, which inhibit peripheral and second-order neuronal transmission; and opioids for acute migraine management (Burstein et al., 2004; Goadsby, Lipton, & Ferrari, 2002; Goadsby & Sprenger, 2010; Matchar et al., 2002; Tfelt-Hansen et al., 2000). For migraine headache pain, multimodal pharmacological approaches are often utilized, such as combinations of triptans, ergots, beta antagonists, NSAIDs, and preventative onabotulinum toxin injections (Attal et al., 2006; Davis, 1999; Dworkin, O'Connor, Audette, Baron, Gourlay, Haanpää, et al., 2010; Jakubowski, Levy, et al., 2005; Schiapparelli et al., 2010). (Table 3) It is not entirely understood how triptan therapy; however, it is the gold standard (93%) for complete relief for acute migraine without allodynia when treated within 2 hours of migraine symptoms (Schreiber, 2006). With the onset of central sensitization, as evident with the presence of allodynia, triptans may be less likely to be successful (15%) in relieving headache pain (Burstein et al., 2004). Therefore, combination treatment strategies have

been explored and implemented (Goadsby, 2009). The following literature was reviewed with these considerations.

Table 3

Migraine pharmacological management.

Medications	**United States Headache Consortium Guidelines For Migraine**	**Acute Migraine** (Goadsby & Sprenger, 2010)
NSAID (First Line for migraine)	Acetaminophen 650-4000mg Diclofenac K 50-100mg Ketoprofen PR 100mg Aspirin 500-100mg Ibuprofen 400-2400mg Naproxen 750-1750mg	Acetaminophen 1000mg (Derry, Moore, & McQuay, 2010) Aspirin 900-100mg (Kirthi, Derry, Moore, & McQuay, 2010) Ibuprofen 400-800mg (Rabbie, Derry, Moore, & McQuay, 2010) Naproxen 100mg (Smith et al., 2005) ketorolac 15 mg (Jakubowski, Silberstein, Ashkenazi, & Burstein, 2005a)
Barbiturate Analgesic	Butalbital 50mg + aspirin 325mg + caffeine 40mg Butalbital 50mg + aspirin 325mg + caffeine 40mg + codeine 30mg Topiramate 100mg	Topiramate 50 mg - 200 mg (Brandes et al., 2006; Silberstein et al., 2006)
ergot alkaloids & derivatives	DHE **(**Dihydroergotamine**)** (SC, IM, IV)1mg DHE (nasal spray) 0.5-4 mg	
triptans (serotonin 1B/1D receptor agonists),	Sumatriptan nasal spray 1-40mg Sumatriptan 25-100mg Sumatriptan (SC) 1-8mg Frovatriptan Naratriptan 1-2.5mg Rizatriptan 5-40 mg Zolmitriptan 1-25mg	Sumatriptan 50-100mg (Smith et al., 2005) Frovatriptan 2.5mg (MacGregor, Pawsey, Campbell, & Hu, 2010; Silberstein et al., 2004) Naratriptan 1mg (Moschiano et al.) Rizatriptan 5 mg (Ferrari, Roon, Lipton, & Goadsby, 2001) Zolmitriptan 2.5mg (Ferrari et al., 2001) Eletriptan 40mg (Ferrari et al., 2001) Almotriptan 12.5mg (Ferrari et al., 2001; Goadsby et al., 2008)

opioids	Acetaminophen (400-650mg) + Codeine 16-25mg) Butorphanol nasal spray 1-2mg Meperidine (IM) 75mg-100mg) Meperidine (IV) 0.4mg/kg) up to 3 doses Methadone 10mg	codeine, oxycodone, morphine and meperidine (Jakubowski, Levy, et al., 2005; Jones, Cormack, Murphy, & Scott, 2009; Law-Koune et al., 2005; Quiney & Cooper, 1996; Rahimi, Alleyne, Vernier, Witcher, & Vender, 2010; Rahimi, Alleyne, Hughes, Witcher, & Vender, 2008; Sudheer, Logan, Terblanche, Ateleanu, & Hall, 2007; Thibault et al., 2007)
Other Muscle paralytic Calcitonin gene-related peptide		botulinum Toxin A (BTX-A) injections (Jakubowski et al., 2006) MK-0974(Ho, 2008)

Silberstein and colleagues (2004) compared placebo with two frovatriptan (serotonin 1B/1D receptor agonist) dosing schedules (once versus twice daily) for women with menstrual-associated migraine (MAM). They found a significantly lower incidence and duration of headache pain ($p < 0.0001$) with either frovatriptan dosing schedule compared to placebo (Silberstein et al., 2004). Smith and colleagues (2005) compared the efficacy of combination sumatriptan 50mg + naproxen to sumatriptan or naproxen alone and to placebo. Patients (65%) who received the combination therapy reported lower pain intensity, required no rescue medications for 24 hours after dosing, and did not have recurrence of moderate to severe pain, compared to other solo pharmacological strategies.

Jakubowski and colleagues (2005) examined two treatment strategies for migraine headache pain with allodynia: 1) sumatriptan + 2 successive 15 mg infusion doses of ketorolac; and 2) ketorolac infusion alone. In both groups, approximately 2/3 of the patients responded to the respective regimens with good relief; 1/3 in each group did not respond. Nine of those who did not respond to either regimen (sumatriptan and ketorolac versus ketorolac alone) reported

using other opioids (codeine, meperidine, oxycodone, or stadol) (Jakubowski, Levy, et al., 2005). These findings suggest that for migraine, the combination of sumatriptan with ketorolac, or ketorolac alone will likely provide relief only if they are not used concurrently with opioid therapy. Jakubowski and colleagues (2006) examined botulinum Toxin A (BTX-A) injections for individuals experiencing migraine headache pain. Those who responded to injections experienced significant decrease in 1) frequency ($p< 0.002$), 2) duration ($p< 0.002$), and 3) intensity ($p< 0.005$). Nonresponders reported no improvement in headache pain. Responders described characteristics of headache pain as either: 1) “imploding” in which they "perceived their skull to be assaulted by external forces, typically described as crushing, clamping or stubbing" (79%); or 2) “ocular,” described as "an eye popping pain" (14%). All nonresponders described their headache pain as “exploding,” or a "build-up of pressure inside as if the skull was about to split open" (Jakubowski et al., 2006). These findings suggest that for migraine, BTX-A injections are more likely to relieve pain if headache pain is “imploding and ocular.” Silberstein and colleagues (2006) investigated the preventive efficacy topiramate 50 mg, 100 mg, and 200 mg doses compared to placebo for migraine. During the 6-month study period, mean monthly migraine frequency decreased with100 mg dose ($p < 0.001$). Similarly, mean monthly frequency decreased from with 200 mg dose ($p< 0.001$). However, no significant decrease in the mean monthly migraine frequency was reported in 50 mg dose or the placebo groups (Silberstein et al., 2006). In a prospective clinical trial of patients (N= 630) undergoing third molar extraction, White et al. (2003) found 96% consumed analgesic medications postoperative day 1, 55% postoperative day 7, and 13% postoperative day 14 (White et al., 2003).

Nonpharmacological Strategies

Nonpharmacologic methods have been considered for a number of reasons, including cost, pharmacologic protocols not being entirely effective, the need to lower the use of potent pharmacologic agents to nontoxic levels or nonaddictive levels, and/or the desire to avoid using pharmacologic agents. McDermott (2006) found that, with neuropathic pain, nonpharmacologic pain management strategies utilized include physical treatments (41.5%), herbs, vitamins and supplements (22.6%), and exercise (35.6%) (McDermott et al., 2006a). Similarly, Tolle et al., (2006) reported nonpharmacologic pain management including physical treatments (30.5%), herbs, vitamins, and supplements (17.1%), devices (9.6%), and exercise (11%) in trigeminal neuralgia (Tölle et al., 2006).

Nonpharmacologic protocols that have been found to be effective for migraine include acupuncture, relaxation, and cognitive-behavioral therapy (Dobos & Tao, 2011; Linde et al., 2009; Nestoriuc & Martin, 2007; Wachholtz & Pargament, 2008). In addition to prescriptive pharmacological protocols for neuropathic pain conditions, including trigeminally mediated pain migraine and postherpetic neuralgia, focus on normal body minerals, specifically magnesium has been explored. Maintenance of normal magnesium levels is important in the normalization of blood sugar, blood pressure (vascular tone), hormone regulation (estrogen), and neurogenic inflammation, all of which have been found to mediate neuropathic pain, including postherpetic neuralgia and migraine (Brill, Sedgwick, Hamann, & Di Vadi, 2002; Fawcett, Haxby, & Male, 1999; Goadsby, 2009; Mauskop et al., 2002; Sun-Edelstein & Mauskop, 2009; Taylor, 2011). Decreased magnesium levels were found during stress with catecholamine release, generally in women, (Schimatschek & Rempis, 2001) and specifically in women with menstrual migraines (Mauskop et al., 2002; Taylor, 2011). In migraine, removal of magnesium from trigeminal

nucleus n-methyl-D-aspartate (NMDA) receptors is considered a primary contributor when neuronal excitability advances to second-order sensitization (Welch, 2003). Magnesium deficiency has been found to contribute to brain dysfunction and headache pain, including migraine (Mauskop et al., 2002).

NMDA receptors activation in neuropathic pain is mostly unrelieved with opioid therapy. However, antagonists such as magnesium stabilize these receptors, enhancing opioid effectiveness. The effect of magnesium for pain management was illustrated in Begon (2002) and colleagues' animal study with mononeuropathic and diabetic neuropathic pain. Researchers found magnesium supplementation alone significantly decreased ($P<0.01$) mechanical pain response, and when supplemented with opioid morphine, analgesic efficacy was augmented, significantly lowering opioid requirement ($P <0.01$) for pain relief, compared to treatment with morphine and saline (Begon, Pickering, Eschalier, & Dubray, 2002). For trigeminally mediated pain such as postherpetic neuralgia, Brill and colleagues (2002) found in a double-blind placebo-controlled crossover study that individuals (N=7) reported significantly lower pain scores at 20-minute ($p=0.016$) and 30-minute ($p=0.016$) intervals following magnesium intravenous infusion (Brill et al., 2002). Studies found that subjects who were administered magnesium therapy for trigeminally mediated migraine experienced 80-86% improvement in pain (Facchinetti, Sances, Borella, Genazzani, & Nappi, 1991; Ginder, Oatman, & Pollack, 2000).

While researchers in pain and headache communities continue to examine and explore pharmacologic and nonpharmacologic protocols, it is clear that identification of effective pain management is elusive and relief is suboptimal (Tölle et al., 2006). One treatment based on physiological findings for trigeminally mediated headache pain has shown great efficacy; prevention of peripheral neuronal activation to central hyperexcitability significantly controls

pain. However, once central processing has occurred, treatment is challenging for monotherapy, typically resulting in multimodal pain management strategies with pharmacologic and nonpharmacologic means. It is not known what medications are currently being prescribed for headache pain following EFS, nor is their perceived efficacy known. Perhaps the reviewed pain management for other trigeminal disorders may be effective for treating EFS headache pain. However, there were no studies found that described what medications or treatment are currently being prescribed for headache pain following EFS and the perceived effectiveness. Levetiracetam (LEV), a newer antiepileptic drug targeting high-voltage N-type calcium channels with established efficacy in epilepsy was evaluated for TN. Self-report questionnaires were used to establish and measure treatment efficacy in TN patients (N=23). A 45.6% weekly reduction in pain was reported, with a decrease in pain from 9.9 to 3.3 ($p < .001$). VAS and patient global ratings of efficacy and safety were significantly increased (177% and 110%, respectively) (Mitsikostas et al., 2010).

Trigeminally Mediated Pain Outcomes

Uncontrolled and undertreated pain has been shown to lead to psychological distress such as extreme anxiety (Polomano, Dunwoody, Krenzischek, & Rathmell, 2008). Additional consequences of undertreated pain include advancement of an acute pain state to a chronic state, delaying healing, prompting unexpected hospitalization, prolonging the recovery, and decreasing patient satisfaction (Carr & Goudas, 1999; Dunwoody, Krenzischek, Pasero, Rathmell, & Polomano, 2008; Good, 1998). Uncontrolled pain may increase morbidity and mortality and is considered inhumane (Werner & Andary, 2002).

Neuropathic pain detrimentally affects emotional status, physical functioning, and productivity, diminishing overall QOL (Jensen, Chodroff, & Dworkin, 2007; McDermott, Toelle,

Rowbotham, Schaefer, & Dukes, 2006c). Specifically, trigeminally mediated pain disorders have been shown to diminish emotional and functional status (Dworkin et al., 2008; Johnson et al., 2010; Lydick, Epstein, Himmelberger, & White, 1995). For example, migraine often leads to days of incapacitation, absenteeism at work, personal loss of social involvement, reduction in productivity, and increasing medical costs (Jensen & Stovner, 2008; Penzien et al., 2002; Steiner et al., 2003; Steiner, 2004). (see Table 4)

Table 4

Headache pain characteristics for migraine

PAIN	**MIGRAINE**
Intensity	Moderate to severe Jakubowski (2006); Borsook, (2006)
Duration	24 to 72 hours and longer Rasmussen (1992); Lipton (2003); Burstein (2004)
Quality	Throbbing, pulsating, pressing Jakubowski (2006); Borsook, (2006)
Location	Unilateral or bilateral headache pain; Imploding or exploding Jakubowski (2006);
Emotional Status	depression, mood changes, emotional distress, anxiety, irritability, frustration, decrease levels of happiness and calmness Lipton, et al. (2003); Magnusson & Becker (2003); Peterlin, et al. (2010)
Functional Status	lower role-physical scores, higher limitations scores - severe impairment and bed rest Burstein, et al. (2000); Lipton, et al. (2003); Cady, et al. (2004); Schreiber, et al. (2004);Goadsby (2005); Stovner & Hagen (2006) Lipton, et al. (2007)

Emotional Status

Emotional health diminishes with trigeminally mediated disorders. In addition, increasing pain intensity further diminishes emotional status. Anxiety, depression, and mood changes are psychological disturbances commonly reported with neuropathic pain disorders (Lipton, Liberman, et al., 2003; Sadosky et al., 2008; Schmader et al., 2008; Tölle et al., 2006). Exploring neuropathic pain disorders, McDermott et al. (2005) found mood, enjoyment in life, and social relations were impaired in trigeminal neuralgia, postherpetic neuropathy, and posttraumatic painful neuropathy (McDermott et al., 2006a). Emotional health significantly decreased ($p<0.001$) for individuals with trigeminal neuralgia (N=82), as measured by the EuroQol Survey, which specifically measures depression and anxiety (Todd, Funk, Funk, & Bonacci, 1996; Tölle et al., 2006). Katz and colleagues (2007) reported that emotional distress and social functioning were significantly diminished for patients with postherpetic neuropathy, as measured by four tools: Beck Depression Inventory, Spiel-berger State-Trait Anxiety Inventory, Mental Health Inventory (an emotional well-being scale), and the Personality Disorder Questionnaire Scale. A significant decline in social functioning ($p<.001$) and an increase in depression ($p < 0.01$) was found in individuals experiencing atypical odontalgia (List et al., 2007).

Schmader and colleagues (2007) found that SF-12 mental scores decreased significantly ($p<0.0001$). With every 1.0 point increase in pain and discomfort intensity, there was a 1.95 point decrease in SF-12 mental scale for individuals with postherpetic neuralgia (Schmader et al., 2007). Similarly, Katz et al. (2004) reported diminished overall emotional distress and decreased social functioning scores compared to control ($p<0.05$) in subjects with postherpetic neuropathy (Katz, Cooper, Walther, Sweeney, & Dworkin, 2004; Schmader et al., 2007). White (2003) reported social functioning returned on postoperative day 3 following third molar extraction.

Chidriac (2001) found anxiety (30.2%), sleep (58.8%) and social life (20.2) were impacted by postherpetic neuralgia. In a prospective cross-sectional study on postherpetic neuralgia pain (N=385), pain interference was assessed on a 10-point scale. Findings included decreased enjoyment of life (4.5 $\pm$ 3.1), mood (4.3 $\pm$ 2.9), and relations with others (3.0 $\pm$ 2.8) (Oster et al., 2005). McDermott et al. (2005) found interference mean on the interference scale of 0-10 due to pain (4.5), mood (2.8), enjoyment in life (3.0), and social relations (2.9) in neuropathic pain disorders (trigeminal neuralgia, postherpetic neuropathy, and posttraumatic painful neuropathy).

The effect of trigeminally mediated pain on emotional status has been most extensively studied in the case of migraine. In a study exploring the relationship between HRQoL and work disability, Lipton and colleagues (2003) compared individuals with (N=200) and without (N=200) migraine. In contrast to those without migraine, those with migraine reported decreased emotional status, which included depression, mood changes, emotional distress, anxiety, irritability, frustration, and decrease levels of happiness and calmness (Magnusson & Becker, 2003; Peterlin et al., 2010). Migraine often results in disruption in social activities (Evans, 2003; Holroyd, Drew, Cottrell, Romanek, & Heh, 2007b; Lipton, Liberman, et al., 2003; Magnusson & Becker, 2003; Peterlin et al., 2010; Quintela, Castillo, MuÃ±oz, & Pascual, 2006; Rasmussen & Olesen, 1992; Terwindt et al., 2000). Terwindt and colleagues (2000) reported higher role limitations and lower emotional status, mental health, and vitality in their study exploring migraine (N=620), as measured by the Rand-36 (Terwindt et al., 2000). Magnusson & Becker (2003) reported that those with more frequent migraine headaches (>21 episodes) had higher depression scores. In addition, those with higher headache pain intensity ($\geq$ 5 on a 0 to 10 scale using a headache diary) reported higher headache-related emotional distress, as measured by the Headache Disability Index (HDI >25). Similarly, those with higher headache pain intensity ($\geq$ 5

(0 to 7 scale) on the Multidimensional Pain Inventory (MPI) reported higher headache-related emotional disability (Magnusson & Becker, 2003).

Lipton and colleagues (2003) compared emotional status changes between individuals with migraine and control group (without migraine). Compared to the control group, migraine pain significantly lowered ($p < 0.05$) role-emotional and social functioning domains, using the SF-36. In addition, the mental health scores, an indication of mood such as happiness, nervousness, depression, and calmness, were significantly lower ($p < 0.05$) in those with migraine. Further, researchers compared disability scores of those with migraine. Scores were determined based on work days missed and work activity reduced by 50%, and were reported as mild (N=98), moderate (N=49), and severe (N=49). Higher disability groups had significantly lower mental component summary scores ($p< 0.05$) and lower social functioning scores ($p< 0.05$) compared to mild disability migraine individuals (Lipton, Dodick, et al., 2003).

Generally, individuals with trigeminally mediated pain disorders, including migraine, experience significant impact on their emotional health. More specifically, because of extensive migraine research, it is further known that those who report more incidents of disability are more likely to experience even greater emotional impact (Lipton, Liberman, et al., 2003; Magnusson & Becker, 2003). It is not known whether emotional status is affected following EFS with resultant headache pain. However, if EFS headache pain is similar to trigeminally mediated migraine, it can be speculated that emotional status will be diminished as it is in migraine.

Functional Status

Paroxysmal or constant severe to excruciating trigeminally mediated neuropathic pain lasting moments to decades reduces functioning, leading to disability, unemployment, and early retirement (McDermott et al., 2006c; Sadosky et al., 2008). Sadosky (2008) reported trigeminal

neuralgia pain interfered with normal functioning at work in 34% full-time employees and up to 28% part-time employees (Sadosky et al., 2008). Similar significant findings included a decrease ($P<0.001$) in functional status, as measured by the modified Short Form Brief Pain Inventory, which included self-care, usual activities, and mobility (Tölle et al., 2006). Fatigue and inability to physically move without pain brought on by postherpetic neuropathy was found to restrict the ability to shop, dress, bathe, eat, and perform normal household activities (Johnson et al., 2010). Marciani (2007) found as result of pain following third molar removal there was a reduction in the ability to maintain oral functioning, including chewing, speaking, and mouth opening. Due to pain, functional limitations, including social activities for 61.5%, recreation for 70.5%, and daily routine for 60%, were impacted. For individuals with atypical odontalgia, there was a significantly reduced role-physical ($P < .001$) and vitality ($P < .004$), when compared to control (List et al., 2007). White (2003) reported trigeminally mediated pain distrupted daily routine and recreation function on postoperative day (POD) 1 for 46% and 63%; POD 2 for 33% and 49%; POD 3 for 23% and 35%; POD 4 for14% and 23%; POD 5 for 9% and 15%; and POD 6 for 5% and 12%, respectively, following third molar extraction (White et al., 2003).

Assessing HRQoL with the EuroQol (ED-5D) in 385 subjects with postherpetic neuralgia, pain interference on a 10-point scale for general activity was 3.7 ± 3.1 and for sleep was 3.8 ± 2.9. As pain severity increased, functioning decreased for usual activities ($p<.001$), as did self-care and mobility, although not significantly (Oster et al., 2005). Similarly, Chidiac (2001) collected data using the Medical Outcomes Short Form -36 and found that there was a decrease in physical activity (36%) and walking time (28.6%) with postherpetic neuralgia pain. Schmader and colleagues (2007) found function, including activities such as getting out of the house, shopping, bathing, and eating, were significant diminished for individuals (N=160) with

postherpetic neuralgia, as measured by Short Form-12 ($p<0.0001$), Zoster Brief Pain Inventory ($p<0.0001$), and the Zoster Impact Questionnaire (ZIQ) ($p<0.0001$). In a sample of those with neuropathic pain of varying etiologies, (N=602), pain intensity had a direct association with poorer outcome ($p<0.001$) illustrated by 43% having disrupted employment, 5.5% having missed workdays in last 30-day work period, and 16% having decreased work time (16%) (McDermott et al., 2006a). Changes in function were identified in a descriptive longitudinal study of a large sample of postherpetic neuropathic pain (N=935). As measured by the Medical Outcomes Study Short Form-36 (MOS SF-36) scale, 36% experienced a decrease in physical functioning, 36% had decreased walking time, and 58% experienced an impact on sleep. Four different distributions were identified in this sample, and findings represented the sample overall, which makes identifying the precise impact on each distribution difficult. However, trigeminally mediated pain in the head and neck region represented over half of the sample (N=500 or 54%), followed by that in the thorax (N=540 or 58%), sacrum (N=89 or 10%), and low back(N=75 or 8%) (Chidiac et al., 2001).

Migraine provides a clear example of the functional consequences of trigeminally mediated pain. Those with migraine pain resulting in severe impairment and bed rest report decreased role-physical and higher limitations scores (Burstein, Yarnitsky, et al., 2000; Cady et al., 2004; Goadsby, 2005; Lipton, Liberman, et al., 2003; Lipton, Bigal, Diamond, Freitag, Reed, Stewart, et al., 2007; Schreiber et al., 2004; Stovner & Hagen, 2006). Magnusson & Becker (2003) found that regardless of the number of days with headache, pain intensity is associated with functional disability. Lipton et al. (2003) found those with migraine headache pain had increased limitations in physical functioning, work-related disability and role-physical scores, compared to those without migraine on SF-36 ($p<0.005$). In another study, individuals with

migraine experienced functional impairments and activity restriction, missed work/school, were unable to perform household work, missed family or social activity, and required bed rest (Lipton, Bigal, Diamond, Freitag, Reed, Stewart, et al., 2007).

In summary, outcomes of trigeminally mediated pain include altered emotional states, subsequently interrupting even the most basic normal everyday activities and self-care. EFS headache pain may have similar trigeminal nerve activation, as seen in the above-reviewed trigeminal disorders, including migraine. It is not known whether emotional and functional statuses are reduced with EFS headache pain. However, if EFS headache is analogous to these trigeminally mediated pain disorders, emotional and functional statuses may be similarly disrupted.

Summary of Trigeminal Nerve Pain Disorders

Only two surgical articles mentioned postoperative headache pain following EFS. No headache pain characteristics or outcomes were described. As suggested, EFS headache results from trigeminal nerve trauma during surgical dissection. Regardless of etiology, in disorders involving this large primarily sensory nerve that innervates the face and forehead, pain is often described as severe with devastating qualities that alter normal mental states, often restricting the ability to maintain normal daily routines. Effective pain management for trigeminally mediated pain disorders, including migraine, continues to be elusive but often involves complex treatment strategies.

Clinical observation and anecdotal reports have revealed that postoperative EFS headache pain is moderate to severe, bilateral, throbbing, and unrelieved with currently prescribed medications, affecting emotional status and functional status. No literature was found that offered any postoperative management following EFS or consideration of effects of headache on

emotional and functional status. Women have a greater propensity to develop trigeminally mediated disorders, suggesting estrogen may be an influencing factor. In migraine, women with stable estrogen levels experience less migraine compared to women with fluctuating estrogen levels, suggesting a greater susceptibility to neuronal excitability with estrogen changes.

Currently, there are no pain descriptions, protocols for treatment, or guidelines for assessing or evaluating EFS headache pain. The goal of this research is examine EFS headache pain to advance our understanding so that outcomes may be improved for our patients in pain.

CHAPTER 4: METHODOLOGY

Introduction

The research methods for this proposed study will describe and enable empirical description of the characteristics, medication efficacy, and emotional and functional outcomes of headache pain following EFS. In addition, correlations between hormone status and headache pain characteristics following EFS will be examined.

Research Design

The study will use a descriptive survey design to examine postoperative headache pain in women undergoing EFS. Based upon the scant clinical reports of EFS headache pain immediately following surgery, time-frame will include the most severe symptoms is from first night to2-7 days.

Sample

Participants will be recruited from ten private independent cosmetic surgeons' offices located in the Orange, Riverside, and San Diego Counties. (Appendix A) As approved by the Institutional Review Board (IRB), the PI will request that surgeons and office staff assist with recruitment. It is estimated that from 15 to 50 women undergo EFS procedures at each site over a six-month period, providing an estimated pool of 105-350 participants from which to draw the sample.

Eligibility Criteria

Women and men who undergo EFS will be included if they 1) are female or male; 2) are 35 to 75 years old; 3) are able to read, write, and understand English; 4) have telephone access; 5) agree to have the PI call to explain the study; and 6) provide their names and telephone numbers where they can be contacted and an alternate person who can be contacted in the event

that the participant is not able to answer the call directly. Upon review of each patient chart, which includes surgeon history and physical, and following telephone pretesting with SF-12v2, participants will be excluded if they 1) have major cognitive or neurological impairments that may impact their ability to participate in the consenting process and complete the study procedures; 2) currently routinely consume pain medications; 3) have allergies to pain medications; 4) have any physical impairments that interfere with normal activities, work days, and social events; 4) are currently being treated for depression or anxiety; or 5) are currently being treated for any pain syndromes. The expected ethnicity for this sample will include women who are predominantly white and between the ages of 40-55.

Sample Size

The target sample will be 30 subjects who undergo EFS. The G-power analyses indicated that the greatest number of measurements (60, with two measurements subject) is required for a correlation testing specific to Aim 5 (pain perception and estrogen levels), based on detecting a negative correlation of 0.35 with a power of 0.8 and a 2-tailed alpha of 0.05 (Lenth, 2006-9). The descriptive aims require a minimum of 27 (t-test) and 28 (Wilcoxon signed-rank) subjects in order to detect a moderate effect size at power of 0.8 and alpha of 0.05. Since 90% of patients are estimated to have pain (based on clinical observation), 3 additional subjects will be recruited an. Furthermore, to allow for a 30% attrition, 9 additional subjects will be recruited an , for a total recruited sample of 42 (Faul, Erdfelder, Lang, & Buchner, 2007).

Measures

Validity Testing

While other pain instruments focus on pain intensity, pain symptoms, and location, the Headache Pain Questionnaire (HPQ) is a highly specified headache questionnaire that also

includes the following pain symptoms: pain qualities, locations, durations, aggravating activities, and autonomic symptoms that frequently coexist with migraine (adapted with permission from Rami Burstein, PhD). The HPQ is a valid way to measure study concepts, and these are measurements of pain characteristics. (Appendix B)

Demographics

The demographics information form will include the following: 1) age; 2) ethnicity; 3) family history of migraine headache, 4) head injury, 5) hysterectomy (with or without ovary removal); 6) HRT (oral or transdermal), and 7) daily medications (name, dose, and frequency). In addition, HRT and spontaneous or surgical menopause information will be accrued as these are all associated factors that could contribute to headache pain (Appendix C)

Headache Pain Perception

Pain Intensity

Pain perception will be operationalized by intensity, location, quality and duration, as measured on postoperative days 1, 3, 7, and 30. The Numerical Rating Scale (NRS) will be used to measure pain intensity. The NRS is an 11-point pain scale with 0=no pain and 10=worst pain (Jensen, Turner, & Romano, 1994). Pain ratings based on the NRS will be scored as follows: mild = 1-4, moderate = 5-6, and severe = 7-10 (Jensen, Smith, Ehde, & Robinsin, 2001; Jensen et al., 1994). Participants will be asked to rate their pain intensity “on the scale of 0 to 10, from 0 = no pain to 10 = worst pain, on the following questions: 1) “How much pain are you having right now?”; 2) “What is the highest pain you had since surgery?”; and 3) “What is the lowest pain you had since surgery?” (Williamson & Hoggart, 2005). The reliability and validity of the NRS is well-established, as evidenced by a high correlation with the Visual Analogue Scale (r=0.94, 95% CI=0.93-0.95). The NRS takes less than 30 seconds and has been used previously to assess

pain intensity in postsurgical and migraine patients (Apfelbaum, Chen, Mehta, Gan, & Tong, 2003; Ashina et al., 2010; Lipton, Dodick, et al., 2003; Rasmussen & Olesen, 1992). (Appendix B)

Location

If the participant is experiencing headache, she will be asked to describe where pain is located. Eleven questions regarding pain locations will be offered in the HPQ for description: right and left forehead, right and left temples, right and left eye, right and left cheek, right and left jaw, and top of head. These questions will take less than 30 seconds to complete. Identifying the pain sites will assist in understanding the distribution of the pain, which may elucidate which branch or branches of the trigeminal nerve are involved. If the right forehead (#1 area) or left forehead (#2 area) is identified as painful, numb, or tingling, respective ipsilateral V1 is involved. If the right temple (area #3) or left temple (#4 area) is identified as painful, numb, or tingling, this would indicate V1 and the zygomaticotemporal nerve are involved. If top of head (#11 area) is identified as painful, numb, or tingling, V1 or superior branch of the trigeminal nerve is involved. If the right (#5 area) or left (#6 area) eye, or right (#7 area) or left (#8 area) cheek is reported to be painful, numb, or tingling, the ipsilateral V2 or middle trigeminal nerve is involved. If right (#9 area) or left (#10 area) jaw is reported as painful, numb, or tingling, this would indicate V3 involvement. (Appendix B)

Quality

The participant will be asked to answer “yes” or “no” to each of the following words or phrases used to describe the quality of headache pain on the HPQ: 1) throbbing, 2) sharp, 3) dull, 4) superficial, 5) deep, 6) imploding inward, 7) exploding outward, 8) continuous, 9) intermittent, 10) headache worsening with bending over, 11) headache worsening with coughing,

12) headache worsening with sneezing, or 13) headache worsening with stair climbing. Each participant will be asked if she feels any general numbness, tingling, or itching, any forehead tenderness, or numbness or tingling in cheek, chin or arm. These word descriptors were previously used in migraine literature and are qualities listed on the HPQ, which includes valid and reliable qualities for characterizing headache pain (Ashina et al., 2010; Burstein et al., 2004; Granella et al., 2004; Jakubowski et al., 2006; Rasmussen & Olesen, 1992). These descriptions will provide information suggesting the etiology of headache pain, branch or branches of the trigeminal nerve involved, and possible presence of central sensitization. This question will take less than 90 seconds.

Participants will also be asked about concurrent symptoms that could affect the intensity and quality of pain experienced. The participant will be asked to say "yes" or "no" to each of the following signs or symptoms: nausea, vomiting, sensitivity to light (photophobia), sensitivity to sound (phonophobia) or sensitivity to smells (osmophobia). These associated symptoms will assist in comparing EFS headache with migraine and identifying whether EFS headache meets ICHD criteria for migraine diagnosis of migraine. Decreased serotonin levels lead to cerebral vascular vasodilation, nausea, and motion sickness. Sensory dysfunction from changes in brain activity resulting in aberrant sensory processing in the thalamus (photophobia) and auditory center (phonophobia). These questions will take less than 60 seconds. (Appendix B)

Duration

Duration will be determined by the number of days the NRS rating for headache pain is not zero. This question will take less than 15 seconds. (Appendix B)

EFS Pain Management

For each prescribed medication, participants will be asked: 1) "What medications have you taken for headache pain?"; 2) "Prior to taking your medication what rating would you give your pain on a scale of 0 to 10?"; 3) "Two hours after taking your pain medication, what would you rate your pain level at on a scale of 0-10?" (Jacob et al., 2003). Any medications prescribed and consumed by study participants will be listed on the Medications and Perceived Relief form in the HPQ.

The following medications are frequently prescribed for migraine and will be listed on the Medication and Perceived form in the HPQ to facilitate recording of responses: opioids (codeine, oxycodone, morphine, meperidine) and nonopioids (acetaminophen; triptans, such as sumatriptan, frovatriptan, and zolmitriptan; nonsteroidal anti-inflammatory drugs, such as ketorolac, anticonvulsants such as topiramate; and Botulinum Toxin A (Jakubowski, Levy, et al., 2005; Jakubowski et al., 2006; Silberstein et al., 2004; Silberstein et al., 2006). This question will take less than 3 minutes to complete. (Appendix B)

EFS Headache Pain Outcomes

Emotional Status

The participant will be asked to answer questions on the Short Form 12 version 2 acute recall questionnaire (SF-12v2) related to emotional status. Health is defined as physical and mental wellness, which includes mental status (emotional status) and body function (functional status). The SF-12v2 items include eight scales resulting in two summary measures, Physical Health (PCS) and Mental Health (MCS). Four subscales, which evaluate emotional status, are (1) Vitality (VT), defined as energy level; (2) Social Functioning (SF), defined as interference in ability to participate in social activities due to current health; (3) Role-Emotional (RE), defined

as interference of current emotional state in work and other daily activities; and (4) Mental Health (MH), defined as current feelings of nervousness and depression. The following questions on the SF-12 specifically relate to emotional status (VT, SF, RE, MH): 1) “How much of the time since your surgery a) have you felt calm and peaceful?; b) did you have lot of energy?; and c) have you felt downhearted and depressed?”; 2) "Since your surgery how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?” Answers to each of these questions will be chosen from the following: 1) "All of the time,” 2) "Most of the time,” 3) "Some of the time,” 4) "A little of the time,” and 5) "None of the time." These questions were previously used in patients with migraine (Ashina et al., 2010; Burstein et al., 2004; Granella et al., 2004; Lipton, Dodick, et al., 2003; Rasmussen & Olesen, 1992). Scores range 0-100, with 0 = poor emotional health and 100 = perfect emotional health, and the test takes less than 2 minutes to conduct. (Appendix D)

Functional Status

To evaluate functional status following EFS, the HPQ and SF-12v2 will be used. (Appendix F) Four subscales that evaluate functional status using the SF-12v2 are (5) Physical Functioning (PF), defined as the ability to perform normal daily activities such as bathing or dressing; (6) Role-Physical (RP), defined as ability to perform work duties with current date of physical health; (7) Bodily Pain (BP), defined as physical pain; and (8) General Health (GH), defined as individual’s perception of health status. The following questions on the SF-12 specifically relate to functional status:

1) “Does your headache now limit you in moderate activities such as moving a table, pushing a vacuum cleaner, bowling, playing golf, or climbing <u>several</u> flights of stairs?”

Responses are either: a) "Yes, limited a lot"; b) "Yes, limited a little"; or c) "No, not limited at all."

2) "Since your surgery, how much of the time have you had any problems with your work or other regular daily activities as a result of your physical health?" Responses are either: 1) "All of the time," 2) "Most of the time," 3) "Some of the time," 4) "A little of the time," or 5) "None of the time."

3) " Since your surgery, how much did pain interfere with your normal work (including both work outside the home and housework)?"

Responses are either: 1) "Not at all," 2) "A little bit," 3) "Moderately," 4) "Quite a bit," or 5) "Extremely".

Scores range 0-100, with 0 = poor functional health and 100 = perfect functional health and no functional limitation. These questions take less than 2 minutes to conduct.

The participant will be asked HPQ questions and to respond "yes" or "no" to each to describe their functional status. The questions are as follows: "Are you able to 1) participate in activities with family/friends like you normally do, 2) work like you normally do, 3) sleep like you normally do, 4) eat and drink like you normally do, 5) perform activities like you normally do?" (Burstein et al., 2004).

The SF-12 has established reliability, test-retest correlations of 0.89 and 0.76, and relative validity coefficients for both physical component summary (0.43 to 0.78, median 0.67) and mental component summary (0.93 to 0.98, median 0.97) (Ware, 2007). (Appendix M) Correct data, correct processing, and reliable interpretation will be obtained with specifically designed QualityMetric certified scoring. Scores for the two summary measures, PCS and MCS, range 0-100, with 0 = lowest level and 100 = highest level. Reports will be interpreted as "at,"

"below," or "above" normal population levels for each of the eight scales. These questions were previously used in migraine evaluation (Lipton et al, 2003; Magnusson & Becker, 2003). These questions will take less than 3 minutes. (Appendix D)

Estrogen

To observe any differences in and relationship between estrogen status and pain perception and outcomes, any estrogen-related data will be obtained on the demographic form. Such data will include surgical removal of ovaries or uterus, history of hysterectomy, and name and routes (oral, transdermal patch, intravaginal gel, cream, or ring) of HRT. The comsumption of exogenous estrogen will not be considered the same as estrogen serum levels. Patient consumption of exogenous estrogen will be obtained for pain experience comparison. While this study may not provide results to compare for statistical significance any relationship between EFS headache and HRT, ovary removal, or hysterectomy, it may identify differences that may be interesting to look at prospectively. (Appendix C)

Procedures

Screening and Recruitment

After Institutional Review Board (IRB) approval is received, the PI will conduct a one-hour educational training session to introduce the study to participating surgeons and one front office staff member at each study site. The trained surgeon or front office person will offer each patient who is going to undergo EFS an IRB-approved recruitment flyer. The flyer provides information about the study (purpose and procedures); spaces to write participant's name and contact phone number, and an alternate name and phone number of the person who may be contacted in the event that the participant is not able to answer the phone; and a statement that, for completion of all 3 telephone interviews, a $75 VISA gift card will be provided to the

participant for compensation of her time. The designated office member will fax completed patient recruitment flyers to PI FAX # (949) 448-0298. To maintain participant confidentiality, the completed flyer will be securely stored in the patient's personal medical record at her surgeon's office. (Appendix E)

Self-report data on the concepts of interest will be accrued by telephone interviews by the PI on postoperative days 1, 3, 7, and 30. This method will allow for data collection from several study participants from multiple office locations with a focus on obtaining valid, consistent results. Telephone interviews have been used successfully in previous research for postoperative pain data collection (Apfelbaum et al., 2003; Chung, Ritchie, & Su, 1997) and were found to be as valid as interviews conducted in person (Rohde, Lewinsohn, & Seeley, 1997). Completion response rates for telephone interviews have been reported to be 42.3- 67.6% (Latremoliere & Woolf, 2009). The data collection method is valid, simple, cost-efficient, and convenient for both interviewee and interviewer, permiting inclusion of geographically distant patients, and minimizes subject burden.

Consenting and Enrollment

In the first telephone interview on postoperative day 1, the PI will read an IRB-approved oral consent form and will give participants the opportunity to ask questions if they wish to. The PI will ask the participant "Would it be okay to proceed with these questionnaires?" The participant will be enrolled when a "yes" response is received and the PI determines she meets all eligibility criteria and informed consent is obtained. For those willing participants who do not meet the eligibility criteria, the interview will not continue. (Appendix F)

Data Collection

The data collection forms described above will be used to guide the interviews. The PI will write the responses on the forms. Five telephone calls will be made to each participant. The first telephone call will be conducted after a completed recruitment study flyer is received with the potential participant's name and telephone number. Once the oral consent is completed, data collection will begin with the completion of demographic information and baseline SF 12v2. This will take approximately 5 minutes. Calls will be made in the privacy of the PI's home office so that participant confidentiality will be maintained. For details of the timeline of the data collection, see Appendix I.

Postoperative Day 1. Eligible study participants will be asked to reply to questions about how they are feeling following surgery. If they mention pain, they will be asked to specify where the pain is. If headache is present, questions will follow about the 1) intensity, location, quality, and duration; 2) medications and perceived relief; and 3) emotional status and functional status. This procedure will take approximately 5 minutes. Participants will be asked what was the worse headache pain intensity for the day (0-10), with 0 = no pain and 10 = worst pain possible. They will be asked if they consumed any prescribed medication for the headache pain. If they did consume medication for headache pain, they will be asked the name of the medication/s and to rate their pain level two hours following consumption. This will provide data on prescribed pain medication efficacy. In the event that the participant is tired or unable to answer the questions, she will be offered two options: 1) a caretaker may act as a relay person to complete the interview; or 2) an hour to rest will be offered, after which the participant will be called again. If a participant or caretaker no longer desire to participate, she will be withdrawn from the study.

Postoperative Day 3. Data collection for postoperative day 3 will be similar to postoperative day 1 and use the NRS, HPQ, and SF 12v2. Information regarding medication taken for headache pain will again be asked about, and present NRS scores will be compared to NRS scores prior to medication consumption and 2 hours after consumption.

Postoperative Day 7. Data collection for postoperative day 7 will be similar to postoperative days 1 and 3 and use the same questionnaires and data collection forms. Information regarding medication taken for headache pain will again be asked about, and present NRS scores will be compared to NRS scores prior to medication consumption and 2 hours after consumption.

Postoperative Day 30. Data collection for postoperative day 30 will be similar to postoperative days 1, 3, and 7 and use the same questionnaires and data collection forms. Information regarding medication taken for headache pain will again be asked about, and present NRS scores will be compared to NRS scores prior to medication consumption and 2 hours after consumption. At the end of the interview, the PI will provide an opportunity for the participant to ask questions and provide comments. At the completion of all interviews, participants will be reminded that the $75 gift card will be provided to them as compensation of their time. The gift card will be available when they return to their respective surgeon's office for their next office visits.

Data Analyses

All data will be entered in SPSS. Descriptive statistics (mean ± SD, frequencies, and median with interquartile range) will be used to describe the demographics of the sample.

Specific Aim 1:

To describe the intensity, location, quality, and duration of headache pain following EFS, descriptive statistics will be used:

Pain intensity – Frequency and percentages will be used to describe the current pain, highest pain, and lowest pain, using the NRS, on postoperative days 1, 3, 7, and 30.

Pain quality – Frequency and percentages will be used to describe the number and percent of participants who indicated "yes" for each of the quality descriptor words.

Pain duration – Frequency and percentages will be used to describe the number of days that pain is felt on postoperative days 1, 3, 7, and 30.

Pain location – Frequencies and percentages will be used to describe the number, location, and percent of participants who indicated "yes" for each location.

Interpretation of data. If findings include moderate to severe intensity, throbbing/pulsating qualities, and unilateral or bilateral locations lasting hours to days, this would suggest EFS and migraine headache pain are similar in characteristics and most likely have similar etiology.

Specific Aim 2

A comparison of EFS and migraine pain characteristics including intensity, duration, location, and quality will be conducted using descriptive statistics.

Pain intensity – Means and standard deviations will be used to describe the current pain, highest pain, and lowest pain, using the NRS, on postoperative day 1 and day 7.

Pain quality – Frequencies and percentages will be used to describe the number and percent of participants who indicated "yes" for each of the quality descriptor words.

Pain duration – Means and standard deviations will be used to describe the number of hours that pain is felt on postoperative day 1 and the number of days that pain is felt from postoperative day 1 to day 3, 7, and 30.

Pain location – Frequencies and percentages will be used to describe the number and percent of participants who indicated "yes" for each location.

Interpretation of data. If findings include moderate to severe intensity, throbbing/pulsating qualities, and unilateral or bilateral headache pain lasting hours to days, this would suggest EFS and migraine headache pain are similar in characteristics and most likely have similar etiology.

Specific Aim 3

To examine and compare prescribed medications consumed and perception of relief on days 1, 3, 7, and 30, descriptive statistics will be used:

Name of Medication – Frequency and percentages will be used to describe the number and percent of participants who indicated having used each medication.

Perceived Relief from Medications – Means and standard deviations will be used to describe amount of relief perceived for the most frequently used medications.

Interpretation of data. Frequencies and percentages will be used to describe what medications were used and which were perceived as effective or not effective for headache pain following EFS. If prescribed medications used following EFS are reported to have little or no perceived relief, current prescribed strategies may be considered ineffective and not the best choice for treatment for headache pain following EFS.

Specific Aim 4

To evaluate the relationship between headache pain intensity and emotional and

functional status frequency, percentages will be used to describe changes from baseline and scores that are below US average (50).

Emotional status – Means and standard deviations will be used to describe emotional status on postoperative days 1, 3, 7 and 30. The range of scores on the emotional subscale of the SF-12 is from 0 indicating poor emotional status to 100 indicating good emotional status. Scores below US average (50) will indicate that participants with high pain also have poor emotional status.

Functional status – Means and standard deviations will be used to describe functional status on postoperative days 1, 3, 7, and 30. The range of scores on the functional subscale of the SF-12 is from 0 indicating poor functional status to 100 indicating good functional status. Scores below US average (50) will indicate that participants with high pain also have poor functional status.

Threats to Internal & External Validity

Threats to Internal Validity

Potential threats to the internal validity of this study are selection bias, history, testing, setting, researcher bias, attrition, and instrumentation bias.

Selection bias. The study sample will be patients selected by convenience from cosmetic surgeons in Orange, San Diego, Los Angeles, and Riverside county areas, limiting interpretability of the results to larger populations outside of these counties.

History. This threat is not a foreseeable issue because this study will only follow participants for 30 days, it is unlikely history will be a threat.

Testing. Testing may be a potential threat to validity. Participants will be asked the same questions at all interviews, thereby familiarizing them with questions. Participants may

remember their previous responses (recall bias) and become more in tune with what the researcher is looking for and tailor their responses in an effort to please the researcher. It is possible that if participants are experiencing headache pain, the length of the interview will be too exhausting for them. The goal of study is to get fresh pertinent data collected from participants' current or recent experiences so that responses accurately depict EFS pain or lack thereof. Any delay between experience and data collection relies on participant recall, which may alter reported description of the actual experience, thus skewing data and diminishing accuracy of study findings.

Setting. There will be setting variations, both among participants' various home surroundings and among the ten cosmetic surgery offices, each with different surroundings, office personnel, and surgeons. Having different surgeons performing EFS and varying anesthesia providers may introduced uncontrollable variables. Subtle differences in the way individual surgeons perform EFS surgery and differences in anesthesia agents may cause varying postoperative pain. These variables may contribute to varying headache experiences but cannot be controlled. Therefore, the results may not be generalizable to all persons who undergo EFS. However, if findings are significant regardless of these variations, this suggests similar results could be expected in other EFS samples.

Researcher bias. Participant will be told that the PI will be conducting all telephone interviews, bonding participants to the study and resulting in greater number of completed questionnaires. Having only one interviewer may result in participants desiring to please or displease the interviewer with their answers. The single interviewer may inadvertently introduce bias during the interview process that will result in data that would prove preconceived study results, thus skewing data and results. Having more than one interviewer might help with this

threat to consistent data. However, for the purposes of the present study, consistency in voice inflection and delivery of questions with the telephone interviews outweighs having two interviewers. Prior to each phone session, the interviewer will need to take a few moments to remember to try not to introduce personal bias during the interview process.

Attrition. Some participants may choose not to complete all interviews, resulting in incomplete data due to participant burden. The number of participants who refuse to participate and who do not complete all interviews will be acknowledged in the final report. Including incomplete data may lead to a misinterpretation of study findings and explain possible study flaws.

Instrumentation bias. The instruments used in this study have evidence of reliability and validity. The SF-12 has established reliability, test-retest correlations of 0.89 and 0.76, and relative validity coefficients for both physical (0.43 to 0.78,median 0.67) and mental (0.93 to 0.98, median 0.97) component summaries (Ware, 2007). The reliability and validity of the NRS is well established, as evidenced by a high correlation with another well-establish scale, the Visual Analogue Scale (r=0.94, 95% CI=0.93-0.95). The questions on the headache pain questionnaire that will be used to guide the telephone interviews were adapted from questionnaires used in other headache populations, namely migraine (Burstein et al., 2004).

Threats to External Validity

Generalizability. There are some limitations in generalizing findings to larger populations, including male EFS patients, other surgeons, surgical techniques, or parts of the country, or alternative settings such as hospitals or free standing surgery centers and varying anesthesia techniques. Since this study only includes women, these findings cannot be generalized to include male EFS patients. Surgery techniques including variations in EFS

fixations and alternative surgical techniques; as well as varying anesthesia techniques may not be evenly represented in this study possibly making generalizing these findings difficult for all EFS patients. This sample includes participants from a small geographical region, which may make it difficult to generalize to larger regions. However, if findings from this study are significant, these findings may be generalizable to larger populations, including males, regardless of surgical techniques.

Protection of Human Subjects

Potential Risks & Discomforts

There is minimal risk to participating in telephone interviews. It may be difficult for participants experiencing headache pain that is incapacitating to participate in the telephone interviews. Holding a phone close to the ear may also cause minimal discomfort while answering questions. Participants will be offered the opportunity to have their caretakers repeat the interviewer's questions and to relay their answers to the interviewer. In the event that study participants are too tired or upset, or not willing to participate in telephone interviews, they will be given an option to decline participation or to be called an hour later to complete the interview/s. Participants will be reminded that participation is voluntary, and there are no penalties for refusing or discontinuing participation in the study. Risk of the wrong person answering the phone when the PI calls may present a risk of privacy and confidentiality.

Risk/Benefit Analyses

There will be no direct benefits to participants. However, the information gained may offer description of headache pain following EFS, as well as the effectiveness or ineffectiveness of current medication strategies, thus exposing the need to develop new guidelines for assessment and management for future EFS patients. New assessment guidelines and medication

strategies may lead to improved emotional status and functional status for patients following EFS.

Confidentiality/Privacy

Survey responses will be available only to the PI and dissertation committee members. Data from this study will have no personal participant identifiers such as names or phone numbers. Numerical codes will be assigned to each participant and will not contain any personal identifying element as part of their code.

Data Security & Physical Safeguards

Each participant will be provided an identification code. The PI will store identification codes in a secure, locked cabinet. Further information such as names, phone numbers and any other contact information will not be disclosed unless essential to conduct the research. All surveys and any other paperwork will not be kept in public places where passers-by may inadvertently gain access to any study participant's content. The UCLA IRB will be notified in the event of data breaches or suspected data breaches. All data and research files will be stored in a locked cabinet. Data or information stored on computer systems will be password protected, and will have built in timeouts that lock access after a set period. An audit trail that records who has access and whether any created or changed information was made to the data will be available.

Record Keeping & Future Access to Data

Any research data will be kept by the PI and an audit trail of any breaches of participant disclosures will be maintained. These records will be kept for six years.

Cost and Payments. Participant will be offered a $75 gift card upon the completion of all three interviews. The gift card will be available upon the completion of the final interview at the office of their surgeon.

Consenting Procedures. An oral consent will be obtained for this study over the phone. This study has minimal risk. Each study participant will be undergoing EFS, and their surgeon or designated front office member in their respective surgeons' offices will offer them a flyer that explains the purpose of the study. At the bottom of the flyer are areas for potential study participants to write their names and phone numbers, or the name and phone number of a caretaker and a time that is convenient for the PI to contact participants by telephone for an interview that evening. The study flyer will contain the PI name (Julia Lassegard), phone number (714-293-3548), and affiliation (UCLA School of Nursing).

In the initial telephone call, the participant will be welcomed to participate in the study. Each potential study participant will be told their participation is voluntary and there are no penalties for refusing or discontinuing participation. They will be told why they are eligible to be in the study and the purpose of the study, which in lay language is to better understand what the postoperative experience following browlift surgery was like for them, including whether they experienced any headache pain. They will be told that there will be minimal if any risk for participating in the study. They will be informed that all information is confidential and no one other than the PI will have access to their personal information. Personal information such as telephone numbers and names will kept in secure cabinets and will not be accessed by anyone besides the PI and coinvestigator.

They will be told what will happen in the study, which is that they will answer questions by telephone about their experience. The interview will last about 5-10 minutes. They will

answer the evening of the surgery (1st postoperative day), postoperative day 3, and postoperative day 7. They will be given the opportunity to ask questions or discuss the study with their caretaker or significant other. If they wish to proceed and accept the opportunity to participate in the study, this will indicate consent to be screened for eligibility criteria and be enrolled if criteria are met. They will then be asked questions related to the inclusion and exclusion criteria. If they are not eligible, they will be told why and the phone interview will be discontinued and all collected personal information, name and telephone number will be destroyed. If they are eligible, questions will proceed, starting with demographic data and followed by questionnaire questions. They will be told the time and day of the next telephone interview. The telephone number for the next interview will be confirmed, and if the study participant prefers a specific interview time, the PI will make every effort to accommodate.

CHAPTER 5: RESULTS

Introduction

The aims were to describe the following: (1 a-d) the nature of headache following EFS, including intensity, quality, location, and duration; (2) the comparison of EFS headache pain with migraine; (3) prescribed pain medications and their perceived efficacy; (4) the impact of headache pain on emotional and functional statuses; and (5) the effect of estrogen levels on headache. Based on anecdotal and clinical experience, it was hypothesized that most women experience postoperative moderate to severe pulsating headache lasting 1-7 or more days, with associated symptoms photophobia and phonophobia, and nausea and vomiting, similar to migraine. Further, it was hypothesized that prescribed pain medications are mostly ineffective, and that emotional and functional statuses deteriorate with postoperative headache. The effects of estrogen (HRT) on postoperative EFS headache were unknown. However, based on anecdote, it was speculated that those on HRT experience less headache pain than those not on HRT.

The findings essentially supported these hypotheses: (1) women experienced moderate to severe pain after EFS; (2) the nature of the headache occurring with EFS was similar to migraine; (3) prescribed pain medications were inconsistent in providing relief, and ineffective in eliminating headache for most women; (4) emotional status and functional status declined postoperatively; and (5) women on HRT experienced lower pain intensity and were almost twice as likely to not meet migraine diagnosis criteria. EFS headache did not disappear for all women by POD #30, but decreased to mild levels for most women. The majority of women experiencing postoperative headache following EFS met ICHD diagnostic criteria for migraine, despite the fact that most did not have a previous history of migraine. The following sections in this chapter

describe the sample, the main findings, including statistical tests for hypotheses, and some secondary analyses that provide further insight into the phenomenon under study.

Sample Characteristics

The sample consisted of 42 women aged 43-74 years of age 59.0 ± 7.9 years [43 to 74], as described in Table 5. Ethnicity was classified as 39 white, two Hispanic, and one other. The enrolled subjects met the inclusion and exclusion criteria of being (1) female; (2) 35 to 80 years old; (3) are able to read, write, and understand English; and (4) have telephone access. Forty-four women were initially screened, consented, and enrolled. However, two subjects dropped out, one due to relocation and one due to excessive pain (ages 51 and 71, one white and one Hispanic). The former was excluded because she moved postoperatively from one location to another, and missed two interviews. The latter participant declined to participate further due to severe pain. She left a voice message saying, "I'm just still hurting too much to continue with the study. I need to see the doctor about getting this headache under control. I'm sorry I just don't feel like I can continue."

Of the 42 participants, 10 had previously undergone hysterectomy surgery, of whom nine had bilateral ovary removal. Fifteen of the 42 women were on HRT prior to EFS surgery. History of migraine existed for twelve women, and eight without personal history of migraine had a close family member (daughter, son, mother, grandmother or sister) with a history of migraine. Four had a history of head injury, all of which resolved without continued medication, therapies, or disabilities.

Table 5

*Sample characteristics. *Does not include two subjects initially enrolled who did not complete the study. †Non-white included one Hispanic and one Armenian.*

Number of Subjects Completed	42*
Women	42 (100%)
Mean Age ± Stdev [range]	59.0 ± 7.9 years [43 to 74]
White	39 (93%) †
History of Migraine	12 (29%)
Family History of Migraine (no personal history)	8 (19%)
HRT	15 (36%)
Hysterectomy	10 (24%)
Hysterectomy with Ovary Removal	9 (22%)
Head Injury	4 (10%)

1. Principle Pain Findings

The first study aim was to describe headache intensity, qualities, and location on postoperative days 1, 3, 7, and 30 following EFS.

1A: Intensity

Headache intensity following surgery was consistent with Hypothesis #1A, namely that women experienced moderate to severe pain after EFS. This pattern was confirmed with a Pearson Chi Square test of independence, which verified severe-to-mild headache pain following EFS ($p < 0.001$). The proportion of women reporting any headache pain was substantial (N=39, 93%) on POD #1 following EFS. (Table 6 and Figure 6) Most (N=35, 83%) continued to

experience pain on POD #7 (N=24, 57%) and POD #30 (N=15, 35.7%). Average pain intensity rating on the 0-10 scale was moderate on POD #1, and declined to mild by POD #30, although substantial variability was present. There was a downward trend in severe pain (46-0%) from POD #1 to POD #30, with an upswing in reports of no pain (5-39%) during the same time period. (Figure 7)

The severity of pain started high and decreased over time ($p < 0.001$, Pearson Chi Square). (Appendix G1) More women experienced headache pain at a level that was severe on POD #1 (45%) as opposed to mild (29%) or moderate (19%). (Table 6) Severe pain reports diminished substantially by POD #7 (7%) and disappeared by POD #30. Incidents of moderate pain increased slightly on POD #3 compared to POD #1 (24% vs. 19%, respectively), decreasing on POD #7 (12%), and remained unchanged on POD #30 (12%). Almost a third of women experienced mild pain on POD #1 (29%). The greatest occurrence of mild pain was on PODs #3 (40%) and #7 (40%); however, levels diminished on POD #30 (29%). There was a considerable increase in women reporting no pain from POD #1 (7%) to POD #30 (60%). On POD #30, no women were experiencing severe pain, with reports of only moderate (12%), mild (29 %) and no pain (60%). In summary, the overall trend for headache pain was a decrease from POD #1 (93%) to POD #30 (41%).

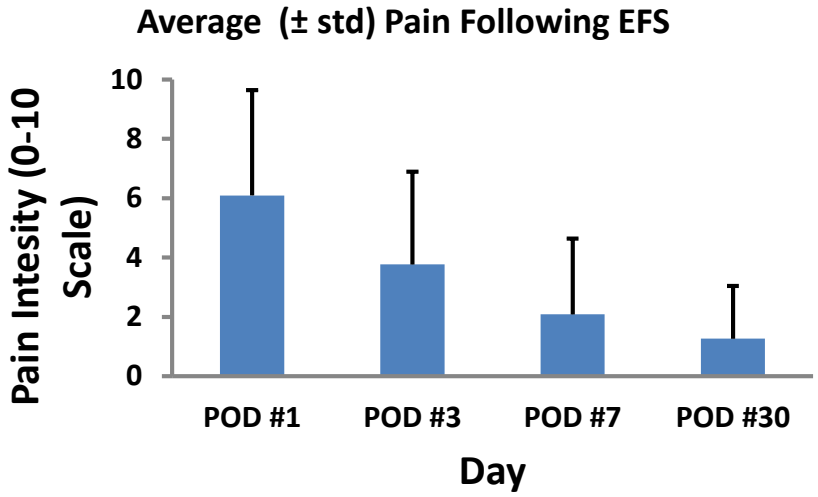


Figure 6.

Pain intensity following EFS PODs #1, 3, 7, and 30 (average ± std).

Table 6

Pain experience distribution on PODs #1

		POD #1	**POD #3**	**POD #7**	**POD #30**
No Pain		7% (N=3)	17% (N=35)	40% (N=25)	60% (N=17)
Any pain		93% (N=39)	82% (N=7)	59% (N=17)	41% (N=25)
Pain categories					
	Severe	45% (N=19)	21% (N=9)	7% (N=3)	0% (N=0)
	Moderate	19% (N=8)	21% (N=9)	12% (N=5)	12% (N=5)
	Mild	29% (N=12)	40% (N=17)	40% (N=17)	29%(N=12)

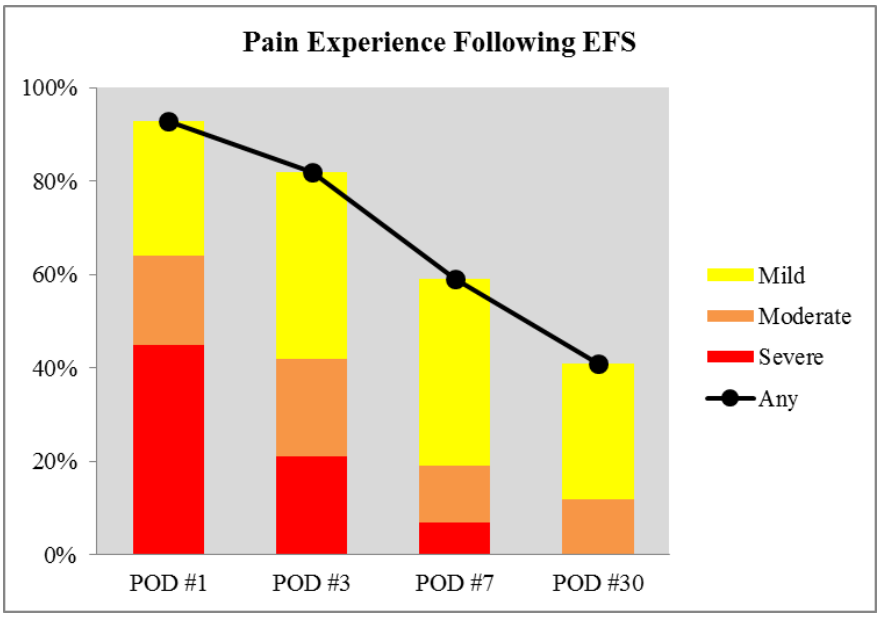


Figure 7.

Pain experience following EFS and Trendline of pain on PODs #1, 3, 7, and 30.

1B: Qualities

The quality of headache pain following surgery was consistent with Hypothesis #1B, namely that women experience headache pain qualities following EFS. Most pain qualities and associated symptoms were experienced on PODs #1, 3, and 7 following EFS. There was a substantial decrease in the prevalence of characteristics by POD #30. Those with moderate (N=5) or mild (N=11) pain intensity continued to experience many pain characteristics and migraine symptoms; migraine symptoms discussed in section "2. EFS Headache Characteristics and ICHD Migraine Criteria" below. (Figure 8)

Specifically, for women with severe pain (N=19) on POD #1, the majority of pain characteristics and associated symptoms were experienced by more than 50% of participants. One women experienced all characteristics and symptoms. With rare exceptions, women with severe pain had more pain qualities at higher incidences than those with moderate and mild levels. (Appendix H, 1-4) Most with severe pain described throbbing (74%), dull (84%), sharp

(58%), imploding (58%), exploding (42%), continuous (58%), and intermittent (42%). In addition, they also experienced associated symptoms of nausea (53%), photophobia (84%), phonophobia (68%), and osmophobia (16%). On subsequent postoperative days, pain characteristics continued to be higher than in other pain groups. For those with severe pain (N=9) on POD #3, pain descriptors included throbbing (56%), exploding (44%), dull (89%), intermittent (33%), continuous (56%), superficial (78%), sharp (22%), and deep (11%). Associated symptoms of nausea (44%), photophobia (89%), phonophobia (67%), and osmophobia (33%) were also experienced. Incidents of nausea decreased on POD #3 from POD #1 (44% vs. 53%, respectively). For POD #7 (N=2), those with severe pain described its characteristics as throbbing (50%), exploding (50%), dull (100%), continuous (50%), intermittent (50%), superficial (50%) and deep (50%), with associated symptoms photophobia (50%) and osmophobia (50%). Reports of nausea were nonexistent on POD #7. For the final postoperative day, there were no reports of severe pain.

Those with moderate pain (N=6) described similar pain qualities as those with severe pain, with two differences: there were no reports of deep characteristic or associated symptom osmophobia. Pain on POD #1 was most often reported as superficial (67%), sharp (38%), dull (50%), continuous (50%), throbbing (17%), and imploding (50%), with lower incidents of exploding pain (38%). Associated symptoms for those with moderate pain included photophobia (38%) and phonophobia (25%).

On POD #3, for those with moderate pain (N=10) most pain characteristics and associated symptoms had diminished significantly. However, throbbing increased substantially from POD #1 to POD #3 (13% vs. 50%). Dull (70%), intermittent (90%), and deep (30%) also increased from POD#1 to POD #3. By POD #7, the moderate group had increased slightly from

POD #1 (N=8 vs. N=10). On POD #7, pain descriptors sharp (25%), dull (100%), and deep (30%) increased from POD #3. From POD #7 to POD #30, the moderate group increased by one participant (N=5). Photophobia (60%), phonophobia (40%), exploding (40%), imploding (30%), and superficial (100%) increased on POD #30, compared to POD #7. Throbbing (40%) decreased from POD #7 (75%), although it was still present.

Women reporting mild pain (N=12) experienced all pain qualities similar to those experiencing severe and moderate pain. Similarly to the moderate group, those with mild pain reported no osmophobia. Pain qualities experienced were superficial (83%), intermittent (42%), throbbing (42%), exploding (25%), sharp (25%), imploding pain (50%), and dull (42%). In addition, the mild pain group also experienced associated symptoms of photophobia (50%) and phonophobia (17%). On POD #1 more participants experienced mild pain than moderate pain. Those with mild pain experienced higher levels of throbbing, photophobia, intermittent, and superficial than those with moderate pain, and only one characteristic, intermittent pain, was higher for those with mild than severe. On the subsequent postoperative day, POD #3, there were more reports of mild pain than either severe or moderate. Comparing POD #1 to POD #3, throbbing (42% vs. 25%), continuous (42% vs. 19%), and superficial (83% vs. 63%) decreased, while osmophobia (0% vs. 6%), dull (42% vs. 56%), and phonophobia (17% vs. 19%) all increased. On POD #7, headache pain described as exploding (29%), dull (59%), continuous (24%), superficial (65%), and deep (24%) all increased compared to POD #3. All other symptoms and associated symptoms had decreased from POD #3. On POD #30, the mild group had four more participants than on POD #7. The pain descriptors sharp (18%), continuous (27%), and deep (27%) increased compared to POD #7. Reports of photophobia doubled (36%) and incidence of phonophobia (18% vs. 0%) increased on POD #30, compared to POD #7.

There were only three study participants who reported no pain on POD #1. Regardless of no overall pain in these subjects, associated symptoms of photophobia (33%), phonophobia (33%), and osmophobia (33%) were experienced on POD #1. One subject reported only one pain characteristic, namely imploding (33%) on POD #1. On POD #3, seven participants reported no pain, and imploding was the only pain characteristic reported by one subject (14%), while associated symptoms photophobia (14%), phonophobia (14%), osmophobia (14%), and nausea (14%) were each reported once by other individuals. On POD #7, 19 participants reported no overall pain, although they did describe the presences of pain-related symptoms of throbbing (11%) and intermittent (5%), with associated symptoms photophobia (16%) and phonophobia (5%). On POD #30, those with no pain (N=26) were the largest group. In the group of women with no pain, only two pain characteristics, imploding (N=1, 4%) and superficial (N=1, 4%), were reported, each by a different subject. In summary, women with higher pain intensity ratings experienced more pain qualities than did those with lower pain intensity ratings at all interview time points following EFS.

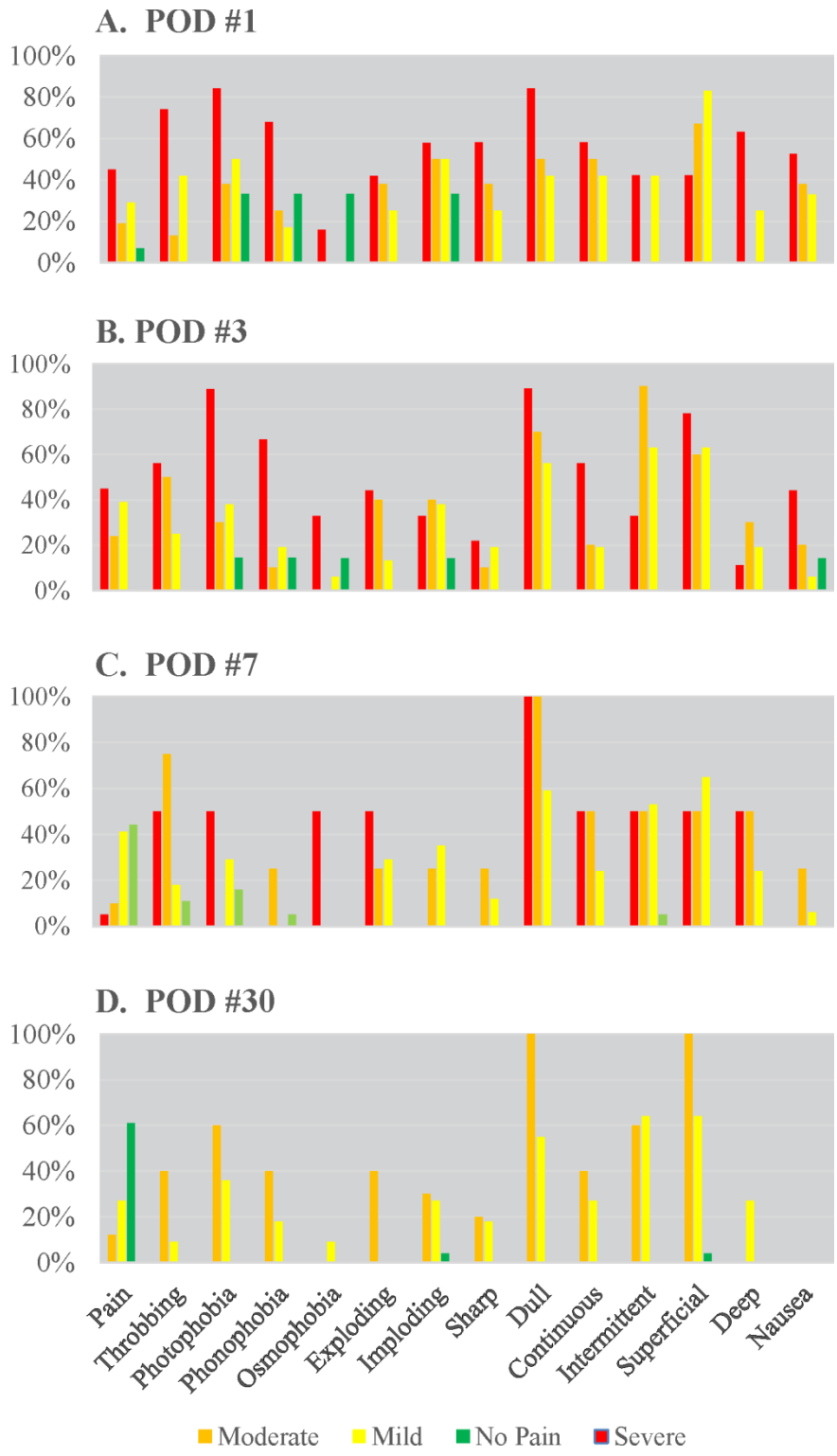


Figure 8

Occurence of pain qualities within each pain intensity classification, on POD #1 to #30 (see A-D). Scale percentages.

1C: Duration

Headache duration following EFS was consistent with Hypothesis #1C, women experience headache pain for hours and days following EFS. The duration was apparent in the overall ratings, as illustrated in Figures 6 and 7 above. Overall, headache was reported for most women following EFS on POD #1 (93%), 3 (83%), and 7 (55%). Over a third (38%) continued to experience headache on POD #30. On POD #1, the majority of women were experiencing severe to mild headache pain (93%). By POD #3, the rate decreased (83%), although most women continued to report headache pain. Headache incidents persists for over half of women on POD # 7 (55%), continuing for over a third of women on POD #30 (38%). Headache pain intensity decreased over the interview time points, but moderate and mild headache pain continued to be experienced on POD #30. (Table 7, Figures 9 and 10)

Individual patterns show that most subjects with any pain on POD #1 reported lower pain intensity on POD #30. Three subjects reported no pain at all, and one subject reported mild pain on POD #1, falling to no pain on POD #7, but returning to mild (4) on POD #30. Three subjects reported an increase from POD #1 to 3, three subjects from POD #3 to 7, and four subjects from POD #7 to POD 30. Thus, approximately one quarter of the sample showed some temporary worsening, but all subjects reported moderate or lower ratings by POD #30. (Figure 11)

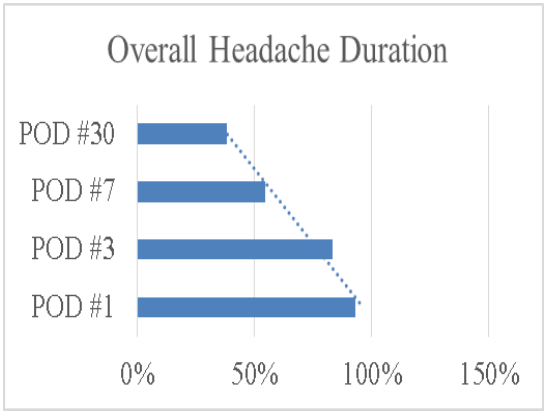


Figure 9.

Duration of pain following EFS. (Percentage of patients with headache on POD 1, 3, 7, and 30.)

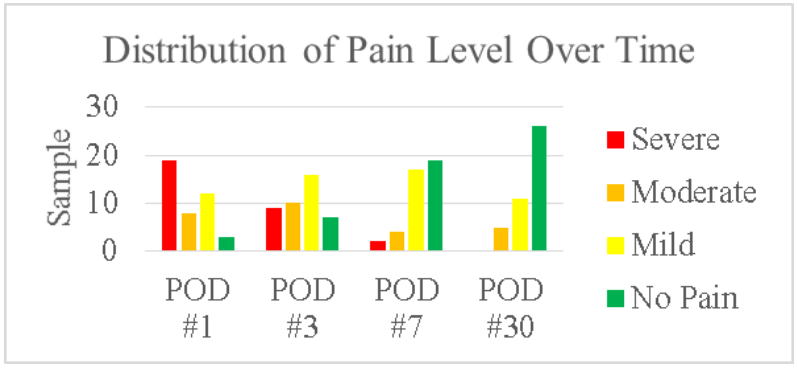


Figure 10.

Duration of headache by intensity following EFS.

	POD #1	POD #3	POD #7	POD #30
Severe	49% (N=19)	26% (N=9)	9% (N=2)	0% (N=0)
Moderate	17% (N=8)	20% (N=10)	14% (N=4)	14% (N=5)
Mild	29% N=12)	37% (N=16)	37% (N=17)	23% (N=11)
No Pain	6% (N=3)	17% (N=7)	40% (N=19)	63% (N=26)

Table 7 *Duration of Pain Intensity and Sample Size*

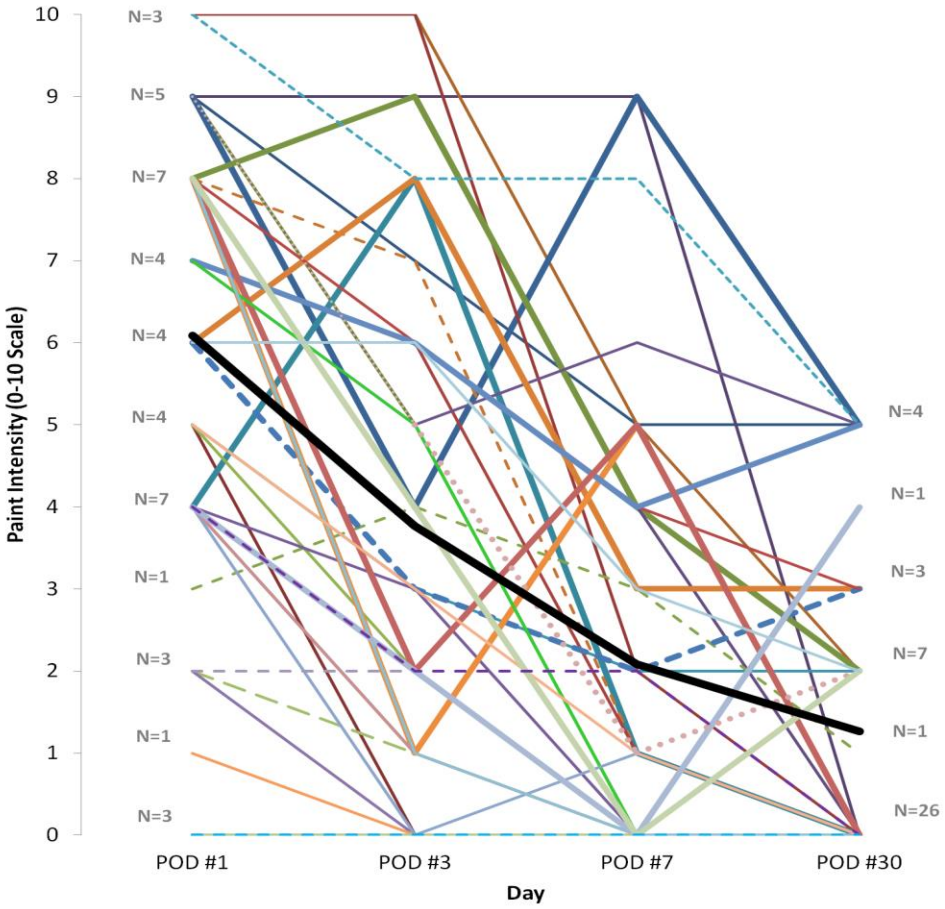


Figure 11.

Pain intensity ratings over time for all 42 subjects (mean in black). Subjects with an increase are plotted with thick black lines (i.e, as plotted in Figure 5). Number of subejcts at each rating for POD #1 and #30 are indicated adjacent to plots.

1D: Location

Location of pain on the first day following surgery was consistent with Hypothesis #1D, women experience headache pain following EFS. Overall, headache pain was reported as consistently higher for all time points following EFS, compared to forehead pain. (Tables 8 and 9) In general, headache was experienced more frequently than was forehead pain, with higher percentages on all days. Both headache (62 %) and forehead (60%) pain were experienced

similarly on POD #1. Forehead (45%) pain decreased more by POD #3, while headache (60%) continued with little change. By POD #7, both headache (36%) and forehead (33%) pain decreased. On POD #30, headache (19%) continued higher than forehead (14%) pain. These findings demonstrate that while forehead and headache pain incidences were similar on POD #1, headache pain (62-19%) was more frequently experienced on all postoperative days than was forehead pain (60-14%).

Table 8

Overall location of headache

	POD #1	POD #3	POD #7	POD #30
Forehead	60%	45%	33%	14%
Headache	62%	60%	36%	19%

Specific regions were identified for headache pain, including right and left forehead, temples, eyes, cheeks, and hairline to crown. There were small differences in pain experienced for both right and left forehead and temples areas, though all decreased similarly over subsequent postoperative days. There were no reports of headache pain in the eye and cheek areas on POD #3 or 7.

Headache pain was reported by the majority of women following EFS on POD #1. The headache pain reports continued for almost half of women on POD #3, and decreasing to a third by POD #7. Incidents of headache pain continued to persist in the forehead, temple, cheek, and hairline to crown regions for all four time points (see Table 9 and Figure 12).

Table 9

Pain locations following EFS

	Right Forehead	Left Forehead	Right Temple	left temple	Right Eye	Left Eye	Right Cheek	Left Cheek	Right Jaw	Left Jaw	Hairline to Crown
POD #1	79%	81%	71%	69%	12%	12%	21%	12%	7%	7%	33%
POD #3	62%	60%	48%	48%	5%	5%	7%	7%	5%	5%	29%
POD #7	57%	55%	40%	38%	0%	0%	5%	5%	0%	0%	21%
POD #30	31%	26%	19%	21%	0%	0%	5%	5%	0%	0%	14%

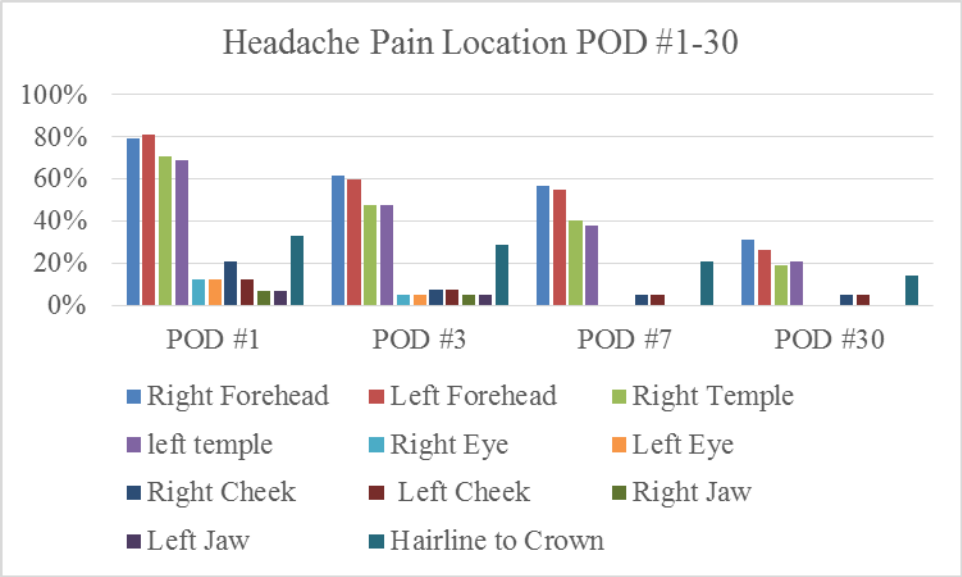


Figure 12.

Location of Pain on postoperative days #1-30. (Based on Table 8).

2. EFS Headache Characteristics and ICHD Migraine Criteria

Headache on the first day following surgery was consistent with Hypothesis #2, namely that women experience headache pain similar to migraine following EFS. Almost half (N=19, 45%) of women met strict ICHD migraine criteria following EFS. (Appendix G2) With the addition of those with probable EFS migraine –like headache (N=14, 33%), the majority of women met migraine criteria (Total EFS migraine –like headache: N=32, 78%) following EFS. (Appendix G3) The International Classification of Headache Disorders (ICHD) criteria for migrainedescribes specific headache characteristics to guide in diagnosing migraine. The ICHD

migraine criteria include headache lasting 4 to 72 hours, unilateral, moderate to severe pain intensity, pulsating quality, aggravated by physical activity, with associated symptoms of photophobia and phonophobia, or nausea and vomiting (IHS, 2010). (Table 10) In this study, three groups emerged for women following EFS.

Table 10

International Headache Society Migraine Criteria

At least 5 attacks fulfilling criteria B-D
Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
Headache has at least two of the following characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (**e.g.**, walking or climbing stairs)
During headache at least one of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia
Not attributed to another disorder

Given the small numbers of study participants, none of the differences were statistically assessed, and the results are presented for descriptive purposes only. The first group, comprising almost half the sample (N=20, 48%), were women who experienced headache symptoms described in the International Classification of Headache Disorders (ICHD) except for initial criteria of a history of 5 headache attacks. (Table 10) The second group were a subgroup of women (N=13, 31%) who, for the most part, met ICHD diagnosis criterions for migraine but

lacked one or two criterions. Some missed having both photophobia and phonophobia concurrently. Others had the associated symptoms, but reported lower than moderate pain intensity with no pulsating. It is speculated that they were probably experiencing EFS-triggered migraine. The third group were women (N=9, 21%) who lacked several migraine criterion for migraine and were consider not experiencing migraine.

In a secondary analysis, differences in subject histories were compared for those with EFS migraine –like headache , with probable EFS migraine –like headache (Table 11 and Figure 13). However, given the small numbers, none of the differences were statistically assessed, and the results are presented for descriptive purposes only. The women in Group 1 (N=20, 48%) met the ICHD migraine criteria for migraine and reported one or more of the following: had a previous history of migraine (N=9, 45%), were on HRT (N=4, 20%), had family members with a history of migraine (N=12, 60%). Women who met the ICHD migraine criteria had the highest rates of previous migraine history compared to Groups 2 (probable EFS migraine –like headache , N=2, 15%) and 3 (no EFS migraine –like headache or probable EFS migraine –like headache , N=1, 11%). Group 1 also had highest rates of family history of migraine (60%) compared to Group 2 (15%) or Group 3 (22%).

Group 2, the second largest group, was classified as probable EFS migraine –like headache (N=13,31%). Compared to group 3, these women were slightly less likely to have a family member with a history of migraine (N=2, 15% versus N=2, 22%) and have a history of migraine (N=2, 15% versus N=1, 11%). Women in this group were more likely to be HRT consumers compared to women in Group 1 (38% versus 20%, respectively), and less likely compared to Group 3 (67%). Women in Group 2 shared traits similar to those with and without EFS migraine –like headache (Group 1 and 3, respectively). Women in Group 2 were less likely

to be HRT consumers and have a history of migraine or have family history of migraine compared to Group 1 and 3.

Group 3 consisted of women with neither EFS migraine –like headache nor probable EFS migraine –like headache , and was the smallest group, with only nine women. Those in Group 3 were least likely to have previous history of migraine (N=1, 11%) than either Group 1 or 2, although they had a slightly higher percentage of family members with history of migraine (N=2, 22%) compared to Group 2. Group 3 included the largest proportion of HRT consumers (N=6, 67%) compared to Groups 1 (N=4, 20%) and 2 (N=5, 38%). In conclusion, those not exhibiting EFS-triggered migraine or probable migraine were less likely to have a previous history of migraine but were the most likely to be a HRT consumer. In summary, women experiencing EFS-triggered migraine were more likely to have a previous history of migraine, have a family member with migraine, and less likely to take HRT, compared to women not experiencing EFS migraine –like headache .

Table 11

ICHD Migraine diagnosis and EFS Participants with history of migraine, HRT, and family history of migraine

Participants on POD #1 with ICHD Migraine Criteria		**History of Migraine**	**HRT**	**Family History of Migraine**
1) All criterion of Migraine	N=20/42 (48 %)	N= 9 (45%)	N=4 (20 %)	N=12 (60%)
2) Probable Migraine: Missing one or two ICHD migraine diagnosis criterion	N=13/42 (31 %)	N=2 (15%)	N=5 (38%)	N=2 (15%)
3) No ICHD Migraine or probable migraine criteria	N=9/42 (21 %)	N=1 (11%)	N=6 (67 %)	N=2 (22%)

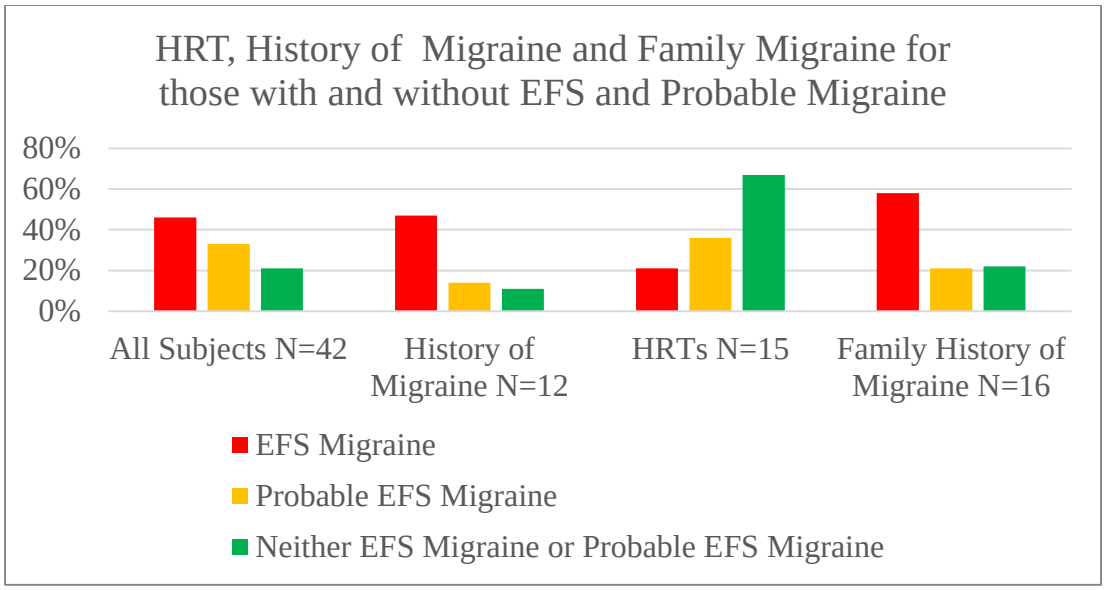


Figure 13.

ICHD migraine diagnosis, history of migraine, HRT, and family history of migraine (based on Table 10).

Therefore, while the majority of women experience migraine and probable migraine following EFS, their history of migraine or family history of migraine did not predict EFS-triggered migraine or probable migraine. A secondary analysis was performed for those in the EFS Total migraine group (those with EFS migraine –like headache and probable migraine –like headache). Among those with EFS Total migraine –like headache , 33.3% reported a history of migraine. EFS Total migraine –like headache was not associated (p=.247) with a history of migraine (Pearson Chi Square test of Independence). (Appendix G4) Among those who did report EFS Total migraine, there was an association (p=.049, Fisher's Exact Test) with HRT. However, among those who did report having EFS Total migraine, only 21.0% reported being on HRT. Of those with EFS Total Migraine, 42.4% had a family history of migraine. Among those who did report EFS Total migraine there was not an association (p=.442, Fisher's Exact Test) with family history of migraine. (Appendix G5) Because of repeated measures, bivariate association time one (POD #1) was only used because none of the covariates varied within

patients over time. Further analysis was performed to predict EFS migraine –like headache or probable EFS migraine –like headache with HRT and history of migraine. In a logistic regression, those consuming HRT had an 83% (1-.168=.832) decrease in odds of EFS and probable EFS migraine –like headache than did those who are not HRT consumers. Those with a history of migraine had 4.2 times the odds of having EFS and probable EFS migraine –like headache compared to those who did not have a history of migraine. Those with a family history of migraine had 2.4 times the odds of having EFS and probable EFS migraine –like headache compared to those who did not have a family history of migraine. (Appendix G6) In summary, these findings suggest those not on HRT having a history of migraine and family history of migraine are more likely to experience EFS migraine –like headache and probable EFS migraine –like headache .

Women with EFS-triggered migraine were four times more likely to have a previous history of migraine compared to those with no EFS migraine –like headache. Those with EFS migraine –like headache were also almost three times more likely to have a family history of migraine than those without EFS migraine –like headache. Those without EFS migraine –like headache were over three times more likely to be HRT consumers than those with EFS migraine –like headache. This suggests that women with a history of migraine or family history of migraine, and not HRT consumer may have a greater potential for EFS migraine –like headache following EFS.

3. Medications Prescribed and Perceived Relief

The type and efficacy of medications prescribed following surgery were consistent with Hypothesis #3 (i.e., prescribed pain medications were inconsistent in providing relief and ineffective in eliminating headache for most women). Mostly opioid medication were utilized

with varying efficacy following EFS. (Table 12) Percocet (oxycodone 5 mg and acetaminophen 325 mg), vicodin (hydrocodone 5mg and acetaminophen 325 or 500 mg), and norco (hydrocodone 5mg and acetaminophen 325 mg) were the most common choices for pain management. Perceived efficacy of prescribed medications was mixed for those reporting severe pain. Vicodin and percocet were effective, somewhat effective, and not effective for different women. Tramadol and norco offered some relief, but never total relief. Hydrocodone and vicodin (both generic and trade name listed as stated by participant to quantify for any differences) were less effective in alleviating pain than oxycodone for those with moderate pain. For mild pain only, norco was completely effective. Percocet, dilaudid, demerol, and hydrocodone were ineffective for severe pain. Vicodin had similar effectiveness for moderate and severe pain, but less for mild headache pain. In summary, success varied for the opioid medication strategies that were prescribed for postoperative pain management, and perceived effectiveness with current prescribed medications for EFS headache was inconsistent across participants.

4. Emotional and Functional Status Following EFS

Emotional and functional statuses following surgery were consistent with Hypothesis #4 (i.e., emotional status and function status declined postoperatively). Both emotional status (Mental Health Score, MHS) and functional status (Physical Health Score, PHS) were above US average (50) preoperatively (56 vs. 57). (Table 13 and Figure 14) The distributions for both

emotional and functional statuses were below US average following EFS. Functional and emotional status were lowest the first day following EFS. Emotional status reports were similarly affected. For more than half of women (52.4%), emotional status on POD #1 was reported at its lowest level following EFS (48 vs. 56 baseline). By POD #3 less than a third of women (31.0%) continued to report emotional levels under US average (50 vs. 56 baseline). Emotional status levels returned to preoperative baseline by POD #7 for most women (78.6%). By POD #30, the majority of women (88%) reported emotional status above US average. (Appendix G7)

Compared to the preoperative baseline, most women experienced deterioration of functional status on POD#1 following EFS. On all PODs, at least one-third of participants' functional status was below US average for the majority of women until POD #30: 88.1% on POD #1; 83.3%, POD #3; 64.3%, POD #7, and 33.3% POD #30. (Appendix G8) The largest decrease in functional status was experienced on POD #1 (31 vs. 57 baseline) than POD #3 (39 vs. 57 baseline) or POD #7 (45 vs. 57 baseline). On POD #30, functional status remained lower than preoperative baseline, though it was above the US average. Emotional status was affected for most women POD #1 and #3 following EFS, whereas functional status was affected more profoundly for a longer period of time.

In summary, women experienced emotional and functional deterioration following EFS. The lowest score for all postoperative interview days was functional score on POD #1. Functional status scores were below the US average on the first three postoperative interview daysFunctional status scores were below the US average on the first three postoperative interview days compared to emotional scores which were below US average only on POD #3.In addition, on all PODs, participants' scores for functional status were lower than those for

emotional status. This indicates that functional status is impacted more than emotional status for a longer period of time following EFS.

Table 13

Emotional and Functional Status following EFS

	Preop	POD #1	POD #3	POD #7	POD #30
MHS	56	48	50	56	56
PHS	57	31	39	45	53

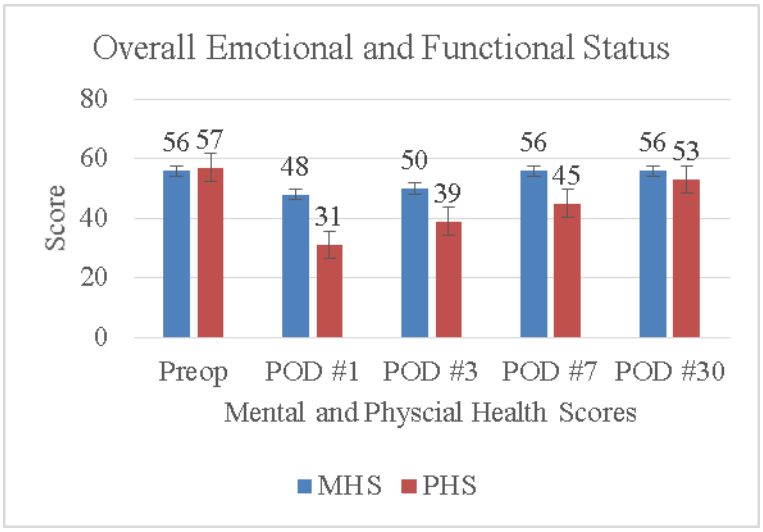


Figure 14.

Overall Emotional and Functional Status Before and Following EFS. (Based on Table 12)

5. Estrogen/Hormone Replacement Therapy (HRT)

The influence of estrogen or HRT on headache pain following surgery was consistent with Hypothesis #5 (i.e., women on HRT had lower intensity and less frequency of headache pain following EFS). Almost a third of the women were on HRT (N=12, 29%). Groups which included women on HRT were: Group #1: migraine (N=3); Group #2: migraine and family

history of migraine (N=1); and Group #3: no migraine or family history of migraine (N=6); and Group #4: family history of migraine and no migraine (N=4). Groups not on HRT included: Group #5: no migraine or family history of migraine (N=15); Group #6: migraine and no family history of migraine (N=1); Group #7 migraine and family history of migraine (N=6); Group #8: family history of migraine and no migraine (N=5). (Table 14)

Table 14

Groups with and without HRT

Group #1 (N=3)	HRT, migraine, no family history of migraine
Group #2 (N=1)	HRT, migraine and family history of migraine
Group #3 (N=7)	HRT, no migraine or family history of migraine
Group #4 (N=4)	HRT, no migraine, family history of migraine
Group #5 (N=15)	No HRT, no migraine, no family history of migraine
Group #6 (N=1)	No HRT, migraine and no family history of migraine
Group #7 (N=6)	No HRT, migraine, family history of migraine
Group #8 (N=5)	No HRT, no migraine, family history of migraine

Pain Intensity: Overall findings for HRT versus No HRT

Women consuming HRT experienced lower headache pain intensity following EFS. In general, women on HRT (N=12, mean age 59; Groups 1-4) reported lower pain intensity levels on PODs #1, 3, and 7 compared to women not consuming HRT (N=30, mean age 59; Groups 5-8) (Table 14) However, on POD #30, headache pain intensity levels had reduced from POD #7 for both groups and were similar. A logistic regression revealed that HRT was a predictor for lower pain intensity on POD #1 ($p > 0.0007$). (Appendix G9)

Women on HRT had lower pain intensity following EFS. (Table 15 and Figure 15) On POD #1, the mean pain intensity was 57% lower for women on HRT compared to those not on HRT (4 vs. 7). Specifically, on POD #1, women reported fewer incidents of severe pain if consuming HRT (25%) than if not on HRT (53%). Women not consuming HRT continued to report higher rates of severe pain than did women consuming HRT on POD #3 (27% vs. 8%) and POD #7 (7%, vs. 0%). For POD #7, women consuming HRT reported higher levels of mild pain (50%) and no pain (50%), while those not consuming HRT reported higher levels of severe (7%), moderate (13%), and mild (37%) pain. On POD# 30, pain intensity ratings were similar for both groups. In a comparison of mean pain intensity, those on HRT reported lower pain intensity on PODs #1 and 3. Levels were comparable for both groups on PODs #7 and 30. In summary, women on HRT reported experiencing lower headache pain intensity following EFS on PODs #1 and 3. (Table 16 and Figure 16)

Table 15

Average NRS for those on HRT and those not on HRT

	POD#1	POD#3	POD#7	POD#30
HRT	4	3	1	1
No HRT	7	4	2	1

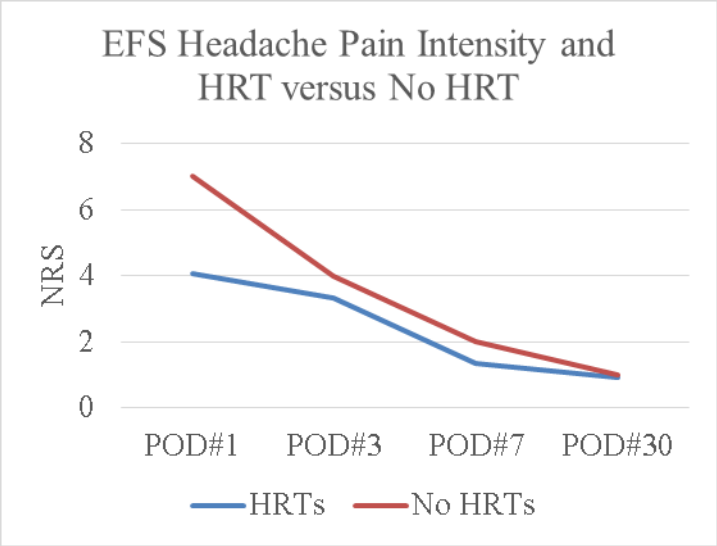


Figure 15.

Average NRS for those on HRT and those not on HRT. (Based on Table 14)

Table 16

Pain Intensity and HRT

		POD #1	POD #3	POD #7	POD #30
Severe	HRT	25%	8%	0%	0%
	No HRT	53%	27%	7%	0%
Moderate	HRT	17%	25%	0%	8%
	No HRT	20%	20%	13%	13%
Mild	HRT	33%	42%	50%	25%
	No HRT	27%	40%	37%	27%
No Pain	HRT	25%	25%	50%	67%
	No HRT	0%	43%	43%	60%

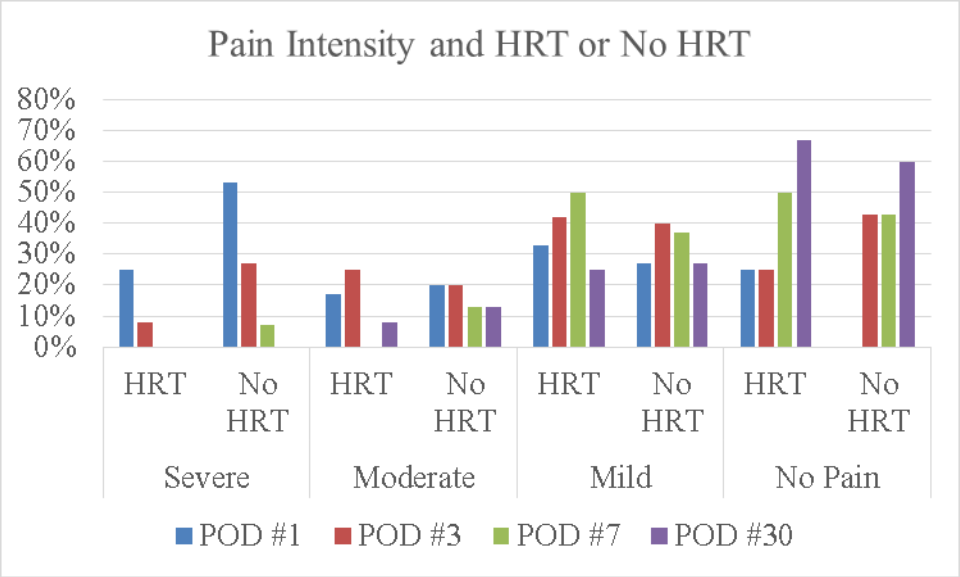


Figure 16.

Overall pain Intensity comparing HRT and no HRT. (Based on Table 15).

Pain Intensity HRT versus No HRT with Preexisting Migraine

Postoperative EFS headache pain intensity with a previous history of migraine and HRT was examined. (Table 17 and Figure 17) There were almost twice as many participants in the groups who had migraine but were not consuming HRT (N=7, Groups 6 and 7) than in the groups who had migraine and were taking HRT (N=4, Groups 1 and 2). Those on HRT with a history of migraine reported slightly higher pain intensity on all interview days compared to those without a history of migraine on HRT. Regardless of the consumption of HRT, women with a previous history of migraine reported higher EFS headache pain ratings on all four interview days than those without a previous history of migraine.

Table 17

HRT and History of Migraine

HRTs	POD #1	POD #3	POD #7	POD #30
History of migraine	5	4	3	3
No history of migraine	4	3	1	1

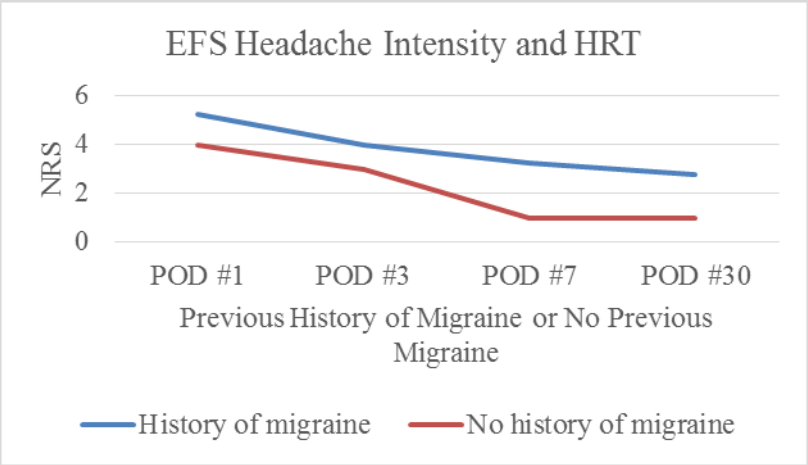


Figure 17.

History of Migraine with and without HRT. (Based on Table 17).

Pain Intensity: HRT vs. No HRT and Family History of Migraine

Headache pain intensity following EFS for women with a family history of migraine varied, whether or not they were consuming HRT. (Table 18 and Figure 18) Overall, consumers of HRT with a history of migraine and family history of migraine experienced lower pain intensity (NRS=4 vs. 7) on postoperative day 1 than did those not on HRT. On POD #3, those on HRT with a history of migraine had the lowest (NRS 3 vs. 4 and 5) pain intensity. Only on POD #30 did women consuming HRT with history of migraine and a family history of migraine report a higher (NRS 3 and 2 vs. 1) pain ratings than those not on HRT. In summary, study participants on HRT with family history of migraine experienced lower pain intensity on 3 out of 4 days, when compared to those not on HRT.

Pain intensity following EFS for those with migraine and a family history of migraine was lower for those consuming HRT. (Table 18 and Figure 18) On postoperative day 1, women consuming HRT reported almost half the pain intensity rating as those not consuming HRT (NRS 4 vs. 7, respectively), regardless of whether they had a history of migraine or family migraine. Overall, regardless of whether the participant was taking HRT, headache pain intensity levels dropped to similar levels. On POD #7, those with migraine and HRT, and those with a family history of migraine and no HRT had the highest pain rating (NRS=3). On POD #30, those with a history of migraine and on HRT had the highest pain intensity (NRS=3). Those consuming HRT who had a family history of migraine had slightly lower pain intensity ratings (NRS= 2); however, this group's scores were higher than those not consuming HRT regardless of whether they had a history of migraine or family history of migraine. In summary, those on HRT with a history or family history of migraine had lower headache pain on POD #1 and their headache pain levels stabilized for subsequent days, changing slightly but sustaining higher levels on POD #7 and 30, compared to those not consuming HRT. Those not consuming HRT had higher headache pain ratings on POD #1 than those consuming HRT, but dropped considerably by POD #3, 7, and 30. Only those groups with history of migraine had a slightly higher headache pain rating on POD #7 regardless of they were on HRT or not. (Table 19 and Figure 19)

Table 18
HRT and Family History of Migraine

	POD #1	POD #3	POD #7	POD #30
HRT	4	4	2	2
No HRT	7	5	3	1

Figure 18.

Family History of Migraine HRT versus no HRT. (Based on Table 17).

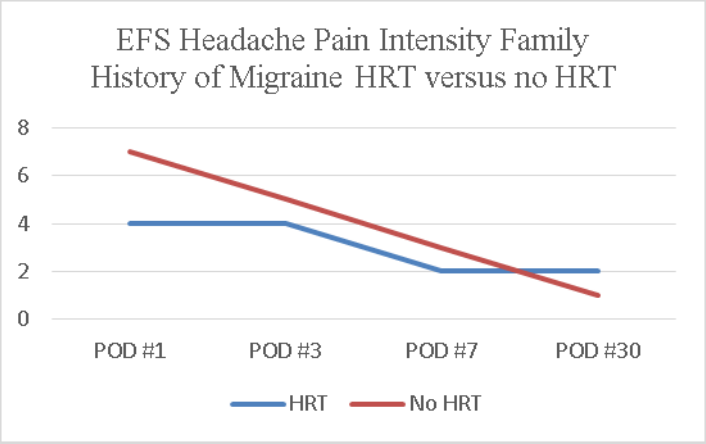


Table 19

Average NRS, HRT, History of Migraine or Family History of Migraine

	1	**3**	**7**	**30**
HRTs + History of migraine	4	3	3	3
HRTs + Family History of Migraine	4	4	2	2
No HRTs + No Family History of Migraine	7	4	2	1
No HRTs + History of Migraine	7	4	2	1
No HRTs + Family History of Migraine	7	5	3	1

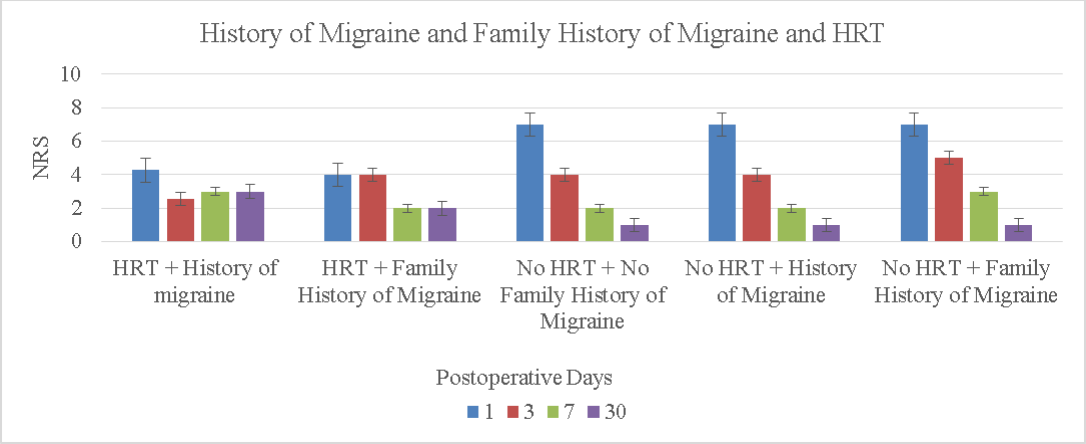


Figure 19.

EFS Headache Pain Intensity for Migraine and Family History and HRT. (Based on Table 18).

Headache Qualities and HRT

EFS headache pain qualities varied depending on whether the women were consuming HRT or not. Women on HRT reported generally lower incidence of pain qualities compared with those not on HRT. Women on HRT described their headache pain more often as continuous than intermittent (33% vs. 27%), as well as dull (60%), superficial (67%), and throbbing (40%), with associated symptoms of nausea (13%), photophobia and phonophobia (40%), and osmophobia (7%) on POD #1. For those not on HRT on POD #1, headache pain was more often described as throbbing (52%), sharp (48%), exploding (41%), continuous (56%), and deep (44%), and more often continuous (56%) than intermittent (44%), with associated symptoms of nausea (56%), photophobia (70%) and phonophobia (37%). (Table 20)

On POD #3, for those on HRT, headache pain was described as throbbing (33%), exploding (33%), and continuous (27%), more often superficial than deep (60% vs. 20%) and more dull than sharp (53% vs. 20%). Photophobia (27%) and phonophobia (20%) were the only associated symptoms experienced for those on HRT. For women not consuming HRT, headache

qualities most often reported were throbbing (30%), imploding (41%), dull (59%), intermittent more than continuous (48% vs. 22%), and with associated symptoms nausea (30%), photophobia (48%), and phonophobia (26%).

On POD #7, many characteristics decreased but did not disappear for both women on or not on HRT. For those on HRT, headache was more often described as dull (53%), imploding (27%) more than exploding (20%), equally superficial (33%) or deep (33%), more intermittent (40%) than continuous (13%), with associated symptoms of photophobia (26%). Those not on HRT described their headache pain as dull (74%), superficial (78%), and more likely continuous (48%) than intermittent (26%), with higher reports of associated symptoms of photophobia (26%) and phonophobia (4%), and nausea (7%).

By POD #30, headache qualities decreased for most women regardless of HRT use, likely because overall pain had declined to low levels for all subjects. Data on HRT and their relation to headache qualities are presented because this information may be of interest, although not part of the initial hypotheses. There were no statistics performed because it was not powered to these comparisons. That said, those on HRT continued to have more reports of throbbing (13% vs. 7%), exploding (13% vs. 7%), imploding (20% vs. 11%), similar dull (27% vs. 26%), and intermittent (33% vs. 26%), compared to those not on HRT. Both associated symptoms photophobia (13% vs. 7%) and phonophobia (20% vs. 7%) were higher for those on HRT. The only qualities higher in those not on HRT were sharp (11% vs. 0%), superficial (30% vs. 27%) and deep (11% vs. 7%). The percentages of headache pain qualities were higher for those on HRT than those not on HRT at POD #30. In summary, the incidence of headache pain qualities and associated symptoms were less for those on HRT compared with those not on HRT.

However, some qualities and associated symptoms persisted at higher percentages on POD #30 for those on HRT.

Table 20

Headache pain qualities for those on HRT and not on HRT. (Percentages)

	POD #1 HRT	No HRT	POD #3 HRT	No HRT	POD #7 HRT	No HRT	POD #30 HRT	No HRT
Throbbing	40	52	33	30	20	52	13	7
Photophobia	40	70	27	48	27	26	13	7
Phonophobia	33	37	20	26	0	4	20	0
Osmophobia	7	15	7	15	0	4	0	0
Exploding	20	41	33	19	20	15	13	7
Imploding	53	48	20	41	27	48	20	11
Sharp	13	48	20	11	7	11	0	11
Dull	60	56	53	59	53	74	27	26
Continuous	33	56	27	22	13	48	7	11
Intermittent	27	44	60	48	40	26	33	26
Superficial	67	59	60	52	33	78	27	30
Deep	13	44	20	11	33	11	7	11
Nausea	13	56	0	30	7	7	0	4

Perceived Headache Pain Relief and HRT

Several pain medication strategies for pain were adopted following EFS, with varying success regardless of HRT consumption. For those on HRT (N=15), vicodin was perceived to offer headache pain relief ranging from total relief to NRS levels 2 or less. (Table 21) Demerol and dilaudid did not relieve headache pain. Percocet provided varying relief, ranging from fewer than two changes in NRS to 4 or more change in NRS. Vicodin was the only medication that offered complete pain relief following EFS for those on HRT.

Table 21

HRT and perceived headache pain relief

HRT			
No change in NRS	**2 or less change NRS**	**4 or more change NRS**	**Complete relief**
percocet	extra strength tylenol	norco	vicodin
dilaudid	excedrin	percocet	
demerol	vicodin	vicodin	
	percocet		
	darvocet		
	tramadol		

Similar for those not on HRT (N=27), medication treatment strategies varied in their perceived effectiveness for relieving headache pain following EFS. Few medications were found to be effective in decreasing NRS by 4 or more. Vicodin had mixed reviews. For some, vicodin relieved headache pain completely while for others it provided much less pain relief. (Table 22)

In summary, several treatment strategies offered some relief, but most were unsuccessful in entirely alleviating headache pain. For both those on HRT and those not on HRT, demerol, percocet, and dilaudid were not effective in relieving headache pain following EFS. In addition, vicodin was the only medication reported to relieve headache pain completely for both groups. However, its effectiveness was not consistent, as some women reported only minimal pain relief with that medication. In conclusion, while some women experienced some relief with their pain medications, there was no one treatment strategy that was consistently effective for all women following EFS, regardless of HRT.

Table 22

Perceived headache pain relief for those not on HRT

No HRT			
No Change in NRS	**2 or less change NRS**	**4 or more change in NRS**	**Complete relief**
percocet	extra strength tylenol	oxycodone	vicodin
dilaudid	excedrin	percocet	
demerol	vicodin	oxycontin	
	percocet	vicodin	
	darvocet	tylenol with codeine	
	tramadol	norco	
	hydrocodone	tramadol	
	norco		

Emotional and Functional Status and HRT

Emotional and functional statuses were affected for women following EFS, consistent with Hypothesis 5A. Emotional status (mental health score, MHS) and functional status (physical health score, PHS) deteriorated both for women consuming HRT and for those not consuming HRT. (Table 23 and Figure 20) Overall preoperative emotional and functional statuses were above US average (50) for those on HRT (56 MHS and 56 PHS) versus those not on HRT (57 MHS and 57 PHS). Functional status was impacted by EFS pain more than emotional status, regardless of HRT consumption. Emotional and functional status scores decreased on postoperative day #1 for both groups. On POD #1, those not on HRT reported lower emotional

and functional status levels (45 and 30, respectively) than those on HRT (53 and 33, respectively). On POD #3, those on HRT had slightly lower emotional scores than those not HRT (49 vs. 50). However, although functional status scores were higher for those on HRT versus not on HRT (42 vs. 38), both levels were below US average. On POD #7, emotional and functional scores were above US average for those consuming HRT. These women had higher emotional and functional scores (58 and 55, respectively) than those not on HRT (56 and 45, respectively). By POD #30, both groups had scores near preoperative levels, with those on HRT being closer to their preoperative levels than those not on HRT.

Overall, both emotional and functional status were affected following EFS, regardless of HRT consumption. Specifically, emotional status score was below US average on postoperative day #3 for those on HRT and on postoperative day #1 for that not on HRT. Functional status was below US average for those on HRT on postoperative days 1 and 3. For those not on HRT functional scores were below US average postoperative days 1, 3, and 7.

Table 23

HRT and Emotional and Functional status

	Preop		POD #1		POD #3		POD #7		POD #30	
	MHS	PHS	MHS	PHS	MHS	PHS	MHS	PHS	MHS	PHS
HRT	56	56	53	33	49	42	58	55	56	53
No HRT	57	58	45	30	50	38	56	45	57	52

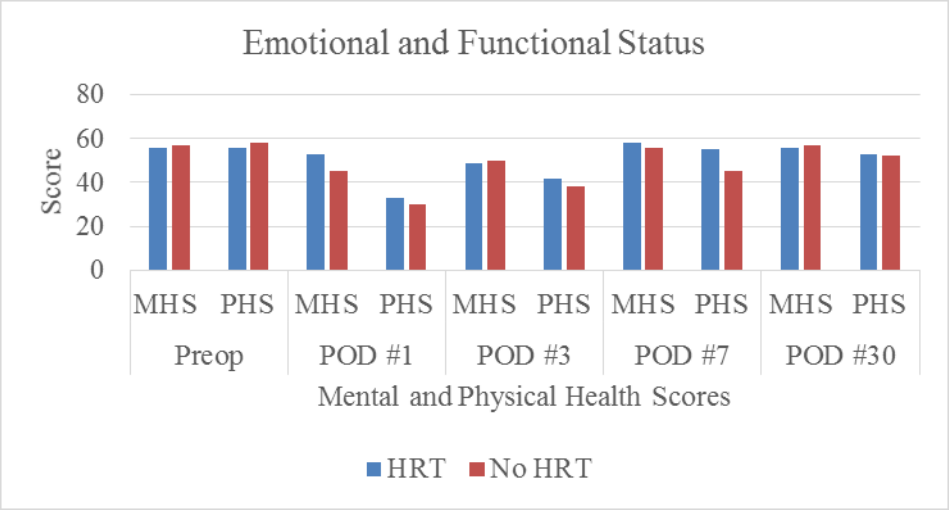


Figure 20.

Emotional and Functional Status with HRT or no HRT. (Based on Table 22).

6. Summary

Following EFS, the majority of women experienced headache with associated symptoms similar to migraine for several days. The majority of women experienced severe to mild headache on postoperative days 1 (93%), 3 (82%), and 7 (59%). The presence of headache decreased by POD #30 (41%). Specifically, higher intensity (severe to moderate) headache was most often described on POD #1 (64%), further continuing on POD #3 by almost half of women (42%). By POD#7, higher intensity headache plummeted (17%), dropping further by POD #30 (12%). Migraine-specific qualities and associated symptoms accompanied EFS headache. Women reporting higher pain intensity ratings often had more pain qualities. EFS headache was more often reported than forehead pain on postoperative days 1 (62% vs. 60%) and 3 (60% vs. 45%). Both headache and forehead pain decreased on subsequent interview days, with headache continuing to be reported more frequently on both PODs #7 (36% vs. 33%) and #30 (19% vs. 14%). In summary, EFS-triggered migraine has similar intensity, qualities, duration, and locations consistent with migraine.

Most women (78%) who underwent EFS reported headache pain that met ICHD migraine criteria as migraine (45%) or probable migraine (33%). Those with EFS migraine –like headache were more likely to have a history of previous migraine (N=9, 47%), family history of migraine (N=11, 58%) and not be on HRT (N=4, 21%). Compared to those with EFS migraine –like headache, those with probable migraine –like headache had lower history of migraine (N=2, 14%), a lower family history of migraine (N-3, 21%), and more used HRT (N=5, 36%). Those with neither EFS migraine –like headache nor probable migraine –like headache had the lowest history of migraine (N=1, 11%) compared to those with either EFS or probable migraine –like headache. The family history of migraine (N=2, 22%) was lower than EFS migraine –like headache and similar to probable EFS migraine –like headache. The group without EFS migraine –like headache or probable EFS migraine –like headache were the highest consumers of HRT (N=6, 67%). HRT consumption was lowest for women experiencing EFS migraine –like headache (21%) and probable EFS migraine –like headache (36%), and highest among those with no EFS migraine –like headache (67%). Women experiencing EFS migraine –like headache were more likely to have a history of migraine and a family history of migraine, and to not consume HRT than those with neither EFS nor probable EFS migraine –like headache .

Those consuming HRT reported different pain experiences compared to those not consuming HRT. Women on HRT reported lower pain intensity only on the first two postoperative interview days compared to those not on HRT (POD #1: NRS 4 vs. 7; POD #3: NRS 3 vs. 4). However, pain intensity levels were identical for both groups of women on subsequent interview days (POD #7: NRS 2 and POD #30: NRS 1). These findings suggest that that the consumption of HRT may contribute to lower intensity ratings following EFS.

A previous history of migraine for women consuming HRT influenced headache pain intensity following EFS. Women on HRT with a previous history of migraine reported higher pain intensity ratings than those women without a previous history of migraine consuming HRT on all four interview days (POD #1: NRS 5 vs. 4; POD #3: NRS 4 vs. 3; POD #7: NRS 3 vs.1; and POD #30: NRS 3 vs. 1). Further, intensity ratings were higher for those on HRT with a history of migraine compared to those on HRT only. This suggests a history of migraine alone may contribute to higher pain ratings, perhaps more than the consumption of HRT.

Intensity ratings reports were similar for those on HRT alone and those on HRT without a family history of migraine. Women on HRT without a family history of migraine reported higher headache intensity on the first three interview days than did women on HRT with a family history of migraine (POD #1: NRS 7 vs. 4, POD #3: NRS 5 vs. 4, POD #7: NRS 3 vs.2, and POD #30: NRS 1 vs. 2) following EFS. These NRS ratings were similar to the broader categories of women on HRT and not on HRT. HRT and family history of migraine intensity were similar. This may suggest that, if women have no family history of migraine, regardless of whether they are using HRT, they can expect to have higher pain intensity following EFS, as compared to women with a family history of migraine. Women on HRT, on HRT with no history of migraine, and on HRT with a family history of migraine had the lowest headache intensity. Women on HRT with a history of migraine had slightly higher intensity ratings. This suggests that women on HRT alone, on HRT with a family history of migraine, and on HRT with no history of migraine may expect to have lower intensity headaches following EFS, compared to other groups.

EFS headache pain qualities and associated symptoms were often less for those consuming HRT. Those on HRT reported lower incidents of pain qualities and associated

symptoms compared to those not consuming HRT. The percentage of headache pain qualities and associated symptoms were higher for those on HRT on POD #3 (46% vs. 54%) and POD #30 (31% vs. 69%). Women not on HRT had higher incidents of headache pain qualities on POD #1 (77% vs. 23%) and POD #7 (62% vs. 38%) compared to women consuming HRT. These findings are inconsistent for suggesting whether HRT contribute to pain qualities and associated symptoms over all four interview days. However, those not consuming HRT had higher frequency at higher percentages on POD #1 and 7. Those on HRT experienced lower percentage of pain qualities on POD #1 and 7 and higher on POD #3 and 30.

Several treatment strategies offered relief, though most did not relieve headache pain entirely. Multiple pain medications were consumed by women following surgery. Vicodin was the only medication reported to offer relief ranging from at least two NRS ratings to total relief, regardless of whether HRT were being consumed. There was no one treatment strategy that was found to be consistently effective for all women following EFS. Some medications were effective for some women but lacked efficacy for others. This suggests that current pain medications strategies not consistently effective in providing pain relief for women following EFS.

HRT consumption influenced emotional and functional statuses for women following EFS. Preoperative emotional and functional statuses were similar for those on HRT and those not on HRT (MHS: 56 vs. 57; PHS: 57 vs. 58). On POD #1, emotional and functional statuses deteriorated below US average, with functional status dropping lower than emotional status for both groups. On POD #3, ratings were inconsistent. Functional status was lower for those not on HRT compared to those on HRT (PHS: 38 vs. 42). Emotional status for those on HRT was slightly lower than for those not on HRT (MHS: 49 vs. 50). Only functional status for those not

on HRT was below US average (PHS: 45 vs. 53). Functional and emotional status returned to US normal levels by postoperative day 30 for both groups. Overall, one emotional and three functional status ratings were reported below US average for those not on HRT, compared to one emotional and two functional status ratings for those on HRT. The ratings were lower for those not on HRT. Each group had one emotional status rating below US average. These findings suggest that those not on HRT may report more decline in functional status than those on HRT, with both groups experiencing similar emotional status deterioration following EFS.

In conclusion, this study sample of women experienced headache pain following EFS. First, most women experienced postoperative headache days following endoscopic foreheadplasty surgery. Second, most women experienced headache characteristics with associated symptoms meeting migraine diagnosis criteria (International Classification of Headache Disorders, 2nd Edition) suggesting evidence EFS headache may be a new migraine-like headache. Third, while a few prescribed medications offered some relief, there were no consistently effective pain management strategies. Consequently, most women continued to experience headache pain with current prescriptive strategies. Fourth, emotional and functional status declined for women following EFS, but returned to US normal levels by postoperative days 7 and 30. Functional status scores were lower than emotional status scores for more postoperative days. Finally, women on HRT, as estrogen measured by exogenous HRT consumptiom and not serum estrogen levels in this study, reported lower headache pain intensity, shorter duration, and fewer pain qualities with associated symptoms following EFS.

CHAPTER 6: DISCUSSION

EFS Headache

Philosophy, Pain Theories, and Headache Following EFS

Empirical data acquired in the present study provide evidence that women experience headache following EFS. Previous articles mentioning headache following EFS were based on case series written by surgeons (Jones & Grover, 2004; Nassif, 2007), and the present data support these surgeons' observations and conclusions.

The present study's hypotheses regarding the etiology and perceptions of pain are supported by several pain theories. The physiological pain theory supports this study's hypothesis that nerve involvement is in some way responsible for migrain- like headache following EFS. Neuropathic pain theory supports the hypothesis that EFS migraine-like headache results from nerve dysfunction and aberrant neuronal activity as result of nerve trauma during surgical dissection. In addition, the Symptoms Management Theory (SMT), a nursing theory, was used to explore and describe headache experience following EFS. This theory supports the current study's predictions. The present study's findings reveal the relationships among the following SMT constructs and EFS concepts: 1) EFS headache pain characteristics (symptoms experience), 2) efficacy of current prescribed medications (symptom management), and 3) the effects of headache pain on emotional and functional status (outcome). In the present study, migraine-like headache was commonly experienced following EFS, and prescribed medications were not consistently effective in relieving headache pain. As headache continued, emotional and functional status deteriorated. Study results also indicate that estrogen was a moderator to EFS headache pain perception, and that those women consuming exogenous estrogen, HRT, reported lower headache pain intensity postoperatively. These results are being

interpreted with caution as those in the HRT group were women who were consuming exogenous estrogen at the time of EFS. No menstrual data was obtained. Group comparison of serum estrogen levels was not conducted. The present study provides evidence that EFS triggered headache may be considered a kind of migraine-like headache because women describe headache characteristics and associated symptoms consistent with ICHD classic migraine diagnosis criteria. These findings introduce a new type of migraine-like headache to the migraine community.

Etiology of EFS Headache

The exact etiology of EFS migraine –like headache is unknown. However, Patel speculated that a potential cause of pain following EFS was trigeminal nerve injury during surgical dissection, resulting in trigeminally mediated pain (Patel, 2006b). This conclusion is supported by the description of surgical structures manipulated during EFS and their innervation. Head and neck pain information is transmitted extracranially via peripheral nociceptors in skin, muscle, periosteum, and arteries, and intracranially (dural and cerebral arteries and veins) by way of the trigeminal ganglion, which innervates the meninges (Agarwal, Gracely, & Silver, 2007; Dubner et al., 1978; Olesen et al., 2009; Zhang et al., 2007). These peripheral extracranial structures have been identified to be involved during EFS dissection (Jones & Grover, 2004; Nassif, 2007; Patel, 2006b). This study found that women are experiencing headache pain (intensity, qualities, duration and location) with associated symptoms similar to migraine following EFS. Not only is EFS headache similar to migraine, EFS headache characteristics sufficiently fulfilled ICHD diagnosis criteria of migraine, supporting a study hypothesis that EFS headache is a trigeminally mediated migraine resulting from trigeminal nerve trauma during surgical dissection (Bennett, 2004; Burstein, 2001; Campbell & Meyer, 2006; Goadsby et al.,

2009; Lipton et al., 2004; Xu et al., 2008). These study findings provide evidence that EFS migraine –like headache is triggered by extracranial peripheral nociceptor activation causing neuronal hyperexcitability, which results in peripheral and central sensitization (Burstein, 2001; Burstein, Cutrer, et al., 2000; Goadsby et al., 2009; Lipton et al., 2008; Olesen et al., 2009). While the exact structure or structures leading to EFS headache are unclear, the similarity to migraine of the pain and associated symptoms mean extracranial activation of the trigeminal pathway leads to EFS migraine –like headache or probable migraine –like headache for most women following EFS.

EFS Headache, Migraine, and Associated Symptoms

The exact etiology of EFS headache is unknown. While no specific aim was included in this study to determine EFS headache etiology, exploring potential sources adds knowledge to better understand EFS migraine –like headache. New theories and hypotheses may then be formulated to assist with the next steps for alleviating pain in women undergoing EFS, development of effective new guidelines for assessment and evaluation of EFS headache and strategizing an effective treatment.

Specific treatment strategies were found to have some effectiveness in eliminating headache, but no strategy consistently provided pain relief. This is in agreement with current strategies for migraine and other trigeminally mediated pain disorders (Dworkin, O'Connor, Audette, Baron, Gourlay, Haanpaa, et al., 2010; Goadsby, 2009). To assess EFS migraine –like headache and strategize potential effective management, a migraine literature review may offer new insight. In selecting an effective pain strategy for migraine, the presence of allodynia, or painful response to normally innocuous stimulus, is critical. The presence of cutaneous allodynia usually takes an hour to develop in migraine (Burstein et al., 2004; Charles, 2009). This

occurrence in migraine is the convergence of nociceptive information that has extended out of the pain area, suggesting central sensitization. To establish the presence of allodynia and central sensitization, specific questions focus on the presence of uncomfortable or painful sensations with hair combing, shaving, or wearing earrings, necklaces or glasses (Burstein, Cutrer, et al., 2000). Triptans, which are 5 HT 1B/1D receptor agonists, are the most common prescribed medications found to be effective in aborting migraine when taken within two hours of symptoms onset (Jakubowski, Silberstein, et al., 2005a).

EFS migraine–like headache patients may benefit from the use of triptans postoperatively. It was challenging to design this study to determine whether EFS headache is peripheral sensitization alone or has components of central sensitization. During interviews, participants were asked if they were experiencing cheek, chin, and upper extremity numbness, tingling, itching, or tenderness. Most study patients had additional facial procedures performed simultaneously, which would likely distort any conclusion that facial sensory alterations were exclusively due to EFS. Further complicating assessment for allodynia with migraine questions was the universal use of full head dressings that covered the ears, eliminating the study participants' possibility of wearing glasses, earrings, and necklaces or combing their hair. These dressings typically remained intact for the first three days following surgery. This may have decreased the number of women reporting symptoms consistent with central sensitization. One study participant, following completion of questionnaires in her final interview on POD #30, commented that she felt severe annoyance, not pain, when her bangs touch her forehead. This may signify the presence of allodynia, providing evidence that central sensitization occurred for this patient postoperatively. There were four reports of altered upper extremity sensations. Two participants expressed tenderness that may have been the result of a blood pressure cuff or upper

extremity positioning during surgery. One had greater left than right hand numbness. It is possible that, if the intravenous catheter was inserted in the hand, there may have been some residual numbness and tenderness. However, this is probably unlikely, as the patient had bilateral numbness. One other patient had tingling in her upper extremities, with more on the right than left. This may be related to allodynia or to intraoperative positioning. It is possible that these instances of altered upper extremity sensation may be allodynia or central nervous system pain resulting from neurological hyperexcitability following EFS (Burstein, Cutrer, et al., 2000).

Interestingly, only a few study participants experienced migraine-associated symptoms without headache following EFS. One woman had photophobia, phonophobia, and osmophobia on postoperative days 1 and 3, although no accompanying headache pain. Another participant reported photophobia without pain on POD #3. A third reported photophobia, phonophobia, and osmophobia without pain on POD #7. On POD #30, she rated her headache pain as mild (NRS=2) and reported experiencing photophobia, phonophobia, and osmophobia. Migraine with associated symptoms and no headache pain has been described (Alstadhaug, 2009). The presence of associated symptoms alone has been attributed to either a decreased inhibition response or an aberrant processing of cortical hyperexcitability (Gierse-Plogmeier et al., 2009). Specifically, the presence of associated symptoms has been described as a form of referred pain resulting from heightened sensitivity of the senses (lights, sounds, and smells), which has been attributed to aberrantly uninhibited or abnormally processed peripheral cutaneous afferent information (Burstein, Cutrer, et al., 2000; Lovati, D'Amico, & Bertora, 2009).

Lakhan and colleagues (2012) explored photophobia and migraine utilizing positron emission tomography. They determined that trigeminal nociception activation alone is not solely responsible for the presence of photophobia following migraine. They identified brainstem nuclei

involvement and demonstrated that cortical excitability was responsible for photophobia continuing after migraine resolved (Lakhan, Avramut, & Tepper, 2013). Photophobia, phonophobia, and osmophobia have been described as a form of referred pain from heightened senses sensitivity and attributed to peripheral cutaneous afferent information that is aberrantly uninhibited or abnormally processed (Burstein, Yarnitsky, et al., 2000; Gierse-Plogmeier et al., 2009; Lovati et al., 2009).

The presence of associated symptoms following EFS without headache in several study participants was an interesting finding. From the above literature, it may be suggested that these women may have been experiencing some type of migraine with no headache pain. They did not meet ICHD criteria for migraine and were not included in either the EFS migraine –like headache or probable migraine –like headache group. That a few women in the study experienced associated symptoms but no headache suggests that, like migraine, EFS migraine –like headache may involve activation of the trigeminovascular system and brainstem nuclei with resulting subcortical dysfunction. These findings further suggest that women who did not meet ICHD criteria but experienced associated symptoms may be having another type of EFS migraine-like induced headache. In this the case, more women are experiencing migraine-like headache following EFS than those who met ICHD criteria. Triptan therapy is one strategy used to manage migraine. EFS migraine –like headache with associated symptoms with or without headache, and involving both peripheral and central sensitization prompted by an extracranial event may benefit from triptan therapy for pain management.

ICHD Migraine Diagnosis Criteria

In this study, twelve different surgeons performed EFS. One surgeon had a patient who did not experience EFS headache. Most patients of the other 11 surgeons experienced

postoperative EFS headache. Conditions in surgical facilities cannot be controlled and may contribute to variation in patient outcome. However, with the majority of women reporting similar postoperative experiences it is unlikely that having patients recruited from twelve different offices skewed study findings.

Risk Factors for PONV

There are several criteria that must be met to suffice ICHD migraine criteria. One of the criteria is experiencing nausea and vomiting. For EFS study participants, there were several factors that could contribute to nausea and vomiting. Opioid pain medications were frequently prescribed to optimize patient outcome following EFS. Nausea and vomiting is a common side effect of opioid pain medications (Smith, Smith, & Seidner, 2012). In all cases, pharmacological strategies were implemented prophylactically to prevent nausea and vomiting from anesthesia and opioids. Some were provided prophylactically preoperatively (scopolamine patch), while others (ondansetron [zofran], phenergan, benadryl, and compazine) were provided intraoperatively and postoperatively, as needed (Table 10). The majority of women reported relief of nausea and vomiting symptoms with prescribed antiemetic medications. The presence of nausea and vomiting is one important criterion to discern EFS migraine –like headache or probable migraine –like headache. If nausea and vomiting was effectively prevented on interview days, then this migraine criterion was not experienced, possibly eliminating a patient from qualifying for EFS migraine –like headache or probable migraine –like headache, which would erroneously skew data findings.

Patient predictive factors, surgery site, preoperative and postoperative surgeon-prescribed medications, and intraoperatively provided anesthetic medications may have contributed to PONV, and its presence may not be solely the result of EFS headache. For many study

participants, these predictive factors were present: female, history of migraine, use of general anesthesia with inhalation agents, and nitrous, opioids, and surgery in similar area as craniotomy. Many study participants experienced PONV (N=14) following EFS. It can be speculated that more incidents of nausea and vomiting would have been reported if patients had not pretreated prophylactically with antiemetic medications. Lack of pretreatment may have resulted in increased nausea and vomiting incidents, leading to more participants meeting strict ICHD migraine diagnosis criteria.

Headache and Ondansetron

The presence of headache is another factor that may have influenced whether EFS headache met ICHD migraine criteria. The recommended pharmacological treatment for PONV is zofran, a 5-HT3 serotonin receptor antagonist in the central nervous system (Gan, 2006). Serotonin receptor antagonist ondansetron (Zofran) is considered the gold standard, and often a first-line pharmacological choice for PONV. Moderate to mild headache is one side effect known to occur with ondansetron (Goodin & Cunningham, 2002). Tramer reviewed 53 clinical trials' patients receiving ondansetron (N=7,177) and placebo controls or no treatment (N=5,712) for PONV. Twenty trials identified postoperative headache in 4,755 patients (Tramer, Reynolds, Moore, & McQuay, 1997). Kim and colleagues compared a new 5HT-3 serotonin receptor antagonist, ramosetron (N=54), with ondansetron (N=54), versus placebo (N=54), in prevention of PONV. Both 5HT-3 antagonists were found to be superior to placebo in treating PONV (33%, 35%, and 63%, respectively). Headache following administration for ramosetron was 20%, ondansetron 17%, and placebo 15% (Kim, Kim, Baek, Ok, & Kim, 2009). Veneziano and colleagues successfully treated chemotherapy-induced nausea with zofran. However, they noted that 42.4% experienced headache as a result (Veneziano et al., 1994). Perez and colleagues found

headache occurred slightly more than 20% when comparing granisetron and ondansetron use following chemotherapy (Perez et al., 1998). In a case report, six children with various cancers experienced post-treatment headache following chemotherapy and ondansetron (for nausea and vomiting). Five of six children met ICHD migraine diagnostic criteria. Headaches were successfully resolved with 1) discontinuation alone (N=1); 2) discontinuation and supplemental gabapentin (N=3); 3) topiramate (N=1); and isometheptene and acetaminophen (Midrin) (N=1) (Khan, 2002). One case report described ondansetron-induced postdelivery headache with complete resolution within hours of discontinuation (Goadsby, 2009). In another case report, a woman with a history of migraine who underwent two similar surgeries reported that ondansetron triggered a migraine following the first surgery (hand wound debridement). In the subsequent anesthetics for surgery, ondansetron was not utilized as a preventive for PONV, thus eliminating postoperative triggering of migraine (Singh, Sinha, & Prakash, 2010). Interestingly, practice review and acute guidelines regarding migraine-induced nausea recommends serotonin receptor antagonists (5HT-3) as a preventive measure for nausea and vomiting (Silberstein & Consortium, 2000; Tepper & Spears, 2009).

Due to ondansetron's potential to cause headache, it may be possible that in the present study, the twelve women on ondansetron were experiencing ondansetron-induced headache and not headache due to EFS. However, because the consumption of ondansetron was limited to morning of POD #1, and pain intensity levels continued for all women on POD #3, two days after ondansetron consumption (N= 9, NRS > 5, N=3, NRS <3), it is unlikely the ondansetron was the cause, or at least the sole cause, of postoperative headache. In this study, 21 EFS participants experienced PONV. Over half (N=15) met ICHD migraine criterions, and seven had previous history of migraine. To treat PONV, the majority consumed ondansetron (N=12), others

were prescribed phenergan (N=1), compazine (N=1), and scopolamine patch (N=1), and some chose to take nothing (N=2) (Table 11). Three women who had consumed ondansetron had a previous history of migraine, suggesting the possibility that the PONV in these cases was the result of a preexisting migraine pattern rather than resulting from EFS. Another possibility is that for those who experienced headache following EFS, the pain was ondansetron induced rather than a result of EFS. From the above review on ondansetron, those with a history of migraine are more likely to experience headache as side effect of ondansetron use. Seven women on ondansetron had history of migraine and therefore may have a greater propensity for headache. The literature reported that within hours of ondansetron discontinuation, the side effect of headache resolved completely. For EFS study participants, ondansetron was provided on surgery day and the morning of POD #1. Interviews were conducted in the early evening on POD #1. It is possible the seven women with a history of migraine who consumed ondansetron were experiencing ondansetron-induced headache on POD #1.

In conclusion, PONV and headache are two ICHD migraine criteria. In the present study, many factors could have influenced the incidents of PONV and headache following EFS. Anti-nausea medications can influence data findings. For example, headache is a side effect for ondansetron, and this may interfere with accurately discerning whether headache is a side effect of ondansetron or a result of EFS. In the review above, these factors have been identified as potential threats to study findings. It is possible these factors could have threatened findings in the present study, although it is unlikely, given that the majority of women continued to experience migraine, probable migraine, and associated factors after POD #1, by which time ondansetron use had been discontinued.

Surgeons and Location

In the initial study proposal, seven surgeon signed letters of support for patient recruitment. Thirty-one surgeons were recruited to assist, with patients ultimately coming from only twelve surgeons. (Appendix J) One surgeon had only one patient in the present study; she had no previous history of migraine, no family history of migraine, and was menopausal but not on HRT. However, she experienced neither migraine nor probable migraine (Table 11). Most patients in the study had either EFS migraine –like headache or probable migraine –like headache, and all of the other surgeons had at least one patient with migraine. These results suggest that postoperative migraine occurs regardless of the surgeon performing the surgery and any technical differences that may exist between surgeons.

PONV, Surgery, and Anesthesia.

PONV continues to be a frequently experienced side effect of anesthesia and surgery and is often referred to as "the big little problem," with reported incidents of 16 - 80% for patients with predicted high risk factors (Apfel, Larra, Koivuranta, Greim, & Roewer, 1999; Gan, 2006; Kapur, 1991; Leslie et al., 2008). These predictive factors include the following: female gender, nonsmoker, history of migraine, history of nausea and vomiting or motion sickness, general anesthesia containing volatile inhalation agents and nitrous oxide, or use of opioids including intraoperative and postoperative opioids (Apfel et al., 2002; Apfel, Stoecklein, & Lipfert, 2005; Gan, 2006; Stadler, Bardiau, Seidel, Albert, & Boogaerts, 2003). Surgical procedures often purported to predict PONV include neurosurgical (craniotomy), head and neck, breast or axilla, gynecological, ear nose and throat, abdominal, and plastic (breast, head and neck) (Apfel et al., 2002; de Oliveira Ribeiro et al., 2013; Fabling, Gan, El-Moalem, Warner, & Borel, 2000; Manninen & Tan, 2002; Ruiz et al., 2010; White et al., 2005). All EFS study participants had predictive factors, suggesting an elevated risk for PONV. EFS participants were female, received

general anesthesia with volatile inhalation agents and nitrous oxide, and received opioids intraoperatively and /or postoperatively, and in several cases, had a history of migraine. This suggest that factors other than EFS migraine –like headache contributed to PONV, possibly skewing these study findings.

Preexisting Migraine and EFS Headache

Based on this present study, there is evidence that with rare exception, women with preexisting migraine will have an EFS migraine –like headache following EFS. Nineteen women had EFS migraine –like headache and fourteen had probable EFS migraine –like headache. Of the twelve women in the study with a history of migraine, nine (75%) met the criteria for EFS migraine –like headache. In contrast, only two (17%) with probable EFS migraine –like headache had a previous history of migraine. Of the twelve with a history of migraine, only one did not have either EFS or probable EFS migraine –like headache. The majority (92%) with a history of migraine had either EFS migraine –like headache or probable EFS migraine –like headache. This suggests that having a history of migraine increases the possibility of having EFS migraine –like headache or probable EFS migraine –like headache, and that those with a history of migraine are more likely to experience EFS migraine –like headache than probable EFS migraine –like headache.

Each woman with a history of migraine was asked if the EFS headache she was experiencing was similar to her preexisting migraine. Only two women stated there was a similarity between their preexisting migraine and their EFS headache. One felt EFS resulted in headache exactly like her preexisting migraine, stating that it was “like someone was beating my head” but worse. She further stated that she felt the migraine deep in her brain with severe throbbing in her brain and behind her eyes and that the surgical pain was more superficial in her

forehead area. Superficial pain characteristic may not be typical of migraine.She stated she felt the surgery made her migraine worse. Following each dose of her usual migraine medication, sumatriptan 100mg, taken once on surgery day and twice on POD #1, her migraine was entirely eliminated. Percocet had some effect on surgical pain (NRS 7 to 5). During the interview on POD #3, she stated that her usual migraine was returning and again she described the migraine as more intensified, commenting she felt it was more intensified due to EFS. She took sumatriptan and experienced subsequent relief. She also took percocet for surgical pain, which had some effect (NRS 3 to 1). She did not have her usual migraine on subsequent interview days. Her NRS was zero for PODs #7 and 30. Another commented that the EFS headache felt like "it wanted to go" into pain similar to her previous migraine but that the headache was not quite the same. Only two women experienced headache sensation similar to their usual migraine, so it can only be speculated that EFS triggers a migraine for a few with preexisting migraine. Based on the second woman's comment that it seemed like her usual migraine was going to occur but didn't, may suggest that EFS headache may have an alternative trigeminal nerve nociceptor processing than her usual preexisting migraine. It may be possible that EFS with a previous history of migraine may trigger a migraine-like headache through preexisting, similar, or alternative abnormal dysfunctional neuronal pathways.

EFS Migraine–like Headache and HRT

HRT Overall

Estrogen levels, as measured by HRT consumption and not serum estrogen levels in this study, were compared dividing the entire sample into two groups: participants on HRT and those not on HRT. Multiple studies provide evidence exogenous estrogen consumed orally, transdermally, topically, or intravaginally (cream) result in increased systemic estrogen levels

(Alexander et al., 2004; Labrie et al., 2009; Rioux, Devlin, Gelfand, Steinberg, & Hepburn, 2000; Sitruk-Ware et al., 2003). Overall, participants not on HRT (N=27) reported headache pain with higher intensity ratings on PODs # 1, 3, 7, and 30, compared to those on HRT (N=15). These study findings suggest that women may expect emotional status and functional changes following EFS, regardless of HRT consumption. Women on HRT may expect to have lower emotional status following EFS, although they may not be as low as those not consuming HRT. Functional status changes may be expected for both those on HRT and those not on HRT. Those not consuming HRT may expect to have more days and a greater impact on functional status than those consuming HRT. These findings further suggest those on HRT may recover closer to preoperative levels by POD #30 than those not on HRT.

In addition to HRT, age is another factor to consider in this study's findings. In general, older women are more likely to use HRT, however, this study sample mean age was similar (HRT, 59.0 ± 7.2 years [48 to 70] versus No HRT, 59.0 ± 8.36 years [43 to 74]) for both those on HRT and not on HRT. Reports and reviews are contradictory whether age is a factor for postoperative pain (Ip, Abrishami, Peng, Wong, & Chung, 2009). Bisgaard and colleagures (2000) reported younger age patients are a predictor for postoperative pain following laparoscopic cholecystectomy (Bisgaard, Klarskov, Rosenberg, & Kehlet, 2001). Gagliese (2005) Elderly (mean age 68-74) post-surgical patients most often report similar pain intensity as younger (mean age 42-54) patients following a wide variety of surgeries (Gagliese, Weizblit, Ellis, & Chan, 2005). In this study, older women reported lower NRS compared to younger on POD #1. The overall mean NRS was 6. The higher mean NRS were reported in younger women 40-50 and 61-65 (NRS = 7, n=13). Lower NRS ratings (NRS 4.9 and 5) in the older age groups (ages 66-74, n=12). The majority of women (n=17) had a mean NRS score of 5.5 and were 51-

60. Age did not appear to have much of influence in this study as the highest and lowest were equally represented with the majority of women in the middle group close to mean. The highest NRS rating group (NRS=7) were reported in women 46-50 and 61-65 and they were less likely to be HRT consumers (25%, n=4), (29%, n=7), respectively. The youngest group included only two women, one on HRT, who also reported the highest mean ratings (NRS, 7) (50%, n=2). (Figure 21)

Specifically, the single woman on HRT had lower pain rating (NRS=6) than the one not on HRT (NRS=8). The middle age groups 51-55 (33%, n=7), 56-60 (40%, n=10), 66-70 (50%, n=-10), and 71=75 (0%, n=2) were higher consumers of HRT with NRS ratings 5-6. NRS ratings were similar for those HRT ages 40-65 (0-7). For women 66-70 pain ratings were lower (0-5). For women not on HRT, pain intensity ratings were higher (1-10) for each age group except for those 51-55 (0-9). This provides evidence that HRT and not age influences pain intensity ratings. (Figure 21 and Table 24) Overall the samples on HRT is small, and only exogenous estrogen consumption was considered and not estrogen levels, these results suggest HRT may be a factor in headache pain intensity following EFS.

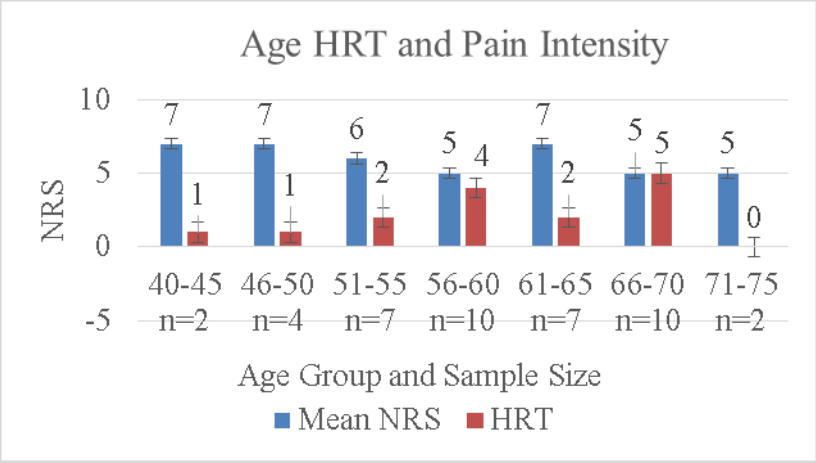


Figure 21. HRT, Age and Pain Intensity.

HRT							
Age Group	40-45 n=2	46-50 n=4	51-55 n=7	56-60 n=10	61-65 n=7	66-70 n=10	71-75 n=2
NRS	6	4	5,7	0,2,7,3	6,7	3,5,0,0	
No HRT							
NRS	8	10,10,10, 4	2,9,3,0,2	9,9,9,0,4,6	9,6,8,10,1	5,4,8,9,8	8,2

Table 24
HRT, Age, and Pain Intensity (NRS) on POD #1.

Preexisting Migraine and Family History of Migraine

Study results suggest that HRT may reduce EFS migraine –like headache symptoms. Regardless of whether participants had preexisting migraine or family history of migraine, headache pain intensity was reported as higher on POD #1 for those not on HRT versus those on HRT. For those with preexisting migraine and family history of migraine who were on HRT, pain levels were almost half on POD #1 than those not on HRT with and without a previous history of migraine and family history of migraine. On subsequent interview days, HRT and migraine was lower on POD #3 and higher on PODs #7 and 30. These findings suggest that HRT may indeed influence EFS migraine –like headache experience on POD #1, regardless of a history of migraine or family migraine. This gives us some potential insight into the effect HRT have on headache pain following EFS.

Compared to those not on HRT, women on HRT experienced less headache pain the first postoperative day following EFS. Specifically, migraine frequency was less and intensity lower for women with migraine on HRT. Estrogen is known to maintain nerve stability and decrease

sensitivity to excitation and neuron hyperexcitability (Brandes, 2006c; Lichten et al., 1996; Loder et al., 2007; Puri et al., 2006; Welch et al., 2006). Although the present study was not powered to identify HRT influences, the fact that women on HRT experienced less pain intensity is consistent with findings on Estrogen's influence on pain in the aforementioned literature.

Headache Management and Opioids

Pain management following EFS is inconsistent warranting new strategies for pain relief. Opioids are typically prescribed followingEFS with varying reports of efficacy. There is evidence that NDMA may have a role in opioids-induce hyperalgesic state, antinociceptive tolerance, and pro-nociceptive process(Chen et al., 2009; Joly et al., 2005). Migraine literature shares similar evidence that opioids are inappropriate for acute and chronic migraine (Bigal & Lipton, 2008). Opioids not only do not relieved migraine but worsened it by increasing sensitization advancing episodic headache to chronic migraine (Bigal & Lipton, 2009). There is new evidence that microglia and astrocytes may have a role in facilitating opioid-induced hyperalgesia resulting in worsening of pain (Johnson, Hutchinson, Williams, & Rolan, 2013). Specifically to anesthesia, remifentanyl and fentanyl, mu-receptor opioid analgesics, provided for analgesic purposes have been found to promote hyperalgesia within fifteen minutes of administration (Waxman, Arout, Caldwell, Dahan, & Kest, 2009). A review of anesthesia records provides information that all patients received fentanyl or remifentanyl preoperatively or intraoperatively. Providing these medications may have predisposed patients to postoperative pain.

Emotional and Functional Status

EFS-triggered migraine resulted in diminishing emotional and functional status, which is consistent with effects of other trigeminal nerve disorders, including migraine (Lipton, Bigal, et

al., 2007b). The present data showed functional and emotional capacities of the women in the present study deteriorated below US averages following EFS. Functional status was impacted more than emotional status for both those on HRT and those not consuming HRT. However, functional status was further below US average for those not on HRT.

Emotional Status

Emotional status diminished for women following EFS. Study participants with EFS-triggered migraine experienced a reduction to emotional status on POD #1. The study participants' experiences were consistent with migraine-related reductions in emotional status consistent with migraine (Lipton, Bigal, et al., 2007a; Magnusson & Becker, 2003; Peterlin et al., 2010). Participants' emotional status improved by POD #3, and by POD #7 had returned to US average or above, illustrating a return to normality in a time-frame consistent with the typical duration of migraine of 4-72 hours.

Functional Status

Women with EFS migraine –like headache experienced more deterioration in functional status for more days than they did in emotional status. On PODs #1, 3, and 7, participants reported lower functional status than emotional status, with both of these levels returning to above US average by POD #30. Functional status scores were more profoundly affected than the emotional scores, which is consistent with migraine's effect on emotional and functional status. The findings in this study are consistent in migraine research by Burstein, Cady, Goadsby, Holroyd, Lipton, and Stovner, all of whom found migraine resulted in severe emotional and functional impairment and total incapacitation with interruptions in home, work, and social activities (Aegidius et al., 2007; Burstein, Cutrer, et al., 2000; Cady et al., 2004; Goadsby, 2005; Holroyd et al., 2007b; Lipton & Bigal, 2007; Lipton, Dodick, et al., 2003).

Limitations

The sample may have been biased due to patient or surgeon choice. Specifically, there may have been bias based on patients chosen and prescreened by the surgeon and or office personnel. The study was reliant on designated trained office staff to provide flyers to prospective participants. When individual offices were contacted to verify procedures and schedules, it was reported that some potential participants were not willing to participate because "they didn't want to be bothered." Routine calls were made to each office monthly to remind designated office staff the study was continuing and ask if there were any EFS patients scheduled in the near future was scheduled for EFS and could be asked to participate in the study. It is unknown the exact number of potential patients not included in the study due to prospective patient choice or surgeon choice. There may have also been bias in such that women with the greatest pain may have been excluded and hence it would bias the findings to reflect a lower pain rating than the true average of the population of interest.

There may have been bias as the PI was the only person interviewing patients postoperatively. The SF-12v2 is a self administered questionnaire that has reliability and validity for telephone interviews, patients may have desired to please the PI with what they considered was the ‘correct’ answer for what the PI wanted to document. This may have contributed to biased study findings.

Postoperative data began with POD #1 to respect patients during surgery day, as it is clinically reported to be most uncomfortable. Although having participants complete questionnaires on surgery day would have provided additional valuable information, IRB protocols require that participants not be burden during what has been often described clinically as the most uncomfortable day following EFS. Some participants were reluctant to participate on

POD #1, as they were experiencing severe pain and were quite uncomfortable. In a few instances, the husband caretaker, who was not aware the wife was participating in the study, was resistant to allowing the PI access to the consented participant because she was in too much pain. The spouse would tell the PI the patient was "not available." Once the spouse was informed that the participant had consented to the study, the husband informed the patient that the PI was calling and questionnaires were completed. There would have been bias if those the caretakers of those patients in extreme pain had refused access, thereby skewing study results. It was important to include as many patient experiences as possible following EFS.

Some potentially important information was missed by starting questionnaires on POD #1. Participants were asked what was the most uncomfortable postoperative day and what was the highest pain NRS for that day. Over half had higher pain ratings on surgery day than POD #1 (N=22, 52%), although some rated pain lower (N=9, 21%) or the same (N=11, 26%). This information supports previous anecdotal reports that most women experience headache pain following EFS on surgery day. Some women (N=8) voluntarily voiced that they were experiencing more associated symptoms on surgery day than on POD #1. Only one revealed she had nausea on surgery day and not POD #1. One participant did not meet ICHD migraine criteria based on NRS ratings information received on POD #1 but did on surgery day. Participants were asked to retrospectively rate their pain on surgery day using the NRS migraine criteria, but other migraine criteria were not asked about. It is possible that with 52% of NRS being higher on surgery day, emotional and functional statuses and associated symptoms would have been higher as well. It is unknown what these statuses were on surgery day.

This study's findings indicate that EFS headache duration is similar to that of migraine pain, lasting from hours to days, supporting the similarities between EFS headache and migraine (Burstein, 2001; Lipton, Bigal, et al., 2007b; Peterlin et al., 2010; Saxena & Tfelt-Hansen, 2006).

Another migraine symptom commonly experienced is headache pain worsening with movement. Surgeon postoperative instructions include minimal activity, specifically no bending over or climbing stairs for fear of increasing the possibility of hematoma. In this study, the majority of women (N=27, 64%) did not know if their headache worsened with movement because they followed surgeon instructions. This may have skewed findings by limiting the number of women who reported pain with activity, which is a hallmark for intracranial nociceptor activation and hypersensitivity (Burstein, Cutrer, et al., 2000).

Questionnaires were useful in gathering many details of the pain experience following EFS. However, some verbal comments made by patients were significant, and the PI gathered many details of the experience via verbal exchange with participants throughout the study process. One participant commented that she seemed so "out of it" on POD #1 that she hoped she answered questions "right." Asking patients to report information when they are under the influence of medication or in pain may taint data. The questionnaire may be less reliable when completed while the subject is in pain. However, information received from study patients was similar for most, regardless of pain level, suggesting the empirical data received reflected the postoperative experience following EFS.

Nursing Implications

Findings from this study provide the medical community with new knowledge of women's experience of migraine-like headache following EFS. Nurses conducting postoperative assessment following EFS can expect women will most likely experience moderate to severe

headache that affects their quality of life. Based on the findings from this study nurses may now anticipate women who undergo EFS on HRT when compared to patients, not on HRT who undergo EFS may experience greater pain intensity with greater deterioration of functional status than emotional status decreasing their quality of life postoperatively. Nurses can now assess and anticipate that those with a history of migraine may have a greater potential to experience EFS migraine –like headache than those without a history of migraine. Nurses can now be aware that current opioid prescriptive strategies are not effective in alleviating headache for most women following EFS and that migraine management may be an effective alternative.

From this study there is now evidence that EFS migraine –like headache is similar to migraine providing nurses with knowledge to assist in strategizing an effective management plan, thus potentially decreasing pain. Finally, these study findings may encourage anesthesia providers and surgeons to consider alternatives to opioids for intraoperative and postoperative EFS headache management, as their use may exacerbate headache, and they may not provide effective postoperative pain management. New future prescriptive intervention studies may now focus on identifying effective pain management strategies in the hopes of improving postoperative outcomes for women following EFS.

Future Research

This study provides a better understanding of EFS headache that may enable the development and testing of data-based strategies for its treatment. For other trigeminally mediated headache migraines, a single treatment protocol continues to be elusive. Animal studies of migraine have enabled further identification of mechanisms, proinflammatory and neuropeptide activity, specific central nervous system anatomical structures and pain pathways, and testing of pharmacological treatments that cannot be conducted on humans (Burstein et al.,

2004; Burstein, Cutrer, et al., 2000; Charles, 2009; Levy, Burstein, Kainz, Jakubowski, & Strassman, 2007; Levy, Jakubowski, & Burstein, 2004). Animal studies duplicating EFS surgical approach that involves dissection of the trigeminal nerve may offer important perspectives on EFS headache pain in humans. Estrogen was found to be a modulating factor in EFS headache, suggesting animal studies to test the effects of estrogen administration preoperatively or postoperatively may be of interest.

A variety of treatments have previously been successfully implemented to treat migraine, including pharmacological (triptans) and nonpharmacological (i.e., magnesium and sublingual feverfew/ginger) protocols (Cady et al., 2011; Dobos & Tao, 2011; Jakubowski, Silberstein, Ashkenazi, & Burstein, 2005b; Linde et al., 2009). Nonpharmacological complementary and alternative treatments for migraine such as meditation and cognitive-behavioral therapy are examples of alternatives to traditional Western medicine (provider-directed drug regimens) migraine treatments (Dobos & Tao, 2011; Linde et al., 2009; Nestoriuc & Martin, 2007; Wachholtz & Pargament, 2008). The migraine like symptoms of EFS-triggered migraine suggests possible benefit of migraine therapy postoperative EFS patients. Future research can explore the efficacy of these interventions to improve EFS headache pain management and outcomes.

Exogenous estrogen in oral contraceptives and HRT may worsen or improve migraine. As complex as this relationship is this study's findings suggest that estrogen may play a role in headache pain experience, responses, and outcomes, suggesting the usefulness of future research that follows hormone fluctuations and serum estrogen levels more closely. While it may seem unreasonable to manipulate preoperative and postoperative estrogen levels, knowledge of perioperative estrogen status (HRT consumption) may help prepare nurses to anticipate headache

pain experiences so that individual pain management may be strategized and provided accordingly. Future studies might also evaluate gender differences in EFS pain and responses. If estrogen plays a role in headache severity for women, EFS responses in men may be unique and less predictable than women's pain.

Future studies could also compare various foreheadplasty approaches, dissections, and fixations. The variations in dissection techniques may translate to more tissue involvement or less nerve involvement (i.e., subperiosteum), thereby altering headache pain experiences. Two popular open brow lifts techniques to be consider for comparison are the "gold standard" coronal browlift (Horn & Thomas, 2006; Puig & LaFerriere, 2002a) and the pretrichal brow lift surgical approach (Tower & Dailey, 2004), both of which may or may not include sub or subgaleal surgical dissections (Thomas, Lee, & Patel, 2007). Study of variations in fixations could prove useful due to their potential impact on postoperative headache. Such variations may include permanent (glues and screws) and temporary (absorbable) devices, some of which that may cause greater tissue reaction than others and therefore increase in patients' pain experiences (Holzapfel & Mangat, 2004; Honig et al., 2008; Sidle et al., 2005). Perhaps most important, findings from this work will offer valuable information for the effective management of EFS headache. If varying surgical dissections and approaches, number of scalp incisions and placement of incisions, time, severity, and fixations are found to promote greater intensity headache pain experiences and resultant emotional and functional deficits, surgical dissection could be adapted that minimize EFS headache pain.

It would be of interest to explore whether HRT and history of migraine have influence on other medical conditions and surgical procedures performed in areas besides the head. Based on present and previous study results, it may be advantageous to limit opioid use intraoperatively

and postoperatively for those undergoing EFS. This alone may actually improve pain outcomes. It may also be of interest to explore whether opioids that are also ineffective in pain relief for other pain conditions, surgical and medical, may also be exacerbating pain. This may warrant pain management strategy modification similar to that for EFS migraine –like headache.

Conclusion

Based on four postoperative interviews with 42 women, this study has established that women are likely to experience headache pain following EFS which meets ICHD migraine criteria providing evidence of a surgically induced extracranial migraine-like headache following EFS. Mechanistically, these findings offer research supporting evidence that EFS triggered migraine headaches may be initiated by extracranial events that activate the trigeminovascular system. Knowing EFS-triggered migraine is similar to migraine suggests that EFS patients may benefit from migraine preventives, and not opioids which are primarily prescribed currently with inconsistent efficacy. For anesthesia providers, this study offers information which suggest opioid for preoperative, postoperative, and postoperative management may be creating a hyperalgesic condition contributing to pain following EFS. These findings may also suggest that those with classic migraine may be experiencing migraine from extracranial etiology requiring a differenct management strategy than migraine with central origin. This study also offers evidence that HRT and a history of migraine both influenced headache episodes and characteristics. These study findings may be the first step to implementing better pain management for women after EFS. Future research can explore the efficacy of current effective migraine strategies to improve migraine-like headache following EFS bettering pain treatment for women. Finding effective EFS treatment may improve to be beneficial for extracranial evoked migraine patients thus improving their lives.

APPENDIX A

Surgeons & Sites of Recruitment

Surgeons	City Location	EFS / 6 Month
1) Robert Wald, MD 100 E. Valencia Mesa Dr. Fullerton, Ca. 92831 714 738-4282	**Fullerton, Ca.**	**15**
2) Bruce Dubin, MD 1401 Avocado Ave., Ste. #501 Newport Beach, Ca. 92660 (949) 640-4911	**Newport Beach, Ca.**	**15**
3) Scott Miller, MD 9834 Genesee Avenue, Suite. #210 La Jolla, Ca. 92037 (858) 453-3133	**La Jolla, Ca.**	**20**
4) Richard Ganges, MD 665 Camino De Los Mares San Clemente, CA 92673 (949) 496-2202	**San Clemente, Ca**	**20-25**
5) Stephen Krant, MD 528 Nautilus Street La Jolla, Ca. 92037 (858) 454-3161	**La Jolla, Ca.**	**20**
6) John Apostolides, MD 528 Nautilus Street La Jolla, Ca. 92037 (858) 454-3161	**La Jolla, Ca.**	**15**
7) Michael Elam, MD 360 San Miguel, Suite # 207 Newport Beach, Ca. 92660 **(949) 721-1113**	**Newport Beach, Ca**	**20**

APPENDIX B

Headache Pain Questionnaire

1. Are you experiencing forehead pain or headache pain? ☐ forehead ☐ headache

2. When was the worse day for your headache pain? _____

3. On a scale of 0-10, what was your pain level? 0= no pain 10= worse pain: 1) what was the worse pain for today?

0.....1.....2.....3.....4.....5.....6.....7.....8.....9.....10

5. Is your forehead, cheek, chin or arm feeling numb, tingling, itching, and tender?

forehead : numb tingling itching tender

cheek: numb tingling itching tender

chin : numb tingling itching tender

arm : numb tingling itching tender

6. Do you have headache which is throbbing? Yes ☐ No ☐

7. Does the headache pain feel: sharp Yes ☐ No ☐

dull Yes ☐ No ☐

8. Does it feel like your head is going to explode outwardly Yes ☐ No ☐

9. Does it feel like your head is going to implode inwardly? Yes ☐ No ☐

10. Does it feel superficial or deep? ☐ superficial ☐ deep

11. Do you have pain around eyes? ☐ above ☐ below

☐ inside ☐ behind

12. Does it feel like someone is pressing a finger in your eye? Yes ☐ No ☐

13. Does it feel like your eye is going to pop outwards? Yes ☐ No ☐

14. Is the headache pain: continuous Yes ☐ No ☐ intermittent Yes ☐ No ☐

15. Does it headache pain worse with:

bending over Yes ☐ No ☐

coughing Yes ☐ No ☐

sneezing Yes ☐ No ☐

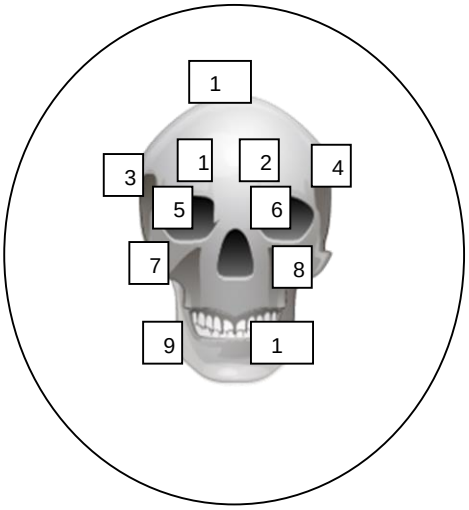
climbing stairs Yes ☐ No ☐

16. Are you experiencing any changes in vision ☐ smells ☐

17. Are you able to take care of yourself? Yes No

20. Do you need assistance with these activities? Yes ☐ No ☐

21. Where is the headache pain?



_____

_____

_____

22. Have you been experiencing?

a. nausea Yes ☐ No ☐

b. vomiting Yes ☐ No ☐

c. tearing of eyes: Right Left Both Neither

d. stuffy/running nose Yes ☐ No ☐

e. red blood shot eyes Yes ☐ No ☐

f. photophobia (sensitivity to light) Yes ☐ No ☐

g. sensitivity to sound (phonophobia) Yes ☐ No ☐

h. sensitivity to smells (osmophobia) Yes ☐ No ☐

Medications and Perceived Relief

Reason: Pain Y N Source:	Medication	Dose	Time	Date	Perceived Relief [0 to 10 NRS]
	Codeine				
	Oxycodone				
	Morphine				
	Meperidine				
	Tylenol with Codeine				
	Excedrin				
	Other				
Reason Nausea Y N How long:	Medication	Dose	Time	Date	Perceived Relief [0 to 10 NRS]
	Zofran				
	Tigan				
	Vistaril				
	Other				

APPENDIX C

Demographics Form

Name or initials: _____

Telephone number: _____

Telephone oral consent obtained Yes ☐ Date: _____ Time: _____

Date of Birth: _____

Race:

☐ White, Not Hispanic origin ☐ Asian or Pacific Islander

☐ Black, Not Hispanic origin ☐ American Indian or Alaskan Native

☐ Hispanic ☐ Other: please specify _____

History of Migraine Headache Yes ☐ No ☐

Medication for Migraine_____

Family History of Migraine Headache Yes ☐ No ☐

History of Head Injury? Yes ☐ No ☐

History of Hysterectomy? Yes ☐ No ☐ Ovaries removed Yes ☐ No ☐

Hormone Replacement Therapy: Yes ☐ No ☐

Hormone Replacement Therapy: Oral or transdermal or Birth Control Treatment

Currently medications, what, why and pattern of consumption: _____

_____

Adapted with permission from: Rami Burstein, PhD

APPENDIX D

SF-12v2™ Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is: 4=Excellent 3=Very good 2=Good 1=Fair 0=Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

2 = Yes, limited a lot 1=Yes, limited a little 0=No, not limited at all

b) Climbing several flights of stairs

2 = Yes, limited a lot 1=Yes, limited a little 0=No, not limited at all

3. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a) Accomplished less than you would like

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

b) Were limited in the kind of work or other activities

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a) Accomplished less than you would like

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

b) Did work or activities less carefully than usual

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

5. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

0=Not at all 1=A little bit 2=Moderately

3=Quite a bit 4=Extremely

6. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week?

a) Have you felt calm and peaceful?

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

b) Did you have a lot of energy?

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

c) Have you felt downhearted and depressed?

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

7. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

4=All of the time 3=Most of the time 2=Some of the time

1=A little of the time 0=None of the time

APPENDIX E

Recruitment Flyer

UCLA SCHOOL OF NURSING

It's Simple... *It's easy*. I call you!

I am a nurse wanting to learn about your experiences following cosmetic surgery. By participating in this research study, you will help me to understand how to provide the best possible care.

1. Fill in your contact information below so I can call you.

2. I will call you this evening & ask basic questions so I can get to know you. This will take about 5-10 minutes.

3. You will receive four other telephone calls on day 1,3,7 and one month after surgery to ask the same questions about your experience following cosmetic surgery. These will each take about 5-10 minutes.

*Following all interviews you will receive a $75 gift card for your time.

*Your information is CONFIDENTIAL and will be protected.

Your Name: _____

Or Name of Contact Person: _____

Phone number: _____ Home

_____ Cell

Best time to call: _____ this evening

**Any questions contact Study Coordinator - Julia Lassegard CRNA, MS (714) 293-3548

Thank you for your Participation

APPENDIX F

Oral Consent Script

PERMISSION TO PARTICIPATE IN A RESEARCH STUDY

Headache Pain Experience in Women Following Endoscopic Foreheadplasty Surgery

PURPOSE

You are invited to take part in a research study. The purpose of the study is to learn how you feel and what medications you are taking following your endoscopic browlift surgery.

PROCEDURES

There will be two telephone calls, one is tonight and one is next week. I will ask you a series of questions about how you are feeling and what medications you are taking following surgery. This may take 10-15 minutes. You may choose not to participate in this study.

RISKS/DISCOMFORTS

Some people may experience discomforts after surgery and may not be willing to answer questions. Holding a phone close to your ear may also cause minimal discomfort while answering questions. You may have your caretaker or someone be a messenger to repeat the questions to you and relay your answers to the questions. In case you are too tired, too upset, or not willing to answer questions, you may stop and I can call an hour later to ask if you would like to continue. You may refuse or discontinue at any time. In case you feel a need for medical assistance (extreme pain, anxiety, bleeding) during the telephone interview, you may contact your respective surgeon, or call 911 in case of emergency.

BENEFITS

You may not experience any direct benefits from being part of this study. However, your answers may help us learn about experiences of patients after cosmetic surgery.

VOLUNTARY PARTICIPATION

You do not have to agree to be in this study, and you may change your mind at any time.

Call the principal investigator, Julia Lassegard, RN, CRNA, MS, at 714 293-3548 if you have questions or complaints about being in this study.

If you have any questions about your rights as a research participant, or if you think you have not been treated fairly, you may call the UCLA Office for Protection of Human Subjects at 323/361-2265.

PERMISSION TO PROCEED

Would it be okay to proceed with these questions? YES NO

Name of Participant: _____

Date and Time: _____ Study Investigator/Interviewer _____

APPENDIX G

Statistics (G1-G8).

G1.Pain Intensity

Frequencies

Time * Severe to Mild Pain Crosstabulation

			Severe to Mild Pain		Total
			No	Yes	
Time	POD1	Count	3	39	42
		% within Time	7.1%	92.9%	100.0%
		% within Severe to Mild Pain	5.5%	34.5%	25.0%
	POD3	Count	7	35	42
		% within Time	16.7%	83.3%	100.0%
		% within Severe to Mild Pain	12.7%	31.0%	25.0%
	POD7	Count	18	24	42
		% within Time	42.9%	57.1%	100.0%
		% within Severe to Mild Pain	32.7%	21.2%	25.0%
	POD30	Count	27	15	42
		% within Time	64.3%	35.7%	100.0%
		% within Severe to Mild Pain	49.1%	13.3%	25.0%
Total		Count	55	113	168
		% within Time	32.7%	67.3%	100.0%
		% within Severe to Mild Pain	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	38.358[a]	3	.000
Likelihood Ratio	40.882	3	.000
Linear-by-Linear Association	37.022	1	.000
N of Valid Cases	168		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 13.75.

G2. <u>EFS Migraine –like Headache</u>

Frequencies

EFS Migraine –like Headache

N	Valid	42
	Missing	0

EFS Migraine –like Headache

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	23	54.76	54.76	52.4
	Yes	19	45.24	45.24	100.0
	Total	42	100.0	100.0	

G3. EFS Migraine –like Headache and Probable EFS Migraine –like Headache

Frequencies

EFS Mig + Probable EFS

N	Valid	42
	Missing	0

EFS Mig + Probable EFS

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	9	21.4	21.4	21.4
	Yes	33	**78.6**	**78.6**	100.0
	Total	42	100.0	100.0	

G4. EFS Mig + Probable EFS * History of Migraine Crosstabulation

			History of Migraine		Total
			No	Yes	
EFS Mig + Probable EFS	No	Count	8	1	9
		% within EFS Mig + Probable EFS	88.9%	11.1%	100.0%
	Yes	Count	22	11	33
		% within EFS Mig + Probable EFS	66.7%	**33.3%**	100.0%
Total		Count	30	12	42
		% within EFS Mig + Probable EFS	71.4%	28.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.711[a]	1	.191		
Continuity Correction[b]	.795	1	.372		
Likelihood Ratio	1.966	1	.161		
Fisher's Exact Test				**.247**	.190
Linear-by-Linear Association	1.670	1	.196		
N of Valid Cases	42				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.57.

b. Computed only for a 2x2 table

G5, EFS Total Migraine and Family History of Migraine

EFS Mig + Probable EFS * History of Family Migraine Crosstabulation

			History of Family Migraine		Total
			No	Yes	
EFS Mig + Probable EFS	No	Count	7	2	9
		% within EFS Mig + Probable EFS	77.8%	22.2%	100.0%
	Yes	Count	19	14	33
		% within EFS Mig + Probable EFS	57.6%	**42.4%**	100.0%

Total	Count	26	16	42
	% within EFS Mig + Probable EFS	61.9%	38.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.224[a]	1	.269		
Continuity Correction[b]	.517	1	.472		
Likelihood Ratio	1.298	1	.254		
Fisher's Exact Test				**.442**	.240
Linear-by-Linear Association	1.195	1	.274		
N of Valid Cases	42				

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 3.43.

b. Computed only for a 2x2 table

G6. Logistic Regression

Classification Table[a,b]

	Observed		Predicted		
			EFS Mig + Probable EFS		Percentage Correct
			No	Yes	
Step 0	EFS Mig + Probable EFS	No	0	9	.0
		Yes	0	33	100.0
	Overall Percentage				78.6

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	1.299	.376	11.938	1	.001	3.667

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	HRT	4.780	1	**.029**
		History of Migraine	1.711	1	**.191**
		History of Family Migraine	1.224	1	**.269**
	Overall Statistics		6.735	3	.081

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	7.466	3	.058
	Block	7.466	3	.058
	Model	7.466	3	.058

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square

1	36.179[a]	.163	.252

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Classification Table[a]

	Observed		Predicted		
			EFS Mig + Probable EFS		Percentage Correct
			No	Yes	
Step 1	EFS Mig + Probable EFS	No	5	4	55.6
		Yes	2	31	93.9
	Overall Percentage				85.7

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	HRT	-1.783	.854	4.364	1	.037	**.168**
	History of Migraine	1.436	1.201	1.431	1	.232	**4.205**
	History of Family Migraine	.855	.959	.795	1	.373	**2.352**
	Constant	1.584	.660	5.764	1	.016	4.873

a. Variable(s) entered on step 1: HRT, History of Migraine, and History of Family Migraine.

G7. Emotional Status Following EFS

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Time * Emotional Status Below US Average	168	100.0%	0	0.0%	168	100.0%

Time * Emotional Status Below US Average Crosstabulation

			Emotional Status Below US Average		Total
			No	Yes	
Time	POD1	Count	20	22	42
		% within Time	47.6%	**52.4%**	100.0%
	POD3	Count	29	13	42
		% within Time	69.0%	**31.0%**	100.0%
	POD7	Count	33	9	42
		% within Time	78.6%	**21.4%**	100.0%
	POD30	Count	37	5	42
		% within Time	88.1%	**11.9%**	100.0%
Total		Count	119	49	168
		% within Time	70.8%	29.2%	100.0%

Time * Emotional Status Below US Average Crosstabulation

					Total
					4
					100.0%
					25.0%
					4
					100.0%
		% within Emotional Status Below US	24.4%	**26.5%**	25.0%
	POD7	Count	33	9	4
		% within Time	78.6%	21.4%	100.0%
		% within Emotional Status Below US	27.7%	**18.4%**	25.0%
	POD30	Count	37	5	4
		% within Time	88.1%	11.9%	100.0%
		% within Emotional Status Below US	31.1%	**10.2%**	25.0%
		Average			
		Count	119	49	168
Total		% within Time	70.8%	29.2%	100.0%
		% within Emotional Status Below US	100.0%	100.0%	100.0%

			Emotional Status Below US Average		Total
			No	Yes	
Time	POD1	Count	20	22	42
		% within Time	47.6%	52.4%	100.0%
		% within Emotional Status Below US Average	16.8%	44.9%	25.0%
	POD3	Count	29	13	42
		% within Time	69.0%	31.0%	100.0%

		% within Emotional Status Below US Average	24.4%	26.5%	25.0%
	POD7	Count	33	9	42
		% within Time	78.6%	21.4%	100.0%
		% within Emotional Status Below US Average	27.7%	18.4%	25.0%
	POD30	Count	37	5	42
		% within Time	88.1%	11.9%	100.0%
		% within Emotional Status Below US Average	31.1%	10.2%	25.0%
Total		Count	119	49	168
		% within Time	70.8%	29.2%	100.0%
		% within Emotional Status Below US Average	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	18.295[a]	3	.000
Likelihood Ratio	18.414	3	.000
Linear-by-Linear Association	17.327	1	.000
N of Valid Cases	168		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 12.25.

Functional Status

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Time * Functional Status Below US Average	168	100.0%	0	0.0%	168	100.0%

Time * Functional Status Below US Average Crosstabulation

			Functional Status Below US Average		Total
			No	Yes	
Time	POD1	Count	5	37	42
		% within Time	11.9%	88.1%	100.0%
	POD3	Count	7	35	42
		% within Time	16.7%	83.3%	100.0%
	POD7	Count	15	27	42
		% within Time	35.7%	64.3%	100.0%
	POD30	Count	28	14	42
		% within Time	66.7%	33.3%	100.0%
Total		Count	55	113	168
		% within Time	32.7%	67.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	35.330[a]	3	.000
Likelihood Ratio	35.732	3	.000
Linear-by-Linear Association	31.863	1	.000
N of Valid Cases	168		

0 cells (.0%) have expected count less than 5. The minimum expected count is 13.75.

G8. Functional Status Following EFS

Time * Functional Status Below US Average Crosstabulation

			Functional Status Below US Average		Total
			No	Yes	
Time	POD1	Count	5	37	42
		% within Time	11.9%	**88.1%**	100.0%
	POD3	Count	7	35	42
		% within Time	16.7%	**83.3%**	100.0%
	POD7	Count	15	27	42
		% within Time	35.7%	**64.3%**	100.0%
	POD30	Count	28	14	42
		% within Time	66.7%	**33.3%**	100.0%
Total		Count	55	113	168
		% within Time	32.7%	67.3%	100.0%

G9. HRT is a predictor for NRS (pain) on POD#1.

* Time 1 analyses regress NRS HRT if Time==1

```
      Source |       SS       df       MS              Number of obs =      42
-------------+------------------------------           F(  1,    40) =    8.04
       Model |  58.3195767     1   58.3195767           Prob > F      =  0.0072
    Residual |  290.251852    40   7.2562963           R-squared     =  0.1673
-------------+------------------------------           Adj R-squared =  0.1465
       Total |  348.571429    41  8.50174216           Root MSE      =  2.6938

------------------------------------------------------------------------------
         NRS |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         HRT |  -2.459259   .8674703    -2.83   0.007    -4.212482   -.7060363
       _cons |   6.592593   .5184127    12.72   0.000     5.544841    7.640344
```

APPENDIX H

Occurence of pain qualities within each pain intensity classification, POD #1 to #30 (1-4)

Pain Severity	Severe	Moderate	Mild	No Pain
	45%	19%	29%	7%
Throbbing	74%	13%	42%	0%
Photophobia	84%	38%	50%	33%
Phonophobia	68%	25%	17%	33%
Osmophobia	16%	0%	0%	33%
Exploding	42%	38%	25%	0%
Imploding	58%	50%	50%	33%
Sharp	58%	38%	25%	0%
Dull	84%	50%	42%	0%
Continuous	58%	50%	42%	0%
Intermittent	42%	0%	42%	0%
Superficial	42%	67%	83%	0%
Deep	63%	0%	25%	0%
Nausea	53%	38%	33%	0%

1. Pain severity, pain qualities, and associated symptoms POD #1.

2. Pain severity, pain qualities, and associated symptoms POD #3.

Pain Severity	Severe	Moderate	Mild	No Pain
	45%	24%	39%	0%
Throbbing	56%	50%	25%	0%
Photophobia	89%	30%	38%	14%
Phonophobia	67%	10%	19%	14%
Osmophobia	33%	0%	6%	14%
Exploding	44%	40%	13%	0%
Imploding	33%	40%	38%	14%
Sharp	22%	10%	19%	0%
Dull	89%	70%	56%	0%
Continuous	56%	20%	19%	0%
Intermittent	33%	90%	63%	0%
Superficial	78%	60%	63%	0%
Deep	11%	30%	19%	0%
Nausea	44%	20%	6%	14%

Pain Severity	**Severe**	**Moderate**	**Mild**	**No Pain**
	5%	10%	41%	44%
Throbbing	50%	75%	18%	11%
Photophobia	50%	0%	29%	16%
Phonophobia	0%	25%	0%	5%
Osmophobia	50%	0%	0%	0%
Exploding	50%	25%	29%	0%
Imploding	0%	25%	35%	0%
Sharp	0%	25%	12%	0%
Dull	100%	100%	59%	0%
Continuous	50%	50%	24%	0%
Intermittent	50%	50%	53%	5%
Superficial	50%	50%	65%	0%
Deep	50%	50%	24%	0%
Nausea	0%	25%	6%	0%

3. Pain severity, pain qualities, and associated symptoms POD #7.

Pain Severity	**Severe**	**Moderate**	**Mild**	**No Pain**
	0%	12%	27%	61%
Throbbing	0%	40%	9%	0%
Photophobia	0%	60%	36%	0%
Phonophobia	0%	40%	18%	0%
Osmophobia	0%	0%	9%	0%
Exploding	0%	40%	0%	0%
Imploding	0%	30%	27%	4%
Sharp	0%	20%	18%	0%
Dull	0%	100%	55%	0%
Continuous	0%	40%	27%	0%
Intermittent	0%	60%	64%	0%
Superficial	0%	100%	64%	4%
Deep	0%	0%	27%	0%
Nausea	0%	0%	0%	0%

4. Pain severity, pain qualities, and associated symptoms POD # 30.

APPENDIX I

TIMELINES & MILESTONES
*EACH YEAR IS DIVIDED INTO 1ST, 2ND, 3RD AND 4TH QUARTERS

Activity	Year 2012				Year 2013				Year 2014	
	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd
IRB Approval & Registration **Study Manual & Personnel Training**	■	■	→							
Patient Screening & Enrollment	■	■	■	→	→	→				
Data Collection	■	■	■			→	→			
Data Entry & Data Verification	■	■	■	■	■	→	→			
Data Analyses	■	■	■	■	■	■	→	→		
Presentations at Scientific Meetings	■	■	■	■	■			→	→	
Complete Chapters 5 & 6	■	■	■	■	■		→	→	→	

July - August 2012

IRB Refinement and set up

Training of Office Personnel

August to December 2012

Recruitment & Consent

Data Collection/Data Entry

February 2013 to November 2013

Data Analyses

Completion of Chapters 5 & 6

February 2014

Final Defense

APPENDIX J

EFS Migraine –like Headache and Probable Migraine –like Headache per Recruiting Surgeon

Surgeons	**Met ICHD Migraine Diagnosis**	**Probable Migraine**
1) Dr. M. B. (N=3)	1	1
2) Dr. G. (N=8)	3	4
3) Dr. B. D. (N=7)	3	4
4) Dr. S. K. (N=1)	1	0
5) Dr. W. (N=1)	1	0
6) Dr. M (N=3)	2	0
7) Dr. B. (N=10)	6	3
8) Dr. K. (N=3)	1	0
9) Dr. W. (N=1)	0	1
10) Dr. A. (N=1)	1	0
11) Dr. H. (N=1)	0	0
12) Dr. D. (N=2)	1	0
Total:	**N=20**	**N=13**

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