Musical Therapy's Effects on Plasma β-endorphin Levels Post-Oral Surgery

Cameron Carlisle

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Professional Abstract

According to the National Institute on Drug Abuse, more than 4.7 million Americans rely on narcotic analgesics (NIDA). These pain killers are prominent in helping manage pain after surgery. Yet, current post-operative pain treatment is relatively expensive and has led to side effects and addiction. Thus, a more effective alternative treatment for post-operative pain management is needed, such as music therapy. This therapy includes a cheap, non-invasive, and non-pharmacological mediation that can lead to less reliance on narcotics for pain relief. Previous music studies relied on the VAS scale (i.e., scale of 1-10), an imprecise quantitative measurement of pain. However, a more appropriate quantitative measurement, plasma β-endorphin levels, are unknown in quantifying the positive effects music therapy has on patients in post-operative pain. Our objective is to measure plasma β-endorphin levels following baroque music therapy and compare that concentration to patients' expressed pain levels following a third molar tooth extraction. An important variable that we will take into account is the amount of pain medication consumed following the tooth extraction in the control and treatment groups. By doing this, we will be able to quantitatively measure the aid music provides in reducing post-operative pain. This will lead to a safe and cheap non-pharmacological method that may complement narcotic consumption to better manage post-operative pain.

NIH Public Audience Abstract

Today, pain affects more Americans than cancer, diabetes, and heart disease combined (NIH). A prominent example of pain that disturbs Americans and individuals around the world is pain following a surgical procedure. According to the Center for Disease Control (CDC), as of 2010, roughly 51.4 million people undergo surgery in the United States per year. As a result, this post-operative pain forces doctors to provide narcotic analgesics. For instance, morphine is commonly given as a pain reliever in post-operative cases, relieving much pain for the patient. However, narcotics cause side effects, lead to addiction, and are expensive. A safe and cheap way that can solve this problem is music therapy following a surgical procedure. Music therapy is recognized to relieve pain levels among subjects in past studies. Although subjects in past studies were able to scale their pain on 1-10 (i.e., VAS scale) following surgery with musical therapy, a more precise measurement of pain could be accounted for. β-endorphins, which are proven to relieve pain and stress, can quantity levels of pain. Plasma β-endorphins within our bloodstream can be precisely measured and would be a viable way to determine the effectiveness of music therapy on post-operative pain levels. Thus, our objective is to measure plasma β-endorphin levels following music therapy and compare that concentration to patients' expressed pain levels following a wisdom teeth procedure in subjects ages 18-25. We will also account for the amount of nar-

cotics given to the treatment group (given music) compared to the control group (no music). Our findings will serve for improved management of pain levels in the near future. In addition, it may also possibly lead to the use of less narcotics in the post-operative setting, leading to less addiction and side-effects associated with narcotic use to manage post-operative pain.

Specific Aims

We hypothesize that β-endorphin levels will rise with the treatment group (i.e., given music therapy), knowing an increase in β-endorphins relieves pain levels in multiple past studies. We also believe that musical therapy treatment following operation will lower pain levels (i.e., on VAS scale) and less pain medication will be taken among subjects, due to music providing a mental block of pain for patients. Specific Aim 1: Measure plasma β-endorphin levels at different time periods for third molar surgery. Blood samples will be drawn in three time periods for each subject. Samples will be obtained at baseline (i.e., before surgery), after surgery when the anesthesia wears off, and lastly, two hours following the procedure. Plasma β-endorphin concentrations will be determined with a radioimmunoassay. Specific Aim 2: Assess the pain levels of subjects with and without baroque music treatment following the oral surgery. Assessment for pain levels will include a visual analogue scale (VAS) questionnaire prior to collection of blood samples. This will occur in the second and third time periods discussed in Aim 1, when the general anesthesia from the surgery wears off and following the music therapy given to the treatment group two hours after the surgery. Ultimately, findings in Aims 1 and 2 will be integrated to quantitatively determine the overall effect of music therapy on post-operative pain. Specific Aim 3: Take into account the variable of pain medicine. This will be assessed by the amount of analgesics administered in both control and treatment groups in the post-operative period. Assessment of analgesic consumption will occur post-surgery following the third molar extraction, in accordance with Aims 1 and 2. The medical charts of both subject groups will be evaluated to observe the quantity of analgesics consumed post-operation. This will reveal the extent to which music therapy compensates for narcotic use in post-operative pain relief compared to without music therapy.

Introduction

According to the National Institute on Drug Abuse, deaths involving prescription opioids have quadrupled since 1999, outweighing the deaths affiliated with cocaine and heroin combined (NIDA). These deaths were most likely due to addiction and or side effects from narcotic analgesics (e.g., morphine). These pain killers are given as an aid in immediate pain relief. Nonetheless, recent research has investigated possible post-operative pain relief through non-pharmacological methods, such as music therapy. Music therapy relieves post-operative pain. For example, Nilsson et al. observed, following a hernia surgery in 125 patients, that music therapy had beneficial effects, lowering post-operative pain intensity among patients who listened to music as a treatment (Nilsson et al. 2003). These findings were based on the VAS scale, an imprecise quantitative measurement of pain. A more precise quantitative measurement, β-endorphin levels, were not implemented, although they correlate with pain according to several studies. The groundbreaking initial research by Dubois et al. in 1981 revealed a robust increase of β-endorphin levels in the post-operative period following surgically induced pain. These results by Dubois et al. led to various studies to also prove the importance in β-endorphins in association

with pain relief. These studies revealed that an increase in β-endorphin levels eases post-surgical pain. Thus, our overall goal is to measure the concentration of plasma β-endorphin levels produced with baroque music therapy and compare that concentration to patients' expressed pain levels following a third molar extraction in subjects of ages 18-25. One of the variables controlled will be the amount of pain medication consumed following the oral surgery among the control and treatment subjects (i.e., treatment with music therapy). This third molar extraction procedure will be the surgery in this study because it is a common surgical procedure (i.e., ten million third molars pulled per year), especially among those in the age group of 18-25, the recommended time that dentists suggest wisdom teeth be removed (Friedman 2007). Measuring the β-endorphin levels in the post-operative period will allow us to quantitatively evaluate the efficacy of music therapy. This may lead to music therapy outweighing narcotic consumption to manage post-operative pain. Although past studies revealed that music therapy eases pain based on the VAS scale, post-operative pain has not been measured with β-endorphins in relation the treatment of music therapy. Our objective is to determine if music is a viable method to raise β-endorphin levels, leading to improved management of post-operative pain. Moreover, our goal is to assess the relationship of the plasma β-endorphin levels to pain incurred and the amount of analgesics expended among subjects following the surgical procedure, an important variable to account for. Understanding these relationships will lead to a safer alternative compared to narcotic pain relief, having associated side effects and possible addiction among certain patients, in addition to being expensive. Music therapy, a non-pharmocoligcal, non-invasive, and rather cheap intervention will be able to compensate for narcotics to effectively manage post-operative pain levels (Heiser et al. 1997). This will ultimately lead to a decrease in the side-effects, addiction, and costs associated with narcotics.

Research Design and Methods

Post-operative pain has been examined with music therapy recently in multiple studies; however, the level of β-endorphins are unknown in relation to music therapy. This study is necessary to examine whether β-endorphins play an important factor with music therapy and managing post-operative pain levels. To observe the effected levels of β-endorphins by music therapy, a comparative study will be conducted to assess the role of music therapy in β-endorphin levels following a wisdom tooth removal. As stated earlier, our hypothesis is the following: We hypothesize that β-endorphin levels will rise with the treatment group (i.e., given music therapy), since music is known to relieve pain levels in multiple past studies. We also believe that musical therapy treatment following operation will lower pain levels (i.e., on VAS scale) and less pain medication will be used among subjects, due to music providing a mental block of pain or patients (Figure 1). To acquire these results, the following experimental designs will be carried out for each of our three specific aims.

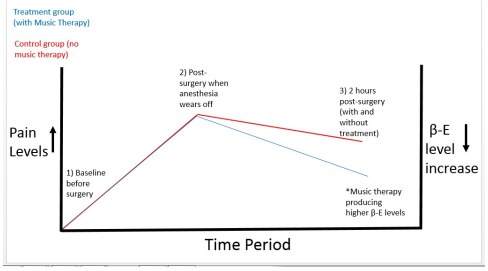

Figure 1: Our hypothesis; we expect to find β-endorphin levels increase following music therapy after the oral surgery in the treatment group (blue) compared to the control group (red). The predicted graph shows β-endorphin levels increase as pain levels decrease throughout the surgical procedure. Specific Aim 1: Measure plasma

β-endorphin levels at different time periods for third molar surgery.

Rationale

Established quantitative research has been conducted on β-endorphin levels and pain; however, only qualitative research has been performed in relation to pain with musical therapy. We will implement the established research on β-endorphin levels to quantify the effects of musical therapy on post-operative pain. We will test the hypothesis (stated earlier) that β-endorphin levels will elevate with the treatment group given baroque musical treatment compared to the control group. We will give the treatment group baroque music, due to its ability to increase the alpha brain wave state (Brewer). Surgeries will be done in in one week to have the same surgeons working on the subjects throughout the five day study. This is vital to limit any outside variables that may negatively affect the data produced.

Experimental Design

To measure the plasma β-endorphin levels in three time periods for the third molar extraction surgery, we will take blood samples for both subject groups (i.e., control and treatment). Blood samples will be taken at 1) baseline, 30 minutes before surgery begins, 2) once anesthesia wears off after surgery and pain begins to collect, and 3) two hours following the procedure for both control and treatment groups. We will not collect blood during surgery because it will not yield a correct measurement of β-endorphins, since patients will be unconscious and sedated under general anesthesia propofol (SFGH). 4mL of blood will be drawn at the antecubital fossa of each subject, the near minimum of blood to extract. This will be done by Phlebotomists using blood draw needles (EXEL, Los Angeles, CA). Once all the samples are collected in blood collection tubes with EDTA (Phoenix Pharmaceuticals, Burlingame, CA), they will be placed in dry ice (Continental Carbonic, Decatur, IL). The tubes will then be centrifuged (Eppendorf, Hamburg, Germany) to separate the red blood cells from the plasma and stored at -80 °C to be analyzed at UCSF. Following the study, the stored plasma samples from the 60 subjects (i.e., 30 from control and 30 from treatment group) will be performed on the same radioimmunoassay (Thermo Fisher Scientific, Waltham, MA) and β-endorphin levels will be determined. The endorphin, beta radioimmunoassay kit will obtain the concentrations of β-endorphins among the three time periods when blood was taken from the subjects (Phoenix Pharmaceuticals, Burlingame, CA).

Analysis

Ultimately, this procedure will allow us to examine how β-endorphin levels start of at baseline and change when pain collects, in addition to when music therapy is applied. We expect to successfully measure β-endorphin levels and examine pain levels. We have tailored the conditions in the study to ensure successful and accurate results, but there could be failure that occurs. For instance, there could be inaccurate readings of β-endorphin levels, not taking the blood samples at the right times throughout the study. However, to ensure accurate readings, the half-life of β-endorphins (i.e., 37 minutes) will be taken into account (Foley et al. 1979). Thus, we will extract the blood at the appropriate times to ensure accurate β-endorphin readings following the radioimmunoassay. Specific Aim 2: Assess the pain levels of subjects with and without baroque music treatment following the oral surgery.

Rationale

Past studies have evaluated pain levels with treatment of music therapy only by use of the visual analogue scale (VAS) in the post-operative period (Nilsson et al. 2003). We will assess pain levels via VAS to examine the relation of pain levels compared to the measured β-endorphins. This will be observed in the control group compared to that of the treatment group with baroque music therapy. Baroque music will be implemented in this study because it is proven to enhance learning and increase alpha brain waves, promoting deep concentration (Brewer). Popular baroque composers include Johann Bach, George Handel, and Antonio Vivaldi, for example. Songs from these artists will be incorporated into the playlist for the treatment group.

Experimental Design

We will evaluate pain levels using a 10-point VAS questionnaire prior to collecting blood samples in the second and third time period (i.e., after surgery when anesthesia wears off and 2 hours following procedure with music given to treatment group). The VAS questionnaire will permit the subjects to rank their pain on a scale of 1 to 10, with the lowest amount of pain felt at 1 and the highest at 10. Both control and treatment groups will have the exact same conditions, but the treatment groups will be listening to baroque music during the 2 hour post-operative period. Songs for the subjects in the treatment group will be in a pre-selected playlist. These songs will be from Bach, Handel, and Vivaldi. Table 1 displays the sequence of tracks that will be played and the time length of each track. All subjects in the treatment group will listen to these songs in the same order shown below.

Composer	Album Title	Song Title	Time (minutes)
Johann Bach (Conductor: Vladimir Feltsman)	Baroque Perspectives: Bach	Keyboad Concerto in D Major, BWV 1054: I. Allegro	7:25
		Keyboard Concerto in D Major, BWV 1054: II. Adagio e piano sempre	6:01
		Keyboard Concerto in D Major, BWV 1054: III. Allegro	3:30
		Sonata for Violin and Chamber Orchestra (arr. From Violin Sonata No. 1) I. Andante	2:45
		Sonata for Violin and Chamber Orchestra (arr. from Violin Sonata No. 1): II. Allegretto	4:01
		Sonata for Violin and Chamber Orchestra (arr. From Violin Sonata No. 1): III. Largo	5:57
		Keyboard Concerto in G Minor, BWV 1058: I. (Allegro)	3:35
		Trio-Sonata: I. Moderato	9:26
George Handel (Conductor: Laurence Cummings)	Handel: Siroe, HWV 24	Siroe, re di Persia, HWV 24: Overture	4:38
		Siroe, re di Persia, HWV 24:Act I: Figli, di voi non meno	3:21
		Siroe, re di Persia, HWV 24:Act I: Aria Se il mio paterno amore	3:36
		Siroe, re di Persia, HWV 24: Act I: Recitative: E puoi, senza arrossirti	4:43
		Siroe, re di Persia, HWV 24: Act I: Aria da capo: D'ogni amator la fede	6:40
		Siroe, re di Persia, HWV 24:Act I: Recitative: Dall'insidie d'Emira si tolga il	5:52
		Siroe, re di Persia, HWV 24: Act I: Aria de capo: Vedesti mai sul prato (Emira)	7:30
Antonio Vivaldi (Conductor: Baltic Baroque)	Vivaldi Senza Basso	Trio Sonata in B-Flat Major, RV 77: I. Allegro	5:09
		Trio Sonata in B-Flat Major, RV 77: II. Andante	4:13
		Trio Sonata in B-Flat Major, RV 77: III. Allegro	3:26
		Trio Sonata in F Major, RV 70: I. Allegro	4:43
		Trio Sonata in F Major, RV 70: II. Larghetto	3:33
		Trio Sonata in F Major, RV 70: III. Allegro molto	3:33
		Trio Sonata in G Major, RV 71: I. Allegro	3:53
		Trio Sonata in G Major, RV 71: II. Larghetto	4:02
		Trio Sonata in G Major, RV 71: III. Allegro	3:48
		Trio Sonata in F Major, RV 68: I. Allegro	4:19
		Trio Sonata in F Major, RV 68: II. Andante	2:21
		Trio Sonata in F Major, RV 68: III. Allegro	3:14

Figure 1: Table 1: Playlist in exact order for treatment subjects. Total time: 2 hours, 5 minutes, 0 seconds.

Analysis

After measuring β-endorphin levels through a series of steps, we will examine the correlation between β-endorphin levels and pain levels. This will be before and after the application of music therapy in the treatment group. In addition, we will look for evident trends observed in β-endorphin and pain levels among the control group. This will be observed by using statistical software to run certain statistical tests, such as a two-sample t-test (SigmaPlot, San Jose, CA). A two-sample t-test will be performed to assess if there is a statistical significance among the control and treatment groups with their β-endorphin and pain levels. A p-value of less than 0.05 will be deemed statistically significant. A potential pitfall may be implementing the same music (i.e., baroque) throughout the whole study, even if we want music to be consistent among treatment subjects in the study. However, if a great difference in β-endorphin levels between treatment subjects is apparent, then it may be due to some subjects not stimulated as much as others by baroque music. To counteract this, we will then perform the study again, allowing subjects to listen to their favorite genre of music, to provide stimulation for all treatment subjects to the songs they enjoy most. Specific Aim 3: Take into the account the variable of pain medicine. This will be assessed by the amount of analgesics administered among both control and treatment groups in the post-operative pain period.

Rationale

To relieve post-operative pain, narcotic analgesics, such as morphine are dealt to treat the pain. The amount of narcotics ingested by subjects will allow us to determine the pain among the control and treatment groups before and after the music therapy is implemented. These numbers have not been related to $\beta\beta$-endorphin levels and pain together, among past studies.

Experimental Design

Following the tooth extraction procedure, nurses will direct the subjects to a large common room. The nurses will situate the subjects and will help the treatment group setting up the baroque music via headphones. These subjects will be lent a 6th generation ipod nano (Ebay, San Jose, CA) and Sony headphones (Sweetwater Sound Inc., Fort Wayne, IN) for the two hour baroque musical treatment. Moreover, the control group will also be monitored by the nurses in the common room. The nurses will be there during the two hour period to monitor the use of analgesics among all subjects in the room. This information will be recorded on their medical charts by the hospital.

Analysis

We will assess the amount of narcotic analgesics used among both the control and treatment group by their medical charts. This will let us see how much the baroque musical treatment compensates for narcotic intake in the two hours post-surgery.

Ethics

Prior to beginning the study, IRB approval from UC San Francisco and San Francisco General Hospital- oral surgery clinic will be obtained. All subjects will sign an informed consent form that includes permission to read the subjects' medical charts. This consent will be done before the study, and I will be the only individual having access to the medical charts to maintain the HIPAA Privacy Rule. In addition, to ensure that personal and medical information collected from the subjects is going to be protected,

we will assign each of the 60 subjects to a number between 1 and 60. That list of information regarding the patients will be on a laptop that will be stored at UCSF for the duration of the 5 day study. For drawing blood thrice in the experiment, $20 cash will be given to subjects as a thank you for participating in the study.

Data Management

The data we will collect in this study will be statistical data in the form of graphs and numerical values. After the data is verified, the left over blood samples will be properly disposed in biohazard wastes (UCSF). Then, once data is produced, it will be saved and kept on several USB hard drives, as a reserve for an emergency (i.e., one USB hard drive becomes misplaced). Data from this research study will be accessible to other researchers, provided they cite the original creator of the data. Redistribution of raw data will be done so only by permission of the author. We will prepare to send out the data via conferences, peer-review and online (e.g., a website).

Project Timeline

Activity	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Recruit volunteers for study	X	X										
Obtain approval to conduct study at SFGH	X	X										
Conduct Experiment			X									
Radioimmunoassay samples from study				X	X							
Statistical Tests and Analysis of Data					X	X	X	X				
Preparation of work to share data via conferences, peer-review, and online.								X	X	X	X	X

Budget

The cost for this three month study will be $23,368.87. We will request approval to use the -80 °C refrigerator and radioimmunoassay equipment from the laboratories at UCSF. Extra equipment left over will be donated to SFGH and UCSF. We will compensate subjects by covering the remaining balance from the surgery that their health insurance does not cover. In addition, we will cover the cost transportation to SFGH for subjects by giving paying them money for gas expenses. If we do not use all of the money for compensating subjects, then the remaining balance will be sent back to NIH.

Category	Product Name	Amount	Price	Company
Equipment	Lavender Vacutainer tubes with EDTA (100 per box)	2	$144.00	Phoenix Pharmaceuticals, Burlingame, CA
Dry ice ($1 per pound)	10	$10.00	Continental Carbonic, Decatur, IL	
Endorphin, beta (Human) - RIA Kit	1	$565.00	Phoenix Pharmaceuticals, Burlingame, CA	
Centrifuge 5810	1	$0.00	Eppendorf (*Provided by UCSF)	
Systat Statistical Software	1	$799.00	SigmaPlot, San Jose, CA	
Exel Multi-Draw Needles; 22G x 1", 1000/Case	1	$128.99	EXEL, Los Angeles, CA	
Lavender Vacutainer tubes with aprotinin (100 per box)	2	$144.00	Phoenix Pharmaceuticals, Burlingame, CA	
-80 °C Refrigerator	1	$0.00	UCSF	
Apple Ipod Nano 6th generation	12	$960	Ebay, San Jose, CA	
	Sony MDR7502 Supra-aural Professional Headphones-Closed	12	$599.88	Sweetwater Sound Inc., Fort Wayne, IN
	RIA Equipment	1	$0.00	UCSF
Personnel	Registered Nurse Morphine SULF 100 MG/5 ML SOLN (Quantity: 30)	2	$33.23 hourly wage (8hr/day for 5 days) = 2,658.00	San Francisco General Hospital
	Phlebotomist	2	$14.50 hourly wage (8hr/day for 5 days)=$1,160.00	San Francisco General Hospital
Miscellaneous	$20 cash incentive for participating in study.	60	$1200	
	Compensation for subjects: covering procedure that insurance doesn't cover and transportation SFGH.	1	$15,000	

Public Health Impact Statement

Millions of individuals face post-operative pain from surgery in the United States and around the world. Music therapy is proven to relieve post-operative pain; how-

ever, there is no quantitative data for it. Therefore, this study will provide quantitative data of musical therapy's effects on post-operative pain by measuring plasma β-endorphin levels. Providing these measurements will hopefully lead to more implementation of musical therapy to reduce post-operative pain, and reduction of side effects, addiction, and costs associated with narcotics.

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Cameron Carlisle

Cameron Carlisle and is a second year Molecular and Cell Biology Major at the University of California, Merced, planning to graduate in the Spring of 2016. He has always had a great interest in the Sciences, such as Biology and Chemistry, since Elementary School. Once in High School, he gained a motivation for attending Medical School, to ultimately become a physician. His plans have changed after being at UC Merced for two years. After joining and working in a faculty research lab, Cameron has found great enjoyment: research and working in a lab to help aid in the pursuit of scientific inquiries. He now plans to attend MD/PhD school following graduation. Outside of the academic arena, Cameron loves to run, play basketball, read, and spend time with friends and family.