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Journal
World Journal of Otorhinolaryngology - Head and Neck Surgery, 6(4)

ISSN
2095-8811

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Publication Date
2020-12-01

DOI
10.1016/j.wjorl.2020.07.005

World Journal of Otorhinolaryngology-Head and Neck Surgery (2020) 6, 235–240

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.keaipublishing.com/WJOHNS; www.wjent.org

Review Article

Appropriate extent of surgery for aspirin-exacerbated respiratory disease

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Received 23 May 2020; received in revised form 19 July 2020; accepted 24 July 2020
Available online 8 September 2020

KEYWORDS
Endoscopic sinus surgery;
Draf III;
Aspirin exacerbated respiratory disease;
Chronic sinusitis;
Nasal polyps;
Extent of surgery

Abstract The current literature lacks strong guidelines regarding surgical management of patients with aspirin-exacerbated respiratory disease (AERD), who present with the clinical triad of chronic rhinosinusitis with nasal polyposis (CRSwNP), bronchial asthma, and aspirin/nonsteroidal anti-inflammatory drug intolerance. To further define the effectiveness of sinus surgery in treating AERD patients, this review article discusses current evidence regarding outcomes associated with more extensive surgery, the benefits of frontal sinus surgery on polyposis, and the role of Draf III intervention. Numerous studies suggest that Draf III frontal sinusotomy may be an efficacious early intervention due to increased neo-ostial patency and subsequent distribution of topical therapies. Future studies that further investigate the efficacy and safety of extensive surgery in AERD patients are warranted.

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.wjorl.2020.07.005

Introduction

CRSwNP, bronchial asthma, and nonsteroidal anti-inflammatory drug (NSAID)/Aspirin (ASA) intolerance comprise the clinical syndrome known as aspirin-exacerbated respiratory disease (AERD), formerly known as Samter's triad.[1] Prevalence of AERD is estimated at 7% among patients with asthma, 14% among patients with severe asthma, 10% among patients with nasal polyposis, 9% in patients with chronic rhinosinusitis, and 0.6%—2.5% of the general population.[2–4] While the definitive mechanisms underlying this disease continue to be elucidated, it is currently thought that a central dysfunction in AERD relates to arachidonic acid metabolism such that inflammatory cysteinyl leukotrienes are over-produced, and their receptors are over-expressed.[5] This imbalance is exacerbated by the use of cyclooxygenase-1 (COX-1) inhibiting drugs (such as aspirin), which block the production of prostaglandin E2, thus disinhibiting 5-lipoxygenase-mediated leukotriene synthesis.[6] The current literature lacks definite guidelines for surgical management of AERD. As such, this manuscript reviews the existing literature to evaluate the appropriate extent of surgery for treating these patients.

Extent of sinus surgery in AERD

Early studies evaluating endoscopic sinus surgery (ESS) found that aspirin-sensitive patients experienced no statistical improvement in sinus symptoms after surgery relative to aspirin tolerant patients, and in fact required more repeat sinus procedures.[7,8] However, a more recent systematic review of 18 studies evaluating adult patients 18 years and older found that ESS contributes to improvement in sinonasal and asthma symptom severity and frequency, radiographic and endoscopy scores, and quality of life after surgery.[1] These studiesalong with their levels of evidence are summarized in Table 1.[6–22] While encouraging, these data were unable to undergo meta-analysis, and did not control for concomitant medical therapies.[23] All but one of these 18 studies were assessed to be grade C or D evidence, with subsequent commentary emphasizing that additional high-quality literature is needed to further define the role and long-term outcomes of ESS in this population.[23,24] To this end, we elected to specifically investigate how the extent of ESS affects clinical outcomes in the AERD population.

In recent years, data has emerged showing that patients with AERD undergoing "complete" sinus surgery bilateral maxillary antrostomies, bilateral total ethmoidectomies, bilateral sphenoidotomies, and bilateral frontal sinusotomies (i.e., Draf IIa, IIb, or III) experience greater quality of life improvements relative to more conservative surgery, and that these quality of life gains are durable with post-surgical aspirin desensitization plus long-term aspirin maintenance.[25,26] This finding is consistent with early studies advocating for more extensive surgery relative to aspirin tolerant patients.[6,27] Although there still exists relatively less data regarding outcomes for revisions ESS, full-house FESS (maxillary antrostomy, total ethmoidectomy, wide sphenoidotomy, and Draf IIa frontal sinusotomy) is generally the minimum extent of surgery. In a study by

Table 1 Studies evaluated by Adelman et al.'s 2016 systematic review on AERD, reporting improvement in sinonasal and asthma symptom severity and frequency, radiographic and endoscopy scores, and quality of life attributed to ESS.

Author, Year	Study Title	Level of Evidence
Amar, 2000	Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad	III
Awad, 2008	Sinonasal outcomes after endoscopic sinus surgery in asthmatic patients with nasal polyps: a difference between aspirin-tolerant and aspirin-induced asthma?	IV
Batra, 2003	Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma	IV
Benninger, 2014	The impact of endoscopic sinus surgery on health care use in patients with respiratory comorbidities	N/A
Cho, 2014	Long-term sinonasal outcomes of aspirin desensitization in aspirin exacerbated respiratory disease	IV
Havel, 2013	Sinonasal outcome under aspirin desensitization following functional endoscopic sinus surgery in patients with aspirin triad	III
Jang, 2014	Aspirin sensitivity does not compromise quality-of-life outcomes in patients with Samter's triad	III
Loehrl, 2006	Long-term asthma outcomes after endoscopic sinus surgery in aspirin triad patients	II
McFadden, 1990	Surgery for sinusitis and aspirin triad. The Laryngoscope	IV
McMains, 2006	Medical and surgical considerations in patients with Samter's triad. American journal of rhinology	IV
Mendelsohn, 2011	Revision rates after endoscopic sinus surgery: a recurrence analysis	III
Nakamura, 1999	Effects of sinus surgery on asthma in aspirin triad patients. Acta oto-laryngologica	IV
Robinson, 2007	Impact of aspirin intolerance on outcomes of sinus surgery	II
Rotenberg, 2011	Postoperative care for Samter's triad patients undergoing endoscopic sinus surgery: a double-blinded, randomized controlled trial	I
Schaitkin, 1993	Endoscopic sinus surgery: 4-year follow-up on the first 100 patients	IV
Smith, 1996	The eicosanoids: cyclooxygenase, lipoxygenase, and epoxygenase pathways	IV

Table 1 (*continued*)

Author, Year	Study Title	Level of Evidence
Young, 2007	Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis	II

Shen et al.,[28] 21 patients with CRS and with at least one prior sinus surgery underwent full-house FESS with significantly improved sinonasal symptoms and endoscopic/radiographic findings 6—24 months postoperatively. It appears that antecedent ESS of total ethmoidectomy with maxillary antrostomy with or without frontal sinusotomy can also help increase tolerance of aspirin desensitization in patients who had previously failed desensitization, and the combination of ESS and desensitization has been noted to decrease overall topical and systemic steroid utilization.[29,30] While quantitative olfactory performance as assessed by Sniffin' Sticks improves in AERD patients following a complete functional ESS (FESS), these patients experience limited olfactory recovery over time relative to aspirin-tolerant patients, and are less likely to become normosmic.[31]

Frontal sinus surgery and polyposis

Following sinus surgery, there is an important need for intranasal corticosteroid administration as well as saline irrigation for inflammatory control and decreasing recurrence of polyposis.[1,32] Topical nasal irrigations which facilitate mucosal healing and clearance of crusts or thick mucus are inexpensive, safe, and effective treatments for improving surgical outcomes and sinonasal symptoms.[32—34] However, sinus obstruction or ostia stenosis can inhibit access to topical irrigations. Grobler et al.[35] have suggested a minimum required sinus ostial diameter of 3.95 mm for guaranteed topical sinus penetration. According to Singhal et al.,[36] a 4.7 mm diameter of ostium patency allows ideal penetration of maxillary and sphenoid sinuses. Another study by Thomas et al.[37] demonstrated that extent of surgery is an important factor in positively impacting topical distribution to the sinuses, and cadaver studies have suggested that without surgery many sinuses remain inaccessible to topical irrigations. Barham et al.[38] utilized cadaver specimens to quantify sinus penetration following Draf IIa versus Draf III surgery, and it was demonstrated that DrafIII was superior for facilitating irrigation, and that this benefit was synergistic with Vertex head positioning. By expanding the ostial pathways, decreasing overall inflammatory load and surface area, and "reshaping" the sinuses, sinus surgery can lead to a more effective delivery of saline, antibiotics, corticosteroids, or alternative agents to address polyposis in both AERD and general chronic rhinosinusitis (CRS) patients.[37]

Among surgical techniques that address polyposis, there is a relative void in literature comparing outcomes based on extent of frontal sinus surgery. Draf IIa and IIb can both improve frontal sinus outflow by widening the frontal sinus ostium from the lamina papyracea to the middle turbinate and nasal septum, respectively.[39] A key variable in deciding between approaches is whether the neo-ostium achieved is sufficiently wide to prevent post-operative stenosis.[40] Interestingly, one retrospective study of frontoethmoidal mucoceles by Dhepnorrarat et al.[41] reported a significantly higher rate of restenosis following Draf IIb (23%) compared to Draf IIa (4%) surgeries, despite the former being utilized more in later years when the authors presumably had more surgical experience and skill. This being said, Turner and colleagues point out that relative comparisons like this may suffer from selection bias, since patients with certain endoscopic anatomical findings may be independently predisposed to stenosis, leading to more aggressive surgery including Draf IIb.[40] For example, restenosis and revision surgery may be predicted by intraoperative frontal ostium size, as well as presence of eosinophilic inflammation.[42] In addition, pre-operated ostia with a diameter below 2 mm may suffer from a significantly increased rate of stenosis.[43,44] Patency outcomes have also been evaluated relative to Draf III(modified endoscopic Lothrop procedure) surgery, where a common frontal sinus cavity is created. In a study comparing Draf IIb to Draf III frontal sinusotomy, where close to 50% of each cohort had nasal polyps, Patel et al.[45] reported no significant difference between restenosis or overall complication rates. Of note, while frontal sinus irrigation is improved by frontal sinusotomy, Draf III-surgery has been suggested to result in less maxillary and ethmoid sinus penetration in some computational fluid dynamic simulations.[46]

The role of Draf III

Draf III can be indicated in patients who are refractory to previous sinus operation(s), or as a primary procedure in those with severe polyposis and other sinonasal comorbidities such as AERD, asthma, Kartagener's or ciliary dyskinesia.[39,47,48] When utilized, Draf III has demonstrated a significant improvement in lowering polyposis recurrence rates; indeed, one retrospective study of 338 patients demonstrated polyp recurrence of 36% after 12 months following Draf III, versus 49% in less invasive frontal sinus surgery.[49]

In general, long-term outcomes of Draf IIIhave been well-studied, including in polypoid disease. One case series of 204 Draf III patients with a long-term follow-up period of 10.2 years reported a 30% rate for re-obstruction requiring revision surgery, the majority of which occurred within 2 years of the initial operation.[50] In contrast, Naidoo et al.[47] retrospectively found 95% of their 229 DrafIII patients avoided revision surgery after 45 months, though allergic fungal sinusitis and recurrent bacterial infections were potential predictors of failure. Another retrospective study of 77 patients undergoing Draf III procedure reported only 12% ultimately required revision.[42]

Despite its benefits, DrafIII can be associated with various morbidities. A recent retrospective study by Patel et al.[45] reported a 12% minor complication rate (e.g., hyposmia, prolonged crusting and adhesion, epistaxis, nasal bone dehiscence) and 12% revision rate. Naidoo et al.'s[47] previously mentioned Draf IIIcohort had a 5% failure rate

requiring revisions, though their cohort had undergone an average of 3 procedures prior to evaluation. This was starkly different than Ting et al.'s[50] aforementioned report of 30% revision within 2 years, which suggests additional studies are needed to further define clinical outcomes on a patient population-specific basis. Furthermore, in some patient populations, Draf II surgery may be adequate for inflammatory control while avoiding morbidity as compared to Draf III. For instance, Jafari et al.[51] have reported higher duration of antibiotics treatment, more clinic visits, increased debridements, and lower rates of improvement in facial/otologic symptoms in patients undergoing Draf III procedures. Despite this, for nasal polyposis Draf III carries high overall efficacy and low morbidity.[47]

The role of Draf III in AERD

The AERD population, representing the most severe inflammation, appears to specifically benefit from more extensive frontal sinus surgery.[48] Early work to this effect was investigated by Bassiouni et al.[49] who performed a retrospective case series of 338 consecutive operations for nasal polyposis in their AERD population and found that Draf III with frontal trephine yielded an 11% recurrence rate of persistent polyps (>3 mos), relative to 55% in patients receiving Draf IIa. For their population overall, the persistent polyposis rates following Draf IIIversus DrafIIa were 16% versus 26%.[49] Subsequent work by Morrissey et al.[52] evaluating all of their Draf III procedures performed from 2001 through 2013 in a sample of 31 AERD patients who had failed more conservative surgery (complete sphenoethmoidectomy, maxillary antrostomies, Draf IIa frontal sinusotomy) showed that DrafIII resulted in 58% polyp recurrence with revision surgery rate of 22.5% overall. By comparison, work by Mendelsohn et al.[16] reported a 90% polyp recurrence rate at 5 years, along with an 89% 10-year surgical revision rate after primary ESS (polypectomy, maxillary antrostomy, ethmoidectomy, sphenoidotomy, or frontal sinusotomy) in their AERD cohort. As such, it appears that more extensive frontal sinus surgery can reduce both the recurrence of polyposis and the need for revision surgery in AERD patients, likely due to increased topical access.

Interestingly, one case series found that the presence of an AERD diagnosis did not contribute to decreased patency of Draf IIIover 35 month follow up, though only 7 of the 72 patients reviewed had AERD.[53] In this study, partial or complete stenosis of the neo-ostium was ultimately seen in 11% of patients overall.[53] One variation in surgical technique is the "outside-in" approach to the Draf III, where dissection of the frontal recess is deferred until the frontal sinus floor is removed.[54] Utilizing this technique, Wong et al.[55] published a case series including 104 patients with inflammatory CRS, and found that while their patients as a whole experienced subjective improvements in olfaction and decreased SNOT 22 scores, the 13 patients with AERD were noted to experience poorer clinical outcome scores on univariate analysis.

With improved powered instrumentation and newer techniques facilitating rapid and safe performance of the procedure, DrafIII may now be considered early in the treatment algorithm for AERD patients. Early unpublished data from a large cohort of AERD patients who underwent Draf III and aspirin desensitization following prior sinus surgery suggests that SNOT-22 scores uniformly improved and were sustained at greater than 3 months of follow up, with overall revision rates under 5%. These results are rather encouraging and suggest that maximal long-term inflammatory control using a multidisciplinary approach of surgery, topical steroid irrigations, and aspirin desensitization appears to provide the best possible outcomes for this recalcitrant disease.

Other procedures for refractory CRS in AERD

Aside from full-house FESS, refractory CRS in AERD may also be amenable to more advanced ESS procedures such as nasalization and the "reboot" procedure. Diffuse and severe nasal polyposis can also be addressed with nasalization, which includes radical ethmoidectomy along with large maxillary antrostomy, sphenoidotomy, frontal sinusotomy, and middle turbinectomy.[56] A study by Jankowski et al. comparing nasalization with ethmoidectomy in the setting of significant polyposis reported that the former had better functional results with decreased asthma symptoms and decreased need for systemic steroids.[27] As such, the authors concluded that nasalization was not more hazardous than ethmoidectomy, and specifically recommended employing more radical surgery when treating challenging polyposis.[27] Lastly, the "reboot" procedure is a novel surgical technique where diseased mucosa is removed from some (partial reboot) or all sinuses including a Draf III (complete reboot), with the aim of allowing healthy re-epithelialization from regions of preserved healthy mucosa on the inferior and middle turbinates.[57] This approach was utilized by Alsharif et al. in a cohort of 84 patients with CRSwNP, and found to significantly reduce recurrence of nasal polyps at 20 months postoperatively relative to mucosal-sparing surgery.[57]

Conclusion

AERD is a challenging clinical entity that can undergo symptomatic improvements following surgical intervention. While more high-quality literature is needed, numerous studies suggest that Draf III frontal sinusotomy may be an efficacious early treatment option for these patients. This benefit can be attributed to the increased efficacy of frontal sinus irrigation following these procedures, which is reflected in more durable neo-ostial patency. The polyposis of AERD patients is also better addressed in the same mechanism following frontal sinus surgery. Patient selection should be made judiciously, as Draf IIIcarries greater comorbidities than less invasive frontal sinusotomy techniques and may decrease efficacy of irrigation throughout the ethmoid and maxillary sinuses. Effective treatment of AERD necessitates a multimodal, interdisciplinary approach to care.

Level of evidence

NA.

Financial disclosure

None.

Declaration of Competing Interest

Edward C. Kuan is a consultant for Stryker. Kalamazoo, MI.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wjorl.2020.07.005.

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Edited by Yu-Xin Fang