

Systematic Review of Topical Vasoconstrictors in Endoscopic Sinus Surgery

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Objective: The objective of this study is to systematically review the literature and examine the safety for the use of topical vasoconstrictors in endoscopic sinus surgery.

Study Design: Systematic review clinical trials.

Method: A systematic literature search was performed in MEDLINE, EMBASE, The Cochrane Library, and National Guideline Clearinghouse, and references in the selected articles.

Results: The search criteria captured 42 manuscripts with relevant titles. A systematic review on the topical use of phenylephrine was found; however, no other systematic review, meta-analyses, or clinical guidelines were identified. Six randomized clinical trials or comparative studies, as well as multiple case reports and review articles were also identified. The literature supports the safety of oxymetazoline and epinephrine when used judiciously in carefully selected patients undergoing endoscopic sinonasal surgery; however, topical phenylephrine is not recommended because of its risk profile.

Conclusion: In sinus or nasal surgery, topical vasoconstrictors should be used in a manner that minimizes the risk of cardiovascular morbidity.

Key Words: Complication, sinus, vasoconstrictor, oxymetazoline, phenylephrine, endoscopic surgery, topical, nasal, epinephrine/adrenaline, xylometazoline, cocaine, phenylephrine.

Level of Evidence: Level 1

Laryngoscope, 000:000-000, 2011

INTRODUCTION

Topical vasoconstrictors are important hemostatic agents for maximizing visualization and minimizing bleeding during endoscopic sinus surgery. However, these topical agents have the potential to have systemic cardiopulmonary effects, and currently there are no guidelines or established protocol that is available to aid the endoscopic surgeon in choosing the appropriate topical vasoconstrictor agent, concentration of topical vasoconstrictors, and contraindications to using these helpful and essential medications during the procedure. Therefore, the objective of this study was to systematically review the literature for safety of topical vasoconstrictor and provide a protocol for the use of topical vasoconstrictors when performing endoscopic procedure in nose and sinuses.

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Editor's Note: This Manuscript was accepted for publication June 22, 2010.

The authors have no financial disclosures for this article.

The authors have no conflicts of interest to disclose.

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DOI: 10.1002/lary.21286

METHODS

Search Strategy

We conducted a systematic literature search of MEDLINE (1966 to July 2008), EMBASE (1980 to July 2008), Cochrane Central Register of Clinical Trials (CENTRAL), Cochrane Database of Systematic Reviews, clinicaltrials.gov, and The National Guideline Clearinghouse databases without language restriction for studies including combined key terms and exploded Medical Subject Headings (MeSH) of the terms *topical*, *vasoconstrictor*, *sinus**, *nasal*, *epinephrine/adrenaline*, *oxymetazoline*, *xylometazoline*, *cocaine*, *phenylephrine*, and *adenoid**. We also scanned the references in the retrieved articles, reviewed abstracts of selected scientific meetings (within the specialties of otolaryngology—head and neck surgery, rhinology, skull base surgery, and anesthesiology), and contacted experts in the field to identify all relevant articles.

Selection Criteria

Two authors (T.H., J.H.) independently screened the titles and abstracts of the search results and identified articles eligible for further review. Inclusion criteria for obtaining the full-text article included original studies, case reports, case series, animal studies, systematic reviews, meta-analyses, or guidelines reporting on intranasal topical vasoconstrictor use. Exclusion criteria included reviews and articles focused on diagnostic nasal endoscopy, transnasal intubation, management of nasal symptomatology, intravenous infiltration, and procedures not involving the sinonasal passages. We resolved any disagreement by consensus. Figure 1 shows the flow chart of article inclusion and exclusion.

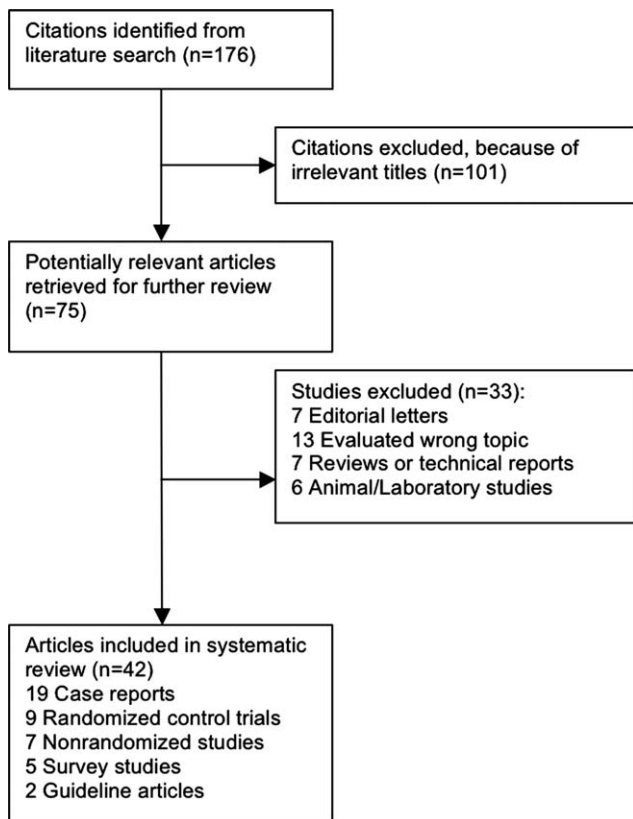


Fig. 1. Flowchart of article retrieval.

Data Extraction

Authors critically appraised the full-text articles using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standards for observational studies, the EQUATOR Network (www.equator-network.org) recommended article for questionnaire studies, and the CONSORT checklist for clinical trials.

RESULTS

Search Results

Figure 1 shows the flow chart of article inclusion and exclusion. The search strategy identified 172 citations and four articles were identified through hand searching the references of retrieved articles. Seventy-five of these citations underwent full-text review. We excluded 33 of these articles for reasons listed in Figure 1. A final number of 42 included articles were used in the systematic review (Tables I–III). The final list of articles included 19 case reports or series, 9 randomized clinical trials, 7 nonrandomized studies, 5 survey studies, and 2 guideline articles.

CASE REPORTS

The search strategy identified 19 case reports (Table I) of morbidity after topical vasoconstrictors use in sinonasal surgery. Table I summarizes the findings from these case reports. Morbidity from topical phenylephrine was reported as myocardial infarction ($n = 1$), hypertensive crisis ($n = 2$), and tachyarrhythmias ($n = 1$).

Topical cocaine was attributed to perioperative myocardial infarction ($n = 6$), tachyarrhythmias ($n = 2$), and acute angle glaucoma ($n = 2$). Topical epinephrine was attributed to one case of cardiogenic shock during septoplasty and one case of postoperative myocardial infarction. The combination of both topical cocaine and epinephrine was attributed to perioperative myocardial infarction ($n = 2$) and tachyarrhythmias ($n = 5$). The combination of topical cocaine and phenylephrine was attributed to hypertensive crisis ($n = 1$) and myocardial infarction ($n = 1$). No case reports reported morbidity from use of topical oxymetazoline.

Clinical Guideline

A clinical advisory report was found from New York State that recommended restricted use of topical intranasal phenylephrine. This report was initiated from a case of a 4-year-old child in New York who died following use of an unknown amount of topical phenylephrine during a routine adenoidectomy. This situation generated a review of the state's records into cases of morbidity with intranasal use of topical phenylephrine. The review identified four pediatric and five adult patients who had hypertensive crisis or pulmonary edema. Two of the pediatric cases and one of the adult cases died after going into cardiac arrest.^{1,2}

Case Series and Nonrandomized Comparative Studies

The case series and nonrandomized studies identified are summarized in Tables I and II, respectively.

Randomized Clinical Trials

The randomized clinical trials identified are summarized in Table III.

Surveys Studies

Five articles^{3–7} were self-completion mail-in survey studies of sinonasal surgeons and their use of topical cocaine. Feehan et al. (1976)³ performed an anonymous survey study of 741 (49% response rate) members of the American Society of Plastic and Reconstructive Surgeons who had reportedly performed 93,004 rhinoplasties using topical cocaine. Eighty percent of respondents reported actively using topical cocaine and reported 225—or 0.24%—mild reactions (no resuscitation required), 14—or 0.015%—severe reactions (resuscitation required), and no mortalities. However, the 7.4% of respondents who had discontinued cocaine use reported twice as many mild reactions (0.4%), 10 times as many severe reactions (0.1%), and 5 fatalities (0.03%). Of these respondents, 48% discontinued topical cocaine because of reports in the literature; 33% reported that the choice for its discontinuation was not based on its risk profile. Seventy percent reportedly used topical adrenaline in place of the discontinued cocaine.

Johns and Henderson (1977)⁴ published a survey study in 1977 of 2,434 questionnaires (with a 58%

TABLE I.
Case Reports.

Author (year)	Age/Gender	Topical Vasoconstrictor(s) (Local injection)	Anesthesia	Procedure	Morbidity	Comments
Topical Cocaine						
Meyers (1980)	32 yo M	Cocaine spray, 10%, 500 mg (Mepivacaine, 80 mg and bupivacaine, 30 mg)	Droperidol Fentanyl	DCR	Tachyarrhythmia	Occurred "following" cocaine spray. Relieved with propranolol. Tachyarrhythmia occurred after cocaine spray. Hypertension occurred after surgeon switched to using topical phenylephrine. Treated with propranolol, chlorpromazine, neostigmine, and atropine.
Chiu (1986)	8 yo F (28 kg)	Cocaine spray, 10%, unknown amount Phenylephrine pack, 2.5%, 125 mg (None specified)	Droperidol Halothane Nitrous oxide Atropine Diazepam	DCR	Tachyarrhythmia Hypertension	
Littlewood (1987)	28 yo F	Cocaine spray, 2 mL and cocaine paste, 25% (1% lidocaine with epinephrine 1:100,000, 15 mL)	Demerol Fentanyl Robinal	Nasal fracture closed reduction Septoplasty	MI	Occurred "soon after" vasoconstrictor application. No comorbidities.
Palon (1989)	44 yo M	Cocaine packing, 1%, 5 mL Epinephrine packing, 1:1000, 2 mL (1% lidocaine with epinephrine 1:100,000, 8.5 mL)	Atropine Fentanyl	Septoplasty	MI	ST segment depression occurred while applying epinephrine packing. Cardiac catheterization revealed coronary artery disease.
Lormans (1992)	64 yo M	Cocaine packing, 160 mg (1% lidocaine with epinephrine 1:200,000, 10 mL)	Midazolam Thiopental Alfentanil Isolurane Vecuronium	Nasal polypectomy Septoplasty	Hypertension, sinus tachycardia V-fib	History of prior MI. Relieved with esmolol. Occurred immediately after topical cocaine and local infiltration, relieved with IV lidocaine. Postoperative workup showed no cardiovascular pathology.
Hari (1999)	17 yo	Cocaine, 4% (7 mL) (0.5% lidocaine with epinephrine 1:40,000, 4 mL)	Propofol Atracurium Isoflurane Not specified	Antral washout and inferior turbinate submucous diathermy DCR	Glaucoma	Occurred 24 hours following procedure.
Wilcsek (2002)	67 yo & 75 yo	Cocaine pack, 5%, Lignocaine with adrenaline 1:200,000	Not specified	Sphenoidotomy Septoplasty	MI Cardiogenic shock	Occurred "soon after" vasoconstrictor application. History of mitral valve prolapse.
Makayrus (2006)	58 yo F	Cocaine, 4% (None specified)	General anesthesia	Nasal surgery	MI	No cardiovascular risk factors. No cocaine abuse.
Torres (2007)	29 yo F	Cocaine				

(Continues)

TABLE I.
(Continued).

Author (year)	Age/Gender	Topical Vasoconstrictor(s) (Local injection)	Anesthesia	Procedure	Morbidity	Comments
Topical Cocaine and Epinephrine						
Young (1946)	20 yo M	Cocaine, 20% Epinephrine, not stated (Not stated)	Not specified	Inferior turbinate submucosal resection	CV arrest, death	
Nicholsin (1995)	9 yo F	Paste, 1 ml of Cocaine, 25% and epinephrine, 0.18% (Not stated)	Atropine Thiopentone Suxamethonium	Nasal surgery FESS	V-fib V-fib	Occurred after paste application and as instruments passed into nose. Occurred between paste application and instrumentation. Occurred after paste application and as instruments passed into nose. Rebound hypertension occurred with lignocaine and labetalol. Incidence: 2/250 (0.08%) nasal surgeries and 1/25 (4%) intranasal pituitary surgeries
Laffey (1999)	18 yo M	Cocaine packing, 3%, 140 mg Epinephrine packing 1:4000, 5 mL	Nitrous oxide Halothane Succinylcholine Nitrous oxide Sevoflurane Vecuronium	Transsphenoidal hypophysectomy Tonsillectomy Nasal polypectomy	Tachycardia, HTN MI	
Badia (2001)	52 yo M	Cocaine packing, 10%, 2 mL (preop) Epinephrine packing, 1:1000 (preop and intraop) (Not stated)	Not specified	Nasal polypectomy	Mydriasis	Noted at end of procedure. Pupil returned to normal in 6 hours.
Topical Cocaine and Phenylephrine						
Ashchi (1995)	23 yo F	Cocaine, 4%, before surgery Phenylephrine, 0.25%, at end of surgery (Not stated)	Not specified	Septoplasty	MI, V-fib	Occurred 15 minutes postoperatively. Initial treatment details not described.
MacMillan (2007)	30 yo M	Cocaine packing, 5%, 2 mL and Phenylephrine packing, 10%, 3 mL (1% lidocaine with epinephrine 1:80,000)	Fentanyl Glycopyrrolate Isoflurane	Lacrimal duct surgery	Severe hyperten- sion, bradycardia	Occurred while packed. Given labetalol, initial improvement but rebound hypertension. Relieved with deeper anesthesia.

(Continues)

TABLE I.
(Continued).

Author (year)	Age/Gender	Topical Vasoconstrictor(s) (Local injection)	Anesthesia	Procedure	Morbidity	Comments
Topical Epinephrine						
Chelliah (2002)	79 yo F	Epinephrine packing 1:1000 (1% lidocaine with epinephrine 1:100,000, 1.5 mL)	Propofol Lidocaine Lidocaine Nitrous oxide Desflurane Propofol	Pituitary surgery for pituitary apoplexy	Severe hypertension	Hypertensive crisis during injection after epinephrine prep. Resolved with esmolol & nitroglycerine.
Schwalm (2008)	29 yo M	Epinephrine packing 1:1000	Propofol	Septoplasty	Cardiogenic shock	Developed hypertensive crisis and wide-complex tachycardia 30 min postoperatively. Given metoprolol with initial improvement but eventual PEA, EF <20%, and need for cardiopulmonary resuscitation.
Topical Phenylephrine						
Hecker (1997)	63 yo F	Phenylephrine, 0.25%, soaked in 4% lidocaine	Fentanyl Sevoflurane	FESS	Myocardial ische- mia, severe hypertension	Chest pain, hypertensive crisis 4 minutes after pledgets placed. Relieved with nitroglycerine.
Nikandish (2007)	18 yo	(1% lidocaine with epinephrine 1:100,000, 8.5 mL) Phenylephrine, 0.25% (Lignocaine with adrenaline 1:200,000, 1.5 mL)	Midazolam Thiopental Halothane	Septoplasty	Mydriasis Hypertensive crisis	Relieved by IV diazoxide and nitroglycerine

References⁴⁻²².

M = male; F = female; yo = years old; DCR = dacryocystorhinostomy; mg = milligrams; mL = milliliters; MI = myocardial infarction; V-fib = ventricular fibrillation; IV = intravenous; min = minutes; PEA = pulseless electrical activity; EF = ejection fraction; FESS = functional endoscopic sinus surgery.

TABLE II.
Summary of Articles: Clinical Guidelines and Nonrandomized Comparative Trials.

Author (year)	Topical Vasoconstrictor(s)	Local injection	Anesthesia	Procedure	Article Characteristics	Comments
<i>Clinical Guideline</i> Groudine (2000) and Jones (1998)	Phenylephrine	N/A	Not specified	Adenoidectomy Septoplasty FESS	Case series and Guideline 4 children (3-9 yo) 5 adults (23-47 yo)	NY State guideline written after the death of a 4-yr-old during adenoidectomy following use of topical phenylephrine and administration of labetalol. 9 cases reported of significant morbidity (hypertensive crisis/ pulmonary edema) or death with topical phenylephrine - 4 children (2 deaths following cardiac arrest) - 5 adults (1 death following cardiac arrest) - 3/3 deaths received labetalol Recommendations of use of phenylephrine in the OR: - Restricted but not banned use of phenylephrine. - Do not use more than 0.5 mg (4 drops of 0.25% solution). - Avoid concurrent beta-blockers or calcium channel blockers. - If beta-blockers are used in error, consider treating with glucagon.
<i>Nonrandomized Comparative Studies</i> Anderhuber (1999)	Epinephrine (1:1000, 1ml)	1% lidocaine with epinephrine 1:100,000, 4 ml (Exp only)	Propofol Fentanyl	FESS Control: Tonsillectomy	Nonrandomized comparative trial Exp: 51 Controls: 12 34 yo (mean)	Results Plasma venous adrenaline levels in experimental group - Before anesthesia: None detectable - After intubation: None detectable - After topical & infiltration of epinephrine: 0.86 nmol/L (95% CI: 0.67 to 1.05) - End of surgery (mean 39 minutes): 0.73 nmol/L (95% CI: 0.53 to 0.94) HR unchanged and similar between groups. BP (systolic and diastolic) decreased in epinephrine group compared to controls ($P < .001$) - Explanation was that the local anesthetic (lidocaine) causes vasodilatation on vessel smooth muscle at clinical levels No adverse reactions occurred, even with known/suspected cardiac/vascular disease. Recommendations - Avoid halogenated hydrocarbon anesthetic (i.e. halothane). - Limit local anesthetic infiltration; increase in venous epinephrine was due to injection. - May use local and topical epinephrine with known/suspected cardiac/vascular disease. - For children <10 yo, adapt epinephrine dosing by weight of child. - For children ≥10 yo, may use normal epinephrine concentration dosing.

(Continues)

TABLE II.
(Continued).

Author (year)	Topical Vasoconstrictor(s)	Local injection	Anesthesia	Procedure	Article Characteristics	Comments
Greinwald (1996)	Cocaine, 4%, 4 ml	Unknown	Not specified	Nasal Surgery	Case Series N = 12 30.4 yo (mean)	Results: - Less than 37% of topical cocaine is absorbed. - Serum cocaine levels were detectable in 2/11.
Kara (2001)	Cocaine, 4%, 5 ml	2% lidocaine with epinephrine 1:100,000, 10 ml	Local	Septoplasty	Case Series N = 60 34.2 yo (mean)	Patients with cardiovascular risk factors excluded. Results: - No change in HR, BP, or ECG characteristics.
Kalyanaraman (1997)	Phenylephrine	Variable	Isoflurane Nitrous oxide	Variable	Case Series N = 6 Ages (yo): 10, 9, 24, 31, 13, 14	Cases of cardiopulmonary compromise with local alpha-agonists written to the AAOHNS. Topical phenylephrine given in 6/12. Other cases mention no topical vasoconstrictors. Results: - Local injection (4/6), hypertension (5/6), pulmonary edema (5/6), cardiac arrest (1/6). - Received beta-blocker (4/6), esmolol (2/6), labetalol (2/6), procardiol (1/6).
Kubo (1995)	Cocaine, 200 mg and Epinephrine, 1 mg	Unknown	Atropine	FESS	Nonrandomized Comparative N = 178 Unknown	Results: - Tachycardia was only complication (26/178). All cases occurred with use of atropine. - No difference in total bleeding with cocaine/epinephrine versus epinephrine alone. - More "minimum bleeding cases" in cocaine/epinephrine group. - Shorter operative duration in cocaine/epinephrine group.
Liao (1999)	Cocaine packing Group I: 160 mg for 10 min Group II: 160 mg for 20 min Group III: 400 mg for 20 min	1% lidocaine with 1:100,000 epinephrine	Not specified	Septoplasty or Septorhinoplasty	Nonrandomized Comparative N = 12 (4 each group) Unknown	Results: - Cocaine absorbed (17% at 5 min, 25% at 10 min, 32% at 15 min, 35% at 20 min). - 2/12 intraoperative hypertension (160/85, 193/128), 1/12 transient ventricular tachycardia (122) in Group III.
Meyer (2000)	Groups: 1: Oxy/lido, 0.05/4% 2: Cocaine, 4%	None	Not specified	DCR (open and endoscopic)	Nonrandomized Comparative Oxy/lido: 27 Cocaine: 28 Unknown	Results: - No difference in mean blood loss (Oxy/lido 6.3 mL vs. cocaine 7.3 mL).

References 23-24, 34-40.

M = male; F = female; yo = years old; DCR = dacryocystorhinostomy; mg = milligrams; mL = milliliters; MI = myocardial infarction; V-fib = ventricular fibrillation; IV = intravenous; min = minutes; PEA = pulseless electrical activity; EF = ejection fraction; FESS = functional endoscopic sinus surgery.

TABLE III.
Summary of Articles: Randomized Controlled Trials.

Author (year)	Topical Vasoconstrictor(s)	Local injection	Anesthesia	Procedure	Article Characteristics	Comments
<i>Randomized Clinical Trials</i>						
Lee (1972)	Epinephrine (1:1000, 1.9 mL) Saline controls	None	Halothane	T&A	RCT Exp: 50 Controls: 50 2-15 yo	Cases - 2/50 had ventricular arrhythmias (1 during emergence from anesthesia 10 minutes following epinephrine use, 1 trigeminy prior to topical epinephrine use) Controls: - 2/50 had ventricular arrhythmias (bigeminy) Surgeon blinded to group allocation. Results: - Significantly higher mean blood loss in group 1 (80 mL vs 36-41 mL). - No difference in vasoconstriction based on mucosal color. - Significantly higher mean SBP and pulse rates in groups 1 and 4.
Delilkan (1978)	Groups: 1: Epinephrine, 1:1000 2: Cocaine, 5% 3: Cocaine, 10% 4: Cocaine/Epi, 5%/1:000	None	Promethazine Petitidine Thiopentone Atropine Suxamethonium Alcuronium	IT surgery	RCT N = 100 (25 in each group) 28 (19-55) yo	Results: - Significantly decreased blood loss in group 2. - Significantly higher cocaine blood levels in groups 2 and 3 (cocaine and epinephrine). - No difference in HR or BP. - No CV toxicity observed.
Lips (1987)	Groups: 1: Cocaine, 25% paste 2: Cocaine, 25% paste + epinephrine, 0.1% paste 3: Cocaine, 25% paste + epinephrine, 0.05% 4: Cocaine, 4% aqueous		Papaveretum Hyoscine Thiopentone Alcuronium	Nasal septum SMR	RCT N = 20 (5 in each group)	Results: - Significantly reduced cocaine absorption in group 2. - No difference in CV toxicity. - Better operative field in group 2.
Pfeiderer (1988)	Groups: 1: Cocaine 2: Cocaine + epinephrine		Not specified	Nasal surgery	RCT N = 30 (15 in each group)	Results: - Significantly reduced cocaine absorption in group 2. - No difference in CV toxicity. - Better operative field in group 2.
Wight (1990)	Cocaine, 10%, 0.1 mL Xylometazoline, 0.1%, 0.1 mL	None	None	Health volunteers, self-controls	RCT Cocaine: 12 Xylo: 12	Results: - No difference in change in blood flow using laser Doppler flowmetry on IT. - Significantly higher nasal airflow with xylometazoline using rhinomanometry
Campbell (1992)	Cocaine, 6%, 2 mg/kg Xylometazoline, 0.1% / Lidocaine, 4% Saline	None	None	Health volunteers, self-controls	RCT Cocaine: 20 Xylo: 20 Saline: 20 18 = 32 yo	Results: - No difference in decongestion among groups, measured as cross-sectional area. - No difference in pulse or SBP among groups. - Significant, but moderate, increase in DBP in cocaine group (+3.25).
Riegle (1992)	Oxymetazoline, 0.05% (O) Phenylephrine, 0.25% (P) Cocaine, 4% (C)	1% lidocaine with epinephrine	Induction: Halothane Thiopental Vecuronium Maintenance: Isoflurane	FESS	RCT O: 19 P: 20 C: 18 6.2 yo (± 4.1)	Results: After 10 minutes: - HR decreased in all subjects. - BP mildly increased (+7.0%) in P subjects. BP stable in other subjects (P = .10). Bleeding subjectively less in O subjects than P or C (P < .02). No arrhythmia in any patients.

(Continues)

TABLE III.
(Continued).

Author (year)	Topical Vasoconstrictor(s)	Local injection	Anesthesia	Procedure	Article Characteristics	Comments
Tarver (1993)	Cocaine Lidocaine/ oxymetazoline (Lido/oxy)	None	None	None	RCT Cocaine: 22 Lido/Oxy: 22	<p>Recommendations: Authors preferred oxymetazoline 0.05% for pediatric FESS. Relative anesthetic contraindications with concurrent use of topical cocaine include: - Halogenated hydrocarbons (i.e. halothane) sensitizes heart to catecholamines - Pancuronium and atropine: induce tachycardia</p> <p>Results: - Significantly less blood flow with Lido/Oxy as measured with laser Doppler placed on the septum Refs: Wight (1990) and Campbell (1992)</p> <p>Results - Higher frequency of "significantly" improved intraoperative hemostasis by surgeons' subjective estimate (67% in epinephrine group vs. 21% in saline group, $P < .001$). - Fewer subsequent packs after study pack to stop bleeding (0.6 vs. 1.2, $P < .001$). - Less frequency of need for electrocautery for hemostasis (22% vs. 45%, $P = .015$). - Shorter procedure time (13 minutes vs. 18 minutes, $P = .043$) - Higher frequency of a slight transient HR rise (41% vs. 21%, $P = .043$) - No "cardiovascular complication demanding intervention during anesthesia." Conclusions Topical racemic epinephrine is safe in pediatric adenoidectomy and helps control intraoperative bleeding, reduces use of electrocautery, and shortens procedural duration.</p>
Teppo (2006)	Racemic epinephrine (1:500) Saline controls	None	Metazolam Alfentanil Lidocaine Propofol Sevoflurane	Adenoidectomy (cold-steel)	RCT Exp: 51 Controls: 42 3 yo (1-6 yo)	

References 25-33.

NY = New York; yo = years old; RCT = randomized controlled trial; Exp = experimental group; mL = milliliter; HR = heart rate; BP = blood pressure; O = oxymetazoline; P = phenylephrine; C = cocaine; IV = intravenous.

response rate) completed by practicing otolaryngologists in the United States. Ninety-two percent of the respondents reported using topical cocaine with 35% using a combination of cocaine and epinephrine. Twenty percent reported observing a “cocaine reaction” (including hyperexcitability, diaphoresis, convulsions, or respiratory arrest). Fifteen deaths were reported, although only one case was documented as being applied nasally.

De et al. (2003)⁵ published a survey study in 2003 of 378 otolaryngologists (with a 65% response rate) in England. Of all the respondents, 77% used cocaine in surgery regularly, 48% used combined topical cocaine and epinephrine, and 43% used cocaine regularly in children. The reasons given for those not using cocaine included “consider it unsafe” (5%), “not available” (3%), and “anaesthetist refused” (1%). The respondents reported one mortality and a total of 39 cases of morbidity, which included CNS excitability, arrhythmias, blood pressure liability, and undefined “cocaine reactions.”

Long et al. (2004)⁶ surveyed 4,017 (54% response rate) active members of the American Academy of Otolaryngology—Head and Neck Surgery in a study published in 2004 and compared its findings to the 1977 Johns and Henderson study. Less respondents in the 2004 study reported using cocaine in surgery (50% vs. 92%, $P < .001$); however, more reported observing an adverse reaction to cocaine (26% vs. 20%, $P < .001$). The survey also found that surgeons in practice less than 10 years were less likely to use cocaine than those in practice for longer (78% vs. 93%, $P < .001$). Fourteen deaths were reported.

Shah et al. (2008)⁷ had an open survey for all Academy of Otolaryngology—Head and Neck Surgery members and only 126 members responded about their experience with topical epinephrine. Their findings were that 12.7% of respondents had experienced a problem, 16.4% had known of errors, 68.9% were concerned of potential errors with epinephrine administration. The survey did not specify the type of surgery in which epinephrine was used, and there is the possibility for selection bias given their marginal response rates—as 65% is the benchmark for acceptability in self-completion postal questionnaires.⁸ The 12.7% complication rate with the use of concentrated topical epinephrine may be high because there was another study that showed a complication rate of 0.1% with the use of topical epinephrine (1:1,000) in 1,998 sinus and nasal procedures.⁹

DISCUSSION

This systematic review provides an overview of the available literature of local vasoconstrictor used in the nose, nasopharynx, or sinuses. The search strategy identified a total of 32 cases of morbidity, including 5 cases of mortality associated with topical intranasal vasoconstrictors. No cases of morbidity were identified with topical oxymetazoline or xylometazoline.

Establishing causation requires rigorous investigation and currently there is no universally accepted method to determine causality of adverse drug reac-

tions.¹⁰ A commonly used set of basic tenants for causality assessment¹¹ include:

1. Temporality (sine qua non). The causative agent precedes the effect.
2. Strength: stronger associations are more likely to be causal than weaker associations.
3. Consistency: the causative agent is associated with the effect on repeated observations.
4. Biologic gradient. The cause–effect relationship follows a dose–response curve.
5. Plausibility: the biologic action of the causative agent could reasonably cause the effect.

The reports of morbidity with topical vasoconstrictors include many of these criteria (most notably temporality and plausibility); however, it is difficult to assess strength, consistency, and dose–response relationships at this time because of the small number of subjects having adverse reactions and the lack of adequately powered comparative studies. Other factors that obscure causality include potential confounding factors, such as the effects of the systemic anesthetic agents, the amount of drug used and absorbed, history of recreational stimulant use, and concomitant local injections. During endoscopic sinonasal surgery, it is difficult to measure the amount used because much of the medication still remains in the pledget after its use and is discarded.

Surgeons generally agree that the use of topical vasoconstrictors is important in minimizing bleeding. However, there is disagreement regarding which topical vasoconstrictor should be used. A few articles provided a crude estimate of the incidence of adverse cardiopulmonary (CP) events using topical vasoconstrictors. Nicholins et al.¹² reported CP events in 0.08% (2/250) of patients undergoing nasal surgery and 4% (1/25) with transphenoidal hypophysectomy using 1 mL of intranasal paste containing 25% cocaine and 0.18% epinephrine. The article did not include a control group, nor did it report if the surgeons also used local injections.

Lee et al.¹³ reported a randomized clinical trial in which 2 out of 50 (4%) children undergoing tonsillectomy and adenoidectomy had ventricular arrhythmias in both the experimental group (receiving topical epinephrine) and the placebo-controlled group. Feehan et al.³ reported in an anonymous survey study that, of 93,004 rhinoplasties performed by surgeons actively using topical cocaine, there were 225 (0.24%) mild reactions (no resuscitation required), 14 (0.015%) severe reactions (resuscitation required), and no deaths. However, the 7.4% of respondents who had discontinued cocaine use reported twice as many mild reactions (0.4%), 10 times as many severe reactions (0.1%), and 5 fatalities (0.03%). Of these respondents, 48% discontinued topical cocaine because of reports in the literature; 33% reported that the choice for its discontinuation was not based on its risk profile; and 70% reportedly used topical adrenaline in place of the discontinued cocaine. Kubo et al.¹⁴ reported that 26 of 178 (15%) patients undergoing FESS using topical epinephrine with and without cocaine had tachycardia at some point in the operation,

but that it only occurred with concomitant use of atropine. Complications are possible even when topical vasoconstrictors are administered properly. Complications can also occur when there is a processing error. Because most topical vasoconstrictors are clear liquid medication that can be often confused with other injectable anesthetic agents that have the same consistency and color, there is a possibility that the topical medicine can be injected.⁸ Therefore, it is important to develop a protocol to differentiate the topical vasoconstrictor from injectable anesthetic. One way to easily remedy this situation is to color the topical medicine with fluorescein or a drop of methylene blue. Other suggestions for safe handling of topical vasoconstrictors include: 1) having the pharmacy prepare the solution, 2) storing only a single concentration, 3) labeling all syringes and storage containers, 4) drawing the medications directly from the vial, and 5) employing a verification process with the operating room staff.

Proposed Protocol

There is a debate regarding the appropriate topical vasoconstrictors to use in endoscopic sinonasal surgery. Some believe that oxymetazoline alone should be used because of its safety record. Others believe that performing safe advanced sinus surgery at times requires better hemostasis than that provided by oxymetazoline and recommend judicious use of topical concentrated epinephrine. The following protocol for topical vasoconstrictors is recommended based on safety profile of the literature reviewed.

1. Do not use topical phenylephrine if possible.
2. Use caution with topical cocaine.
3. Avoid β -blockers for intraoperative hypertension after topical vasoconstrictor use.
4. Avoid halogenated hydrocarbon anesthetic agents (i.e., Halothane) when using topical vasoconstrictors.
5. If possible, avoid using concentrated topical cocaine or epinephrine in patients with history of cardiovascular disease.
6. For neonate to 85 pounds or 12-year-old child: consider using 0.05% oxymetazoline first. If adequate visualization or hemostasis is not achieved then consider 1:2,000 topical epinephrine with judicious use.
7. For 85 pounds to 17 years of age: use oxymetazoline or 1:2,000 epinephrine with judicious use.

8. 18 years or older: use 1:2,000 or 1:1,000 epinephrine with judicious use.

Based on the current literature, it is difficult to recommend a safe amount of topical vasoconstrictors to use because the absorption rate is difficult to measure. At the present time judicious use is recommended.

Future Studies

Future studies need to be randomized clinical trials with adequate subject samples. Because the rate of adverse effects from intranasal topical vasoconstrictors is extremely low, the sample size would need to be quite high.

CONCLUSION

In sinus or nasal surgery, topical vasoconstrictors should be used in a manner that maximizes hemostasis while limiting the risk any risk or morbidity such as a cardiovascular event.

BIBLIOGRAPHY

1. Groudine SB, Hollinger I, Jones J, et al. New York State guidelines on the topical use of phenylephrine in the operating room. *Anesthesiology* 2000; 92:859–864.
2. Jones J, Greenberg L, Groudine S, et al. Clinical advisory: phenylephrine advisory panel report. *Int J Ped Otorhinolaryngol* 1998;45:97–99.
3. Feehan HF, Mancusi Ungaro A. The use of cocaine as a topical anesthetic in nasal surgery. A survey report. *Plast Reconstruct Surg* 1976;57:62–65.
4. Johns ME, Henderson RL. Cocaine use by the otolaryngologist: a survey. *Trans Sect Otolaryngol Am Acad Ophthalmol Otolaryngol* 1977;84: 969–973.
5. De R, Uppal HS, Shehab ZP, et al. Current practices of cocaine administration by UK otorhinolaryngologists. *J Laryngol Otol* 2003;117:109–112.
6. Long H, Greller H, Mercurio-Zappala M, et al. Medicinal use of cocaine: a shifting paradigm over 25 years. *Laryngoscope* 2004;114:1625–1629.
7. Shah RK, Hoy E, Roberson DW, et al. Errors with concentrated epinephrine in otolaryngology. *Laryngoscope* 2008;118:1928–1930.
8. Kelley K, Clark B, Brown V, et al. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care* 2003;15:261–266.
9. Orlandi RR, Warriar S, Han JK. Concentrated topical epinephrine is safe in endoscopic sinus surgery. *Am J Rhinol Allerg* 2010;24:140–142.
10. Agbabiaka TB, Savović J, Ernst E. Methods of causality assessment of adverse drug reactions: a systemic review. *Drug Saf* 2008;31:21–37.
11. Rothman KJ, Greenland S, ed. Causation and causal inference. In: *Modern Epidemiology*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:7–29.
12. Laffey JG, Neligan P, Ormonde G. Prolonged perioperative myocardial ischemia in a young male: due to topical intranasal cocaine? *J Clin Anesthesiol* 1999;11:419–424.
13. Lee JH, Sigel M, Paisner HM, et al. Use of topical epinephrine in tonsillectomy and adenoidectomy with halothane anesthesia. *Anesth Anal* 1972; 51:64–68.
14. Kubo N, Nakamura A, Yamashita T. [Efficacy and complications of topical cocaine anesthesia in functional endoscopic sinus surgery]. *Nippon Jibiinkoka Gakkai Kaiho* 1995;98:1263–1269.