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REVIEW ARTICLE

Dexmedetomidine improves the quality of the operative field for functional endoscopic sinus surgery: systematic review

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Abstract

Background: Intra-operative bleeding diminishes visualisation during functional endoscopic sinus surgery and can cause unfavourable outcomes. Dexmedetomidine is a potent alpha-2 agonist, with sympatholytic effects. This systematic review aimed to assess whether dexmedetomidine decreases intra-operative bleeding and improves operative field quality.

Methods: All randomised, controlled trials that assessed the ability of dexmedetomidine to provide good operative fields for functional endoscopic sinus surgery were identified from Medline and Embase. The outcomes of interest were: operative field quality, intra-operative bleeding, operative time and adverse events.

Results: Five studies (254 patients) met the inclusion criteria. When compared to saline, dexmedetomidine improved the quality of the operative field. The operative time was similar between groups. When compared to other drugs, dexmedetomidine was as effective as esmolol and remifentanil. There were no adverse incidents.

Conclusion: Dexmedetomidine is beneficial in providing good visibility during functional endoscopic sinus surgery. Controlled hypotensive anaesthesia with this medicine decreases intra-operative bleeding and enhances surgical field quality.

Key words: Dexmedetomidine; Paranasal Sinuses; Sinus Surgery

Introduction

For successful functional endoscopic sinus surgery (FESS), with good surgical outcomes and no major complications, surgeons need to have a good knowledge of nasal and paranasal sinus surgical anatomy, and excellent operative field visualisation. Intra-operative bleeding is the main reason for a poor quality surgical field.

While haemostasis for head and neck surgery relies on vessel ligation and extensive cauterisation, haemostasis for FESS differs in that it relies on vasoconstriction and clotting mechanisms. Controlled hypotension is used to minimise intra-operative blood loss during surgery and improve surgical field quality.[1] Various agents have been used for this purpose, including vasodilators (e.g. sodium nitroprusside[2] and nitroglycerine[3]), beta-adrenergic antagonists (e.g. propranolol and esmolol),[4] high doses of potent inhaled anaesthetics (e.g. isoflurane)[5] and magnesium sulphate.[6] Major disadvantages caused by these agents are reflex tachycardia, tachyphylaxis and rebound hypertension, which may enhance venous bleeding and reduce visibility. High doses of inhalation anaesthetics may prolong the hospital stay.[7] Other drawbacks are cyanide toxicity due to sodium nitroprusside[8] and myocardial depression due to esmolol.[2]

Dexmedetomidine is a potent, highly selective alpha-2 adrenoceptor agonist, with a receptor affinity eight times higher than that of clonidine.[9] Central nervous system stimulation of postsynaptic alpha-2 receptors leads to the inhibition of sympathetic activity, which decreases noradrenaline release, blood pressure and heart rate. It also causes sedation, analgesia and vasoconstrictive effects.[10] The hypotensive action and hemodynamic stability thereby reduce intra-operative bleeding. In addition, dexmedetomidine has no effects on the respiration system,[11] and its use decreases the requirement for other anaesthetics and analgesics. Dexmedetomidine is a more effective sedative and analgesic agent than clonidine. The most common adverse effects of dexmedetomidine are hypotension and bradycardia, which are usually related to the rate of administration and dosage.[12]

This study aimed to systematically review randomised, controlled trials that investigated dexmedetomidine and its effectiveness on operative field quality for FESS.

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TABLE I
CHARACTERISTICS OF INCLUDED STUDIES

Study	Year	Pts (*n*)	Surgery	Intervention	Comparison	Outcome(s)
Guven *et al.*[17]	2011	40	FESS	Dexmedetomidine	Saline	Intra-operative bleeding & operative field quality scores, operative time
Ke & Pen[18]	2013	60	FESS	Dexmedetomidine	Saline	Number of patients with intra-operative bleeding
Gao *et al.*[16]	2012	48	FESS	Dexmedetomidine	No treatment	Intra-operative bleeding & operative field quality scores
Shams *et al.*[20]	2013	40	FESS	Dexmedetomidine	Esmolol	Intra-operative bleeding & operative field quality scores, intra-operative blood loss volume, operative time
Lee *et al.*[19]	2013	66	FESS	Dexmedetomidine	Remifentanil	Intra-operative bleeding & operative field quality scores, intra-operative blood loss volume, operative time

Pts = patients; FESS = functional endoscopic sinus surgery

Materials and methods

Electronic systematic searches for randomised, controlled trials were conducted, without language, publication year or publication status restrictions. The date of the last search was 9 May 2014. A literature search was performed using Ovid Medline and Embase databases, with the following Medical Subject Heading terms and key words: 'endoscopic sinus surgery' in combination with 'dexmedetomidine', 'Precedex', 'Dexdor' and 'Dexdomitor'.

Randomised, controlled trials that fulfilled the following inclusion criteria were included: (1) studies that comprised an adult population aged 18 years or older; (2) studies that involved patients undergoing FESS; (3) studies that involved a comparison of the use of dexmedetomidine with placebo, no treatment or other anaesthetic agents; and (4) studies that reported on the quality of the operative field. References of included studies and additional sources were searched to identify any missing published or unpublished trials.

When studies were sufficiently homogeneous, data were pooled for meta-analysis. The primary outcomes were operative field quality and intra-operative bleeding. Secondary outcomes were operative time and adverse events. Standardised mean difference and 95 per cent confidence intervals (CIs) were used for the continuous data. Risk ratio and 95 per cent CIs were used for the dichotomous data. A random effect model was used. Statistical assessments were performed using Review Manager ('RevMan') software, version 5.1.6.[13] The significance of any discrepancies in estimates of treatment effects from different trials was assessed by means of Cochran's Q test for heterogeneity and by a measure of the I^2 statistic. I^2 values of less than 40 per cent, 40–60 per cent, or greater than 60 per cent represent low, moderate or substantial heterogeneity respectively.[14] The quality of included studies was assessed by evaluating risks of bias, guided by the *Cochrane Handbook for Systematic Reviews of Interventions*.[14]

Results

Study selection

A total of 794 articles were retrieved from Ovid Medline and 159 were retrieved from Embase; 729 of these were removed in first-level title screening because they were duplicate or irrelevant studies. Eight studies were removed after screening of the abstracts. One additional study was excluded as it was presented at a conference without publication, and essential data could not be obtained.[15] Five studies were included in the review.[16–20] Characteristics of the five included studies are displayed in Table I. A flow chart of study retrieval and selection is shown in Figure 1.

Participants

There were 254 participants in total in the included studies. The mean patient age (reported in four of the trials[17–20]) was 26.3 years; 56.1 per cent of the patients (reported in four of the trials[16–19]) were men.

Comparisons and effects of interventions

Two studies compared dexmedetomidine with saline.[17,18] One study compared dexmedetomidine plus sevoflurane with sevoflurane alone.[16] Two studies compared dexmedetomidine with other anaesthetic drugs.[19,20]

Four studies[16,17,19,20] scored the quality of the surgical field using a predefined six-point scale, as per Fromme *et al.*,[21] as follows: 0 = no bleeding; 1 = slight bleeding with no suctioning of blood required; 2 = slight bleeding with occasional suctioning required (surgical field is not threatened); 3 = slight bleeding with frequent suctioning required and bleeding that threatens the surgical field seconds after suction is removed; 4 = moderate bleeding with frequent suctioning required and bleeding that threatens the surgical field directly after suction is removed; and 5 = severe bleeding with constant suctioning required and bleeding that appears faster than can be removed by suction, with the surgical field severely threatened.

Intra-operative bleeding was reported in three studies.[18–20] Two studies reported the volume of blood loss,[19,20] while the other reported the number of cases with nasal bloody exudate.[18] The operative time was reported in three studies.[17,19,20] Adverse events were reported in four studies.[16,17,19,20]

Dexmedetomidine versus placebo. Two studies compared the use of dexmedetomidine with saline.[17,18]

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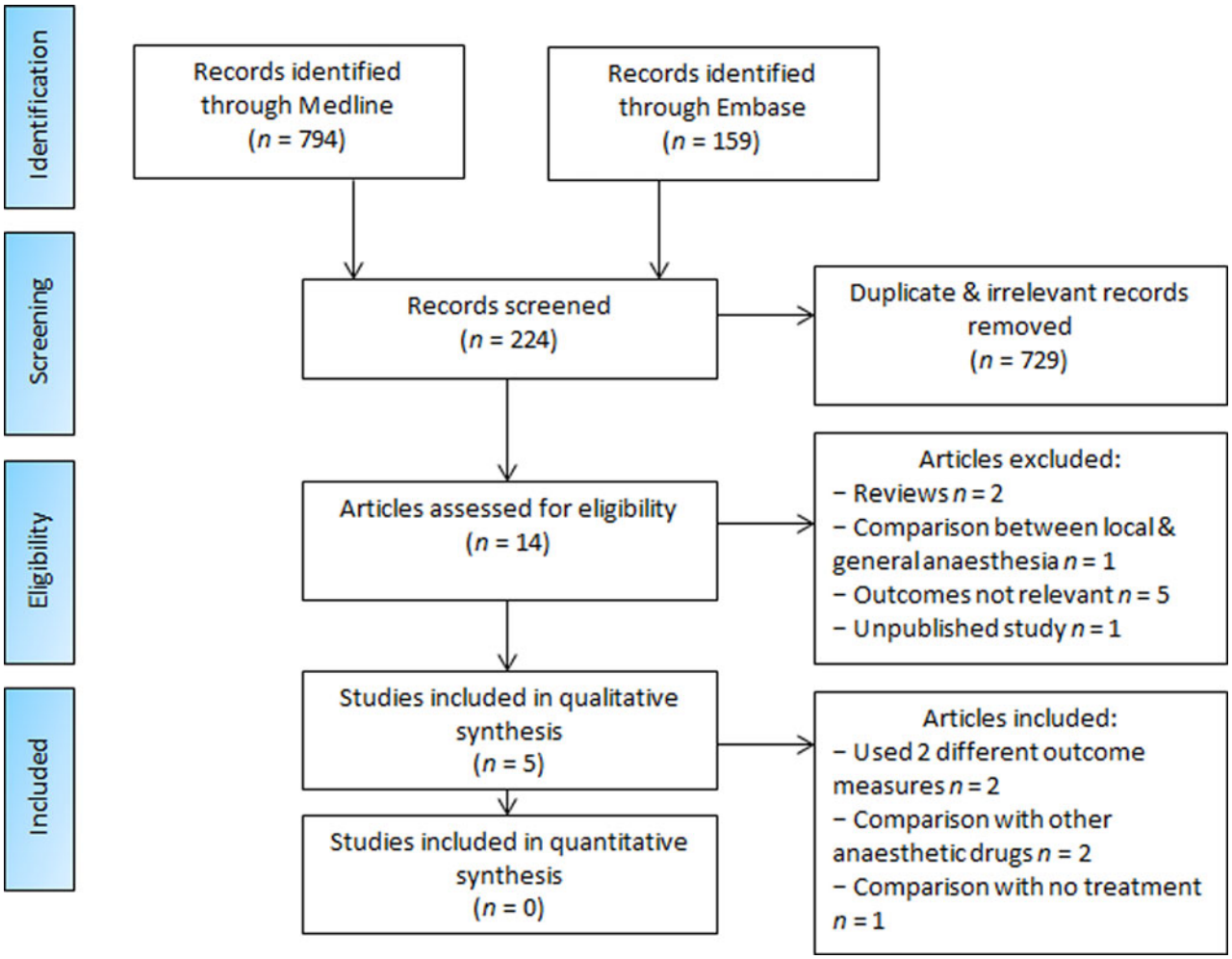

FIG. 1
Flow chart of study retrieval and selection.

The benefit of dexmedetomidine over placebo was shown in both studies; however, data could not be pooled for meta-analysis.

Guven and colleagues[17] assessed the surgical field using the Fromme *et al*. scale.[21] Surgical field visibility was better in the dexmedetomidine group (scores of 1.4 ± 1.27 *vs* 3.15 ± 0.74; $p = 0.019$).[17] The operative time was similar between groups (92.25 ± 27.21 minutes *vs* 90.75 ± 19.34 minutes; $p = 0.13$).

Ke and Pen[18] reported the number of patients with significant bleeding. The results favoured the use of dexmedetomidine, as none of the patients in the dexmedetomidine group required packing.[18] Sixty per cent of the dexmedetomidine group, compared to 90 per cent of the saline group, had intra-operative bleeding ($p < 0.05$). Operative time was not assessed.

Dexmedetomidine versus no treatment. One trial compared dexmedetomidine plus sevoflurane with sevoflurane alone.[16] The operative field quality score was significantly better in the dexmedetomidine plus sevoflurane group (score of 1.25 ± 0.4) than in the sevoflurane alone group (score of 2.34 ± 0.6) ($p < 0.05$). Operative time was not assessed.

Dexmedetomidine versus esmolol. One trial compared dexmedetomidine with esmolol.[20] Shams and colleagues concluded that both drugs enabled hypotensive anaesthesia and provided a good quality operative field for FESS, with similar surgical field scores (2.81 ± 0.74 *vs* 2.53 ± 0.93; $p = 0.18$) and intra-operative blood loss (214.69 ± 158.78 ml *vs* 186.47 ± 176.98 ml; $p = 0.50$). The operative time was similar in both groups (61.19 ± 26.6 minutes *vs* 65.12 ± 23.05 minutes; $p = 0.52$).

Dexmedetomidine versus remifentanil. One trial compared dexmedetomidine with remifentanil.[19] Lee and colleagues concluded that both dexmedetomidine and remifentanil were effective in providing a good quality operative field, with similar surgical field scores (2.0 ± 0.5 *vs* 2.0 ± 0.5; $p > 0.05$) and similar intra-operative blood loss (130.6 ± 26.8 ml *vs* 131.4 ± 22.5 ml; $p > 0.05$). The operative time was similar between the two groups (88.1 ± 14.3 minutes *vs* 90.0 ± 13.6 minutes; $p > 0.05$).

Heart rate and mean arterial pressure. Heart rate and mean arterial pressure data for the dexmedetomidine

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TABLE II
HEART RATE AND MEAN ARTERIAL PRESSURE IN DEXMEDETOMIDINE AND CONTROL GROUPS

Study	Year	Comparison	Heart rate (bpm)			Mean arterial pressure (mmHg)		
			Dexmedetomidine group (mean ± SD)	Control group (mean ± SD)	*p*	Dexmedetomidine group (mean ± SD)	Control group (mean ± SD)	*p*
Guven *et al.*[17]	2011	Placebo	70.0 ± 12.8	90 ± 19.2	0.04	72.5 ± 16.0	83.3 ± 7.8	0.005
Ke & Pen[18]	2013	Placebo	61.2 ± 2.5	65.5 ± 2.7	<0.05	65.3 ± 7.2	71.5 ± 6.9	<0.05
Gao *et al.*[16]	2012	No treatment	66.0 ± 10.2	91.2 ± 18.5	<0.05	80.4 ± 6.7	90.7 ± 7.0	<0.05
Shams *et al.*[20]	2013	Esmolol	70.0	80.0	>0.05	80.0	90.0	>0.05
Lee *et al.*[19]	2013	Remifentanil	72.7 ± 7.2	64.6 ± 8.8	>0.05	69.7 ± 4.2	71.4 ± 9.8	>0.05

Bpm = beat per minute; SD = standard deviation

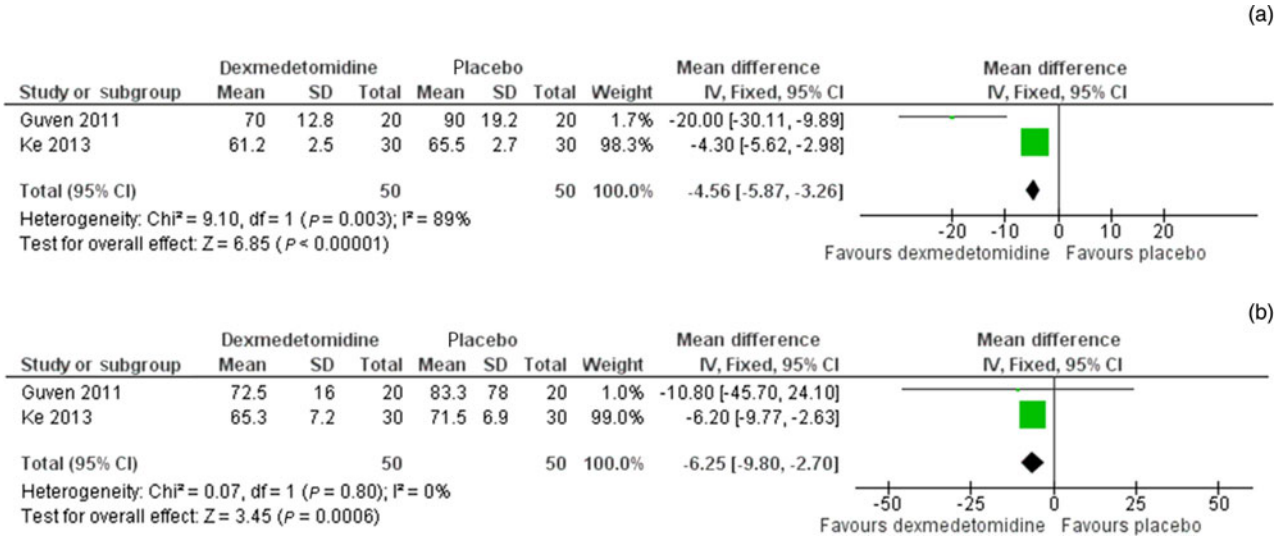

FIG. 2
Forest plots comparing dexmedetomidine with placebo groups for (a) heart rate and (b) mean arterial pressure. SD = standard deviation; IV = inverse variance; CI = confidence interval

groups and control groups of the individual studies are displayed in Table II. When compared to the placebo or 'no treatment' groups, dexmedetomidine significantly decreased heart rate and mean arterial pressure. When compared to esmolol or remifentanil, there was no significant difference between groups. When data were pooled for meta-analysis, the pooled results significantly favoured dexmedetomidine over placebo in terms of the control of heart rate (mean difference −4.56 bpm; 95 per cent CI −5.87, −3.26) and mean arterial pressure (mean difference −6.25 mmHg; 95 per cent CI −9.80, −2.70) (Figure 2).

Adverse events

Adverse events were reported in four studies.[16,17,19,20] All events were minor and successfully managed. When compared to the placebo group, Guven *et al.* reported fewer events in the dexmedetomidine group for nausea, vomiting and tachycardia, but a greater number of hypotension events.[17] When compared to the no treatment group, Gao *et al.* reported a significantly lower number of events in the dexmedetomidine group for delirium, pain, chill and respiratory inhibition.[16] When compared to esmolol and sevoflurane, there were no significant differences in the number of adverse events reported in any of the dexmedetomidine groups.[19,20]

Quality of included studies

Two studies could not be assessed because of language difficulties.[16,18] All three studies assessed for quality had a low risk of randomisation and allocation concealment.[17,19,20] Two studies were double blind.[17,19] Shams and colleagues performed a single-blind study; however, the anaesthetist in that study (who was not blinded) assessed other objective outcomes that were not the outcomes of interest.[20] Intra-operative bleeding and operative field quality were assessed by the surgeon who was blinded to the agent used.[20] There was no drop-out in any studies because all studies investigated intra-operative outcomes. All studies had a low risk of reporting bias. A summary of the risks of bias for each study are displayed in Figure 3.

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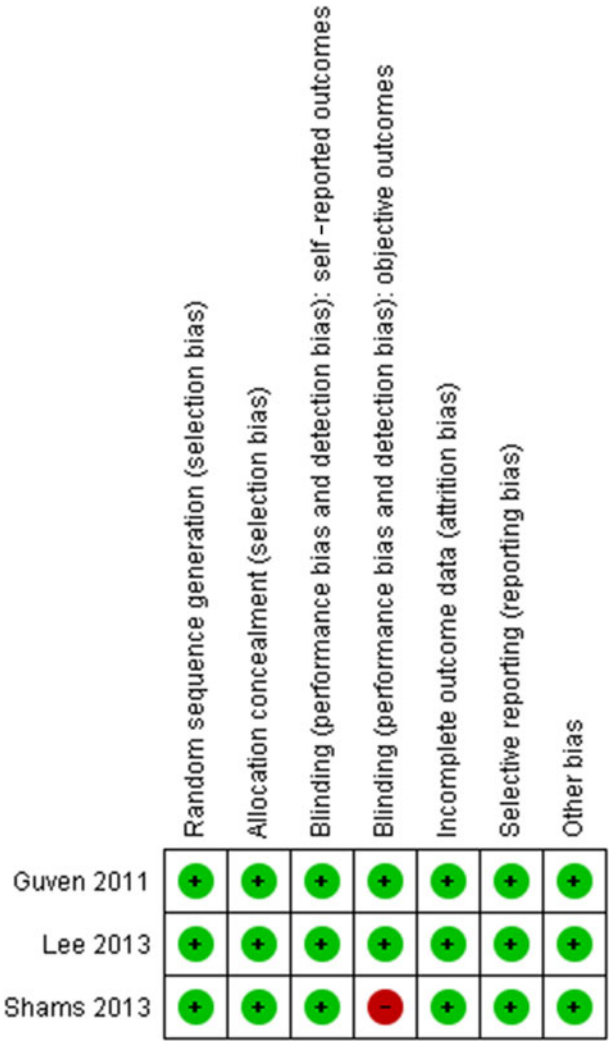

FIG. 3
Summary of risks of bias for each relevant study.

Discussion

Dexmedetomidine has been shown to be beneficial in decreasing intra-operative blood loss and improving the quality of the operative field for FESS. This is because dexmedetomidine is a potent alpha-2 adrenoceptor agonist and its action inhibits noradrenaline release. This causes decreased heart rate and lower blood pressure, with vasoconstrictive effects. This hemodynamic stability leads to better visualisation of the surgical field. In contrast to alpha-2 adrenoceptor agonists, inhalational anaesthetics decrease blood pressure, causing vasodilatory effects and resulting in reflex tachycardia. Simply decreasing mean arterial pressure does not always bring about improved visibility, particularly when patients have increased heart rate and vasodilatation in nasal mucosa. Jacobi and colleagues reported that controlled hypotension did not improve surgical field conditions or intra-operative blood loss when sodium nitroprusside was used in FESS, although mean blood pressure was around 65 to 75 mmHg throughout the surgery.[22]

The findings revealed that dexmedetomidine use did not reduce operative time compared to placebo. Although the visibility of the operative field does improve, this may not be sufficient to affect the speed of surgery. Another possibility is that operative time correlates with the extension of FESS. 'Full-house' FESS (entire paranasal surgery) may not proceed as initially planned if the visibility of the operative field is compromised. Surgeons may instead perform limited FESS or terminate the procedure in order to prevent further complications.

Esmolol is a beta-adrenergic antagonist that produces negative chronotropic and ionotropic effects, resulting in a decrease of cardiac output. Once cardiac output is decreased, arterial blood pressure is also decreased, and a stable course of controlled hypotension and an excellent operative field can be achieved.[1,2] Remifentanil hydrochloride is a potent, short-acting synthetic opioid analgesic drug. It provides higher surgical field visibility because of its ability to decrease heart rate, cardiac output and blood pressure.[2,23,24] When compared to esmolol and remifentanil, dexmedetomidine was reported as similarly effective for improving visualisation.

Better quality of the operative field in the dexmedetomidine group than the saline group was also reported by Malhotra and colleagues ($p = 0.011$; assessed using the Fromme *et al.* scale[21]).[15] However, that study, presented at the European Society of Anaesthesiology Congress, has only been published in abstract form, and data could not be obtained; hence, the study was not included. Operative time was not assessed.

Two additional randomised trials assessed the effect of dexmedetomidine on intra-operative bleeding and improved operative field quality for septoplasty.[25,26] Similar findings of the beneficial effects of dexmedetomidine were reported.

Midazolam is commonly used as a sedative for sinonasal surgery performed under local anaesthesia. There have been two randomised trials comparing midazolam with dexmedetomidine.[27,28] Although the aim was to investigate the sedative effect, dexmedetomidine was shown by these two studies to have decreased intra-operative bleeding and improve the operative field quality as a result of the hemodynamic stability it produced.

Major adverse events of dexmedetomidine use have not been reported. However, dexmedetomidine may induce bradycardia and hypotension. It is recommended that patients given dexmedetomidine are closely monitored. Bradycardia of less than 50 beats per minute and mean arterial pressure of less than 50 mmHg should be corrected.

One limitation of this systematic review is that there are co-interventions of other anaesthetic drugs and rescue medicine. These confounders may have affected the outcomes. However, these confounders were given to both arms of the studies. Furthermore, group allocation was random and the outcome assessors were

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blinded. In addition, the studies included were of good quality, with no bias.

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References

1 Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodium nitroprusside- and esmolol-induced controlled hypotension for functional endoscopic sinus surgery. *Can J Anaesth* 1995;**42**:373–6
2 Degoute CS, Ray MJ, Manchon M, Dubreuil C, Banssillon V. Remifentanil and controlled hypotension; comparison with nitroprusside or esmolol during tympanoplasty. *Can J Anaesth* 2001;**48**:20–7
3 Degoute CS, Dubreuil C, Ray MJ, Guitton J, Manchon M, Banssillon V *et al*. Effects of posture, hypotension and locally applied vasoconstriction on the middle ear microcirculation in anaesthetized humans. *Eur J Appl Physiol Occup Physiol* 1994;**69**:414–20
4 Degoute CS. Controlled hypotension: a guide to drug choice. *Drugs* 2007;**67**:1053–76
5 Pavlin JD, Colley PS, Weymuller EA Jr, Van Norman G, Gunn HC, Koerschgen ME. Propofol versus isoflurane for endoscopic sinus surgery. *Am J Otolaryngol* 1999;**20**:96–101
6 Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. *Br J Anaesth* 2006;**96**: 727–31
7 Dal D, Celiker V, Ozer E, Basgul E, Salman MA, Aypar U. Induced hypotension for tympanoplasty: a comparison of desflurane, isoflurane and sevoflurane. *Eur J Anaesthesiol* 2004; **21**:902–6
8 Amaranath L, Kellermeyer WF Jr. Tachyphylaxis to sodium nitroprusside. *Anesthesiology* 1976;**44**:345–8
9 Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care* 2001;**7**:221–6
10 Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. *Ann Pharmacother* 2007;**41**:245–52
11 Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. *Curr Opin Anaesthesiol* 2008; **21**:457–61
12 Easley RB. Sedation challenges in the pediatric ICU: is dexmedetomidine the solution? *Indian Pediatr* 2009;**46**:761–3
13 Review Manager (RevMan) v. 5.1.6 ed [computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011
14 Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 (updated March 2011). The Cochrane Collaboration (online), 2011
15 Malhotra SK, Kumar S, Arora S, Gupta A. Effect of dexmedetomidine on the quality of surgical field and requirement of hypotensive agents during endoscopic sinus surgery under general anesthesia. *Eur J Anaesthesiol* 2013;**30**:27
16 Gao GJ, Xu YY, Wang B, Lv HM, Yang WY, Shang Y. Feasibility of dexmedetomidine assisting sevoflurane for controlled hypotension in endoscopic sinus surgery [in Chinese]. *Jie Fang Jun Yi Xue Za Zhi* 2012;**37**:45–8
17 Guven DG, Demiraran Y, Sezen G, Kepek O, Iskender A. Evaluation of outcomes in patients given dexmedetomidine in functional endoscopic sinus surgery. *Ann Otol Rhinol Laryngol* 2011;**120**:586–92
18 Ke J, Pen X. The effect of dexmedetomidine on post-operative blood pressure after controlled hypotension in endoscopic sinus surgery [in Chinese]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2013;**27**:478–80
19 Lee J, Kim Y, Park C, Jeon Y, Kim D, Joo J *et al*. Comparison between dexmedetomidine and remifentanil for controlled hypotension and recovery in endoscopic sinus surgery. *Ann Otol Rhinol Laryngol* 2013;**122**:421–6
20 Shams T, El Bahnasawe NS, Abu-Samra M, El-Masry R. Induced hypotension for functional endoscopic sinus surgery: a comparative study of dexmedetomidine versus esmolol. *Saudi J Anaesth* 2013;**7**:175–80
21 Fromme GA, MacKenzie RA, Gould AB Jr, Lund BA, Offord KP. Controlled hypotension for orthognathic surgery. *Anesth Analg* 1986;**65**:683–6
22 Jacobi KE, Bohm BE, Rickauer AJ, Jacobi C, Hemmerling TM. Moderate controlled hypotension with sodium nitroprusside does not improve surgical conditions or decrease blood loss in endoscopic sinus surgery. *J Clin Anesth* 2000;**12**:202–7
23 Eberhart LH, Folz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. *Laryngoscope* 2003;**113**:1369–73
24 Manola M, De Luca E, Moscillo L, Mastella A. Using remifentanil and sufentanil in functional endoscopic sinus surgery to improve surgical conditions. *ORL J Otorhinolaryngol Relat Spec* 2005;**67**:83–6
25 Ayoglu H, Yapakci O, Ugur MB, Uzun L, Altunkaya H, Ozer Y *et al*. Effectiveness of dexmedetomidine in reducing bleeding during septoplasty and tympanoplasty operations. *J Clin Anesth* 2008;**20**:437–41
26 Durmus M, But AK, Dogan Z, Yucel A, Miman MC, Ersoy MO. Effect of dexmedetomidine on bleeding during tympanoplasty or septorhinoplasty. *Eur J Anaesthesiol* 2007;**24**:447–53
27 Balaraju TC, Pathan R, Thomas R, Kantha S, Sheetal D, Yogesh B *et al*. A study of dexmedetomidine compared with midazolam for sedation in endoscopic dacryocystorhinostomy. *Indian J Public Health Res Dev* 2013;**4**:185–9
28 Ragab A, El Shamaa H, Ibrahim M. Dexmedetomidine, morphine, propofol vs midazolam, morphine, propofol for conscious sedation in rhinoplasty under local anesthesia. A prospective, randomized study. *Egyptian J Anaesth* 2013; **29**:181–7

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