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Original Article

Effectiveness of dexmedetomidine in reducing blood loss during middle ear surgery under general anaesthesia: a randomised controlled trial

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Abstract

Background: Maintenance of relatively dry bloodless field is favoured by surgeons during middle ear surgery under operating microscope as it produces better visibility, ease of operation and reduces operating time. A highly selective alpha2 adrenergic agonist like dexmedetomidine, by virtue of its central sympatholytic, sedative and analgesic-sparing effect may provide such desired operating conditions.

Methods: A randomised double-blind, placebo-controlled study was conducted to evaluate whether dexmedetomidine reduces blood loss in middle ear surgery under general anaesthesia and improve operative field visibility. Fifty-four patients aged 18-40 years, posted for elective middle ear surgeries were randomly divided into two groups. Patients of Group D (n=27) received dexmedetomidine in a loading dose of 1mcg/kg over 10 minutes before induction of anaesthesia followed by steady infusion at 0.4mcg/kg/hr. Group P (n=27) patients received corresponding volumes of normal saline as placebo. The operating surgeon assessed the intraoperative bleeding by a four-point Bleeding Score at the 10-minute interval and the Final Opinion on Bleeding Score at the end of surgery. For the test of statistical significance, a value of p less than 0.05 was chosen.

Results: In Group D, the Bleeding Scores and the Final Opinion on Bleeding Score were significantly lower when compared with Group P ($p < 0.05$).

Conclusions: Dexmedetomidine was found to significantly reduce intraoperative bleeding. This, in turn, improves operative field visibility and increases surgeon's satisfaction during middle-ear surgery under general anaesthesia.

Keywords: cortical mastoidectomy; dexmedetomidine; intraoperative bleeding; tympanoplasty.

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Introduction

At present, otorhinolaryngologic surgery is routinely being done under the operating microscope.[1,2] Surgical bleeding during these procedures can markedly reduce the visibility of the operative field. To reduce bleeding during middle ear surgery, maintaining deliberate hypotension (mean arterial pressure < 60 to 80 mmHg) has been a popular technique.[3] This helps to improve the visibility of the operative field, reduce blood loss, ensure greater ease of operation and reduce the operating time. Several techniques have been advocated to achieve deliberate hypotension to reduce blood loss and improve intraoperative visibility.[4,5] These range from the use of inhalational agents like halothane, isoflurane; vasodilators like sodium nitroprusside[2], glyceryl trinitrate, prostaglandin E_1; beta-adrenergic blocker like esmolol[2] to alpha adrenergic agonist like clonidine.[3]

In comparison to clonidine, dexmedetomidine is highly selective $alpha_2$ adrenergic agonists having several beneficial actions during the perioperative period. In addition to central sympatholytic action, dexmedetomidine also decreases the requirement of opioids and anaesthetic drugs and provides adequate sedation, analgesia as well as vasoconstrictive effect.[6,7,8] Stimulation of central postsynaptic alpha2-adrenergic receptors causes reduced sympathetic outflow leading to hypotension and bradycardia probably by reducing norepinephrine release.

In view of the favourable effects of dexmedetomidine on the central nervous system and cardiovascular system, the present study was designed to evaluate whether it plays any significant role in reducing blood loss during middle ear surgery when performed under general anaesthesia.

Methods

After obtaining Institutional Ethical Committee approval and informed consent from each patient, a prospective, double-blind, randomised controlled clinical trial was conducted. The study included 54 adult patients of either sex, of ASA Grade I and II aged 18 to 40 years undergoing tympanoplasty or cortical mastoidectomy under general anaesthesia. Patients were assigned either to dexmedetomidine group (Group D, n=27) or placebo group (Group P, n=27) using a computer-generated randomization table. Patients with a history of significant systemic comorbidities, psychiatric disorder, substance abuse, history of known allergy to study drug, systolic blood pressure more than 160 mm Hg, bradycardia, patient receiving regular opioid or any other analgesic drug one day prior to surgery were excluded from the study. The study was conducted from September 2012 to August 2013 in the ENT operation theatre of IPGMER, Kolkata.

The sample size was calculated based on the following assumptions. For an effect size of 30% (test group: 5% and control group: 35%), the power of 80% and alpha of 0.05 with equal allocation ratio, we needed 27 subjects in each arm, a total of 54 subjects would be enrolled in the study. The effect size has been calculated based on the proportion of subjects in each group who have a score of either 2 or 3 (severe bleeding) in the Bleeding Score.

After receiving the patients in the operating room, an intravenous line was established with an 18 G intravenous cannula and infusion of lactated ringer's solution was started.

Study drugs were prepared in identical looking 100 ml 0.9% normal saline vials by an anaesthesiologist who then handed them over to the attending anesthesiologist blinded to the nature of drug given to him or her. 100 mcg of Dexmedetomidine was dissolved in 100 ml of 0.9% normal saline hence obtaining a drug concentration of 1mcg/ml. All personnel involved in perioperative anaesthetic care along with the surgical team excluding the anaesthesiologist who was involved in preparing the drugs were blinded to the study group and the drug administered. A single surgeon operated on all the study patients to maintain uniformity of clinical assessment. Furthermore, to eliminate bias, the surgeon was kept unaware of the hemodynamic status of the patient. Intraoperatively, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation, electrocardiogram (ECG) and capnogram were monitored.

Patients in Group D received dexmedetomidine infusion, initiated 15 minutes before induction with a loading dose of 1 mcg/kg over 10 minutes followed by a maintenance infusion of 0.4 mcg/kg/hr diluted in 100 ml of normal saline as a continuous infusion via micro drip infusion set from the same vial. Patients in Group P received corresponding volumes of 0.9% normal saline as placebo in the form of bolus loading and the continuous infusion. In both the groups, the drugs were administered 15 minutes before induction slowly over ten minutes. The protocol of induction was similar in both the groups. Each patient received fentanyl 2mcg/kg and propofol in titrated doses after adequate preoxygenation and vecuronium 0.1 mg/kg was administered to facilitate tracheal intubation. Anaesthesia was subsequently maintained with nitrous oxide, oxygen, isoflurane (1%) and appropriate boluses of vecuronium under controlled mechanical ventilation. The drug infusions were stopped 5-8 minutes prior to the end of surgery.

Blood loss was assessed intraoperatively by the Bleeding Score (BS)[3] and Final Opinion on Bleeding Score (FOBS). The Bleeding Score was taken as the primary outcome of the study whereas FOBS, haemodynamic parameters and awakening time were considered as secondary outcomes. BS was assessed at ten minutes interval , starting from the time of incision and ending with closure of wound, by asking the surgeon, on a four-point scale from 0 = no bleeding (excellent surgical conditions), 1 = minimum bleeding (sporadic suction), 2 = diffuse bleeding (repeated suction) and 3 = abundant (troublesome) bleeding (continuous suction). FOBS was assessed by the surgeon at the end of operation on a five-point scale from 1 = very low, 2 = low, 3 = average, 4 = high, 5 = very high. MAP and HR were recorded at different time points starting from basal values followed by values just before intubation, at intubation, at 1,3,5 minutes after intubation, at the start of surgery, at 10,20,30,40,50,60,70 and 80 minutes intraoperatively, at extubation and finally at 1 & 5 minutes after extubation.

Infusion of the study drug was stopped immediately when the patient developed bradycardia (HR less than 50 beats/min) or significant hypotension (MAP less than 30% of preoperative value). Atropine (0.01 mg/kg) and phenylephrine were used for treating bradycardia or significant hypotension respectively.

Infusion of study drug was stopped after completion of graft placement. On conclusion of surgery, neostigmine 50mcg/kg and atropine 20mcg/kg was given to antagonise residual neuromuscular blockade. The time in seconds from the administration of neuromuscular block reversal agent till the patient is able to demonstrate sustained (> 5 seconds) eye opening on command was noted. This was defined as awakening time. Any other obvious side effects were also noted.

All raw data were subsequently entered into a Microsoft Excel spreadsheet and analysed using Microsoft excel 2007, Statistica software version 10. The variables were summarised using either Mean±SD for parametric data and Median ± Inter Quartile Range (IQR) for nonparametric data. For comparing the outcome variables between groups- Independent sample t-test was used for parametric data and Mann-Whitney U test for non-parametric data. Categorical data were compared using Fisher's Exact test or Pearson Chi-Square test as applicable. The value of $p < 0.05$ was taken to be statistically significant.

Results

Fifty-eight patients were assessed for eligibility of which four patients were excluded as three patients did not fulfil the inclusion criteria and one patient declined to participate. Randomization and analysis were done with 54 patients, 27 patients in each group. (Figure 1)

The patients in both groups were comparable with respect to demographic profile such as age, gender, body weight.

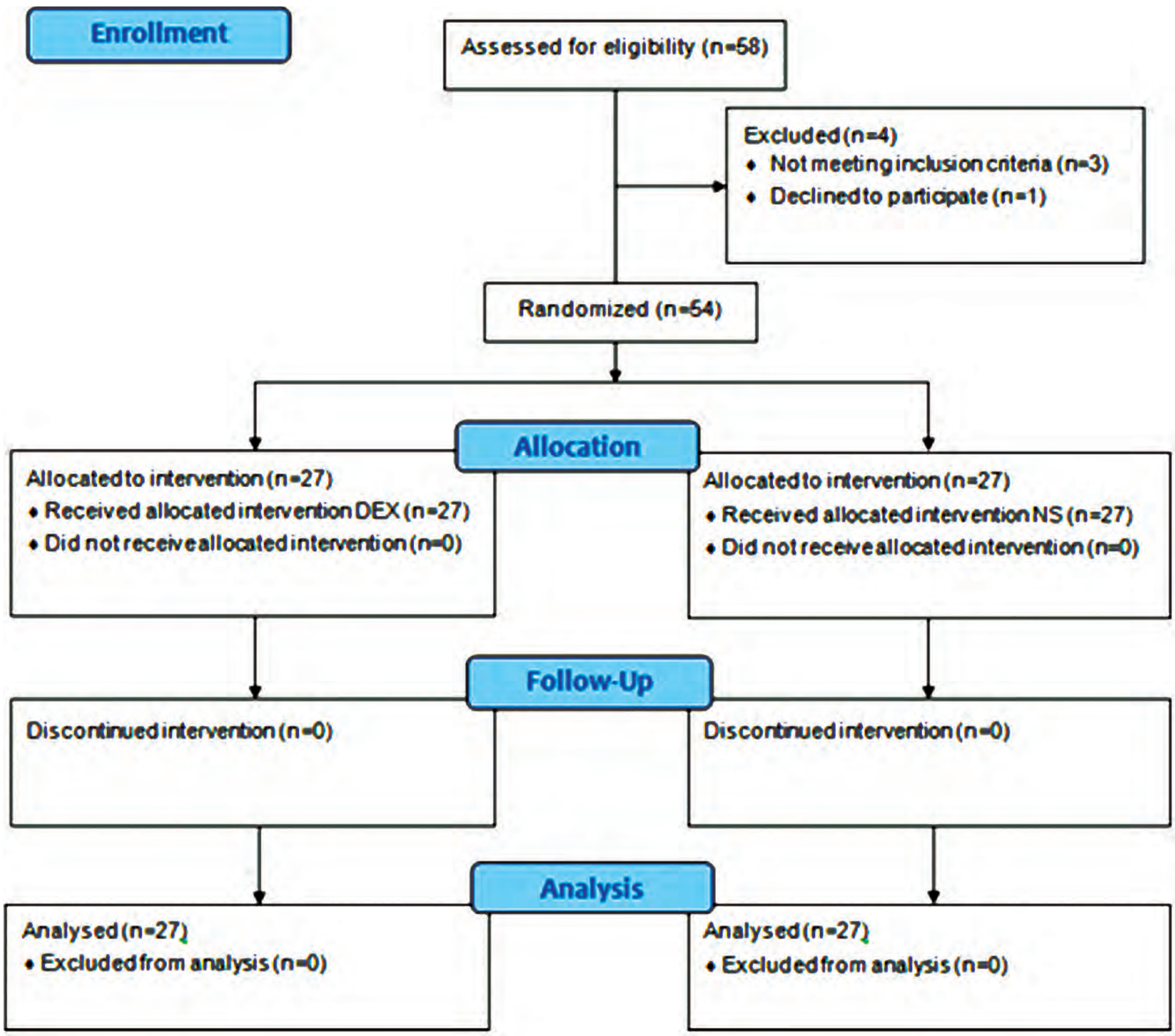


Figure 1: CONSORT 2010 Flow diagram

The duration and the type of surgery performed in both the groups were comparable (Table I).

Table I: Demographic characteristics of the patients in two groups

Variable	Group D	Group P	p-value
Age (years)	25.67±5.328	26.15±5.376	0.742
Gender (M/F)	17:10	15:12	0.580
Weight (Kg)	47.19±4.844	44.703±6.201	0.108
Duration of surgery (minutes)	107.78±16.251	103.70±14.974	0.343
Types of operation (tympanoplasty: cortical mastoidectomy)	15:12	16:11	0.500

Final Opinion on Bleeding Score (Table II) and Intraoperative Bleeding Score (Table III) was significantly higher in Group P in comparison to Group D.

Table II: Final opinion on bleeding score (FOBS)

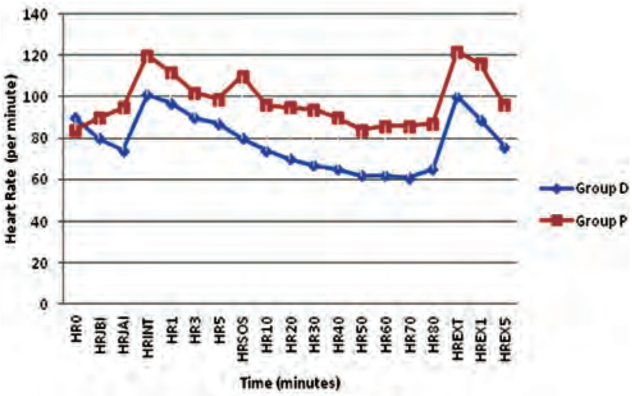
Groups	Median	I.Q.R	minimum	Maximum	p-value
D	2	1-2	1	2	0.000
P	4	3-4	3	5	

Table III: Intra-operative bleeding score

Time Scale	Group	Median	I.Q.R	p- Value
At 10 minutes	D	1	1.00-1.00	0.000
	P	2	2.00-3.00	
At 20 minutes	D	1	1.00-1.00	0.000
	P	2	2.00-2.00	
At 30 minutes	D	1	1.00-1.00	0.000
	P	3	2.00-3.00	
At 40 minutes	D	1	1.00-1.00	0.000
	P	3	2.00-3.00	
At 50 minutes	D	1	1.00-2.00	0.000
	P	2	2.00-3.00	
At 60 minutes	D	1	1.00-2.00	0.000
	P	3	2.00-3.00	
At 70 minutes	D	2	1.00-2.00	0.000
	P	3	2.00-3.00	
At 80 minutes	D	1	1.00-2.00	0.000
	P	3	2.00-3.00	
At 90 minutes	D	1	1.00-2.00	0.000
	P	2	2.00-3.00	
At 100 minutes	D	1	1.00-2.00	0.000
	P	2	2.00-3.00	
At 110 minutes	D	1	1.00-2.00	0.002
	P	2	2.00-3.00	
At 120 minutes	D	1	1.00-2.00	0.002
	P	2	2.00-3.00	
At 130 minutes	D	1	1.00-2.00	0.027
	P	3	2.00-3.00	

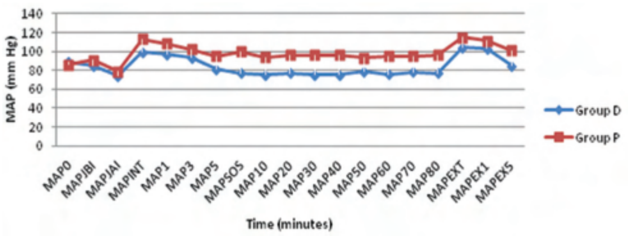
In Group D, the HR and MAP were maintained at significantly lower levels in comparison to Group P throughout the intra-operative period and even at extubation (Figure 2 and 3).

Figure 2: Comparison of Heart rate between two groups



HR0-basal heart rate, HRJBI-heart rate just before intubation, HRINT-heart rate at intubation,HR1,3,5-heart rate at 1,3,5 minutes after intubation, HRSOS- heart rate at start of surgery, HR10,20,30,40,50,60,70,80 - heart rate at 10,20,30,40,50,60,70 and 80 minutes intraoperatively, HREXT- heart rate at extubation, HREXT1 & HREXT5 - heart rate at 1& 5 minutes after extubation.

Figure 3: Comparison of Mean Arterial Pressure between



two groups

MAP0 – basal mean arterial pressure, MAPJBI- mean arterial pressure just before intubation, MAPINT- mean arterial pressure at intubation, MAP1,3,5- mean arterial pressure at 1,3,5 minutes after intubation, MAPSOS- mean arterial pressure at start of surgery, MAP10,20,30,40,50,60,70,80 - mean arterial pressure at 10, 20,30,40,50,60,70 and 80 minutes intraoperatively, MAPEXT- mean arterial pressure at extubation, MAPEXT1& MAPEXT5- mean arterial pressure at 1 & 5 minutes after extubation.

The awakening time (Table IV) was comparable between the two groups (p value= 0.749).

Table IV: Awakening time (in seconds)

Groups	Median	Minimum	Maximum	I.Q.R	P value
D	145	85	210	120-170	0.749
P	140	90	205	110-180	

None of the patients in both groups developed significant bradycardia and significant hypotension that required treatment anytime during the study period.

Discussion

Nowadays, middle ear surgeries are routinely performed under operating microscope. The highly magnified view of the operative field can be easily obscured with even a slight increase in surgical bleeding. Under such conditions, identification of anatomical landmarks is difficult and surgery becomes technically more demanding and time-consuming. So in middle ear surgery, the technique of anaesthesia should be such that produces minimal bleeding providing the surgeon with a relatively dry bloodless field.

Intraoperatively, acute elevations in arterial blood pressure may lead to increased capillary oozing in the operating field. On the other hand, very low arterial blood pressures may expose the patient to a number of hazards like prolonged awakening, cerebral thrombosis, extensive cerebral and cerebellar infarction, oliguria and anuria.

Therefore, achieving hemodynamic stability in intra-operative period is very important. Maintenance of adequate depth of anaesthesia throughout the intraoperative period is also important to avoid sudden surges in blood pressure and thus reduce intraoperative blood loss and produce a relatively dry operative field. During hypotensive anaesthesia, mean arterial pressure is lowered by about 30% of preoperative basal values and is maintained at that level throughout the surgical period.

Generally, middle ear surgeries are done under local anaesthesia. The surgeon infiltrates local anaesthetics with adrenaline in the operative field to reduce bleeding and provide analgesia. The advantage of this technique is that the hazards of general anaesthesia are avoided, patient's cooperation is ensured and turnover of surgical case load is also faster.

But this technique has got several disadvantages also. Patient has to lie motionlessly throughout the intra-operative period. Some patients may not cooperate. This will produce an unsteady operative field. The patient will also require some form of systemic sedative and analgesic like an intramuscular injection of opioids. This may be hazardous in a patient whose airway is not secured.

It is often difficult to maintain blood pressure within desired range in patients undergoing general anaesthesia. Blood pressure usually increases in a light plane of anaesthesia, following a change in surgical stimulation, airway suctioning etc. This may lead to excessive bleeding and subsequent worsening of operating condition for the surgeon.

Pharmacological intervention is a popular technique in avoiding intraoperative surges in blood pressure. Drugs like halothane, esmolol[2], clonidine[3], glyceryl trinitrate, sodium nitroprusside[2] are commonly used to decrease blood pressure to the desired level. An ideal hypotensive agent should possess certain desirable characteristics like short duration of action, easy titrability, and predictable reversibility with no significant interactions with drugs usually administered in the perioperative period.

Dexmedetomidine is a novel α_2 agonist with multifaceted desirable effects. It has sedative, analgesic and anxiolytic properties, reduces anaesthetic drug requirements[4,9-13] in intraoperative period and has been found to maintain hemodynamic stability in cardiovascular[14,15], gastro intestinal[16], genitourinary and gynaecological surgeries[11,12,17] in various studies. Among other major advantages are its faster onset of action and short half life[18,19] that allow effective titration of drug dose.

The role of the α_2 adrenergic agonist on blood vessels in humans is yet to be established. The mechanism by which it reduces perioperative blood loss is probably by decreasing norepinephrine release, rate-pressure product, oxygen demand and maintenance of stable haemodynamics which together counteract the α_2 receptor-mediated anti-ischemic effect.[20,21]

In the present study, it was observed that intraoperative dexmedetomidine infusion decreases bleeding and hemodynamic response to certain noxious stimuli like intubation, skin incision and attenuated the hemodynamic response during emergence from anaesthesia. The main mechanism is attributed to the attenuation of the sympathetic activity and stimulation of peripheral alpha 2 adrenoceptors of vascular smooth muscle. Reduction of the blood pressure and heart rate decreases bleeding within the surgical field thereby providing bloodless surgical site[13]. Moreover, it has its advantages over other hypotensive anaesthetics as it does not cause any respiratory depression. There are still inadequate studies stating the direct effect of Dexmedetomidine on blood vessels and this needs further research.

The loading and maintenance dose of dexmedetomidine in this study is comparable to doses used in similar previous studies.[4,13,22-26] Aho and colleagues[12] found that a dose of 0.3mcg/kg/hour as maintenance infusion on patients posted for gynaecological surgery was ineffective in attenuating HR and SBP. On the other hand, in another study, they observed that a higher dose of dexmedetomidine infusion in the range of 0.6mcg/kg/hour resulted in hemodynamic instability[17]. So, a dose of 0.4mcg/kg/hour as continuous infusion of dexmedetomidine was selected for this study.

However, Hilal et al[22] provided contrasting findings on effects of intraoperative surgical bleeding during tympanoplasty and septoplasty. They noted that dexmedetomidine played a significant role in reducing both intraoperative bleeding and fentanyl dosage requirement in septoplasty whereas in tympanoplasty, attenuation in intraoperative bleeding was not found to be significant The authors attributed these findings to either inadequate sample size or the fact that blood loss is less in tympanoplasty than septoplasty operations generally.

After bolus administration of dexmedetomidine, SBP and HR were significantly decreased. This result corroborates the findings of previous studies that loading dose of dexmedetomidine decreases heart rate and blood pressure significantly.[18,27] Though HR and SBP had fallen significantly in all patients in dexmedetomidine group, the changes were not severe enough to warrant the use of vasopressors or atropine. All patients were haemodynamically stable. In numerous studies with dexmedetomidine (general or gynaecological surgery), the authors have reported increased incidence of bradycardia and hypotension that was seen most often after rapid bolus administration in young healthy volunteers.[18] The explanation for this observation lies in the fact that in this study the bolus dose of dexmedetomidine was administered over a period of ten minutes as recommended in literature.[10]

Another important finding of the present study was that the awakening time was not prolonged with the use of dexmedetomidine in patients of Group D. The reason can be attributed to the unique fact that unlike other sedatives and inhalation agents[28,29], in dexmedetomidine-induced sedation the patients remain easily arousable.

In this study, the amount of actual blood loss was not measured during surgery which might be direct evidence for the effectiveness of dexmedetomidine in reducing blood loss, as the blood loss in middle ear surgery is of very small quantity. Invasive arterial pressure, bispectral index, neuromuscular monitoring and drug plasma concentrations measurements were not done. These were the limitations of the study.

This study was limited to two types of middle ear surgery: cortical mastoidectomy & tympanoplasty, as these are the most commonly performed middle ear surgical procedures under general anaesthesia in the study institution. Further studies are required for other types of middle ear surgery.

It is concluded that dexmedetomidine significantly reduces intraoperative bleeding, improves operative field visibility and increases surgeon's satisfaction in patients undergoing middle ear surgery under general anaesthesia.

Informed consent: Informed consent was obtained from all- individual participants included in the study.

Conflicts of interest: None

Acknowledgement: None

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