

Dexmedetomidine over Labetalol for oligemic surgical field in middle ear microsurgeries- A prospective randomized clinical trial

C.N. Navya¹, Ranganathan V.¹, A.P. Sambandan²

¹Department of Anesthesiology, Sri Muthukumaran Medical College Hospital and research institute, MGR University, Tamil Nadu

²Department of ENT, Sri Muthukumaran Medical College Hospital and research institute, MGR University, Tamil Nadu

Abstract

Background: Maintenance of relatively 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. Primary objective of this study was to evaluate and compare the effectiveness of dexmedetomidine and labetalol in providing better quality of the surgical field during middle ear surgeries under general anesthesia.

Methods: Seventy patients aged 18-65 years of ASA Grades I and II, of both gender were randomised into two comparable equal groups of 35 patients each for middle ear surgery under general anaesthesia with standard anaesthetic technique. Patients of Group D (n=35) received dexmedetomidine in a loading dose of 1mcg/kg over 10 minutes before induction of anaesthesia followed by incremental doses of 1/4th loading dose over 2mins if required and group L (n=35) received bolus dose of labetalol 0.3mg/kg over 2 min and increments of 1/4th loading dose (5mg) over 2 min till the required mean arterial pressure was achieved. All patients were assessed intra-operatively for bleeding at surgical field, haemodynamic changes, mean end tidal isoflurane concentration, surgeon satisfaction, post-operative analgesia requirement time, sedation and side effects.

Results: Patients receiving dexmedetomidine had significantly lesser bleeding at surgical field and better surgeon satisfaction score (P < 0.05). The mean arterial pressure did not show any significant difference between the groups. Mean time required for postoperative analgesia was significantly higher with dexmedetomidine group.

Conclusion: Dexmedetomidine and labetalol can be used to provide hypotensive anesthesia and hence oligemic field for middle ear microsurgery. Dexmedetomidine was found to significantly reduce intraoperative bleeding, which improved operative field visibility and increased surgeon's satisfaction during middle-ear surgery under general anaesthesia than labetalol. Mean end tidal isoflurane and post-operative shivering was significantly lower with dexmedetomidine than labetalol group. Time requirement of analgesics for post-operative pain was higher with dexmedetomidine group.

Keywords: Dexmedetomidine; labetalol; operative field visibility; middle ear surgery; end tidal isoflurane.

Introduction

The practice of middle ear surgery under anesthesia has undergone a revolution with the introduction of hypotensive anesthesia to provide a relatively bloodless field while using an 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 has been a popular technique. This helps to improve the visibility of the operative field,

reduce blood loss, ensure greater ease of operation and reduce the operating time. Innumerable techniques/agents have been advocated to achieve hypotension during anesthesia. These have ranged from the use of inhalational agents such as halothane, isoflurane, intravenous (IV) propofol infusion, vasodilators like sodium nitroprusside, glyceryl trinitrate (GTN), prostaglandin E1, remifentanyl, magnesium sulphate, beta-adrenergic blocker like esmolol, labetalol, metoprolol to alpha adrenergic agonist like clonidine

Address for Correspondence:

Dr. Navya C. N.

Department of Anesthesiology, Sri Muthu kumaran Medical College Hospital and research institute, Chennai, Tamil Nadu

E-mail: dr.cnavya@gmail.com

and dexmedetomidine.^[3-10]

Dexmedetomidine is highly selective alpha₂ 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^[11-13].

Labetalol is a combined alpha and beta adrenoceptor antagonist used in the medical treatment of hypertension. The alpha-adrenoceptors of the capacitance vessels may be blocked with resultant vasodilatation, and a reflex increase in heart rate and cardiac output may be prevented by the simultaneous blocking of the beta-receptors.^[14]

There are no studies comparing the effectiveness of dexmedetomidine over labetalol given in intermittent doses to provide relatively dry surgical field. Therefore, this randomized study was planned using these drugs for inducing and maintaining controlled hypotension, thereby optimizing surgical field in patients undergoing middle ear surgeries under general anaesthesia. The secondary objectives were to assess intraoperative blood loss, surgeon satisfaction, end tidal isoflurane (Etisoflurane) requirement, post operative requirement of analgesia time, sedation and side effects.

Materials and Methods

This prospective, single blind, randomized clinical trial was conducted after obtaining Institutional Ethical Committee approval and registered in Clinical Trial Registry of India as CTRI/2018/02/012012. Written informed consent was taken from each patient. The study included 70 adult patients of either sex, of ASA Grade I and II aged 18 to 65 years undergoing middle ear surgeries under general anaesthesia. Patients with history of allergy or contraindications to either dexmedetomidine or labetalol, concomitant use of medications which may exaggerate the heart rate response of dexmedetomidine including digoxin or β-adrenergic antagonists, coronary artery disease, ischemic heart disease, rhythm disturbances, bronchial asthma, history of sleep apnoea, renal insufficiency, cerebral insufficiency, liver impairment, hypertension, diabetes mellitus, bleeding disorders, administered medication for psychiatric diseases, chronic or acute intake of sedative or analgesic drugs and patients on medications affecting coagulation system were excluded from the trial.

Patients were allocated to dexmedetomidine group

(Group D, n=35) or Labetalol group (Group L, n=35) using a computer-generated randomization table. Allocation concealment was performed using sequentially numbered, sealed envelopes.

Patients were premedicated with oral alprazolam 0.25 mg night before surgery and kept nil per oral for 6 hours prior to surgery. On arrival in the operating room, routine standard monitors such as continuous ECG, blood pressure and pulse oximeter were established and the patients' baseline heart rate, blood pressure and oxygen saturation (SpO₂) were recorded after 5 min settling in the operative room. A 20G intravenous cannula was inserted for drug and continuous fluid administration.

All patients were premedicated with intravenous (IV) glycopyrrolate (0.05mg/kg), IV midazolam (0.03mg/kg), IV Fentanyl (2µg/kg) for analgesia. All the patients received loading dose of the study drug before induction and maintenance dose was given to achieve the target MAP during the surgery. Before induction, patients in Group D: received dexmedetomidine loading dose of 1 µg/kg diluted to 10 ml with NS, infused over 10 min, followed by increments of 10-20mcg over 2min (1/4th of loading dose) and patients in group L received bolus dose of labetalol 0.3mg/kg diluted to 10ml with NS, over 2 min and increments of 5-10 mg till the required mean arterial pressure was reached. After pre-oxygenation, patients were induced with IV propofol at 1-2 mg/kg until loss of verbal response. After ensuring ability to ventilate patients were relaxed with IV vecuronium 0.1mg/kg and ventilated for 3min. Laryngoscopy using Macintosh laryngoscope and appropriate sized cuffed endotracheal intubation was done. Patients were maintained with oxygen and Nitrous oxide in 60:40, Isoflurane and Vecuronium. All patients were given head elevation of 15°, infiltration of adrenaline (1: 50,000 or 1: 200,000) and a PEEP of 5cm H₂O.

The heart rate through ECG, mean arterial pressure mm/Hg, SpO₂ using pulse oximeter, continuous ECG were monitored every 3min and recorded by the principal investigator at baseline, after administration of study drugs, at intubation and every 15min till the end of surgery. End tidal Concentration of isoflurane was recorded in percentage every 15 min till conclusion of surgery. Hypotension was defined as MAP was ≤65 mm Hg or fall >25% of baseline MAP, which was treated by decreasing the dial concentration of isoflurane and 6mg of ephedrine was used if needed. When heart rate (HR) was ≤50bpm, 0.6 mg IV atropine was used to combat bradycardia.

All the patients were operated by the same surgical team, who were unaware of the study drug, and the quality of surgical field was estimated by the surgeon every 15 min during surgery using the following scale: Grade 0-no bleeding, excellent surgical conditions; Grade I-minimum bleeding, sporadic suction needed; Grade II-diffuse bleeding, repeated suction needed; and Grade III-considerable, troublesome bleeding, and continuous suction was needed.

Thirty minutes before the end of surgery IV ondansetron 0.15mg/kg was given. After surgery, the residual neuromuscular blockade was reversed with neostigmine (0.05 mg/kg) and IV glycopyrrolate (0.008 mg/kg). Patients were extubated after observing adequate motor recovery and spontaneous breathing efforts. The total blood loss was measured from the suction apparatus and wet gauze. At the end of surgery surgeon was asked to score according to Surgeon

satisfaction Criteria Score (4-Excellent; 3-Good; 2-Fair; 1-Poor)

The incidence of post-operative adverse events respiratory depression, shivering, bradycardia (HR <60 bpm), hypotension (fall in MAP >25% of baseline mm Hg), nausea, vomiting, sedation using Ramsay sedation score (1-Anxious or restless or both; 2-Cooperative, orientated and tranquil; 3-responding to commands; 4-Brisk response to stimulus; 5-Sluggish response to stimulus; 6-No response to stimulus) or any other drug-induced side-effects or complications were recorded. Patients were considered ready for discharge from the PACU when the modified Aldrete score was ≥9. Patients were transferred to the ward after being discharged from PACU.

The sample size was calculated by considering confidence level of 95%, test power of 90%, standard deviation 1 and least significant difference between

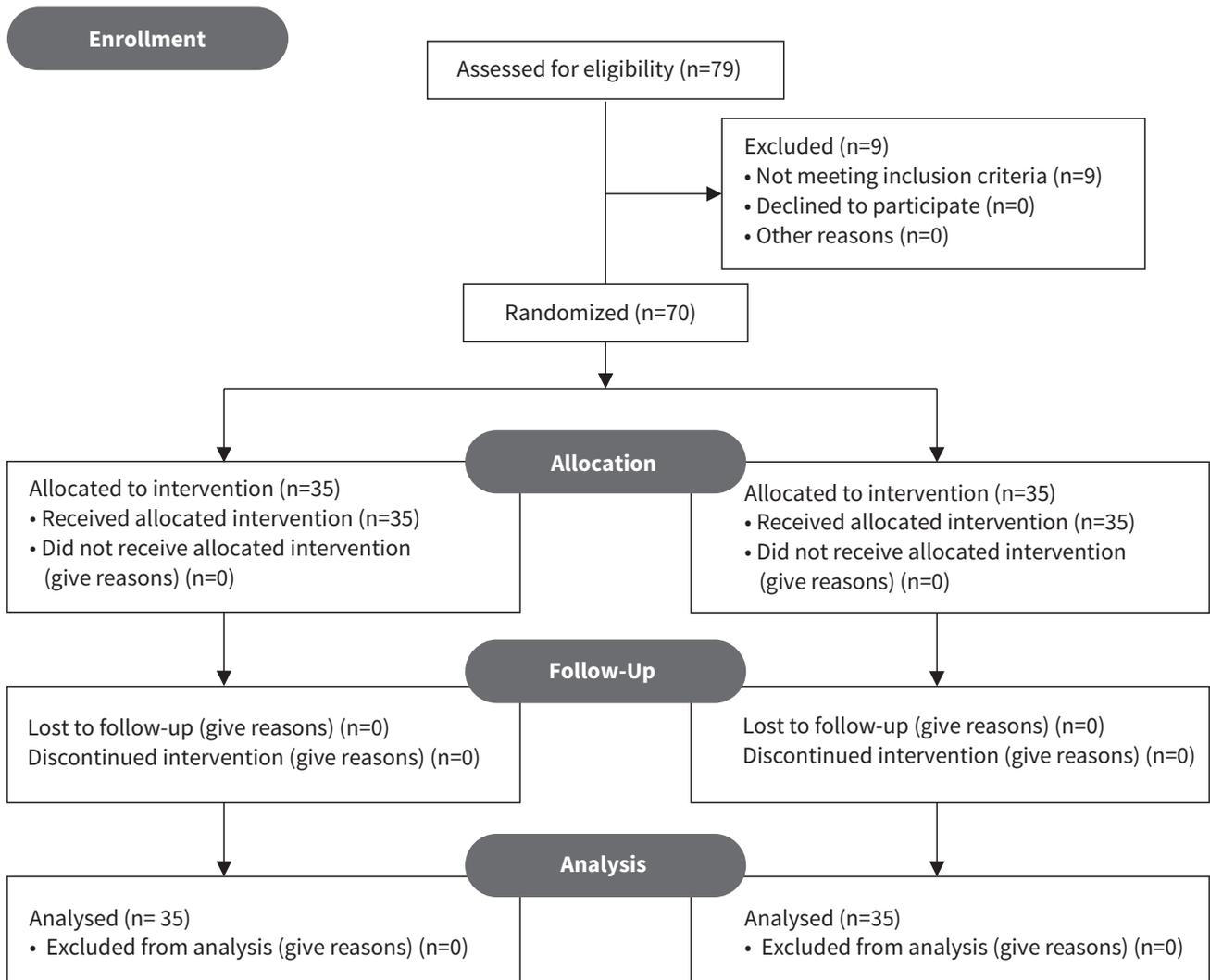


Figure 1: CONSORT flow diagram of patients included in the study

two groups as 0.8. Thirty four subjects were required in each arm, we rounded sample size to 35 considering drop outs, a total of 70 subjects were enrolled in the study. All raw data were subsequently entered into a Microsoft Excel Data was transferred to statistical package of social sciences (SPSS) version 16. Descriptive statistics was done and presented in tables. To compare dexmedetomidine and labetalol, independent sample t test was used. Data was presented as mean and standard deviation with confidence interval of 95% and $P < 0.05$ was considered as statistically significant.

Results

Figure 1 shows flow diagram for this study where 79 patients were assessed for eligibility and 70 patients were included and their results were analysed. The demographic data of age, sex, and weight were comparable between the groups (Table 1).

Table 1: Patient demographic data

Parameters	Group D	Group L
Age (y)	35.54±10.91	32.74±12.60
Female(n)	23	21
Male (n)	12	14
Weight (kg)	78.3 ± 12.7	76.5 ± 11.4

Data as mean±Standard deviation

There was statistically significant decrease in HR and MAP in group D than group L, immediately after administration of study drugs till 10 min of intubation($P < 0.000$). The HR and MAP were comparable between both the groups from 15min post intubation till end of surgery (figure 2 and 3).

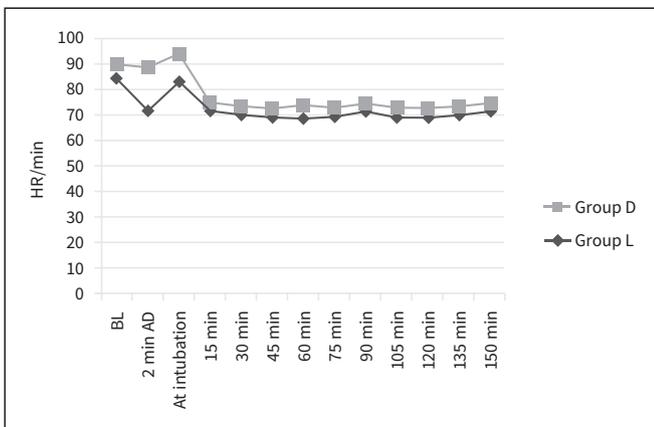


Figure 2: Comparison of mean Heart Rate between Group D and Group L

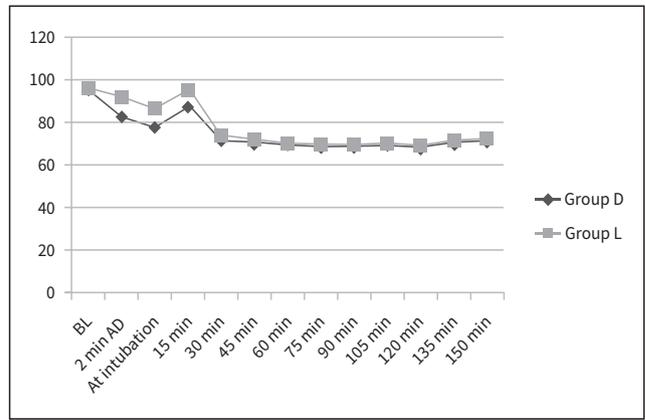


Figure 3: Comparison of Mean Arterial Pressure between group D and group L

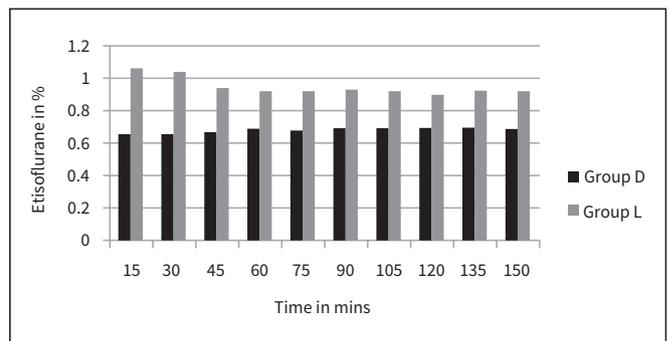


Figure 4 : Comparison of Etisoflurane between group D and group L

Figure 4 shows the required percentage of end tidal isoflurane concentration was significantly less ($P < 0.05$) to maintain the desired mean blood pressure in patients of Group D than group L.

Patients in group D were more sedated than group L. But none of the patients in group D were restless or agitated. (Figure 5)

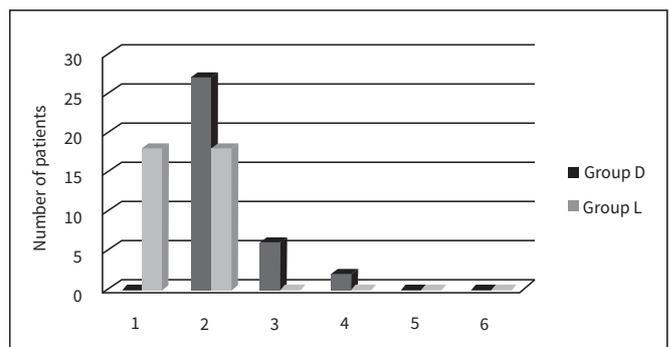


Figure5: Comparison of Ramsay sedation score in group D and group L

Table 2: Assessment of intraoperative bleeding by surgeon (n=70)

Grade	Suction requirement	Group D	Group L
0	No bleeding, No suction	1	0
1	Minimum bleeding, Sporadic suction	31	29
2	Diffuse bleeding, Repeated suction	3	6
3	Trouble bleeding, Continuous suction	0	0

The operating microscope was used throughout the middle ear surgery and surgeons observed Grade 1 bleeding (minimum bleeding with sporadic suction) at surgical site in majority of patients of Group D. The mean difference in bleeding at surgical site was statistically significant (1.06 ± 0.338 vs 1.29 ± 0.572 ; $p=0.047$) between the groups (Table 2).

Table 3: Comparison of variables at the end of surgery between group D and group L

Parameters	Group D	Group L	P value
Blood loss(ml)	109.86 ± 44.100	144.00 ± 41.643	0.00
Surgeon satisfaction score	$3.14 \pm .494$	$2.71 \pm .572$	0.040

Table 4: Comparison of studied variables in recovery room

Parameters	Group D(n=35)	Group L(n=35)	P value
Requirement of post-operative analgesia time (min)	23.54 ± 6.368	6.34 ± 3.280	0.000
Shivering	2	8	0.041
Nausea	3	6	0.291
Vomiting	1	3	0.310
Hypotension	1	0	0.150
Bradycardia	2	0	0.160

The blood loss was significantly lower with group D and surgeon satisfaction score was better with group D than group L (Table 3). The time required for post-operative analgesia showed a significant difference between both the groups ($p=0.000$). Group D had lesser incidence of shivering when compared to group L. There was no significant difference between either of the groups with respect to other side effects (Table 4).

Discussion

Even small amount of blood can obscure the microscopic operating field and decreasing the extravasation of blood may improve the results of surgical procedures.^[1] Different techniques, to minimise intra-operative blood loss during middle ear

surgery are used.^[2-10] There are no comparative report about dexmedetomidine and labetalol, so, to the best of our knowledge, the present study is the first study to assess the efficacy of dexmedetomidine and labetalol to provide oligemic surgical field in middle ear surgeries.

Dexmedetomidine is a highly selective α_2 adrenergic agonist and used as adjuvant in anaesthesia to reduce the intra-operative anaesthetic and analgesic requirement. It regulates the autonomic and cardiovascular systems by acting on blood vessels and inhibiting norepinephrine release at sympathetic terminals, thereby attenuating the heart rate and blood pressure responses to intra-operative stressful events of anaesthesia. It effectively minimises the surgical blood loss and improves the surgical field visibility. Its haemodynamic effects are predictable and dose-dependent.^[11,12] The intermittent dexmedetomidine regime was followed according to study done by Rayan A^[13] which showed that compared to the conventional infusion of dexmedetomidine, administration of intermittent doses had fewer side effects, significantly decreased total amount of dexmedetomidine consumed, had short time to emergence, and better modified Aldrete scores.

Labetalol is an antihypertensive drug that antagonizes both alpha- and beta-receptors. This drug affects beta-receptors 5 to 10 times more specifically than other receptors. This property hinders reflex tachycardia that usually emerges after inducing controlled hypotension by other antihypertensive vasodilator drugs. In a study conducted by Eltringham^[14] et al., there was no significant difference in decreasing the volume of bleeding between the labetalol and nitroglycerine in middle ear microsurgery. They concluded that both drugs were the useful choices to induce hypotension and decrease blood loss in such surgery. Yeasmeen^[15] et al., evaluated the effects of labetalol and nitroglycerine on 2 groups of patients undergoing spinal surgery and found a significantly higher score for surgical field quality and less bleeding in labetalol group. It is also interesting that they achieved these results with a much lower dose of labetalol. Cope^[16] suggested that Labetalol would appear to be a useful agent for controlled hypotension in cardiac patients. Scott^[17] and others have shown that it reduces peripheral resistance, decreases heart rate and reduces cardiac output minimally in healthy patients.

In our study isoflurane requirement was significantly high in labetalol group which could have resulted in

restlessness or agitation in immediate postoperative period. Our study was similar to Aho^[18] and Khan^[19] where the mean EtIsoflurane requirement was reduced with dexmedetomidine usage.

Conclusion

Both dexmedetomidine and labetalol were effective to induce hypotension with similar hemodynamics during middle ear surgeries, but findings in the present study revealed that intraoperative bleeding at the surgical site in dexmedetomidine group was lower than labetalol group. In addition, surgeon satisfaction score was better with dexmedetomidine. Mean end tidal isoflurane was significantly lesser in dexmedetomidine group. Other findings revealed that in dexmedetomidine group, post-operative shivering was lower and time required for post-operative analgesia was longer than labetalol group.

Acknowledgements: Our sincere thanks to Dr V Srisantanakrishnan, M D community medicine, for his statistical expertise in data analysis.

References

- Kerr AR. Anesthesia with profound hypotension for middle ear surgery. *Br J Anaesth.* 1977 May; 49(5):447-452.
- Jellish WS, Owen K, Edelstein S, Fluder E, Leonetti JP. Standard anesthetic technique for middle ear surgical procedures- A comparison of desflurane and sevoflurane. *Otolaryngol Head Neck Surg.* 2005 Aug; 133(2):269-274.
- Fairbairn ML, Eltringham RJ, Young PN, Robinson JM. Hypotensive anesthesia for microsurgery of the middle ear. A comparison between isoflurane and halothane. *Anesthesia.* 1986 Jun; 41(6):637-640.
- Hessen M, Dietrich GV, Boldt J, Zeiler D, Alberts CH, Hempelmann G. Beta 2-adrenoceptor density of human lymphocytes after nitroprusside-induced hypotension. *Anesth Analg.* 1995 Dec; 81(6):1250-1254.
- Bajwa SJ, Kaur J, Kulshrestha A, Haldar R, Sethi R, Sing A. Nitroglycerine, esmolol and dexmedetomidine for induced hypotension during functional endoscopic sinus surgery: A comparative evaluation. *J Anaesthesiol Clin Pharmacol.* 2016 Apr-Jun; 32(2):192-197.
- Degoute CS. Controlled hypotension: a guide to drug choice. *Drugs* 2007; 67(7):1053-76.
- Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. *Br J Anaesth.* 2006 Jun; 96(6):727-731.
- Richa F, Yazigi A, Sleilaty G, Yazbeck P. Comparison between dexmedetomidine and remifentanyl for controlled hypotension during tympanoplasty. *Eur J Anaesthesiol.* 2008 May; 25(5):369-374.
- Hashimoto S, Kobayashi A. Clinical pharmacokinetics and pharmacodynamics of glyceryl trinitrate and its metabolites. *Clin Pharmacokinet.* 2003; 42(3):205-221.
- Toivonen J, Kaukinen S. Clonidine Premedication: A useful adjunct in producing deliberate hypotension. *Acta Anaesthesiol Scand.* 1990 Nov; 34(8):653-657.
- Nasreen F, Bano S, Khan RM, Hasan SA. Dexmedetomidine used to provide hypotensive anesthesia during middle ear surgery. *Indian J Otolaryngol Head Neck Surg.* 2009 Sep; 61(3):205-7.
- Ayoglu H, Yapakci O, Ugur MB, Uzeen L, Altunkaya H, Ozer Y, et al. Effectiveness of dexmedetomidine in reducing bleeding during septoplasty and tympanoplasty operations. *J Clin Anesth.* 2008 Sep; 20(6):437-41.
- Rayan AA. Controlled hypotensive anesthesia for functional endoscopic sinus surgery: a new protocol for dexmedetomidine administration. *Ain-Shams J Anaesthesiol* 2016; 9:57-65.
- Eltringham RJ, Young PN, Littlejohns PA, Robinson JM. A comparison of glyceryltrinitrate and labetalol as hypotensive agents in microsurgery of the middle ear. *Eur Heart J.* 1988 Jan; 9:201-203.
- Yeasmeen S, Siddique MRU, Islama A, Aktaruzzaman AKM, Banik D, Hye A. Use of labetalol and glyceryl trinitrate for induced hypotension in spine surgery- A comparative study. *J Bangladesh Society of physiologists.* 2009 Jan; 22(2):48-53.
- Cope DHP, Crawford MC. Labetalol in controlled hypotension- Administration of labetalol when adequate hypotension is difficult to achieve. *Br. J. Anaesth.* 1979 Apr; 51(4): 359-365.
- Scott DB, Buckley FP, Littlewood DG, MacRae WR, Arthur GR, Drummond GB. Circulatory effects of labetalol during halothane anaesthesia. *Anaesthesia.* 1978 Feb; 33(2): 145-56.
- Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effect of intravenously administered dexmedetomidine on perioperative haemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology.* 1991 Jun; 74(6):997-1002.
- Khan ZP, Munday IT, Jones RM, Thornton C, Mant TG, Amin D. Effects of Dexmedetomidine on isoflurane requirements in healthy volunteers. I: Pharmacodynamic and pharmacokinetic interactions. *Br J Anaesth.* 1999 Sep; 83(3):372-380.

Conflict of interest: Nil

Source of funding: Nil

Date received: May 31st 2018

Date accepted: June 26th 2018