



Esmolol and dexmedetomidine for controlled hypotension in middle ear surgeries-a prospective, open labeled, single centre study.

Kakade BL¹, Bhalerao PM²

Abstract

Background and Aims: Controlled hypotension has been used to reduce bleeding, the need for blood transfusions and provide a satisfactory bloodless surgical field. Esmolol, a short acting cardioselective beta blocker and dexmedetomidine, a central α -2 adrenergic agonist both cause controlled hypotension. The aim was to study the effect of dexmedetomidine and compare it to esmolol for controlled hypotension, surgical field, dose requirement of induction agent, requirement of inhalational agent and muscle relaxant in middle ear surgeries. **Method:** This study is a prospective, open labeled, single center study. Hundred patients of American Society of Anesthesiologists physical status I and II (ASA) scheduled for middle ear surgeries lasting for 2-3 hours under general anaesthesia were included. Patients were divided into two groups of 50 each by computer generated random numbers. Group E (n=50) patients received esmolol infusion and Group D patients received dexmedetomidine infusion. **Results:** The two groups were comparable in terms of haemodynamic parameters and surgical field assessment. The thiopentone dose requirement was 494 ± 12.93 milligrams (mg). in group E and 354.50 ± 17.26 mg in group D (p-0.022). The mean isoflurane concentration used in group E and group D was 45.30 ± 5.85 millilitre (ml) and 13.79 ± 4.51 ml respectively (p-0.002). The requirement of vecuronium was 11.19 ± 0.71 mg in group E and 4.58 ± 0.46 mg in group D (p-0.009).

Conclusion: The drugs provide controlled hypotension, good surgical field and reduce pressor response equally. In addition, dexmedetomidine reduces the dose requirement of induction agent, inhalational agent and skeletal muscle relaxant.

Key words: Controlled hypotension, esmolol, dexmedetomidine, middle ear surgery.

Introduction

Controlled hypotension has been used to reduce bleeding, the need for blood transfusions, and provide a satisfactory bloodless surgical field for half a century.[1] Ear surgeries under the microscope warrant a bloodless clear field for appropriate visualization. Esmolol, a cardioselective beta blocker is devoid of partial agonistic or membrane stabilizing action. It can be titrated easily with its short duration of action and has been found to be useful for controlled hypotension.[3] Dexmedetomidine, a central α -2 adrenergic agonist provides controlled hypotension and gives a satisfactory operative field by reducing intraoperative bleeding in middle ear surgeries.[2,3] Thus the two drugs were

compared.

Methods

The study was conducted in collaboration with a tertiary care level institute. A synopsis of the study protocol was submitted to the institutional ethics committee and approval was obtained. Prior to inclusion in the study, subjects were given all information and details about the surgical procedure, technique of anesthesia and drugs used. A written informed consent was obtained from each subject. All patients received glycopyrrolate 5 microgram/kilogram (mcg/kg) intramuscular, ondansetron 0.08 milligram/kilogram (mg/kg) midazolam 0.03 mg/kg and pentazocine 0.3 mg/kg intravenously as premedication 15-20 minutes prior to induction of anaesthesia. In addition, patients in group E received esmolol 1mcg/kg intravenous over ten minutes as loading dose and group D received intravenous dexmedetomidine as

loading dose 500 mcg/kg/min over ten minutes.

Preoxygenation was done with 100% oxygen for three min minutes. Induction was done with injection thiopentone (5-7 mg/kg) till the loss of eyelash reflex and injection succinylcholine (2mg/kg) as muscle relaxant. After laryngoscopy the patient was intubated with appropriate sized endotracheal tube and maintained on 50:50 O₂:N₂O, inhalational isoflurane and injection vecuronium as skeletal muscle relaxant.

In addition, group E received injection esmolol (50mcg/kg/hr) and group D received injection dexmedetomidine infusion (0.1-0.5 mcg/kg/hr). The infusion was continued up to 15-20 minutes prior to the end of surgery. Skeletal muscle relaxant was administered as per the train of four ratio (TOF). At the end of surgery, reversal with glycopyrrolate 10mcg/kg and neostigmine 0.04 mg/kg intravenous was done once spontaneous respiratory attempts and eye opening were present.

The patient was extubated once respiration was spontaneous and adequate, patient was

¹Department of Anaesthesiology, BJ Government Medical college and Sassoon General hospitals, Pune, Maharashtra, India

²Government medical college Miraj, Maharashtra, India.

Corresponding Author:

Dr. Pradnya Milind Bhalerao
D-15/10-11, Saritanagari-2, Off Sinhad road, Pune 411030
E-mail: dr.pradnyabhalerao@gmail.com

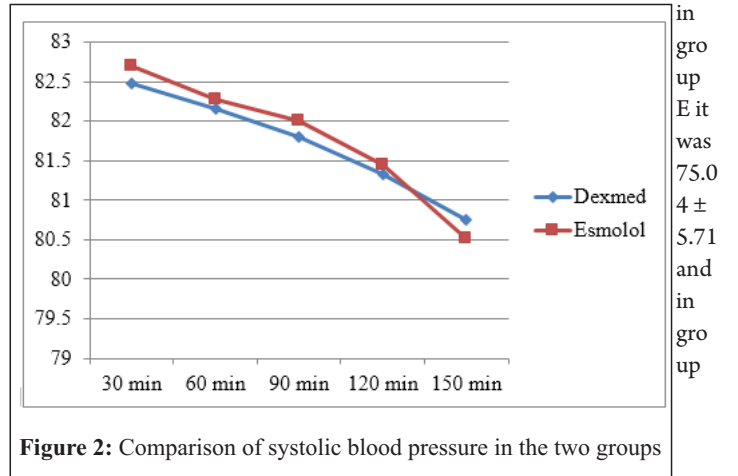
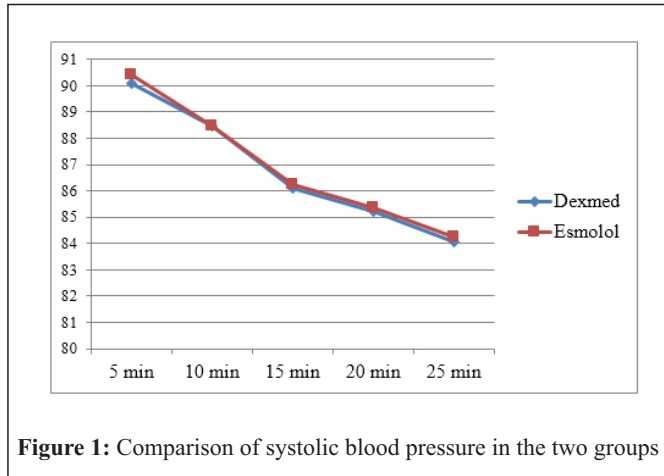


Figure 1: Comparison of systolic blood pressure in the two groups

Figure 2: Comparison of systolic blood pressure in the two groups

obeying commands and had good muscle tone and power. We monitored heart rate (HR) and systolic blood pressure (BP) every minute initially till loading dose of dexmedetomidine and esmolol was being administered, every minute during induction, every minute till five minutes after intubation followed by every five minutes for the next 30mins. Then it was measured every 15mins throughout surgery. The amount of induction agent required was calculated and response to laryngoscopy and intubation was noted. TOF ratio was evaluated every 30mins. The amount of inhalational agent and skeletal muscle relaxant required was noted. The Dions formula was used to calculate the amount of isoflurane required. The surgical field was assessed by the surgeon using the surgical field assessment score. It was scored as; 0-no bleeding, 1-Bleeding so mild that there was no surgical nuisance, 2-Bleeding a nuisance, but no interference with appropriate dissection, 3-Moderate bleeding, moderate compromise of surgical dissection, 4-Bleeding heavily, compromising with dissection but controllable, 5-Uncontrolled bleeding.

The primary objective was to compare the two drugs in terms of fall in blood pressure,

surgical field, dose requirement of induction agent, requirement of inhalational agent and muscle relaxant. The secondary objective was to note side effects if any. The data was analysed by using SPSS® version 17. All means were expressed as mean ± standard deviation (SD). Two independent sample t-test was used for quantitative data, and the χ^2 was used for qualitative data. A difference was regarded as significant at a p value of < 0.05. Preliminary sample size estimation showed that approximately fifty patients should be included in each group considering power of 80% and alpha error of 5% (95% confidence interval).

Results

We found that the two groups were comparable with regards to mean age (years), sex (male/female) and weight (kilograms) by using 2 independent sample t-test (p-values > 0.05). Mean baseline blood pressure in group E it was 123.56 ± 6.81 and in group D was 124.12 ± 7.76 (p-0.237). Similarly during induction mean heart rate was 77.60 ± 5.74 in group E (p- 0.790) and in group D was 78.24 ± 5.98 . Mean blood pressure in group E was 101.32 ± 3.55 (p-0.603) and in group D it was 101.44 ± 3.25 during induction.

D was 74.96 ± 4.73 (p-0.255). During intubation mean blood pressure in group E it was 95.12 ± 5.17 and in group D was 94.88 ± 4.96 (p-0.524). At 2min following intubation mean blood pressure in group E was $95.56 \pm (5.50)$ and in group D was $95.12 \pm (4.55)$ (p-0.251). Thus the mean baseline blood pressure and heart rate, blood pressure and heart rate at induction, during and after intubation did not show any statistical significance between the two groups. During the intraoperative period there was a fall in blood pressure in both the groups [Figure 1, 2] but with a p value of <0.05 which shows that there is no significant difference between these study groups.

The thiopentone dose requirement was 494 ± 12.93 mg in group E and 354.50 ± 17.26 mg in group D with the p-value of (0.022) which was statistically significant [Table 2]. Similarly the mean isoflurane required in group E and group D was $45.30 (\pm 5.85)$ ml and $13.79 (\pm 4.51)$ ml respectively with a p-value of <0.002 which was statistically significant. [Table 2] The requirement of vecuronium in milligrams was 11.19 ± 0.71 in group E and 4.58 ± 0.46 in group D. The p-value was (0.009) thus making it significant. [Table 2] There was no statistically significant difference in the adequacy of the surgical field between the two groups. (p-0.091)

Discussion

Controlled hypotension has been used to reduce bleeding and the need for blood transfusions, and provide a satisfactory bloodless surgical field. It is defined as a reduction of the systolic blood pressure to 80-90 mm Hg, a reduction of mean arterial pressure (MAP) to 50-65 mm Hg or a 30%

Table 1: Requirement of induction agent, inhalational agent and muscle relaxant in the two groups

Requirement of	Study group		P value
	Esmolol	Dexmed	
Induction agent (mg)	494.00 ± 12.93	354.50 ± 17.26	0.022**
Inhalational agent (ml)	45.30 ± 5.85	13.79 ± 4.51	0.002**
Skeletal muscle relaxant (mg)	11.19 ± 0.71	4.58 ± 0.46	0.009**

*Data presented as Mean ± SD. **P value < 0.05 considered significant

During intubation mean heart rate in group E was 75.52 ± 4.45 and in group D it was 73.76 ± 4.09 (p-0.317). At 2min following intubation the mean heart rate

reduction of baseline MAP. [1, 3] Middle ear surgeries require good surgical field visibility. Oozing blood obscures vision during ear microsurgery and can make correct graft placement difficult. The primary methods to minimise blood loss during middle ear surgery included mild head elevation of 15°, and infiltration or topical application of epinephrine. [2, 4] Pharmacological agents used for controlled hypotension include those agents that can be used successfully alone and those that are used adjunctively to limit dosage requirements and, therefore, the adverse effects of the other agents. Agents used alone include inhalation anaesthetics, sodium nitroprusside, nitroglycerin, trimethaphan camsilate, alprostadil (prostaglandin E1), adenosine, remifentanyl, and agents used in spinal anaesthesia. [3] Agents that can be used alone or in combination include calcium channel antagonists and beta-adrenoceptor antagonists. Agents that are mainly used adjunctively include angiotensin converting enzyme inhibitors (ACE) inhibitors and clonidine. New agents and techniques have been recently evaluated for their ability to induce effective hypotension without impairing the perfusion of vital organs. Esmolol is a cardioselective beta blocker which can be titrated easily with its short duration of action and has been found to be useful for controlled hypotension with an effect of capillary vasoconstriction due to unopposed alpha-adrenergic action on the mucous membrane vasculature. [5] Dexmedetomidine is a central α -2 adrenergic agonist with sedative, analgesic and hypnotic properties maintaining respiratory stability. It provides controlled hypotension which gives the satisfactory operative field by reducing intraoperative bleeding in middle ear surgeries. Dexmedetomidine has been shown to decrease the induction dose of intravenous anaesthetics, decrease intraoperative opioid, muscle relaxant and volatile anesthetic requirements. [6] With an emphasis on multidimensional features of dexmedetomidine, the present study was designed to compare the effect of this drug and compare it to esmolol in middle ear surgeries in context with its effect to provide controlled hypotension, pressor response, hemodynamic changes, effect on requirement of anesthetic agent, opioids and skeletal muscle relaxant.

The two groups were comparable with regards to age, sex and weight of the patients. Our results showed that both esmolol and dexmedetomidine decreases the mean heart rate and mean blood pressure and prevent the hemodynamic and sympathoadrenal responses to laryngoscopy and tracheal intubation. The results of our study are consistent with the results obtained in other studies. [7, 8] Similarly in the intraoperative period the blood pressure remained at a lower level with a systolic blood pressure between 80-90mmHg. Thus it is clear that esmolol and dexmedetomidine provides controlled hypotension in middle ear surgeries of 2-3 hr duration. However the difference between the two groups was statistically not significant. [Figure 1, 2] The results of our study are consistent with the results obtained in another study. [9] In modern anesthetic practice, we are using a variety of agents with different pharmacokinetic and pharmacodynamic profiles in order to maximize their benefits and minimize their adverse effects. Thus it would be desirable to use an adjuvant which would reduce the requirement of the anesthetic agents and thus reduce the resultant side effects. By reducing the requirement of induction agent, inhalational agent, skeletal muscle relaxant and opioids, dexmedetomidine decreases the total dose of drugs that the patient is subjected to and thus decreases the risk of dose related adverse effects. In the present study, the thiopentone dose requirement was and 494 ± 12.93 in group E and 354.50 ± 17.26 mg in group D with the p-value of (0.022) which was statistically significant. [Table 2] Our results are in accordance with previous studies who observed a similar reduction in the dose requirement of thiopentone. [7] The mean amount of isoflurane used in group E and group D was 45.30 ml (± 5.85) and 13.79 ml (± 4.51) which is a 71.12% difference with a p-value of <0.002 which was statistically significant. [Table 2] We used the Dions formula for calculation of amount of isoflurane used in millilitre. [10, 11] Isoflurane has been found to be a good agent for ear surgeries. We observed a significant reduction in isoflurane use in the dexmedetomidine group as compared to esmolol group. [7, 12] Dexmedetomidine produces a decrease in activity of the

projections of the locus ceruleus to the ventrolateral preoptic nucleus. This increases GABA and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections. The α 2 agonists seem to inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels. It thus produces subcortical depression which reduces the requirement of maintenance agent. A 62.5% reduction in the induction dose of propofol, with a 30% less end-tidal concentration of isoflurane requirement for maintenance of anesthesia was noted in other studies. [13, 14, 15] Similarly there was a definite decrease in the requirement of vecuronium in the dexmedetomidine group than esmolol group and the difference was statistically significant. [Table 2] There is no direct interaction of dexmedetomidine with the neuromuscular junction but it is a known fact that deepening the plane of anesthesia reduces the requirement of muscle relaxant. It suggests a cortical action as cortical depression promotes unconsciousness, leading to immobility, which is opposed by ambient stimulation and the excitatory effects of pain projected on the cortex. Dexmedetomidine provides both hypnosis and analgesia. Thus the cortical stimulation for purposeful movement is suppressed. The drug provides a more stable anesthetic plane by attenuation of the stress response. This could explain the reduced requirement of the neuromuscular blocking agent. But the fact that we have observed a reduced requirement of non-depolarising neuromuscular blocking agents (NMBA) by monitoring the train of four (TOF) ratio shows that there should be some other explanation for the prolongation of the duration of the NMBA like post synaptic augmentation. Further studies are required to draw a definitive conclusion. In addition to this pharmacodynamic interaction which we assume to be present, there could be an explanation in relation to the pharmacokinetic interaction. The effect of dexmedetomidine on neuromuscular blockade with rocuronium was studied. It was concluded that the change in twitch tension was the result of the increased rocuronium concentration. The reason for the increase in plasma rocuronium concentration in the presence of

dexmedetomidine was not clear. That dexmedetomidine may have altered the biodisposition of rocuronium was proposed. The clearance of rocuronium decreased by 6% over the course of dexmedetomidine infusion, which suggests that dexmedetomidine influences the pharmacokinetics of rocuronium. The above studies suggest that there could possibly be a pharmacokinetic interaction between dexmedetomidine and NMBA. [16] Adequacy of surgical field in terms of pulsatility and oozing was noted by the surgeon in both the groups. By improving the surgical field esmolol as well as dexmedetomidine provides better operating conditions for the surgeon and reduces the blood loss, thus decreasing the requirement of blood transfusion and its attending risks. We have carried out a subjective assessment

by the surgeon (who was blinded) of adequacy of surgical field. [17] However, there was no statistically significant difference between the two groups.

The possible explanation could be that dexmedetomidine reduces the amount of circulating catecholamines and thus reduces the pulsatility and oozing from the surgical field. This effect could be attributed to the sympatholytic effect and hypotension and bradycardia associated with the use of dexmedetomidine. [18, 19, 20]

A possible limitation of our study may have been the use of subjective criteria to determine dose of thiopentone and isoflurane for each patient. Estimating anesthesia depth by changes mediated by autonomic nervous system is difficult during dexmedetomidine infusion as it increases the hemodynamic stability. Intraoperative Bispectral index (BIS)

monitoring would have been definitely more objective in deciding the depth of anesthesia and the requirement of anesthetic agent. It was not done because of practical difficulty. Measurement of the end-tidal isoflurane concentration would have been ideal to indicate the depth and for quantifying decrease in utilization between the groups.

Conclusion

Both the drugs esmolol as well as dexmedetomidine provide controlled hypotension in middle ear surgery, reduce the stress response associated with intubation and surgical stimulation and minimize the intra-operative hemodynamic alterations. However in addition as compared to esmolol, dexmedetomidine had an advantage in terms of decrease in the dose of induction agent and intraoperative requirement of inhalational agent as well as muscle relaxant.

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