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COMPARING HYPOTENSIVE PROPERTIES OF DEXMEDETOMIDINE AND CLONIDINE FOR INDUCED HYPOTENSION DURING SINUS SURGERY: A RANDOMISED, DOUBLE-BLIND STUDY

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ABSTRACT

Background: Functional endoscopic sinus surgery (FESS) has been proposed as a selected treatment used in patients with chronic sinusitis. Due to the nature of the location of endoscopic sinus surgery, even a small amount of bleeding can reduce the operative visibility and thus cause surgeon dissatisfaction and prolong the operation trauma. This study was conducted to compare the hypotensive effectiveness and haemodynamic stability of dexmedetomidine and clonidine in patients undergoing elective FESS. **Methods:** 72 patients in 25-45 years age-group, posted for ambulatory FESS procedures under general anesthesia were randomly divided into two groups (n = 36 each) receiving dexmedetomidine 1µg/kg and clonidine 2µg/kg, respectively; both diluted in 10 ml saline solution 15 min before anesthetic induction. Nasal bleeding and surgeon's satisfaction score; amount and number of patients receiving nitroglycerine for analgesia and deliberate hypotension, duration of hypotension, hemodynamic parameters and side effects were recorded for each patient. **Results:** Nasal bleeding score,though non significant amongst the groups, was lesser with clonidine group. Again due to less bleeding and excellent operative condition, surgeon's satisfaction score was better in clonidine treated group than dexmedetomidine pretreated group but it was found to be non significant. Side effects such as nausea, vomiting, shivering were all comparable among two groups, but bradycardia and hypotension were significantly higher in Group B ($P < 0.05$). **Conclusions:** Dexmedetomidine found to be providing more effectively controlled hypotension and analgesia, and thus, allowing less nasal bleeding as well as more surgeons' satisfaction score than Clonidine with less hemodynamic alterations.

KEYWORDS: Clonidine, controlled, dexmedetomidine, hypotension, functional endoscopic sinus surgery; mean arterial pressure.

INTRODUCTION

Functional endoscopic sinus surgery (FESS) has been proposed for patients with chronic rhinosinusitis, and is widely used in patients where conservative management has failed. Due to the nature of such surgeries, intra-operative bleeding, of even a small amount, can leave a negative effect on the vision of the surgeon leading to many problems in establishing a proper surgical field; thus, surgery becomes harder and longer.[1] Impaired visibility due to excessive bleeding is a major hurdle that has been reported for FESS under general anesthesia (GA).[2] Intraoperative bleeding may be reduced most effectively by induced systemic hypotension. There are several important advantages of using the intentional hypotensive anesthetic technique during FESS like reduction in blood loss; hence, reduction in blood transfusion rate, improvement in the surgical field, and reduction of the duration of surgery.

Therefore, controlled hypotension, which is a technique in which the arterial blood pressure is lowered in a controlled manner to minimize blood loss and associated complications, and also to enhance the operative field visibility, is used.[3,4] In hypotensive anesthesia, the patient's baseline mean arterial pressure (MAP) is reduced by 30% or MAP is kept at 60-70 mm Hg.[5,6] For achieving controlled hypotension, several agents such as nitroglycerine,[7] higher dose of inhaled anesthetics,[8] vasodilators[9,10] and β blockers have been used either alone or in combination with each other; however, an ideal agent for inducing controlled hypotension cannot be asserted. The ideal agent used for controlled hypotension must have the characteristics, such as: ease of administration, short onset time, effect that disappears quickly when administration is discontinued, rapid elimination, nil or negligible effects on vital organs, and predictable, dose-dependent effects.[11,12]

Clonidine is also a selective α-2 adrenergic agonist with some α-1 agonist properties and acts by decreasing the

sympathetic nervous system output from the central nervous system. In clinical studies on FESS, preoperative intravenous (IV) administration of clonidine can reduce surgical time and improve surgical results through a less bloody field.[13] Oral clonidine premedication also yielded similar results during FESS.[14,15] Various studies have found that preoperative administration of clonidine decreases mucosal bleeding in FESS, which improves surgical field visibility and reduces the duration of surgery.[16-18]

Dexmedetomidine is highly selective (8 times more selective than clonidine),[19] specific, and potent α_2 - adrenergic agonist having analgesic, sedative, antihypertensive, and anesthetic sparing effects when used in the systemic route.[20] It binds to trans-membrane G protein-binding adreno-receptors and has a unique property among sedatives, as it produces sedation without causing respiratory depression, anxiolytic, and sympatholytic property in anesthesia.[21] The sympatholytic performance of dexmedetomidine is manifested by reduced arterial blood pressure, heart rate, cardiac output, and reduced release of norepinephrine.[22] Prior administration of dexmedetomidine can also provide a hypotensive anesthesia, a better surgical field, and finally an abbreviated operative duration.[23,24] It acts through central α-2A and imidazoline type 1 receptors. The activation of these central receptors results in a decrease in norepinephrine release, which leads to a decrease in blood pressure and heart rate.

Dexmedetomidine and clonidine both have been used for checking of haemodynamic response to laryngoscopy and tracheal intubation.[25,26] The aim and objective of this study was primarily to compare the efficacy for producing controlled hypotension by preoperative IV dexmedetomidine and clonidine during FESS in adults in an ambulatory care setting. Primary objective being to assess and compare the hypotensive effectiveness and haemodynamic stability of dexmedetomidine and clonidine in FESS by comparing the haemodynamic parameters from the baseline at different time intervals within each group (intragroup) and between both the groups (intergroup). The secondary objectivewes to assess and compare the quality of the intraoperative surgical field, emergence time, sedation score, visual analogue scale (VAS) score and time to first rescue analgesic demand in the post-operative period and to compare the proportion of cases with side effects.

MATERIAL AND METHODS

A hospital-based prospective, double-blinded, randomised double-blind interventional comparative study was conducted during a period of 6 months on a total of 72 adult patients, in SMGS Hospital, Jammu. Patients were randomly allocated to two equal groups (36 in each group) using computer generated random number list. A written informed consent was obtained from all participants. Ethical clearance was duly obtained from institutional ethical committee before the start of the study. Preoperative assessment was done by an anaesthetist the day before surgery. Demographic data such as age, weight, height, body mass index were also recorded.

Inclusion Criteria: All patients with ASA I and II, aged between 25 and 45 years, of both gender, undergoing FESS under GA, were enrolled in the study.

Exclusion Criteria: Patients with ASA physical status classification III, IV; Patients having a history of hypertension, coronary artery disease, heart blocks, autonomic neuropathy, renal dysfunction, hepatic dysfunction, recurrent sinus surgery and allergy to study drugs were excluded from the study. Patients with any known hypersensitivity or contraindication to clonidine, dexmedetomidine, nitroglycerine, fentanyl; pregnancy, lactating mothers, hepatic, renal or cardiopulmonary abnormality, alcoholism, diabetes, patients on calcium channel blockers, and bleeding diathesis were excluded from the study. Patients having a history of significant neurological, psychiatric, or neuromuscular disorders were also excluded.

Double blinding was done in such a manner that the anaesthesiologist who administered anaesthesia was different from the anaesthesiologist who recorded study variables. A routine pre-anaesthetic check-up was done a day before surgery. Resident doctors keeping records of different parameters were also unaware of group allotment.

First group: Group A, received dexmedetomidine 1 µg/kg in 10 ml of saline over 10 min followed by 1 µg/kg/h infusion. Second group: Group B, received clonidine 2 µg/kg in 10 ml of saline over 10 min followed by 1 µg/kg/h infusion. Loading dose of study drugs were given 10 min before induction of general anaesthesia (GA), and its maintenance dose infusion was started soon after induction of anaesthesia and continued intra-operatively until 5 min before the completion of surgery or stopped on the occurrence of hypotension below our target, whichever was earlier.

Patients were premedicated withinj. glycopyrrolate 4 µg/kg and inj. tramaol1mg/kg intravenously. Anaesthesia was induced with inj. thiopentone sodium 5 mg/kg and inj. succinylcholine 1.5 mg/kg and maintained on oxygen-nitrous oxide (40:60), isoflurane (0.4%–1%) and intermittent boluses of atracurium. Muscle relaxation was maintained with intermittent IV atracurium (0.2 mg/kg) as and when required. Controlled ventilation was maintained manually with 33% oxygen in 66% nitrous oxide and isoflurane up to 1-2 MAC.

A solution containing 40 mg/2 mL lidocaine hydrochloride + 0.025 mg/2 mL epinephrine was applied directly or through soaked cotton to the nasal side of both the medial and lateral conchae, for topical vasoconstriction/ local anesthesia.

When preoperative MAP was ≥70 mm of Hg, 50 µg of nitroglycerine was applied; again when MAP was ≤55 mm Hg, 6mg of mephentermine was applied. When heart rate (HR) was ≤50, 0.6 mg IV atropine was applied to combat bradycardia.

Intraoperative haemodynamic parameters such as heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP) and oxygen saturation (SpO_2) were recorded at baseline, after the loading dose, after induction, 1 min after intubation, 5 min after intubation and thereafter every 10 min until shifting ofthe patient to the recovery area.

At the completion of surgery, the residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV, and patient was extubated. After extubation, all patients were transferred to the postanesthesia care unit (PACU).

The severity of bleeding was calculated by using the average category scale proposed by Fromme and Boezaart.[27,28] [score 0 = no bleeding; score 1 = slight bleeding; score 2 = slight bleeding, occasional suctioning required; score 3 = slight bleeding, frequent suctioning required; score 4 = moderate bleeding, frequent suctioning required, bleeding threatens surgical field directly; score 5 = bleeding appears faster than can be removed by suction, surgical field severely threatened].

Post-operatively, patients were kept in the recovery room, haemodynamic parameters, emergence time and sedation score were recorded every 30 min. Sedation was assessed by using Ramsay Sedation Score.[29] Post-operative pain was assessed by VAS score every 15 min until the patient reached a VAS score of3. Time to first rescue analgesia was noted and patients were given intravenous diclofenac 75 mg as rescue analgesia. Post-operative complications like nausea, vomiting, shivering, dryness of mouth, hypotension and bradycardia were also recorded.

Microsoft Excel 2010 software was used for data analysis, and for statistical evaluation, of categorical variables/proportion of cases like the occurrence of complications was analyzed using Chi-square test. Normally distributed continuous variables were analyzed using the independent sample *t*-test and $P < 0.05$ was considered statistically significant.

Hypotension was defined as MAP <65 mmHg and was treated by stopping hypotensive agent and giving fluid bolus and inj. mephentermine 6 mg bolus as per need. Bradycardia was defined as HR <50/min and treated with intravenous atropine 0.6 mg if not resolved by stopping study drug infusion.

RESULTS

There were no dropouts out of the 72 patients enrolled. The age, sex distribution, body weight, height, ASA status, preoperative Hb, and duration of surgery were found to be comparable between the two groups without any significant difference. (Table 1)

Table 1: Demographic profile of both groups.

Characteristics	Group A (*n*=36)	Group B (*n*=36)	*P*
Age (Years), Mean±SD	33.54 ± 6.22	34.83 ± 7.29	0.806
Gender: Male/Female (No.)	19/17	18/18	0.832
Weight (kg), Mean ± SD	60.47 ± 6.93	59.62 ± 5.63	0.480
Height (cm)	163.1 ± 6.2	161.8 ± 5.8	0.657
ASA Physical Status- I/II	28/8	27/9	0.746
Hemoglobin (g%) Mean ± SD	10.12 ± 2.04	10.26 ± 2.73	0.559
Duration Of Surgery (min), Mean ± SD	65.33 ± 5.49	73.27 ± 6.48	0.028*

Group A: Dexmedetomidine 1 µg/kg; Group B: Clonidine 2 µg/kg
*P<0.05 = significant

Mean arterial pressure (MAP) were significantly decreased ($P < 0.05$) at all observation time points after giving a loading dose of study drugs in comparison to baseline in both the groups, however, it was significantly lower in Group A in comparison to Group B.

Table 2: Mean arterial pressure (MAP) (mmHg) and Heart Rate (HR).

	MAP			HR		
Time point	**Group A (*n*=36)**	**Group B (*n*=36)**	**p-value**	**Group A (*n*=36)**	**Group B (*n*=36)**	**p-value**
Baseline	90.56 ± 4.39	91.61 ± 5.03	0.420	84.2 ± 5.6	85.2 ± 5.0	0.649
After induction	80.04 ± 3.92	84.62 ± 4.66	0.025*	80.4 ± 5.8	81.8 ± 4.4	0.547
5 min after intubation	73.22 ± 3.74	79.83 ± 6.19	0.010*	76.2 ± 4.3	77.3 ± 5.2	0.317
10 min	68.15 ± 4.03	75.62 ± 5.79	0.001*	71.0 ± 5.2	75.8 ± 6.5	0.043*
20 min	63.22 ± 4.65	72.87 ± 4.07	0.009*	69.4 ± 8.9	71.1 ± 5.7	0.119
30 min	62.43 ± 3.85	68.76 ± 5.17	0.029*	62.8 ± 6.8	68.2 ± 6.7	0.028*

40 min	61.82 ± 3.43	66.58 ± 5.93	0.037*	61.2 ± 6.0	67.7 ± 8.8	0.064
50 min	63.18 ± 4.77	68.42 ± 6.65	0.038*	60.3 ± 5.4	65.3 ± 6.2	0.029*
60 min	68.92 ± 4.93	71.78 ± 5.16	0.051	65.5 ± 5.3	69.6 ± 4.1	0.041*

**P<0.05* = significant

However, nasal bleeding score was not significant (P >0.05) amongst the groups, and side effects such as nausea, vomiting, shivering were also comparable among two groups, but bradycardia and hypotension was found significantly higher in Group A (P < 0.05). (Table 3)

Table 3: Bleeding Score.

Nasal Bleeding Score	Group A (n=36) (%)	Group B (n=36) (%)	P-value
0	4	2	0.180
1	12	8	
2	14	13	
3	4	7	
4	2	5	
5	0	1	

**P<0.05* = significant

Mean time to first rescue analgesia was significantly longer in group A (98.97 ± 10.46 min) as compared to group B (79.03 ± 10.45 min) (*P*< 0.001). Post-operative complications were statistically comparable between the two groups.

DISCUSSION

In developing countries, most of the patients avoid bearing expenses of prolonged hospital stay. At the same time, infrastructure in these countries is not organized uniformly to smoothly deliver the day care procedures. In the day care scenario, hemorrhage in the immediate postoperative period is the most common cause of delayed recovery and discharge after ambulatory surgery and most frequent (even extending up to 8.8%) cause of unplanned admission and subsequently delayed return to work.[30] FESS is usually done for the treatment of patients with acute as well as chronic sinonasal disease who do not respond to the conventional medical treatment. Good visibility during FESS is necessary because of nasal tiny anatomical structures, which are full of vessels and limit the nasal endoscopic access. In such situation, even a minor bleeding can lead the surgical procedure left unfinished.[31]

In this study, we had chosen a target MAP 60-70 mm Hg to provide the best surgical conditions without the risk of tissue hypoperfusion depending on a review of literature conducted by Barak et al. with a MAP of 50-65 mm Hg during major maxillofacial surgeries.[32] Hypotensive anesthesia induced by using sodium nitroprusside or nitroglycerine in mandibular osteotomy to achieve MAP 60-70 mm Hg was found to be absolutely safe and associated with no significant increase in pyruvate, lactate, or glucose levels.[33]

Clonidine is effective by the stimulation of pre- and post-synaptic α2 -agonists in many areas of the central nervous system leading to sedation, analgesia, and reduction of sympathetic tone.[34] Single preoperative administration of clonidine can reduce surgical time and improve surgical results through a less bloody field resulting in lower patient morbidity and improvement of operating room resources.[35] But, dexmedetomidine, is a more highly specific α2 -adrenoreceptor agonist (α2 /α1 = 1620/1) than clonidine (α2 /α1 = 220/1), has been approved by Food and Drug Administration as a short-term sedative for mechanically ventilated Intensive Care Unit patients.[36]

Dexmedetomidine causes a reduction in blood pressure, slowing of HR, sedation and analgesia. The fall in blood pressure is mainly due to inhibition of central sympathetic outflow and due to stimulation of presynaptic α-2 adrenoceptors decreasing norepinephrine release.[37] Dexmedetomidine has a very minimal respiratory depressant effect with potent sedative and analgesic effects compared with opioids and other sedatives. The important problem involved in FESS is bleeding from the sinuses. Controlled hypotension has a definitive role in FESS as it reduces bleeding during surgery and improves visibility of the surgical field, which can decrease the duration of surgery and anaesthesia. There are several studies comparing dexmedetomidine with other agents for FESS but very few directly comparing it with clonidine.

In the present study, we found that though induced hypotension was achieved with both the drugs, dexmedetomidine produced more stable haemodynamics with lower readings of MAP and HR along with more prolonged post-operative analgesia and conscious sedation in comparison to clonidine. These results were consistent to Suggala*et al.*[38], who also noted that the time to first rescue analgesic request was significantly prolonged in the dexmedetomidine group along with higher sedation scores as compared to clonidine.

Kim *et al.*,[39] in a meta-analysis of randomised controlled trials comparing the perioperative administration of hypotensive agents, found dexmedetomidine to be a superior agent. They also concluded that systemic use of dexmedetomidine reduces intraoperative bleeding and operating time, provides relatively stable haemodynamics by alleviating stress response and reduces the fentanyl requirement significantly, which was quite similar to our observations.

Moshiri *et al.*[40] compared dexmedetomidine with propofol and found that the desired surgical field is made possible by reducing HR rather than vasoconstriction. In

our study, the HR was comparativelyless fluctuating in the dexmedetomidine group, which is in favour of more stable haemodynamics and blunting of response to sympathomimetic stimuli by dexmedetomidine.

In our study, nausea, vomiting, and shivering were comparable among two groups. But, the bradycardia was more in the clonidine group in a significant manner than dexmedetomidine group but the patients receiving atropine for bradycardia was again comparable among two groups. Similar results were observed by Guven *et al*. While doing a study on dexmedetomidine versus magnesium sulfate for producing controlled hypotension for the patients undergoing FESS.[41] Again, dexmedetomidine producing hypotension was significantly less than clonidine. Quite similar results were found while administering preoperative IV clonidine by Zalunardo *et al*. in their placebo-controlled study for attenuating stress response during emergence from anesthesia.[42]

It is quite evident that durations of surgery and anesthesia were quite comparable among the two groups. These results were very similar to the study with same two drugs, conducted by Mariappan *et al*.[43] At the same time, they found that the recovery was similar among two groups, but in our study, PACU recovery and hospital discharge was significantly earlier in dexmedetomidine group than clonidine. In our study, duration of controlled hypotension was prolonged in Group D than Group C but the difference was clinically insignificant. Similar result was also found by Mariappan *et al*.[43]

Missing out a control group can be a limitation of our study, however it is not possible not to try to control bleeding in FESS where surgical field visibility may be compromised due to bleeding. However, a larger study with larger sample size needs to be conducted to establish the author's point of view with solidarity.

CONCLUSION

The study concludes dexmedetomidine provides better haemodynamic stability in comparison to clonidine, for providing controlled hypotension, rendering an excellent surgical field with higher surgeon's satisfaction and lesser analgesic requirement without major hemodynamic alteration. Both the drugs achieve ideal operative field visibility and decrease in blood loss; however, dexmedetomidine provides an additional benefit of prolonged analgesia and conscious sedation with less hemodnamic alterations.

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