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Dexmedetomidine Nasal Drops in Endoscopic Sinus Surgery: Does It Have A Benefit?

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ABSTRACT

Background: Although functional endoscopic sinus surgery (FESS) allows better visualization during surgical dissection, the occurrence of intraoperative bleeding may hinder this advantage. Controlled hypotension is recommended to decrease intraoperative bleeding, and it could be achieved by multiple medications that have some undesirable side effects. Dexmedetomidine, an alpha-2 agonist, is known to induce hypotension and its intranasal administration is understudied. The current trial aims to evaluate its beneficial impact on intraoperative and postoperative parameters during FESS.

Patients and methods: A prospective, randomized study was conducted on eighty patients, who were divided into two equal groups; Group D received 1 ml (100 µg) dexmedetomidine nasal drops, and Group F received fentanyl (1.5 µg/kg) as nasal drops. Both medications were administered after installing local anesthesia.

Results: We noted no significant differences between both groups regarding demographic variables and operative time. However, the severity of intraoperative bleeding, heart rate, and mean blood pressure decreased markedly in Group D. The sedation level was comparable between the two groups. As regards the analgesic profile, Group D showed a marked decline in postoperative pain scores (two and three hours after surgery) with a significant prolongation of the time to the first rescue analgesic. However, the percentage of patients requiring rescue analgesia was comparable between the two groups. **Conclusion:** The intranasal administration of dexmedetomidine during FESS has several advantages, manifested by the decrease in intraoperative heart rate, MAP, and bleeding severity and better postoperative analgesic profile compared to fentanyl.

Keywords: Dexmedetomidine; Intranasal; Controlled hypotension; Sinus surgery.

INTRODUCTION

The current otorhinolaryngology practice has witnessed great popularity and advances in the field of functional endoscopic sinus surgery or FESS. The enhanced illumination and magnification provided by endoscopy allow better operative field visualization[1]. Nonetheless, excessive intraoperative bleeding during FESS may hinder visualization and increase the possibility of surgical complications[2]. Therefore, controlled hypotension is recommended during these procedures to minimize the bleeding and improve surgical field quality[3]. Multiple pharmacological agents have been described to induce controlled hypotension during FESS, including high-dose inhalational anesthesia (isoflurane), B adrenergic antagonists (esmolol and propranolol, and vasodilators (nitroglycerine and sodium nitroprusside) [4]. However, the previous agents have their disadvantages. High doses of inhalational anesthesia may delay patient recovery after the surgery [5, 6], while esmolol may induce myocardial depression. In addition, systemic vasodilators can induce reflex tachycardia and rebound hypertension, along with the risk of cyanide toxicity with nitroprusside administration [7].

Dexmedetomidine, an alpha-2 adrenergic receptor agonist, has a higher affinity compared to clonidine (about eight times) [8, 9]. By its action on central alpha receptors, it has sympatholytic effects. Also, it has analgesic, anxiolytic, sedative, and peripheral vasoconstrictive actions [10, 11]. If administered during surgery, it induces a decline in both heart rate and blood pressure without a significant effect on the cardiac output as long as its concentration is below 5.1 mcg/ml/ [12]. Additionally, it does not compromise the respiratory center [12, 13]. Furthermore, it has other advantages including a decrease in postoperative nausea, vomiting, and delirium [14-16].

Although the beneficial effects of dexmedetomidine have been widely described in the literature, there is a clear paucity of studies handling its pharmacokinetics and bioavailability with intranasal administration. That is why we conducted the present trial to elucidate the effects of intranasal administration of 100 µg dexmedetomidine on intraoperative blood pressure, bleeding severity, and postoperative sedation in FESS patients.

AIM OF THE WORK

Our study aims to investigate the effect of 100 µg of dexmedetomidine nasal drops in FESS on systemic blood pressure, heart rate, and sedation.

PATIENTS AND METHODS

After receiving the included participants' informed written consent and receiving approval from our university institutional review board, this prospective, randomized study was carried out at Mansoura University Hospitals (IRB code: R.21.06.1351.R1.R2).

Inclusion criteria: Adult patients between the ages of 18 and 60 scheduled for FESS were targeted for the

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study, which took place from August 2021 to February 2022.

Exclusion criteria: We excluded patients with uncontrolled coagulation disorders, a history of opioid addiction, chronic clonidine therapy, chronic liver disease, renal impairment, significant cardiac disease (heart failure and symptomatic ischemic heart disease), pregnancy, or a history of previous allergy to the study medications. We also excluded patients with a history of nasal allergy or requiring revisional nasal surgery.

We estimated the required sample size via the Priori G Power analysis, using an effect size of 0.6 to evaluate the mean arterial blood pressure (MAP) difference between the two groups. A sample of 72 patients in the two groups was yielded to achieve an 80% power and 5% alpha error, and that sample was increased to 80 patients for the expected 10% dropout. Hence, our study included 80 patients (40 in each group). All patients received the standard preoperative assessment. Additionally, all participants were reviewed by the anesthesia team and classified according to the "American Society of Anesthesiologists" or ASA class. Patients with ASA more than II were excluded from the current trial.

The included patients were randomly assigned into two equal groups; Group D included 40 patients who received 1 ml (100 µg) dexmedetomidine nasal drops after installing local anesthesia by the operating surgeon and Group F included 40 patients who received fentanyl (1.5 µg/kg) as nasal drops after installing local anesthesia. The randomization was done via the sealed envelope method. All procedures were performed under general anesthesia that was induced by propofol (1.5 – 2 mg/kg), IV fentanyl (1 µg/kg), and rocuronium (1 mg/kg) to facilitate endotracheal tube insertion. Anesthesia was maintained by isoflurane (0.1 – 1.5 MAC) in an air/oxygen mixture with a 40% FiO2.

5 min. before the surgical dissection, all patients were infiltrated by 4 ml bupivacaine (0.5%), 4 ml lidocaine (2%), 1 ml epinephrine (1:50000), and either 1 ml dexmedetomidine (100 µg) or fentanyl (1.5 µg/kg) as nasal drops in each nostril, according to group allocation. Baseline heart rate and MAP were recorded in all patients, then they were measured and recorded every 15 minutes during the procedure. The severity of intraoperative bleeding was determined by the Boezaart grading scale to assess the intraoperative surgical field [17]. The duration of the surgical procedure was recorded in both groups.

After the procedure ended, the patients were transferred to the Post Anesthetic Care Unit (PACU). Their sedation level was assessed via the "Richmond Agitation Sedation Scale" or RASS [18]. Then, they were transferred to the internal ward after completing the criteria for discharge. They were closely monitored and postoperative pain was assessed via the "visual analog scale" or VAS [19], which is an 11-point scale with zero for no pain sensation and 10 for the worst pain. VAS was recorded at PACU, then one, two, three, six, and 12 hours following the procedure.

Postoperative analgesia was achieved by IV ketorolac (30 mg/ 12 hours) and IV acetaminophen (1gm/8 hours). If the patients reported a VAS > 3, IV fentanyl (25 – 50 µg) was administered. The percentage of patients requiring rescue analgesia and the duration till requesting it were recorded in both study groups.

The main outcome of our trial was intraoperative hemodynamic changes, while secondary outcomes included the severity of intraoperative bleeding, postoperative sedation, and postoperative analgesic profile.

Ethical consideration:

Initially, the study protocol was approved by the Institutional Review Board (IRB) of Mansoura University, code R.21.06.1351.R1.R2, and all patients agreed to the terms of our research after explaining the benefits and possible drawbacks of each intervention. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans[20].

Statistical analysis

The SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA) was used to tabulate and analyze the collected data. While categorical variables were expressed as numbers (with percentages), quantitative data were expressed as mean (and standard deviation). The former data type was compared between the two groups using Fisher exact or Chi-square tests, while the latter type was compared using the student t-test. Any p-value less than 0.05 was considered statistically significant.

RESULTS

Starting with patients' demographic data, patients in Group D had a mean age of 35.28 years, compared to 35.7 years in Group F patients. As regards their gender, the male gender was more prevalent in both groups as they represented 62.5% and 52.5% of patients in Groups D and F respectively. Patients with ASA class I represented 77.5% and 85% of participants in the same two groups respectively, whereas the remaining patients had ASA class II. The statistical analysis did not reveal any significant difference between the two groups regarding either of the previous parameters (**Table 1**).

The duration of the surgical procedure had a mean value of 86.38 minutes in Group D versus 88.75 minutes in Group F, with no significant difference between the two groups. There was a marked decrease in the severity of intraoperative bleeding in Group D, as Boezaart grade IV was encountered in 7.5% of its cases, versus 25% of Group F patients ($p = 0.025$). RASS had mean values of 0.48 and 0.88 in Groups D and F respectively, with no significant difference in statistical analysis (**Table 1**).

Table (1): Demographic criteria, operative time, intraoperative blood loss, and RASS in the study groups.

		Group D (n= 40)	Group F (n= 40)	P
Age (years)		35.28 ± 9.318	35.70 ± 8.340	0.830
Gender	**Male**	25 (62.5%)	21 (52.5%)	0.366
	Female	15 (37.5%)	19 (47.5%)	
ASA	**1**	31 (77.5%)	34 (85.0%)	0.390
	2	9 (22.5%)	6 (15.0%)	
Operating time (minutes)		86.38 ± 13.204	88.75 ± 11.309	0.390
Intraoperative bleeding (Boezaart grade)	**II**	13 (32.5%)	5 (12.5%)	**0.025**
	III	24 (60.0%)	25 (62.5%)	
	IV	3 (7.5%)	10 (25.0%)	
RASS score at PACU		0.48 ± 1.132	0.88 ± 0.822	0.099

As shown in **Table 2**, although the two study groups had comparable baseline heart rates (p = 0.632), the subsequent intraoperative heart rate readings tended to have significantly lower values in Group D (p < 0.05).

Table (2): Changes in heart rate in the two groups

Heart rate (bpm)	Group D (n= 40)	Group F (n= 40)	P
Baseline	85.30 ± 10.400	86.60 ± 13.570	0.632
15 minutes	82.73 ± 10.915	88.78 ± 14.487	**0.038**
30 minutes	78.63 ± 9.826	90.90 ± 14.681	**< 0.001**
45 minutes	78.75 ± 10.541	91.48 ± 14.772	**< 0.001**
60 minutes	78.83 ± 10.865	91.50 ± 15.135	**< 0.001**
75 minutes	78.83 ± 11.112	91.60 ± 15.460	**< 0.001**
90 minutes	80.11 ± 9.857	93.57 ± 16.039	**0.003**

MAP showed similar changes in heart rate (**Table 3**). Baseline MAP did not express any significant differences between the two groups (p = 0.969). Nonetheless, intraoperative readings showed a marked decreased MAP in Group D compared to Group F (p < 0.05).

Table (3): Changes in MAP in the two study groups.

MAP (mmHg)	*Group D (n= 40)*	*Group F (n= 40)*	*P*
Baseline	***93.43 ± 5.467***	***93.38 ± 5.982***	***0.969***
15 minutes	***88.75 ± 5.714***	***95.83 ± 6.275***	***< 0.001***
30 minutes	***84.40 ± 6.201***	***98.00 ± 6.679***	***< 0.001***
45 minutes	***84.75 ± 6.625***	***98.45 ± 7.802***	***< 0.001***
60 minutes	***84.45 ± 7.214***	***98.20 ± 8.486***	***< 0.001***
75 minutes	***84.63 ± 7.510***	***98.28 ± 8.218***	***< 0.001***
90 minutes	***85.17 ± 6.474***	***96.87 ± 8.719***	***< 0.001***

Although our two groups expressed no significant difference regarding postoperative VAS either at PACU or one hour after the operation, the two- and three-hour readings were markedly decreased in Group D (p = 0.03 and 0.02 respectively). The duration till the first rescue analgesia showed a marked prolongation in Group D (3.49 vs. 2.33 hours in Group F – p = 0.03). However, the same groups had a comparable incidence in the patients requiring rescue analgesia (87.5% vs. 97.5% in Groups D and F respectively). **Table 4** summarizes the previous data.

Table (4): Analgesic profile during the postoperative period in the two study groups.

		Group D (n= 40)	*Group F (n= 40)*	*P*
VAS	***PACU***	***2.10 ± 0.810***	***2.28 ± 1.132***	***0.556***
	1 hour	***2.75 ± 0.981***	***2.85 ± 1.210***	***0.772***
	2 hours	***3.35 ± 1.167***	***4.10 ± 1.646***	***0.030***
	3 hours	***3.53 ± 1.320***	***4.35 ± 1.406***	***0.020***
	6 hours	***4.72 ± 1.450***	***4.33 ± 1.700***	***0.150***
	12 hours	***3.85 ± 1.494***	***3.68 ± 1.366***	***0.621***
Patients who required rescue analgesia		***35 (87.5%)***	***39 (97.5%)***	***0.090***
First analgesics request (hours)		***3.49 ± 2.501***	***2.33 ± 2.298***	***0.030***

DISCUSSION

Bleeding during FESS could impair intraoperative visibility leading to disastrous problems during the procedure. Therefore, it is crucial to maintain controlled hypotension to minimize blood loss during such procedures [21].

So, we evaluated if intranasal dexmedetomidine could have a beneficial impact on intraoperative hemodynamics and surgical field quality in FESS patients. This idea is poorly discussed in the literature, which poses a great advantage for our study.

On looking at our preprocedural data, the reader could notice almost no significant difference between our two groups. This indicates our proper randomization technique, and that should also nullify any bias skewing our findings in favor of one group rather than the other. That poses a second advantage of our study.

In our study, although heart rate and MAP showed comparable findings between the two groups at baseline, the subsequent intraoperative readings showed a marked decline of the previous two parameters in Group D compared to group F.

Other multiple studies confirmed the effects of dexmedetomidine on both heart rate and blood pressure [22-24]. It mediates the previous two actions by its agonistic action on alpha-2 receptors leading to sympatholytic action via decreasing the circulating norepinephrine concentrations [25].

The systemic effects of dexmedetomidine could be explained by its absorption through the nasal mucosa that has a rich blood supply, and that has been documented in previous studies that confirmed its safe and effective transmucosal absorption through both nasal [26] and oral mucosae [27].

In our study, we noted a significant decline in the bleeding severity in association with dexmedetomidine, indicating a decreased intraoperative loss with that medication. That could be secondary to the controlled hypotension secondary to the systemic absorption of the drug, or its local peripheral vasoconstrictive action mediated by its action on alpha-2B receptors present in the vascular smooth muscles [28]. Of course, the decreased intraoperative bleeding has multiple advantages including better visualization of the anatomical structures, easier dissection, and decreased risk of injury to the nearby structures.

In line with our findings, **Tang *et al***. noticed a marked decline in intraoperative blood loss during FESS. It had mean values of 60 in the dexmedetomidine group and 78.2 ml in the placebo group ($p = 0.03$). Also, the operating surgeon showed more satisfaction with the operative field quality in the dexmedetomidine group [22].

Although RASS was statistically comparable between our two groups, Group D had decreased RASS values compared to Group F indicating more sedation in association with dexmedetomidine administration. That could be explained by the central action of the drug on alpha-2 receptors leading to the decline of central nervous system excitation, especially in the locus coeruleus [29]. The absence of statistical differences could be attributed to the small sample size.

In the current trial, we noticed a marked decline in postoperative pain scores one and three hours after the procedure in Group D compared to Group F. As we believe in the concept of "preemptive analgesia", we intended to install the drug before surgery to prevent sensitization and decrease pain sensation after the procedure [30, 31].

Pain after FESS is mediated through surgical trauma to the nasal and sinus mucosa leading to the release of proinflammatory cytokines including interleukin 6 and tumor necrosis factor, which induce pain sensitization [32-34]. One study has proved the effect of dexmedetomidine in decreasing the previous inflammatory markers [22]. However, we did not measure the previous markers in our study, and that poses a limitation of this trial.

Furthermore, dexmedetomidine can induce inhibition of pain-transmitting fibers including the C- and Aα-ones. Also, the decreased release of norepinephrine results in hyperpolarization of the presynaptic membranes leading to decreased pain transmission to the brain [35]. The previous facts could elucidate how dexmedetomidine provided a better analgesic profile compared to the other group, which was also manifested by the increased duration till the first analgesic request.

All in all, we recommend the administration of intranasal dexmedetomidine during FESS because of its multiple advantages to both the surgeon and anesthetist, without significant major drug-related side effects.

Limitations of the study:

Finally, one should mention the limitation of our study. We included a small sample of patients who were collected from a single institution.

CONCLUSION AND RECOMMENDATION

The intranasal administration of dexmedetomidine during FESS has several advantages, manifested by the decrease in intraoperative heart rate, MAP, bleeding severity, postoperative pain, and prolongation of the time to the first rescue analgesic, with no significant side effects compared to the fentanyl group. Also, we recommend measuring stress biomarkers along with serum dexmedetomidine levels to evaluate the degree of systemic absorption with mucosal administration. More studies should be performed in the future to overcome the previous limitations.

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