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A comparative study between the effect of intravenous versus intranasal dripping of dexmedetomidine on intraoperative blood loss during functional endoscopic nasal sinus surgery

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ABSTRACT

Background: Functional endoscopic sinus surgery (FESS) is considered one of the most common ENT procedures. The main obstacle is impaired vision owing to excessive bleeding. Many drugs have been used to control such issues. Dexmedetomidine has a great affinity to α^2-adrenergic receptors. This research evaluated the hypotensive effect of intravenous against the intranasal dexmedetomidine in FESS.

Materials and methods: Patients randomized into 2 equal groups:Dexmedetomidine intravenous group (IV group) ($n = 35$): IV dexmedetomidine 1 µg/kg in 100 ml of normal saline (0.9%) was infused 15 min before starting anesthesia, followed by 0.5 µg/kg/h. At the same time, intranasal saline was given as a placebo.Dexmedetomidine intranasal group (IN group) ($n = 35$): IN dexmedetomidine (2 µg/kg) was given 15 min before induction, 1 ml in each nostril. At the same time, the patient received 100 ml of saline (0.9%)15 min before anesthesia, followed by IV saline as a placebo. The primary outcome was Boezaart's grading scale. Other outcomes were the recorded hemodynamics, surgical satisfaction, sedation score, and adverse events.

Results: The calculated blood loss and Boezaart's scale were lower in the IV group (p value < 0.001). Also, the IV group's mean arterial blood pressure (MAP) and heart rate were significantly lower. The total intraoperative fentanyl dose was lower in the IV group. Surgeon satisfaction and sedation scores were significantly higher in the IV group.

Conclusions: Intravenous dexmedetomidine provides a better surgical field, more surgeon satisfaction, and lower blood loss for FESS.

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Dexmetomedine; intranasal; FESS; α2-adrenergic receptors; boezaart scale

1. Background

Functional endoscopic sinus surgery (FESS) is considered one of the most common ENT procedures [1]. The main obstacle is impaired vision owing to excessive bleeding, which is rare. However, even scarce bleeding could impair vision, increasing complications such as damage to arterial branches or other adjacent anatomical structures [2]. Consequently, deliberate hypotension is required to control intraoperative bleeding effectively. Many pharmacological drugs, such as nitroglycerine, sodium nitroprusside, vasodilators, high MAC of inhaled anesthetics, and B-blockers, have been used [3]. However, each of these drugs had many side effects.

Dexmedetomidine has a great affinity to α^2-adrenergic receptors. The dose-dependent effects of dexmedetomidine are sedative effect, analgesic effect, sympathetic inhibition, and reduced stress with preservation of respiration. It has a dual effect on blood pressure, depending on the dose [4].

Intravenous dexmedetomidine had been used effectively for deliberate hypotension in the FESS against the placebo group under local anesthesia [5]. Also, during general anesthesia against esmolol [6], magnesium sulphate [7], nitroglycerine [8]or remifentanil [9]. These studies have revealed it as an efficient and safe alternative to other agents.

Intranasal dexmedetomidine has been used for pain relief and sedation in healthy volunteers [10] and third molar extraction surgery [11]. Recently, it has been used in FESS, resulting in improved surgical field and less bleeding [12].

Regarding English literature, no clinical studies has compared the ideal application of dexmedetomidine intravenous or intranasal. Therefore, this research evaluated the hypotensive effect of intravenous against the intranasal dexmedetomidine in FESS, with the primary outcome of calculating the intraoperative blood loss and its impact on intraoperative conditions.

2. Patients & methods

This prospective double-blinded randomized study was investigated at the ENT division of the hospitals affiliated with Mansoura University. Seventy consecutive

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candidates scheduled for FESS were enrolled in the study. The clinical part of the research was started after getting permission from the Institutional Research Board (IRB)of Mansoura Faculty of Medicine coded with MS.210401452. Eligible patients of both sexes, aged between 18 and 60 years, classified as either class I or II according to the American Society of Anesthesiologists (ASA), were selected to be enrolled in the study.

The following were considered as exclusion criteria: patient refusal, hypertensive individuals, pregnancy, neuromuscular illnesses (such as myopathies and myasthenia gravis), hematological diseases, and abnormalities. Also, the participants with psychiatric conditions, known hypersensitivity to the study medicines, use of analgesics or sedatives within 24 hours before surgery, known heart conditions, and calcium channel blocker users were excluded.

2.1. Blinding and randomization techniques

The registered patients were allocated to two equal groups by a computer-generated tables constructed using the Statistical Package for the Social Sciences (SPSS) version 22. The group assignments were hidden within consecutively numbered sealed and non-transparent envelopes. Before enrolling patients, an impartial anesthesiologist, who had no involvement in the study, unsealed the envelopes holding patient data. The pharmacist in charge of drug compounding did not participate in the study activities.

3. Dexmedetomidine intravenous group (IV group) (*n* = 35)

Intravenous dexmedetomidine (precedex® Pfizer, ample 2 ml, 100 µg/ml.) 1 µg/kg in 100 ml of normal saline (0.9%) was infused over 10 min as a loading dose 15 min before starting anesthesia, then the rate of infusion 0.5 µg/kg/h as maintenance in 50 ml saline via a syringe pump immediately after starting of anesthesia till the end of the operation [13]. At the same time, intranasal saline (2 ml) was given 1 ml in each nostril through dripping by a syringe 15 min before induction as a placebo.

4. Dexmedetomidine intranasal group (IN group) (*n* = 35)

Intranasal dexmedetomidine (2 µg/kg) was given 15 min before induction, prepared at a volume of 2 ml with saline, and 1 ml was dripped in each nostril in the supine position with a syringe [12]. At the same time, the patient received 100 ml of 0.9% normal saline over 10 minutes, 15 minutes before anesthesia, followed by a 50 ml saline infusion by a syringe pump as a placebo.

Every patient was evaluated pre-operatively by history, clinical examination, and laboratory investigations (blood picture, clotting profile, liver, and kidney functions). Informed written consent was signed by the participating patient during the preoperative visit after thoroughly explaining the study.

4.1. Anesthetic management

On the patient's arrival at the theatre, essential monitoring (5 leads ECG, blood pressure (non-invasive), and pulse oximetry) were connected, and the peripheral vein was cannulated with an 18 G venous cannula. Premedication was performed with 0.03 mg/kg midazolam and 2 µg/kg fentanyl. The patients received 10 ml/kg Ringer acetate.

Anesthesia was induced similarly in both groups after preoxygenation with 100% O_2, with intravenous administration of propofol (2 mg/kg). A cuffed endotracheal armored tube of adequate size was inserted and facilitated by 0.5 mg/kg of atracurium besylate, an oropharyngeal pack was inserted, and the head was elevated by 30 degrees. Oxygen, 50% in the air mixture, was used during surgery. Patients were ventilated by volume-controlled mode. The minute volume was adjusted to keep $ETCO_2$ ~30–35 mmHg. Anesthesia was maintained by TIVA and propofol infusion (1.5–2.5 mg/kg/h). The bi-spectral index (BSI) confirmed the anesthetic depth, keeping its value between (40 and 60). Atracurium besylate 0.1 mg/kg every 20:30 min and fentanyl 50µ as bolus dose when needed (greater than a 20% increase from the baseline in either the heart rate or mean arterial blood pressure). The target MAP was maintained approximately at 55–65 mmHg by controlling the infusion rate of propofol. If the mean blood pressure decreased by 20% or greater from the baseline, ephedrine bolus (3–6 mg) was used and repeated when needed. An increment of 0.3 mg atropine was given if the heart rate (H.R.) reached 50 bpm or less. Each nostril received two cotton balls squeezed and soaked in epinephrine at a concentration of 1:100,000. The surgical procedures followed a similar stepwise methodology and were carried out by the same rhinology surgeon unaware of the different study solutions. The extubation was done after a complete reversal of muscle relaxation with 0.04 mg/kg and 0.02 mg/kg of neostigmine and atropine, respectively.

4.2. Monitoring and collected data

The primary outcome was the amount of intraoperative blood loss using Boezaart's grading scale. Where 0:no bleeding,1:slight bleeding, 2:slight bleeding, occasional evacuation of blood is

required;3:slight bleeding, frequent evacuation of blood is required,4:moderate bleeding, frequent evacuation; and 5:vigorous bleeding needs evacuation constantly [14].

The secondary outcomes were the recorded hemodynamics. Both mean arterial pressure (MAP) and heart rate (HR.) were recorded as basal, immediately after intubation, after 5 min, then every 15 min till the end of the surgery, and immediately after tube removal. The surgical satisfaction was measured using a 5-point Likert scale [15]. Ramsey's sedation score was used to assess patients' sedation scores immediately after PACU transfer [16].

Postoperative adverse events (nausea, vomiting, bradycardia, tachycardia, and hypotension), duration of surgery, and total consumption of intraoperative fentanyl, ephedrine, and atropine were recorded. Time of recovery was calculated as the time between the closure of an anesthetic infusion and the patient's ability to maintain normal oxygenation without mechanical assistance.

4.3. Sample size calculation

Power Analysis and Sample Size (PASS) software program, version 2021 for Windows used to calculate the sample size. This calculation was based on data collected from a pilot trial including 12 patients, with the primary outcome being the estimated blood loss measured in milliliters. Based on the pilot study, the IV group experienced a total blood loss of 143.14 ± 22.4 ml, whereas the IN group had a total blood loss of 163.67 ± 21.3 ml. A sample size of 31 patients in each group was necessary to attain a power of 95% (1-β) for the proposed investigation. This study will employ a two-sided, two-sample t-test with a significance level (α) of 5%. To account for an expected attrition rate of 10%, 35 individuals were recruited for each group.

5. Statistical analysis

The statistical data analysis was performed using the (SPSS) software, especially version 22. The data was presented utilizing the mean (± standard deviation) for quantitative data and frequency and proportion for qualitative data. A Shapiro-Wilk test was performed to evaluate the normality of the data distribution. The unpaired student-t test was used to compare numerical variables between groups, given that its assumptions were satisfied. Alternatively, the non-parametric Mann-Whitney test was employed. The chi-square test was utilized to examine categorical data. A difference or change was considered statistically significant if it had a probability (P) of less than 0.05, reflecting a confidence level of 95%.

6. Results

On study time, 81 patients were evaluated for eligibility; five didn't match the designed study's inclusion criteria, and six refused to join the trial. The remaining 70 cases were involved in the study, and their data were sufficient for analysis (Figure 1)

As presented in Table 1, demographic data and duration of surgery were comparable among the two studied groups, while recovery time was statistically significant shorter in the Intranasal group (7.17 ± 2.32 Vs 10.80 ± 2.91, p-value < 0.001). The calculated blood loss was statistically significantly lower among the IV group (141.14 ± 22.462 Vs162.57 ± 21.467, p value < 0.001).

Boezaart's scale showed a statistically significant lower grade in the IV group ranging from 1–2 versus the intranasal group, which ranged from 2–3 with p value < 0.001(Figure 2).

Regarding mean arterial blood pressure (MAP) and heart rate, statistically significant lowered values were found among the IV group vs. the IN group. In contrast, both groups showed comparable basal readings as shown in Figures 3 and 4, respectively.

The calculated total dose of intraoperative fentanyl was statistically significantly lower among the IV compared with the intranasal group (45.71 ± 28.105 Vs. 75.71 ± 35.087, p-value < 0.001) (Table 2).

The total consumption of ephedrine and atropine was comparable between the two studied groups (Table 2). Surgeon satisfaction was statistically significantly higher in the IV group than in the IN group, with p value < 0.009 (Table 2). Ramsay sedation score was statistically significantly higher in the IV group than the IN group, p-value < .001 (Table 3). The postoperative complications were comparable among the two groups (Table 3).

7. Discussion

Endoscopic sinus surgery is a method that is performed with little invasion, speed, and safety. However, the success of the surgery is heavily influenced by the characteristics of the operating area. The present study assessed the disparities in the delivery of dexmedetomidine using intravenous and intranasal routes in patients having functional endoscopic sinus surgery.

Upon examining our preprocedural data, it becomes apparent that there is a minimal disparity in the demographic data of the groups. This suggests that our randomization procedure was executed correctly, eliminating any potential bias favoring one group over the other.

Our study showed that administration of intravenous DEX can decrease the amount of intraoperative bleeding and improve surgical conditions and surgeon

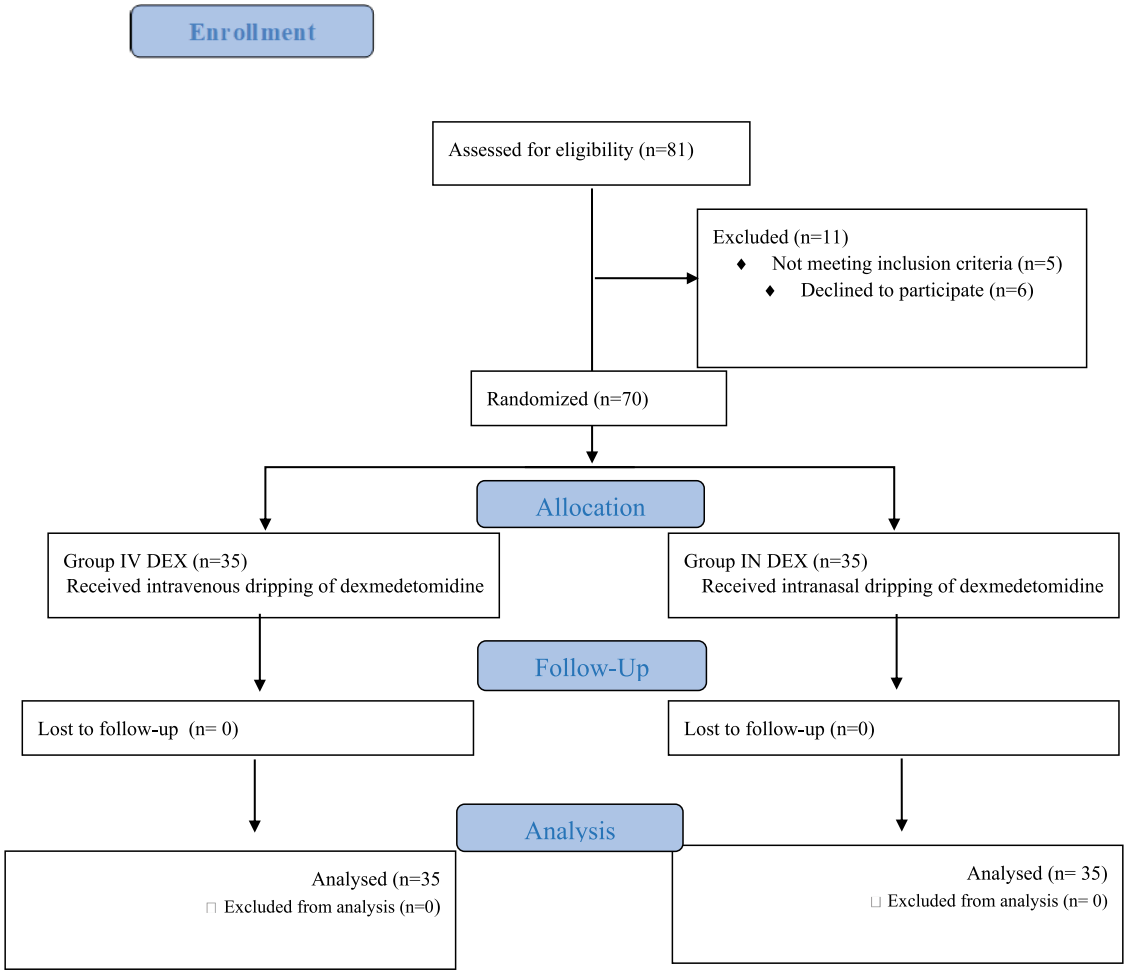

Figure 1. Consort flow chart.

Table 1. Demographic characteristics, ASA classification, duration of surgery, and estimated blood loss.

		Group IV ($n = 35$)	Group IN ($n = 35$)	95% CI	P
Age (years)		42.26 ± 11.44	38.86 ± 9.75	− 1.67, 8.47	0.18
Gender	Male	17 (48.6%)	21 (60.0%)	-	0.33
	Female	18 (51.4%)	14 (40.0%)		
Weight (kg)		77.57 ± 14.25	76.53 ± 14.68	− 5.86, 7.95	0.76
Height (m)		1.72 ± 0.07	1.71 ± 0.06	− 0.03, 0.04	0.825
BMI (kg/m^2)		26.12 ± 3.65	25.93 ± 4.25	− 1.70, 2.09	0.83
ASA	I	15 (42.9%	20 (57.1%)	-	0.23
	II	20 (57.1%	15 (42.9%)		
Duration of surgery (min)		101.57 ± 21.24	104.14 ± 24.65	− 13.55,8.41	0.64
Estimated blood loss (ml)		141.14 ± 22.46*	162.57 ± 21.46	− 31.9, − 10.9	< 0.001
Recovery time (min)		10.80 ± 2.91	7.17 ± 2.32*	2.37, 4.89	< 0.001

Data were expressed as mean ± standard deviation or as percentage and frequency—95% CI: 95% confidence interval of the difference between both groups. IV: intravenous dexmedetomidine, IN: intranasal dexmedetomidine, BMI: body mass index.ASA: The American Society of Anesthesiologists (ASA) physical status classification system.

satisfaction more than intranasal DEX; also, there was more lowering in heart rate and blood pressure, more postoperative sedation, longer recovery time, and less consumption of fentanyl in IV DEX group.

The Boezaart scale was consistently lower in the IV group compared to the intranasal group at all research time points, and this difference was statistically significant. This can be ascribed to higher DEX absorption and plasma levels in the intravenous (IV) group. The decrease in bleeding score can be attributed to the controlled decrease in blood pressure resulting from the medicine being absorbed into the bloodstream, or its ability to constrict blood vessels in the surrounding tissues by acting on alpha-2B receptors in the smooth muscles of the blood vessels [17]. Undoubtedly, reduced intraoperative bleeding has several benefits, such as improved clarity in observing anatomical features, easier dissection without complications, and a decreased likelihood of injuring neighboring tissues.

Our study demonstrated a noteworthy decrease in heart rate and mean blood pressure (MBP) in the intravenous group compared to the intranasal group at all time points throughout the study, from the moment of induction until after extubation. The intranasal group

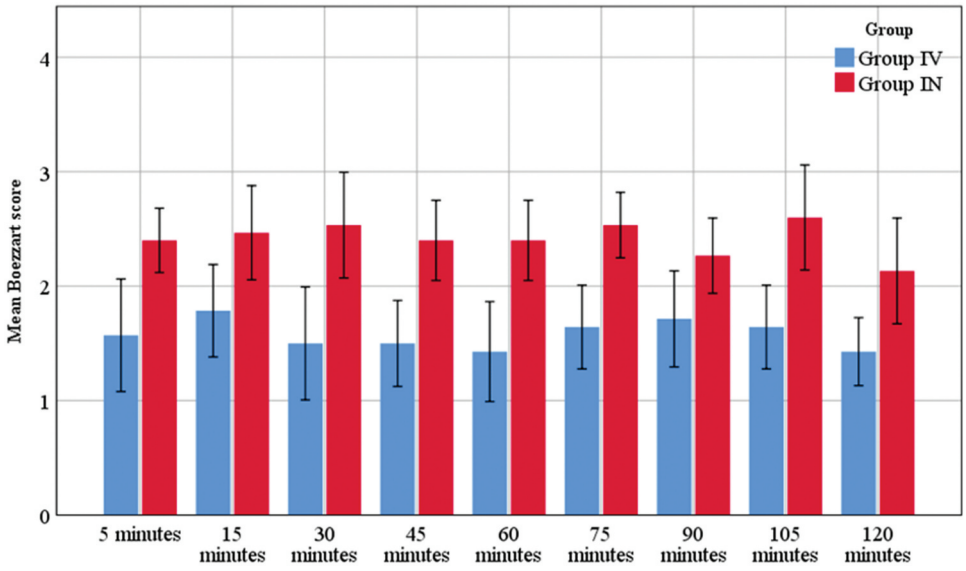

Figure 2. Intraoperative boezzart scale comparison between the studied groups.

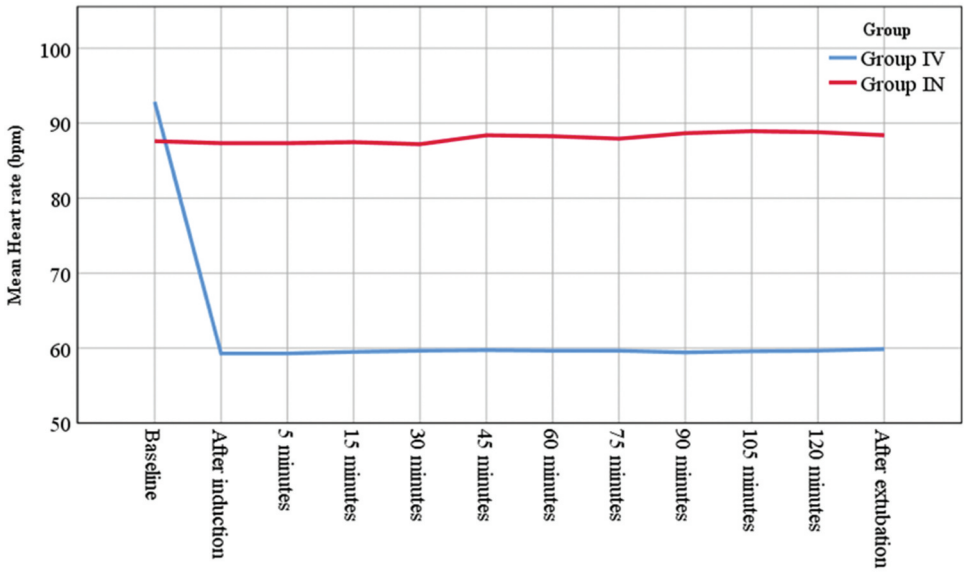

Figure 3. Intraoperative heart rate comparison between the two studied groups.

did not experience a significant decrease in heart rate (H.R.) and mean blood pressure (MBP) because the absorption of DEX into the bloodstream was reduced compared to intravenous (IV) administration of DEX.

Additional research has corroborated dexmedetomidine's impact on heart rate and blood pressure [18–20]. It achieves the preceding two activities by activating alpha-2 receptors, which reduces circulating norepinephrine levels and decreases sympathetic activity [21].

In the present investigation, the recovery duration was notably extended in the intravenous (IV) group compared to the intranasal group. Dexmedetomidine elicits sedative effects in humans that are dependent on the dosage administered. Recall and recognition start to decline as the dosage of dexmedetomidine is raised [22]. Patients administered with therapeutically significant dosages of dexmedetomidine maintain the ability to be awakened and engage in communication [23]. The sedative properties of dexmedetomidine appeared to be triggered inside deep brain areas. Their dissemination is limited to the cerebral cortex solely at elevated drug concentrations, hence accounting for the protracted recuperation period associated with IV DEX [24].

Eghbal et al. validated our findings and conducted a study including 100 patients to examine the impact of labetalol and DEX in reducing intraoperative bleeding and improving FSE field conditions. The labetalol group exhibited a shorter recovery time compared to the DEX group [1]. Consistent with our findings, Qiao et al. reported that the post-anesthesia care unit (PACU) duration was greater in the intranasal DEX group than in the placebo group [12].

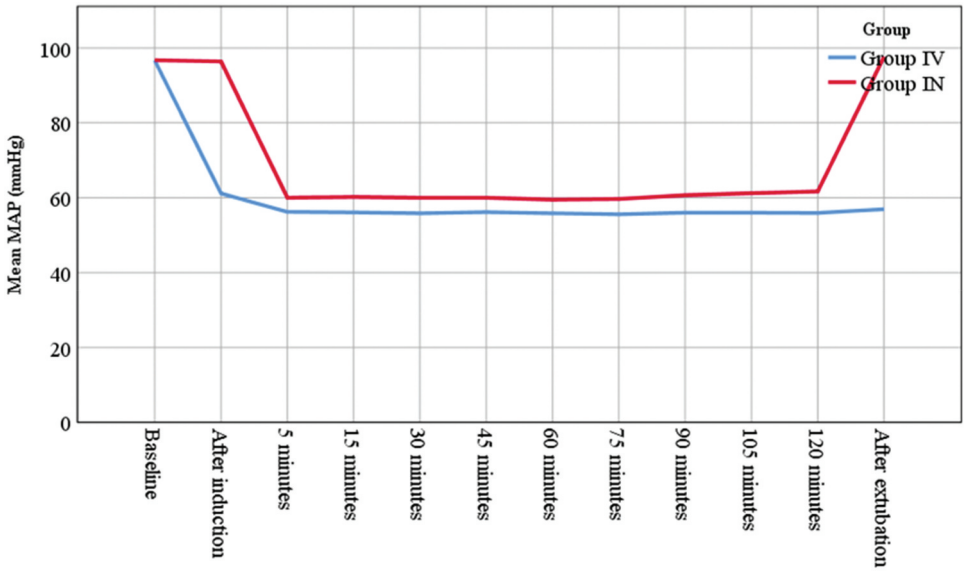

Figure 4. intraoperative comparison of mean arterial blood pressure (MAP) of the two studied groups.

Table 2. Intraoperative events of the studied groups and surgical satisfaction.

	Group IV ($n = 35$)	Group IN ($n = 35$)	P	95% CI
Total intraoperative consumption of fentanyl (ug)	45.71 ± 28.105*	75.71 ± 35.087	< 0.001	− 45, −14
Intraoperative need of Atropine n (%)	2 (5.7%)	0 (0.0%)	0.151	0.869, 1.023
Intraoperative need of Ephedrine n (%)	5 (14.3%)	2 (5.7%)	0.232	Odds ratio = 2.75, CI .49,15.2
Surgical satisfaction(likert scale)				
2	1 (2.9%)	3 (8.6%)	0.009	
3	5 (14.3%)	15 (42.9%)		
4	17 (48.6%)	10 (28.6%)		
5	12 (34.3%)	7 (20.0%)		

N; number of patients.ug; microgram.Surgeon satisfaction was recorded according to a 5-point Likert scale. Data were expressed as mean ± S.D. or as percentage and frequency. 95% CI: 95% confidence interval of the difference between both groups. The odds ratio was calculated for group IN compared to group IV.

Table 3. Ramsay sedation score of the studied groups and postoperative complications.

Ramsay sedation scale	Group IV ($n = 35$)	Group IN ($n = 35$)	P
1	0 (0%)	1 (2.9%)	< 0.001*
2	12 (34.3%)	31 (88.6%)	
3	21 (60%)	3 (8.6%)	
4	2 (5.7%)	0 (0.0%)	
Postoperative complications			
Nausea	2 (5.7%)	5 (14.3%)	0.23
Vomiting	0 (0.0%)	2 (5.7%)	0.15
Bradycardia	1 (2.9%)	0 (0.0%)	0.31
Tachycardia	0 (0.0%)	1 (2.9%)	0.31

Ramsay Sedation Score: score divides a patient level of sedation into 6 categories ranging from severe agitation to deep coma. Data were expressed as number (%).

In the current study, the total intraoperative consumption of fentanyl was significantly decreased in the IV group than in the intranasal group. Dexmedetomidine has sedative and analgesic properties, and there is a higher plasma concentration of DEX in the IV group than the intranasal group, and this may explain the lower dose of fentanyl in the intravenous group.

In the current study, Surgeon satisfaction was significantly higher in the IV group than in the intranasal group. That could be secondary to the more deliberate hypotension mediated by DEX. action on alpha-2B receptors in the vascular smooth muscles [17]. This finding validated by multiple studies [12,13].

Ramsay sedation score was significantly higher in the IV DEX group (p-value < .001). Shams et al. agreed with our results and confirmed that Ramsay's sedation score was significantly lower in the esmolol group at the 15th and 30th minutes after the surgery than in the DEX group [25].

The drug's impact on alpha-2 receptors is the main reason for decreased central nervous system stimulation, particularly in the locus coeruleus [26].

Our findings showed no statistically significant difference in the postoperative incidence of complications as regard: Nausea, vomiting, bradycardia, and tachycardia.

8. Conclusion

This study concluded that intravenous dexmedetomidine provides a better surgical field, more surgeon satisfaction, and lower blood loss for FESS. However, Intranasal DEX provides a more down recovery time and a nearly constant heart rate.

9. Study limitations

One of the significant drawbacks in the current investigation was the very expensive cost of DEX. The absence of a standardized approach for evaluating surgical visibility complicates the ability to compare findings with earlier research. It has the potential to yield contentious outcomes. Additional research conducted on a significant number of patients utilizing varying dosages of dexmedetomidine will determine the optimal effective doses that enhance surgical field visibility.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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