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Comparison of Intranasal and Intravenous Dexmedetomidine as Premedication for Hypotensive Anesthesia in Adult Functional Endoscopic Sinus Surgery: A Randomized Triple-Blind Trial

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ABSTRACT

Controlled hypotension is frequently employed during Functional Endoscopic Sinus Surgery (FESS) to improve surgical field visibility. Intranasal (IN) administration of dexmedetomidine provides a noninvasive alternative with lower peak plasma concentrations and milder pharmacodynamic effects, including reduced hypotension, bradycardia, and sedation, compared to intravenous (IV) delivery. This study compared IN and IV dexmedetomidine in the context of hypotensive anesthesia for FESS.In a randomized, triple-blind, controlled trial, 60 patients scheduled for FESS were randomly allocated into two equal groups. The IN group received 1 μg/kg dexmedetomidine in 10 mL of 0.9% saline intranasally 45–60 minutes before anesthesia, whereas the IV group received the same dose in 10 mL of 0.9% saline infused over 10 minutes. The primary endpoint was total atropine usage, while secondary endpoints included hemodynamic changes preoperatively, intraoperatively, and postoperatively at defined intervals. Operative field quality, sedation levels, adverse events, and post-surgical hemostatic requirements were also evaluated. Findings revealed a significant reduction in atropine consumption in the IN group. Ramsay Sedation scores were similar at baseline (T0), T5, T50, and T60, but were lower in the IN group between T10 and T40. Mean arterial pressure showed no difference at T0, T5, and T60, yet was lower in the IV group from T10 to T45. Both groups demonstrated comparable satisfaction, postoperative sedation, operative field quality, hemostatic needs, and incidence of complications. In conclusion, intranasal dexmedetomidine is an easy-to-administer and effective option that avoids first-pass metabolism. Its slower onset relative to IV administration necessitates preoperative administration about one hour before surgery, making it suitable for adult patients who require mild sedation prior to FESS.

Keywords: Analgesia, Quality of operative field, Bioavailability, Intravenous, Intranasal, Dexmedetomidine

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Introduction

Chronic rhinosinusitis (CRS) frequently requires intervention due to its substantial negative effect on quality of life [1]. Functional Endoscopic Sinus Surgery (FESS) is considered the most effective treatment for refractory CRS and related conditions [2]. FESS is minimally invasive but typically performed under controlled hypotensive anesthesia [3]. Excessive intraoperative bleeding can increase the risk of complications, including blindness, cerebrospinal fluid (CSF) leakage, meningitis, and longer operative times [4, 5]. Severe bleeding may occasionally necessitate early termination of the procedure. Therefore, optimizing visibility while limiting blood loss is a key objective in FESS [6, 7]. Controlled hypotension, achieved by reducing mean arterial pressure (MAP) by approximately 30% or maintaining it between 65–70 mmHg, is commonly employed to improve surgical field clarity, though it carries risks such as decreased cerebral perfusion and ischemic injury to vital organs [8].
Various pharmacologic agents, including direct vasodilators and alpha-2 adrenergic agonists such as clonidine and dexmedetomidine, have been used effectively to induce hypotension under general anesthesia [9].

Dexmedetomidine, a highly selective α2-adrenoceptor agonist with greater affinity than clonidine, exhibits potent sedative and anxiolytic properties [10]. Its pharmacokinetics include a redistribution half-life of approximately 6 minutes and an elimination half-life near 2 hours, making it suitable for precise intravenous titration [11]. Potential benefits include reduced requirements for additional anesthetics and analgesics, while common adverse events include hypotension, bradycardia, nausea, atrial fibrillation, and hypoxia [12].
Intranasal (IN) dexmedetomidine offers a noninvasive, effective alternative, providing reliable sedation and analgesia during surgery [13]. Pharmacokinetic studies show IN administration yields lower peak plasma concentrations than IV dosing, resulting in attenuated pharmacodynamic effects such as hypotension, bradycardia, and sedation [14]. Comparisons between IN and IV dexmedetomidine have been conducted in various surgical contexts [15–17], but limited data exist regarding FESS, where hypotensive anesthesia is crucial for evaluating operative field conditions. This study was designed to compare IN and IV dexmedetomidine for hypotensive anesthesia in patients undergoing FESS.

Materials and Methods

This randomized, prospective, controlled, triple-blinded clinical trial enrolled 60 patients over 21 years old of both sexes, classified as ASA I–III, scheduled for FESS. The study was conducted from November 2022 to March 2023 at Al-Azhar University (Damietta) Hospitals. Written informed consent was obtained from all participants. The study protocol was approved by the Ethical Committee of Al-Azhar University (Damietta) Hospitals (approval code: IRB 00012367-22-011-001) and registered at clinicaltrials.gov (ID: NCT05604599, first registration March 11, 2022).
Exclusion criteria included BMI >30 kg/m², recent or active severe illness, contraindications to dexmedetomidine, significant cardiovascular risk factors, history of coronary artery disease, genetic susceptibility to cardiovascular disease, substance abuse, drug allergies, psychiatric or cognitive disorders, systemic conditions requiring anticoagulation, nasal pathologies such as recurrent epistaxis or tumors, and previous FESS.

Randomization and blinding
Participants were randomly assigned to two equal groups using computer-generated numbers. The IN group received intranasal dexmedetomidine preoperatively along with saline infusion, while the IV group received dexmedetomidine infused over 10 minutes along with intranasal saline. Randomization was ensured by sealed, opaque, sequentially numbered envelopes handled by a chief nurse not involved in the trial. Patients, observers, and outcome assessors were blinded, and medications were prepared by a clinical pharmacist who did not participate in subsequent procedures. All study solutions were visually identical.

Preoperative preparation
Patient history, clinical examination, and routine laboratory tests were performed for all participants. During preoperative assessment, the Visual Analog Scale (VAS) for discomfort and pain (0 = no pain, 10 = maximum pain) was explained. Venous access was established for drug administration and management of potential side effects. Radial artery catheterization allowed continuous blood pressure monitoring and blood sampling. Patients were connected to monitors for noninvasive blood pressure, pulse oximetry, 5-lead ECG, capnography, and temperature.
Forty-five to sixty minutes before surgery, the IN group received 1 μg/kg dexmedetomidine in 10 mL 0.9% saline intranasally, while the IV group received 10 mL 0.9% saline intranasally to maintain blinding. The IV group received 1 μg/kg dexmedetomidine over 10 minutes or saline infusion in the IN group prior to induction of general anesthesia. Hemodynamic parameters, SpO_2, respiratory rate, and ECG were continuously monitored. Preoperative sedation scores were recorded at five-minute intervals.

Intraoperative management
Patients were transferred to the operating room, and intravenous infusion of 8–10 mL/kg Ringer's solution was initiated. No additional sedatives were administered as premedication. General anesthesia (GA) was induced using 1 μg/kg fentanyl and 2 mg/kg propofol intravenously, followed by 0.15 mg/kg IV cis-atracurium to facilitate endotracheal intubation. Anesthesia maintenance was achieved with 1–1.5% isoflurane in 50% oxygen, and

supplemental doses of cis-atracurium (0.03 mg/kg) and fentanyl were administered as needed. Mechanical ventilation settings were adjusted to maintain end-tidal CO_2 between 30–35 mmHg.
If heart rate (HR) or mean arterial pressure (MAP) increased by ≥20% from baseline, an additional 1 μg/kg IV fentanyl was given. Induction doses of fentanyl and ongoing isoflurane administration were recorded intraoperatively. Following intubation, patients were positioned in a reverse Trendelenburg at approximately 30°, and standard local vasoconstriction with 1:200,000 adrenaline was applied to the nasal mucosa.
All surgeries were performed by the same surgeon, who was blinded to the type of hypotensive agent, to maintain consistency in operative field assessment. Study drugs were discontinued 15 minutes before the anticipated end of surgery to facilitate hemostasis. MAP and HR were recorded at baseline and every 5 minutes until the conclusion of surgery.
Intraoperative bleeding was assessed using the Fromme-Boezaart 6-point scale [18]: 0 = no bleeding; 1 = minimal bleeding, no suction required; 2 = mild bleeding, occasional suction needed; 3 = moderate bleeding, frequent suction required; 4 = severe bleeding, surgical field compromised, continuous suction required; 5 = massive bleeding preventing dissection.
Neuromuscular blockade reversal was achieved using atropine (0.05 mg/kg) and neostigmine (0.02 mg/kg). Postoperative analgesia included 1 g IV paracetamol every 8 hours, with rescue analgesia of 50 mg IV pethidine if VAS exceeded 3. Time to first analgesic request and cumulative 24-hour pethidine consumption were recorded. Adverse events such as nausea, vomiting, hypotension (MAP <20% of baseline, treated with 5 mg IV ephedrine and IV fluids), and bradycardia (HR <60 bpm, treated with 0.5 mg IV atropine) were documented. Atropine usage was recorded. Postoperative swelling from hemostatic packing was graded: 1 = tolerable, 2 = barely tolerable, 3 = intolerable. Sedation was evaluated at 15, 30, and 60 minutes after recovery using the Ramsay Sedation Score (RSS: 1–6). Patient satisfaction was assessed immediately postoperatively and at 24 hours using a 5-point Likert scale ranging from "very dissatisfied" to "very satisfied."
Primary outcome: total atropine consumption. Secondary outcomes: hemodynamic parameters (HR, MAP) from preoperative baseline through intraoperative and postoperative intervals, operative field quality, adverse reactions, and hemostatic packing tolerance.

Sample size determination

Sample size was calculated using G*Power 3.1.9.2 (Universitat Kiel, Germany). A pilot study including 5 patients per group indicated mean ± SD atropine consumption of 0.3 ± 0.27 mg in the IN group versus 0.6 ± 0.4 mg in the IV group. With an effect size of 0.87, 95% confidence, 90% power, and a 1:1 allocation ratio, a minimum of 29 patients per group was required. To account for potential dropouts, one patient was added per group, resulting in a total of 60 participants.

Statistical analysis

Data were analyzed using SPSS v. 28 (IBM, Armonk, NY, USA). Normality was assessed via the Shapiro-Wilk test and visual inspection of histograms. Parametric quantitative variables were expressed as mean ± SD and compared between groups using unpaired Student's t-test, and within groups using paired t-test. Non-parametric quantitative variables were presented as median (IQR) and compared using Mann–Whitney U test between groups and Wilcoxon signed-rank test within groups. Categorical data were expressed as frequencies or percentages and analyzed using Chi-square or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Results and Discussion

Out of 76 patients initially assessed for eligibility, 11 did not meet inclusion criteria and 5 declined participation. The remaining 60 participants were randomly assigned to two groups in a 1:1 ratio, with 30 patients in each group, and all randomized cases were included in the analysis **(Figure 1).**
Demographic and baseline characteristics, including age, sex, BMI, ASA classification, and duration of surgery, were similar between the two groups **(Table 1).**
Preoperative Ramsay Sedation Scores (RSS) were comparable at T0, T5, and T60 ($p > 0.05$). However, at T10, T15, T20, T30, and T40, sedation scores were significantly higher in the IV group compared to the IN group ($p < 0.001$) **(Figure 2).**

Mean arterial pressure (MAP) values at T0, T5, and T60 were similar across groups, but at T10, T15, T20, T30, and T45, the IV group exhibited significantly lower MAP than the IN group. Within-group analysis showed that MAP in the IN group decreased significantly at T45 and T60 compared with baseline, whereas in the IV group, the decline began at T10 and persisted through T60 **(Table 2).**

Heart rate (HR) measurements were comparable at T0, T5, T45, and T60, while T10, T15, and T30 were significantly lower in the IV group relative to the IN group. Intragroup comparisons demonstrated that HR in the IN group decreased significantly from T30 to T60 relative to baseline, whereas in the IV group, HR reduction began at T10 and continued until T60 **(Table 3).**

During surgery and recovery, MAP and HR did not differ significantly between groups at any time point **(Figures 3–6)**. Postoperative assessments showed comparable patient satisfaction, RSS, hemostatic packing tolerance, and incidence of complications in both groups **(Table 4).**

Preoperative and recovery respiratory rates and SpO_2 values were similar between groups and did not differ significantly from baseline at any time point **(Figures 7–10).**

Analgesic requirements, including total pethidine consumption, time to first rescue analgesic, and operative field quality, were comparable between groups. Notably, total atropine consumption was significantly lower in the IN group compared to the IV group **(Table 4).**

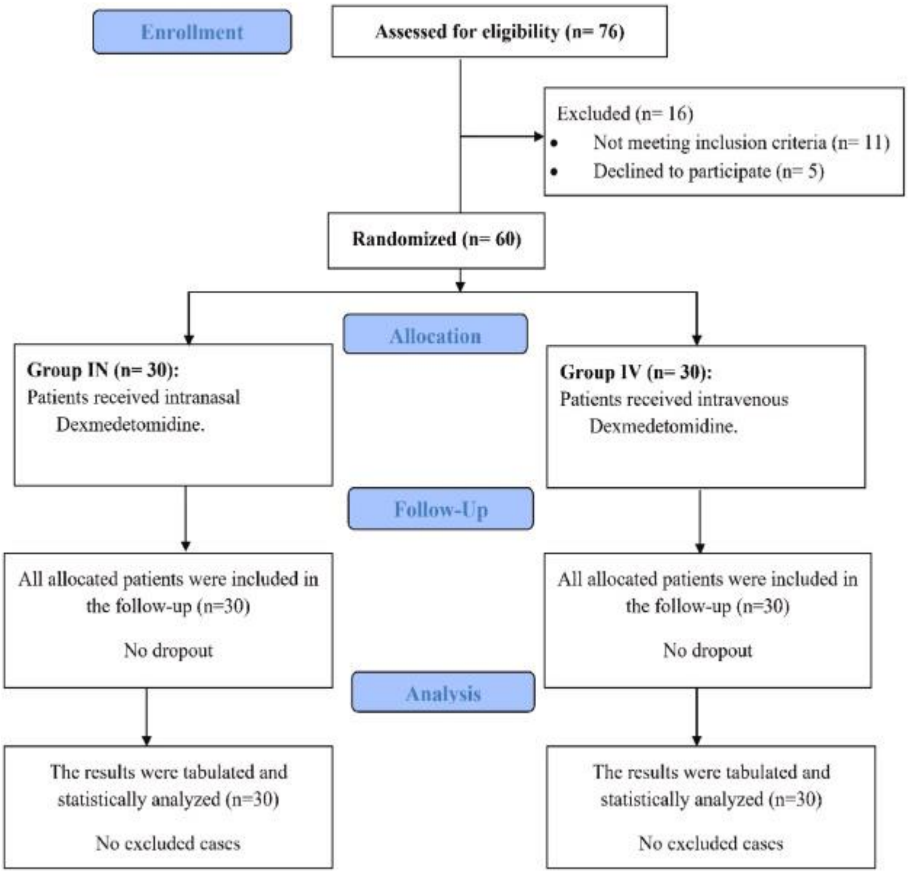

Figure 1. CONSORT diagram illustrating the enrollment, randomization, and analysis of study participants.

Table 1. Baseline characteristics of participants, including demographics, ASA classification, and operative duration, presented as mean ± SD or number (percentage). Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

		Group IN (n = 30)	Group IV (n = 30)	P value
Age (years)		43.9 ± 10.12	44.7 ± 11.96	0.781
Sex	**Male**	22 (73.33 %)	25 (83.33 %)	0.347
	Female	8 (26.67 %)	5 (16.67 %)	
BMI (kg/m^2)		26 ± 2.82	25.3 ± 2.55	0.317
ASA	ASA I	8 (26.67 %)	4 (20 %)	0.197
	ASA II	22 (73.33 %)	26 (86.67 %)	

Duration of surgery (min)	90.4 ± 8.97	86.8 ± 16.26	0.359

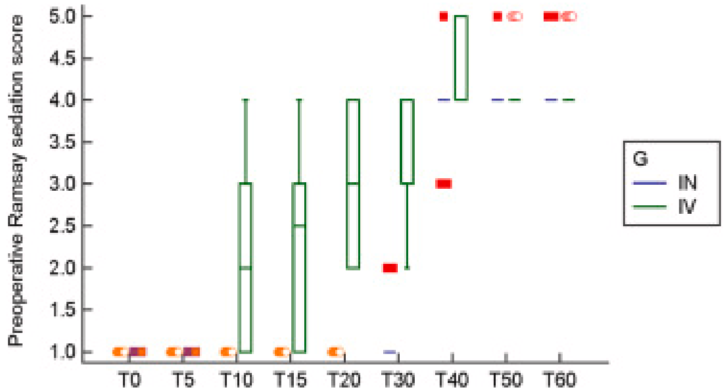

Figure 2. Comparison of preoperative Ramsay Sedation Scores between the two study groups.

Table 2. Preoperative MAP of the studied groups.

Time interval	Group IN (n = 30)	Within group comparison	Group IV (n = 30)	Within group comparison	Comparison between IN and IV groups
T0	89 ± 12.09	–	85.8 ± 13.59	–	0.339
T5	84.9 ± 4.56	0.094	82.9 ± 3.21	0.303	0.051
T10	85 ± 7.11	0.057	81.2 ± 6.33	0.02*	0.032*
T15	84.6 ± 4.33	0.061	80.6 ± 4.4	0.031*	0.0001*
T30	85.2 ± 6.33	0.073	80.8 ± 5.9	0.037*	0.006*
T45	84.2 ± 2.91	0.047*	81.2 ± 6.32	0.045*	0.022*
T60	82.7 ± 5.09	0.004*	78.8 ± 14.52	0.035*	0.177

Data are presented as mean ± SD, *: Significant when P value ≤ 0.05.

Table 3. Preoperative HR of the studied groups.

Time interval	Group IN (n = 30)	Within group comparison	Group IV (n = 30)	Within group comparison	Comparison between IN and IV groups
T5	81.4 ± 4.16	0.054	79.3 ± 5.66	0.103	0.118
T10	80.9 ± 6.39	0.067	69.5 ± 8.57	<0.001*	<0.001*
T15	81.2 ± 5.54	0.106	69.6 ± 8.14	<0.001*	<0.001*
T30	69.8 ± 7.54	<0.001*	63.5 ± 7.89	<0.001*	0.002*
T45	65 ± 9.75	<0.001*	60.3 ± 9.44	<0.001*	0.063
T60	57.6 ± 11.32	<0.001*	58.7 ± 10.09	<0.001*	0.702

Data are presented as mean ± SD, *: Significant when P value ≤ 0.05.

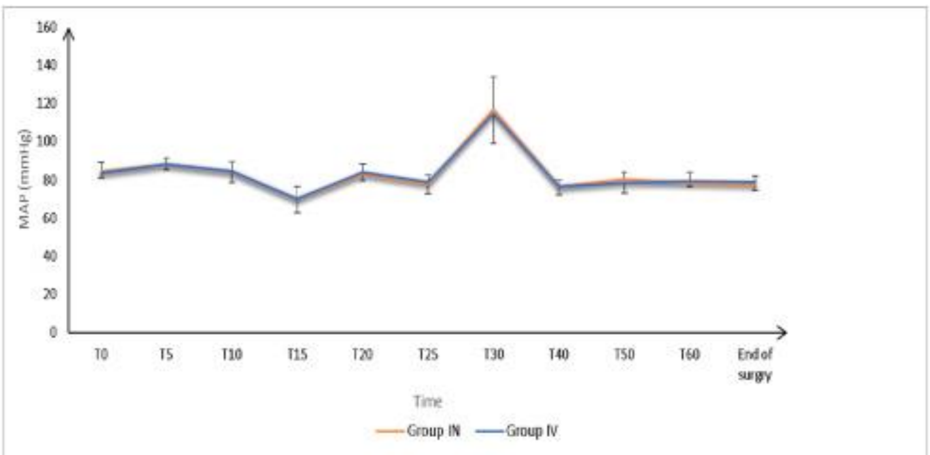

Figure 3. Intraoperative mean arterial pressure (MAP) trends in the two study groups.

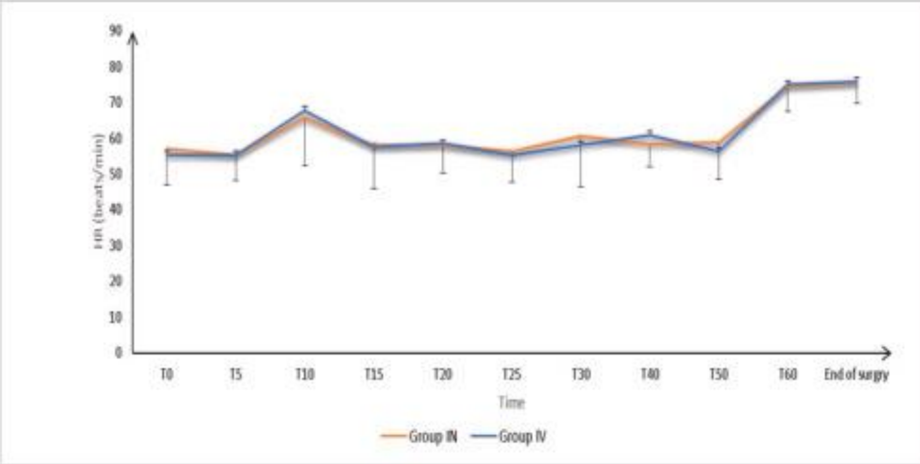

Figure 4. Intraoperative heart rate (HR) measurements in both study groups.

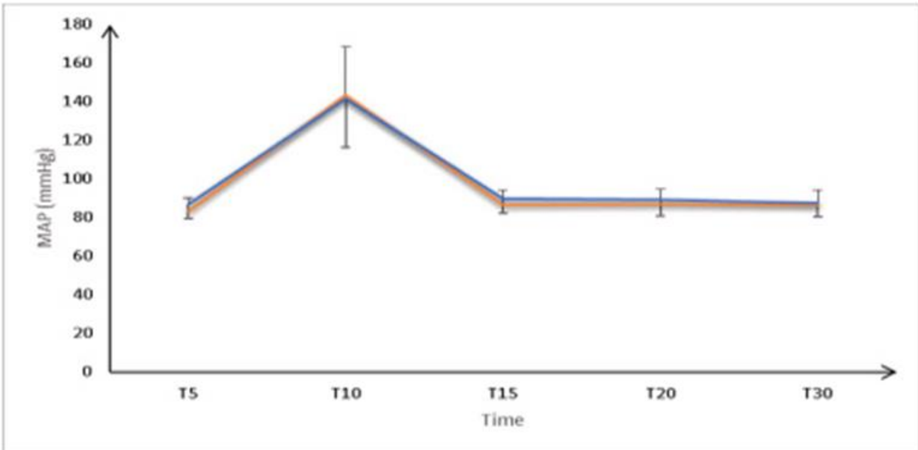

Figure 5. Postoperative (recovery) mean arterial pressure (MAP) in both study groups.

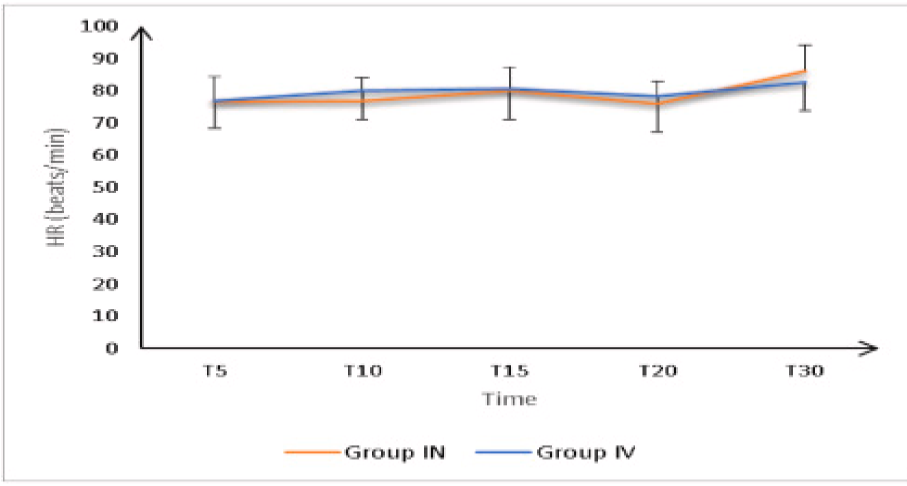

Figure 6. Postoperative (recovery) heart rate (HR) in both study groups.

Table 4. Satisfaction, postoperative Ramsey sedation, hemostatic suffering, analgesic effect, quality field, atropine consumption and complications of the studied groups.

		Group IN (n = 30)	Group IV (n = 30)	P value
Postoperative Satisfaction		4 (4–4)	4 (4–4)	0.646
Satisfaction post 24 h		4 (3–4)	4 (3–4)	0.775
Postoperative Ramsey sedation	Ramsey (1)	26 (86.67 %)	25 (83.33 %)	0.718
	Ramsey (2)	4 (13.33 %)	5 (16.67 %)	

Hemostatic suffering	No swelling, can tolerate	14 (46.67 %)	11 (55 %)	0.604
	Swelling, can barely tolerate	14 (46.67 %)	14 (70 %)	
	Swelling, cannot tolerate	2 (6.67 %)	4 (13.33 %)	
Pethidine (mg)		100 ± 50.85	106.7 ± 44.98	0.593
Time to first rescue (hours)		2 ± 1.1	2.3 ± 1.12	0.355
Quality field	**Quality field 1**	6 (20 %)	10 (50 %)	0.422
	Quality field 3	8 (26.67 %)	5 (16.67 %)	
Atropine (mg)		0.2 ± 0.34	0.7 ± 0.55	<0.001*
Complications		Vomiting	4 (13.33 %)	0.853
		Nausea	2 (6.67 %)	

Data are presented as frequency (%), or as median (IQR) or mean ± SD *: Significant when P value ≤ 0.05.

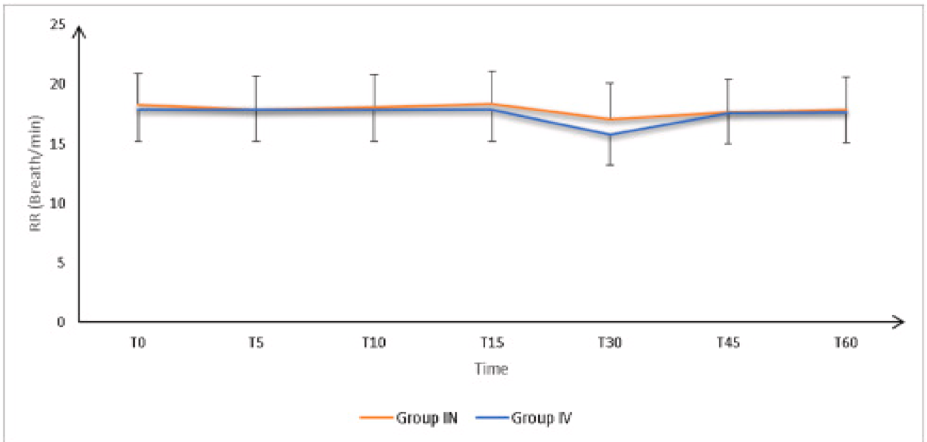

Figure 7. Preoperative respiratory rate measurements in the two study groups.

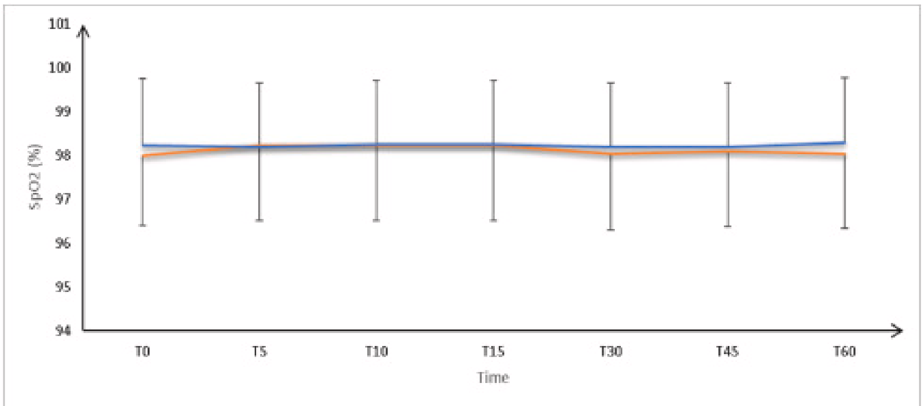

Figure 8. Preoperative peripheral oxygen saturation (SpO_2) in both study groups.

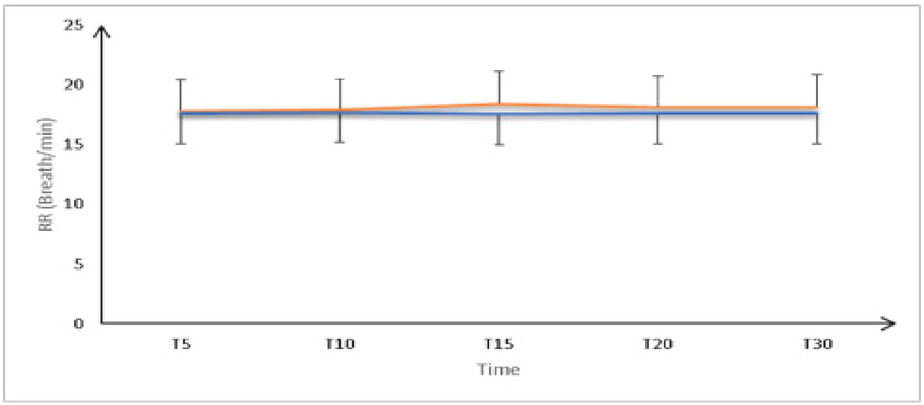

Figure 9. Postoperative (recovery) respiratory rate in both study groups.

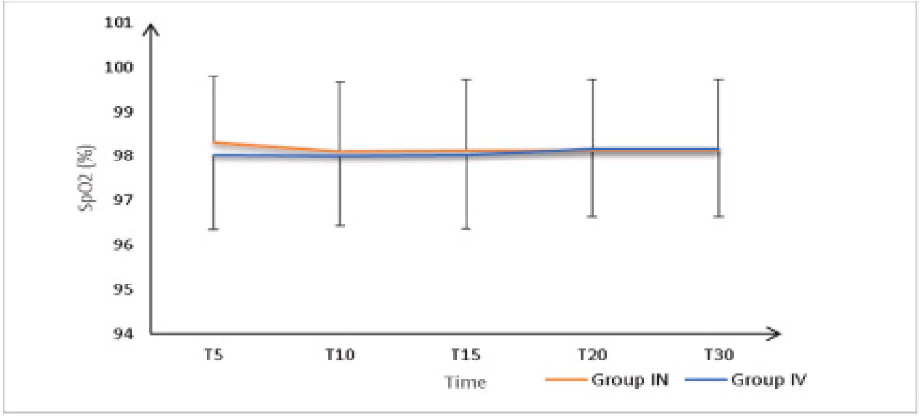

Figure 10. Postoperative (recovery) peripheral oxygen saturation (SpO_2) in the two study groups.

Functional endoscopic sinus surgery (FESS) under general anesthesia can be complicated by significant intraoperative bleeding, which may limit visibility and increase the risk of adverse outcomes [19]. Controlled hypotension is widely used to minimize blood loss and optimize the surgical field [3, 20]. Previous studies have shown that intranasal (IN) drug delivery is an effective premedication route [21–23], although most research has focused on oral administration [24]. IN administration offers a simple, noninvasive approach with high bioavailability and reduced first-pass metabolism [25], representing an important advancement in translational medicine [26].

IN dexmedetomidine has demonstrated efficacy and patient compliance in healthy volunteers and has been proposed as an alternative to oral midazolam in pediatric premedication [14, 27, 28]. This study aimed to compare IN versus intravenous (IV) dexmedetomidine for hypotensive anesthesia in adults undergoing FESS.

Our findings showed that preoperative Ramsay Sedation Scores (RSS) were similar between groups at T0, T5, T50, and T60, whereas sedation was significantly lower in the IN group at T10, T15, T20, T30, and T40. Adequate premedication is essential, as preoperative anxiety can exacerbate stress-related hemodynamic fluctuations and complicate anesthesia induction [29]. Dexmedetomidine, a selective α2-adrenoceptor agonist, provides sedative, hypnotic, and analgesic effects by modulating both central and spinal sympathetic activity [30]. Additionally, it has organ-protective effects, including attenuation of renal and myocardial injury [31].

Previous pharmacokinetic studies reported peak plasma concentrations of IN dexmedetomidine at 38 (15–60) minutes with 65% absolute bioavailability, compared to higher and faster peaks with IV administration [14, 27]. These findings align with our observation of more gradual onset with IN delivery, making it suitable for adult patients requiring mild sedation. IV administration, by contrast, produced higher Cmax values and more pronounced early sedation. The onset of IN sedation typically occurs within 30–45 minutes, suggesting that administration should be timed approximately one hour before surgery [27, 32].

In terms of hemodynamics, preoperative MAP and HR were generally higher in the IN group compared to IV at several time points, consistent with the slower systemic absorption of IN dexmedetomidine [14]. During surgery and recovery, MAP and HR did not differ significantly between groups, reflecting the similar elimination half-life of both routes [14, 28]. Analgesic requirements, time to first rescue analgesia, and operative field quality were comparable. Notably, atropine consumption was lower in the IN group, likely due to the lower early peak concentrations of dexmedetomidine and reduced incidence of bradycardia with IN administration [33, 34].

Neither route affected respiratory rate or oxygen saturation, consistent with prior reports [35, 36]. Limitations of this study include its single-center design and short follow-up period. Larger multicenter trials with extended monitoring are needed to generalize these findings.

Conclusion

Intranasal dexmedetomidine is a simple, noninvasive, and effective option for premedication in adults undergoing FESS, providing stable sedation with fewer cardiovascular side effects and reduced atropine requirements compared to IV administration. Due to its slower onset, it should be administered approximately one hour before surgery, making it particularly suitable for adults who require only mild preoperative sedation.

Impact of research findings on patients

- Intranasal dexmedetomidine can be effectively used for hypotensive anesthesia during Functional Endoscopic Sinus Surgery (FESS) in adults, offering lower preoperative sedation.
- This route provides analgesic efficacy comparable to intravenous administration while reducing adverse effects during FESS.
- Intranasal delivery is practical, noninvasive, and demonstrates high bioavailability with diminished first-pass hepatic metabolism.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: The research was conducted in adherence to the principles outlined in the Declaration of Helsinki. Each patient gave informed consent in writing. The study was conducted subsequent to receiving approval from the Ethical Committee of Al-Azhar University (Damietta) Hospitals (approval code: IRB 00012367-22-011-001) and registration of clinicaltrials.gov (ID: NCT05604599).

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