The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4340-4348

Preemptive Nebulization of Dexmedetomidine versus Ketamine for Postoperative Analgesia in Nasal Surgeries

Zainab Abd Alkhader Mabrouk Alshame*, Maha Ebrahem Eldesouky, Mohammed Saad Ahmed Mousa, Doaa Mohammed Farid

Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Zainab Abd Alkhader Mabrouk Alshame,

Mobile: (+20) 01008864059, **E-mail:** Zezoworfaly@gmail.com

ABSTRACT

Background: Nasal backing and the actual surgical trauma are responsible for mild to severe postoperative pain following nose operations.

Aim: To evaluate analgesic effectiveness of nebulized ketamine against nebulized dexmedetomidine for patients undergoing nose operations.

Patients and methods: 105 adult patients for elective nose operations were divided into three groups. Patients in each group were given the drug via nebulization 15 minutes before to surgery; in the case of group D, patients received 50 μg of dexmedetomidine (0.5 ml + normal saline 0.9% up to 3 ml), group K, 50 mg of ketamine (1 ml + normal saline 0.9% up to 3 ml), and group C, 0.9% (3 ml) of normal saline. Hemodynamics, intraoperative opioids, the first-time analgesia was requested, the total amount of postoperative rescue analgesia administered, and side effects were all included in the outcome measures. Version 20 of SPSS was used to code and analyses the data that had been gathered.

Results: There was statistically significant ($p< 0.05$) reduction in intraoperative fentanyl needs in D group < K group < C group and also significant decrease in postoperative ketoprofen needs. The first time to rescue analgesia was delayed ($p< 0.05$) in D group > K group > C group. Postoperative complications were lower in D and K groups < C group ($p< 0.05$).

Conclusion: Preemptive nebulization of dexmedetomidine produces extremely good analgesia in nasal surgeries, when compared with other groups it can effectively reduce the intra- and postoperative opioid consumption.

Keywords: Preemptive Analgesia, Dexmedetomidine, Ketamine, Nasal nebulization

INTRODUCTION

Nasal surgeries are usually associated with mild to severe postoperative discomfort, due to both nasal backing and surgical damage. The administration of opiates to treat this pain may result in respiratory depression, hypoxia, decreased alertness, nausea, and vomiting [(1)].

Nebulization of analgesics across the nasal mucosa plays a major role in pain control and is generally favored because it is safe and simple for the patient to receive, with delivering the medication to the lower airway with less risk of aspiration [(2)].

Dexmedetomidine is a selective α-2 adrenergic agonist action**.** As it is highly lipid soluble agent, it has good systemic absorption on trans mucosal administration **[(3)].** It induces hypotension, bradycardia, sedation, and analgesia by activating spinal cord and brain receptors [(4)]. Dexmedetomidine has a distribution half-life of about 6 min and a terminal elimination half-life of about 2 h (2-compartment model). It has a quick onset and short duration of action. Dexmedetomidine is extremely lipophilic and about 94% protein bound. It is nearly completely biotransformed, and is excreted in feces (4%) and urine (95%) [(5)].

Ketamine is an N-methyl D-aspartate (NMDA) receptors antagonist, it acts on the limbic system and the central nervous system to cause drowsiness and analgesia [(6)]. It has various routes of administration including intramuscular, intravenous, oral, nasal, intrathecal subcutaneous, intraosseous and rectal gargles **[(7)].** Nebulized ketamine has anti nociceptive anti-inflammatory properties **[(8)].**

This study aimed to assess the efficacy of good postoperative pain management with a less rescue analgesia by using either nebulization of dexmedetomidine or ketamine in patients undergoing nasal surgeries.

PATIENTS AND METHODS

The Zagazig University Hospitals conducted this prospective, randomly, controlled clinical trial between September 2022 and March 2023. 105 cases were separated into three groups with 35 cases in each category, according to the open Epi program's calculation of the sample size. A prior study found that the test has an 80 percent power at 95% confidence interval. Depending on heart rate (HR) measurement it was assumed that mean HR was 83.39±11 vs 77.76±7.88 beat/min in ketamine vs dexmedetomidine group **[(7)].**

In this study, elective nasal operations on adult patients between the ages of 21 and 60, of either sex, who were ASA I and ASA II patients, BMI ≥18≤30 kg/m² and scheduled for these procedures, were included. Exclusion criteria for this study included patients with advanced respiratory, renal, hepatic, neurological, or psychiatric disease, pregnant or nursing women, patients with a history of allergies to any study drugs, patients who had used central nervous system depressants or analgesics within the previous 24 hours, and patients with hypertension, hypotension, or bradycardia.

Received: 13/11/2022
Accepted: 15/01/2023

Study design

A computer-generated randomization table randomly separated the trial participants into three groups based on the preemptive nebulized medication used in each group: group of dexmedetomidine (group D): Patients received dexmedetomidine 50 μg (0.5 ml + normal saline 0.9% up to 3 ml), ketamine group (group K) received ketamine 50 mg (1 ml + normal saline 0.9% up to 3 ml), and control group (group C) received normal saline 0.9% (3 ml), 15 minutes prior to surgery. Prior to surgery, patients were taught how to rate their own pain using a VAS scale from 0 to 10 (where 0 indicates no pain and 10 the worst possible pain). Intravenous access was controlled inside the pre-medication room. Heart rate (HR), oxygen saturation, and mean arterial blood pressure (MAP) baseline readings were recorded. Each patient received a nebulization of either the study medication (ketamine or dexmedetomidine) or plain saline 15 minutes prior to the onset of general anesthesia. After nebulization, the HR, oxygen saturation, and MAP were immediately recorded. Nebulization was performed using compressed O_2 at 8 l/min, then fentanyl 1-2 g/kg, propofol 1-2 mg/kg (given in 20 mg increments as determined by verbal contact), and atracurium 0.5 mg/kg to aid in endotracheal intubation were intravenously administered to begin the induction of general anesthesia. The HR was adjusted to be maintained 20–25% lower than the baseline values or mean arterial blood pressure (MAP) maintained at 50–65 mmHg in order to maintain anesthesia with isoflurane 1- 1.2% (minimum alveolar concentration) in oxygen/air mixture. Atracurium, given every 20 minutes at 0.1 mg/kg, maintained the muscles adequately relaxed.

When the HR or MAP values increased over the specified level or when the HR increased by more than 20% from baseline values, an additional bolus dose of fentanyl (0.5 g/kg) was administered intraoperatively. The mechanical ventilation's parameters were adjusted to maintain the end-tidal CO_2 level between 30 and 35 mmHg. Following intubation, intraoperative data were collected and continuously monitored every 15 minutes throughout the procedure. Moreover, the total dosages of intraoperative opioids and propofol used for induction and maintenance were documented. After the procedure, the patient had bilateral nasal packing. The anesthetic was then turned off, and atropine and neostigmine were slowly infused intravenously (I.V); neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were administered to reverse neuromuscular relaxation. Then patients were turned aside in the recovery position. After the protective airway reflexes returned and the patient met the requirements for extubation, awake extubation was conducted. The VAS was used to measure the patients' pain at rest at the following intervals: 15 minutes, an hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 16 hours, 18 hours, and 24 hours postoperatively. All patients in all groups received a standardized analgesic of paracetamol 1 gm I.V infusion/8 h (maximum dose of 4 gm/day). If the VAS scores were at least 3, ketoprofen 1.5 mg/kg intramuscular was administered. The initial need for rescue analgesics and the total dosage of ketoprofen administered to each patient within the first 24 hours following surgery were determined and recorded.

Within the first 24 hours following surgery, any significant adverse effects were noted and treated, including, Bradycardia was treated with (0.5 mg to 1 mg) atropine IV, while hypotension was treated with 0.9% normal saline or with ephedrine IV (5 mg to 10 mg). Hallucinations, Reassure and antipsychotic drug might help to treat. Tachycardia was treated with analgesia,and others. At the end of the 24-hour trial period, patients' satisfaction with their analgesia was graded as very satisfied, mildly satisfied, or not satisfied[(3)].

Ethics approval:

The Institutional Review Board has reviewed and assessed the study (IRB#9682/3-8-2022) regarding the potential risks and benefits based on the World Medical Association's code of ethics for experimentation on humans; the Helsinki Declaration. Patients' written informed consent was also obtained.

Statistical Analysis

Data collection was done., processed, and statistically evaluated using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative data were described using the mean, standard deviation, and (range), and qualitative data were described using absolute frequencies (number) and relative frequencies (percentage). To compare more than two independent groups of normally distributed data, the one-way ANOVA test was performed. with a post hoc test ,**Tukey test** to compare between groups. The Chi-square test was used to compare categorical variable percentages. Each test contained two sides. The threshold for statistical significance was set at 0.05.

RESULTS

The eligibility of 115 individuals who were scheduled to have elective nasal surgeries were evaluated,10 patients were excluded from them (6 patients did not meet the eligibility criteria while the remaining 4 patients refused to participate), so 105 patients signed a consent form and were divided into three groups, each with 35 patients: the control group (C), the ketamine group (K), and the dexmedetomidine group (D) (Figure 1).

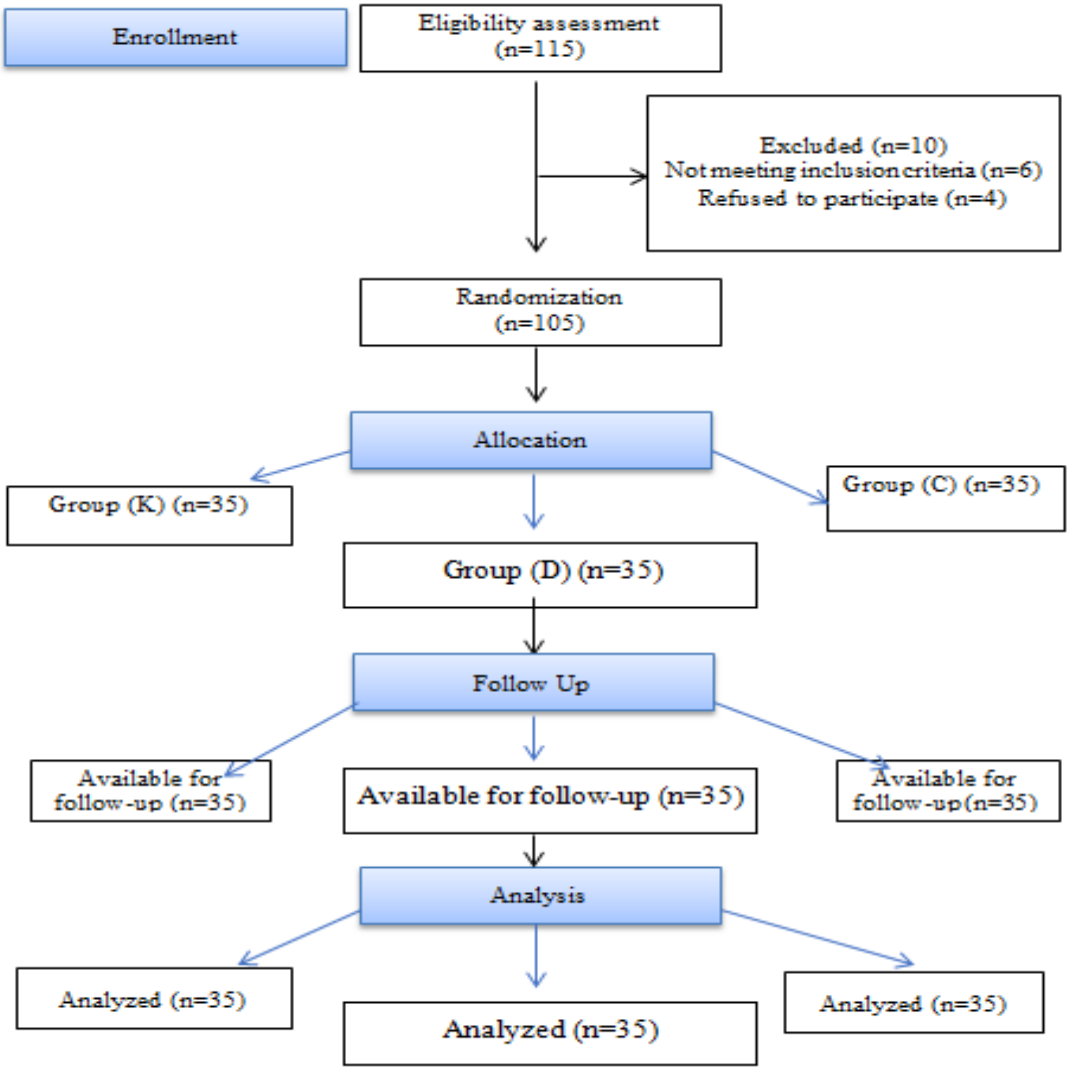

Figure (1): Flow chart demonstrates the experimental design of the study

Table 1 shows that there were no significant differences between the study groups in terms of age, BMI, and sex. The operation time was significantly higher in D group than the other 2 groups.

Table (1): Patients' basic data of the studied groups

Variable		Group C (n=35)		Group D (n=35)		Group K (n=35)		Test P value
Age (years) Mean± SD		34.23±7.40 (23-46)		31.11±7.20 (21-45)		30.86±7.33 (21-44)		0.105
		No.	%	No.	%	No.	%	
Sex	**Male**	19	54.3	17	48.6	19	54.3	0.858
	Female	16	45.7	18	51.4	16	45.7	
BMI (kg/m^2) Mean± SD		24.21±3.32 (18.6-30)		24.92±3.46 (18.6-30)		25.47±2.93 (21-29.3)		0.268
Operation time (minutes) Mean± SD		46.1±6.3		50±7.2		49±7.1		0.21

K= Ketamine, D=Dexmedetomidine, C=Control, P for comparison between 3 groups,

Figure 2 shows that there was a statistically significant difference between the groups under study with respect to heart rate changes at different intervals where C group showed higher mean heart rate and group D had the least values.

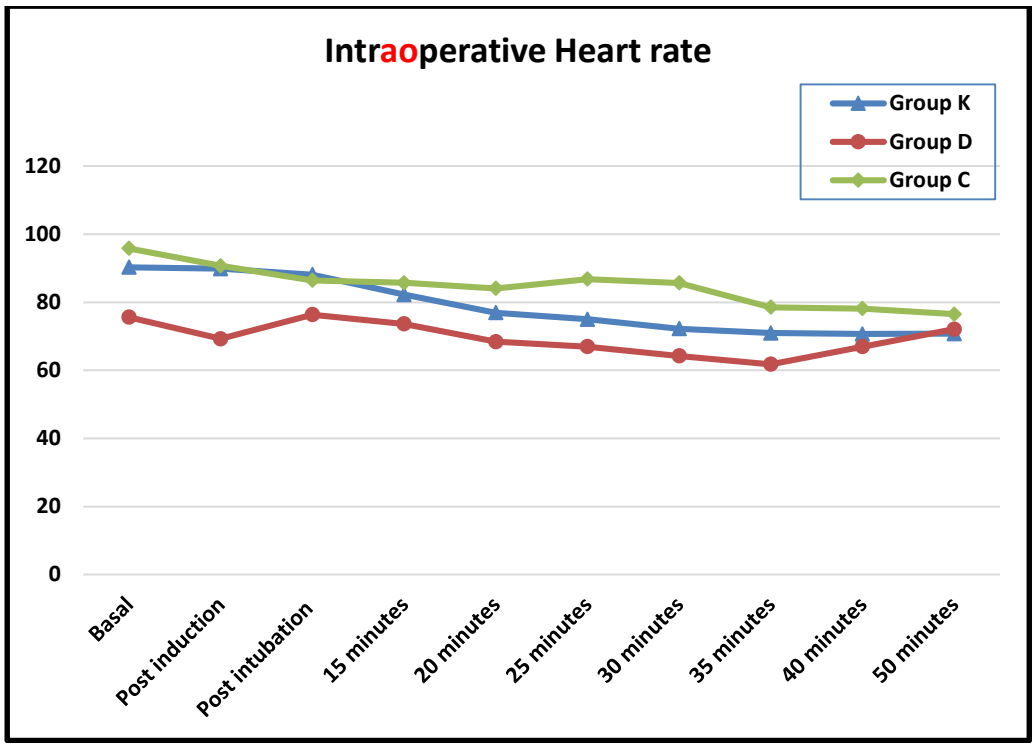

Figure (2): Intraoperative heart rate changes at different intervals between the studied groups

Figure 3 shows that there was a statistically significant difference between the groups studied in terms of postoperative heart rate changes at different intervals, where C group showed higher mean heart rate than other groups. Group D showed the lowest values regarding postoperative heart rate.

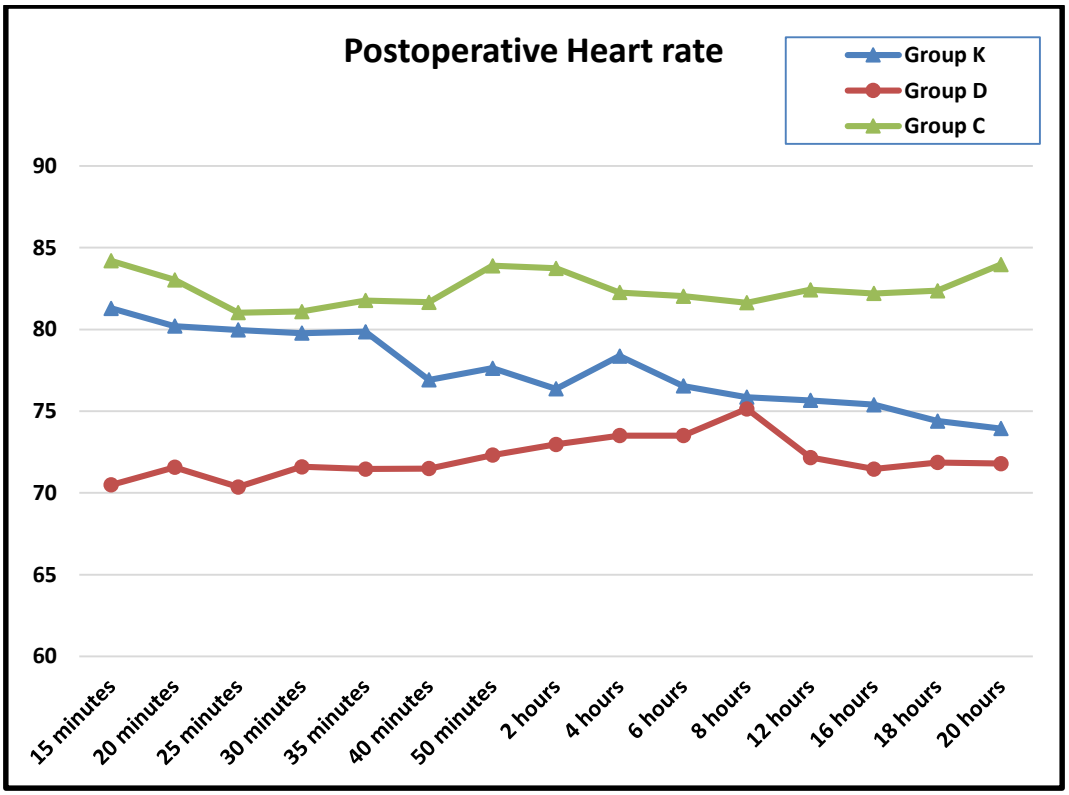

Figure (3): Postoperative heart rate changes at different intervals between the studied groups

As shown in figure 4, there was statistically significant difference in the studied groups regarding intraoperative mean arterial pressure changes at most intervals (basal, post induction, post intubation, 15, 25 and 50 minutes), where C group showed higher mean arterial pressure than other groups.

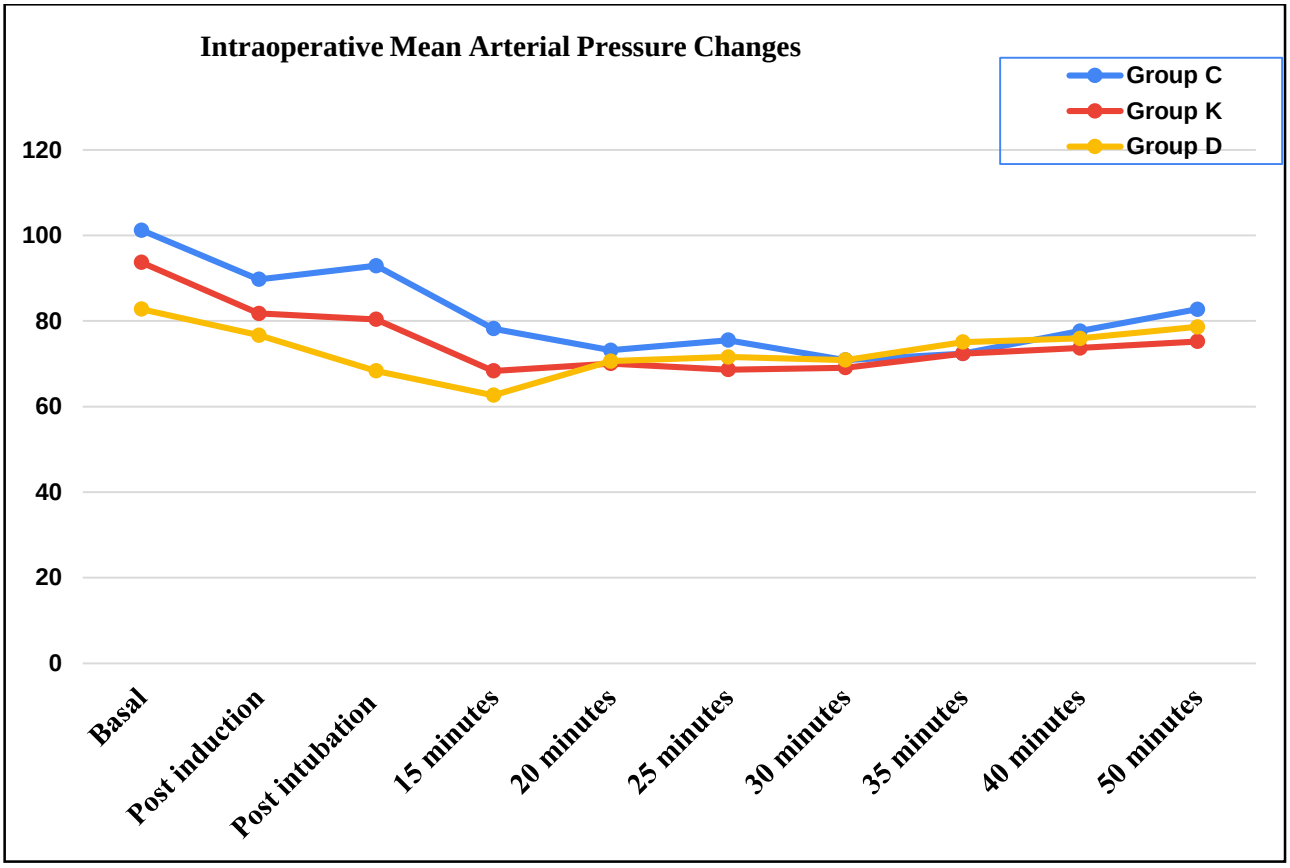

Figure (4): Intraoperative mean arterial pressure changes at different intervals between the studied groups

As shown in figure 5, there was statistically significant difference between the studied groups regarding postoperative mean arterial pressure changes at different intervals, where D group showed lower recorded mean postoperative arterial pressure than other groups.

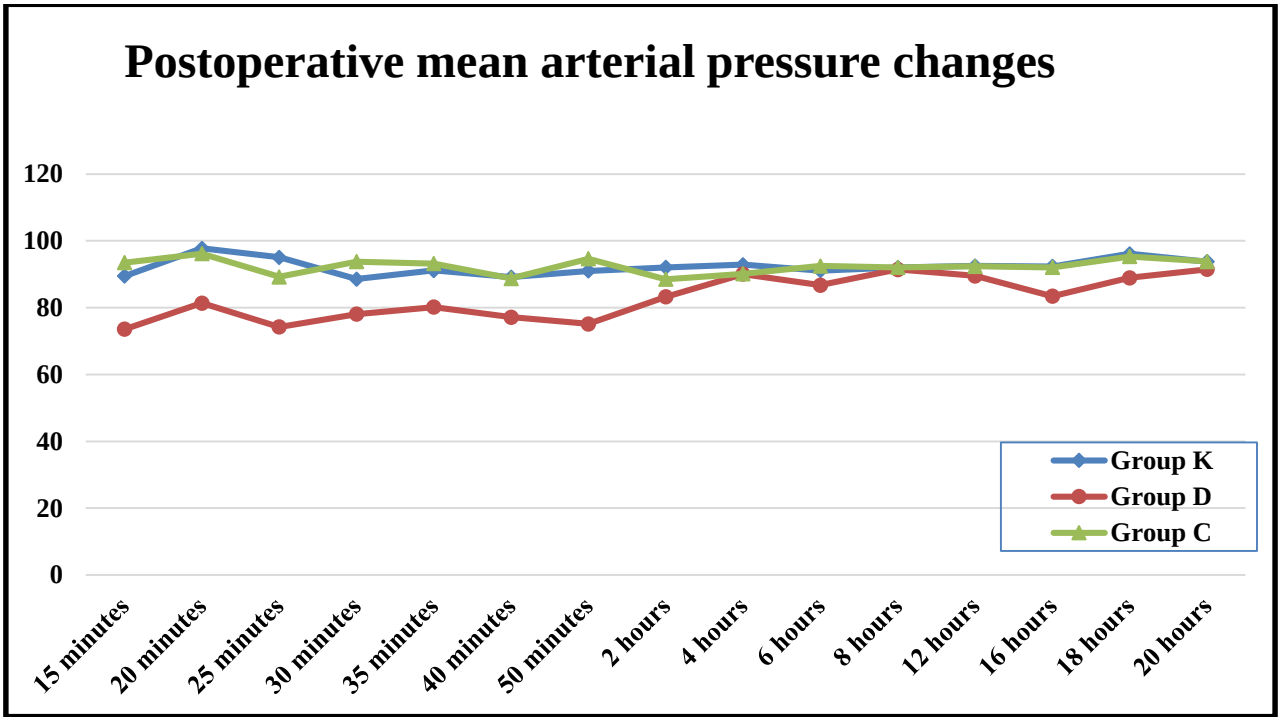

Figure (5): Postoperative mean arterial pressure changes at different intervals between the studied groups

Figure 6 shows that there was a statistically significant difference between the groups tested in terms of VAS changes at different intervals, where group D showed the lowest mean score<K group<C group, at 16 h, 18 h and 24 h than other groups.

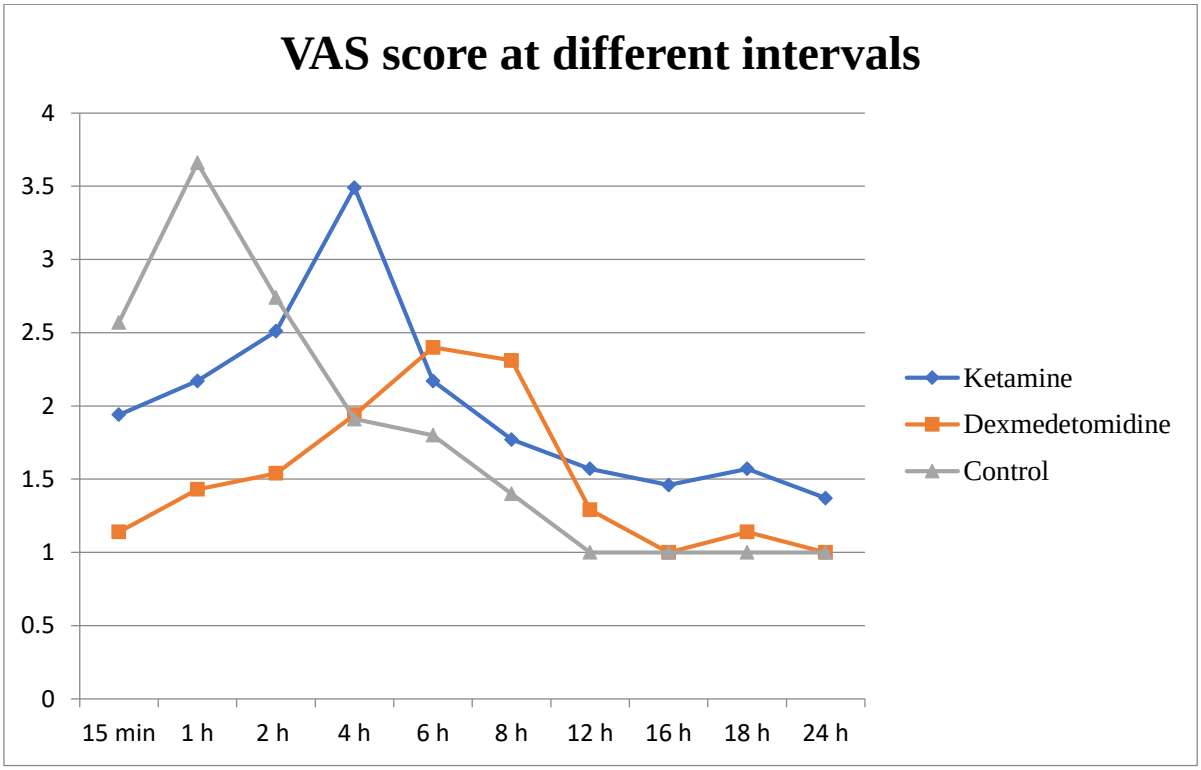

Figure (6): Line graph showing mean VAS score of the studied groups at different intervals

Table 2 shows that there was a statistically significant difference between the tested groups in terms of maximum breathed isoflurane%, with group D having the lowest concentration, followed by group K, and finally group C. Across the groups that were evaluated, there were statistically significant difference in the need for fentanyl dose, where D group needed fentanyl less than K group and group C. There was a statistically significant difference in using analgesia and first time of rescue (ketoprofen), where cases of C group needed analgesia and had the shortest time to take the first analgesic followed by group K who needed analgesia within a shorter time than group D. Also, between the examined groups, there was a statistically significant decreased in total amount of rescue/24 h, as group D needed least amount, followed by group K, then group C with the highest total amount.

Table (2): Intraoperative fentanyl, first time of rescue, and total dose of rescue and intraoperative fentanyl dose of the studied groups

Variable	Group C (n=35)	Group D (n=35)	Group K (n=35)	P value
Maximum inhaled isoflurane % Mean± SD	1.95±0.16 (1.7-2.5)	1.28±0.26 (1-2)	1.69±0.15 (1.5-2)	<0.001*
P-value of post Hoc test	---------	P1<0.001*	P2<0.001*	
	----------	P3<0.001*	---------	
First Time of Rescue(h) (ketoprofen), Mean± SD	1.23±0.43 (1-2)	09±1.02 (6-8)	3.77±0.43 (3-4)	<0.001*
P-value of Tukey test	---------	P1<0.001*	P2<0.001*	
	----------	P3<0.001*	---------	
Total amount of rescue /24h (mg) Mean± SD	95±18.34 (60-150)	81.36±21 (50-100)	90.86±17.04 (60-100)	0.034*
P-value of Tukey test	----------	P1<0.001*	P2 0.003*	
	----------	P3 0.009*	---------	
Intraoperative fentanyl dose (µg)	150.89±0.22	100.0±0.17	110.3±0.41	<0.001*
P-value of Tukey test	----------	P1<0.001*	P2 0.009*	<0.001*
	----------	P3<0.001*	----------	

K= Ketamine, D=Dexmedetomidine, C=Control, P value for comparison between 3 groups, Post hoc test: comparison between each 2 groups, *= Significant
P1 =K group vs. D group, P2 =K group vs. C group, P3 = D group vs. C group.

Table 3 shows that there was statistically significant difference between the studied groups regarding different anesthesia complications. Bradycardia and hypotension were statistically significantly higher in D group than other groups. Hallucination was statistically significantly increased in K group and tachycardia was statistically significantly increased in C group.

Table (3): Anesthesia complication within the studied groups

Variable		Group C (n=35)		Group D (n=35)		Group K (n=35)	
		No.	%	No.	%	No.	%
Hallucination	**No**	35	100	35	100	26	74.2
	Yes	0	0	0	0	9	25.7
P-value of Tukey test		------		--------		P1<0.001*	
		---------		----------		P2<0.001*	
Bradycardia	**No**	35	100	26	74.3	35	100
	Yes	0	0	9	25.7*	0	0
P-value of Tukey test		-------		P1<0.001*		--------	
		----------		P3<0.001*		--------	
Hypotension	**No**	35	100	30	85.7	35	100
	Yes	0	0	5	14.3*	0	0
P-value of Tukey test		---------		P1<0.001*		---------	
		----------		P3<0.001*		-------	
Tachycardia	**No**	20	57.1	34	97.1	31	88.6
	Yes	15	42.9*	1	2.9	4	2.9
P-value of Tukey test		P2<0.001*		--------		P1 0.009*	
		P3<0.001*		--------		--------	

K= Ketamine, D=Dexmedetomidine, C=Control, P value for comparison between 3 groups, Post hoc test: comparison between each 2 groups, *= Significant, P1 =K group vs. D group, P2 =K group vs. C group, P3 = D group vs. C group.

The result of present work showed that there was statistically significant increase in patient satisfaction ($p<0.05$) across the examined groups in D group (77.1%) > K group (51.4%) > group C (17.1%).

DISCUSSION

In this study, we tried to evaluate the analgesic effectiveness of nebulized ketamine against nebulized dexmedetomidine for patients undergoing nasal procedures. Moreover, preemptive medication administration was carried out in an effort to research the effects on hemodynamics during intubation and intraoperatively.

Regarding **basic demographic data,** age, BMI, sex, and operating time,there was no statistically significant difference between the analysed groups. Regards to intra- and postoperative SPO_2, there was no discernible difference between the groups under study, With Regarding **intra- and postoperative hemodynamic parameters**, our study found that the dexmedetomidine group had the lowest heart rate and mean postoperative arterial pressure values. Also, about (25.7%) of **dexmedetomidine** group complained of **bradycardia** and (14.3%) were **hypotensive** as an anesthetic complication.

In our study, MAP and HR were comparable in the three studied groups at baseline reading and at intubation. The MAP and HR increased immediately following the surgical incision, between the three studied groups, with a statistically significant difference (C group > K group > D group). Additionally, the D group had greater intraoperative hemodynamic stability than the K group or C group. These results agreed with **Shafa *et al.*** [9] who found that there was significant reduction of hemodynamic response to intubation as well as fiberoptic bronchoscopy in the dexmedetomidine group more than lidocaine group and placebo group.

Furthermore**, Singariya *et al.*** [10] reported that there was dexmedetomidine's cardio-depressant impact caused a drop in HR and SBP from baseline in that group, whereas ketamine's sympathetic stimulant qualities caused a modest increase in HR and SBP from baseline in that group.

The findings of the current investigation did not coincide with those of **Misra *et al.*** [11]**,** who employed nebulized dexmedetomidine at a dose of 1 g/kg to attenuate the rise in heart rate but not blood pressure after laryngoscopy; this may be due to low dose of dexmedetomidine used in the previous study.

As regards **maximum inhaled isoflurane%**, there was a statistically significant difference between the analyzed groups in the current investigation, with

group D reporting the lowest concentration levels followed by groups K and C.

According to **Misra *et al.* [11],** the isoflurane needs were considerably lower in the dexmedetomidine group than in the placebo group (P = 0.013), which is consistent with the findings of the current investigation.

As regards total fentanyl dose in the current study, there was statistically significant reduction in D group < K group < C group (100.0±0.17µg vs.110.3±0.41µg vs. 150.89±0.22µg respectively). Also, the total ketoprofen requirement in the first 24 hours was statistically significant in D group < K group < C group (81.36 ± 21 mg vs. 90.86 ± 17.04 mg vs. 95± 18.34 mg respectively). While, there was delayed 1st time to rescue analgesia **(P <0.05)** in D group > K group > C group (7.09±1.02h vs. 3.77± 0.43h vs.1.23 ± 0.43h respectively).

These results were consistent with those of **Schnabel *et al.* [12],** who demonstrated that perioperative opioid use, including intraoperative fentanyl and postoperative morphine, was markedly reduced **(P< 0.05)** in the dexmedetomidine group compared to the control group in the first 12 hours but morphine requirements of the 2 groups were comparable in the following 12 hours. Also, the dexmedetomidine group experienced delayed rescue analgesia compared to the placebo group, with a statistically significant difference **(P< 0.05)** between the two groups.

Abdel-Ghaffar *et al*. [13] compared the efficiency of analgesics of nebulized ketamine (1 and 2 mg.kg1) with intravenous ketamine (0.5 mg.kg1) and saline placebo in children having elective tonsillectomy, which is in line with the findings of the current work. They claimed that nebulized ketamine used in advance was successful in relieving post-tonsillectomy pain. It can be viewed as a potent substitute for intravenous ketamine.

The results of the current study were not in agreement with the outcomes of **Ahmad *et al.* [14],** no difference was found among groups dexmedetomidine, ketamine and dexmedetomidine. Thirty minutes after surgery, an analgesic requirement for ketamine was noted, with the majority of patients receiving rescue analgesia based on VAS values. Perhaps as a result of the patient group differing from that of pediatric patients having tonsillectomies

As regards the postoperative visual analogue scale (VAS), there was a significant statistical reduction in both D and K groups when compared to C group, also there was statistically significant reduction in VAS in D group when compared to K group. VAS score was significantly lower in D group < K group < C group.

These results coincide with the results of **Abd Ellatif and Mowafy [3]** who demonstrated that the VAS scores were statistically significant lower **(P <0.05)** in the dexmedetomidine group than in the control group (saline) in all time intervals.

Moreover **Motamed *et al.* [15]** claimed that there was significant reduction **(p <0.05)** in postoperative VAS scores in the dexmedetomidine group than in the ketamine group in all time intervals.

There was a statistical significant increased between the three studied groups as regards bradycardia (25.7%) and hypotensive (14.3%) that were statistically significantly high in D group more than other groups. As regards hallucination, it was statistically significantly increased in K group; about (17.1%). As regards tachycardia, it was statistically significantly increased in C group, about (42.9%) .

According to **Ali and Mahmoud [16],** who also found findings that are consistent with those of the current investigation, bradycardia and hypotension were considerably more common in the two groups that received different doses of dexmedetomidine.

Also, the outcomes of the current investigation concur with **Kronenberg [17]** who reported that when used; nebulization of ketamine in high doses can be associated with some complications such as hallucinations.

As regards the patient satisfaction in the present work, there was statistically significant increase in the patient satisfaction in D groups > K group> C groups, where (77.1%) of D group were satisfied versus (51.4%) of K group and (17.1%) of group C.

A drawback of this study were nebulization timing and safe dosages should be further investigated because in this trial, far lower doses were employed than those that were associated with adverse outcomes.

CONCLUSION

Preemptive nebulization is simple, non-invasive, and easy-to-learn. Delivering the medication to the lower body is advantageous for both patient comfort and convenience during administration airway with little chance of aspiration.

Preemptive nebulization of dexmedetomidine produces excellent analgesia in nasal surgeries when compared with other groups. It can effectively reduce the intra- and postoperative opioid consumption, produce better intraoperative hemodynamic stability, delay postoperative rescue analgesia, reduce the postoperative VAS pain score, reduce the complications, and increase the patient satisfaction.

RECOMMENDATIONS

Preemptive nebulization of dexmedetomidine in nasal surgeries as it is simple, less invasive, and produces excellent analgesia when combined with general anesthesia.

Use of dexmedetomidine nebulization as preemptive analgesic technique in prevention of chronic postsurgical pain after nasal surgeries. Only few studies were done, so further studies are required to assess its efficacy in preventing chronic postsurgical pain.

Further studies are required to assess the efficacy of dexmedetomidine nebulization with other ASA (III or IV) in nasal surgeries.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflicts of interest: There are no conflicts of interest.

REFERENCES

1. **Parthasarathy S, Krishnapriyanka K, Saravanan B (2022):** Effectiveness of pre-emptive nerve block on opioid consumption in patients undergoing nasal surgery under general anaesthesia: A double-blinded randomised controlled study. Indian J Anaesth., 66(2): 133-136.
2. **Prasant N, Mohapatro S, Jena J *et al.* (2021):** Comparison of preoperative nebulization with 4% lignocaine and ketamine in reduction of incidence of postoperative sore throat. Anesth Essays Res., 15(3): 316-314.
3. **Abd Ellatif S, Mowafy S (2019):** Pre-emptive nebulized ketamine versus nebulized lidocaine for endoscopic nasal surgeries. Research and Opinion in Anesthesia and Intensive Care, 6(4): 408-409.
4. **Cai Y, Xu H, Yan J *et al.* (2014):** Molecular targets and mechanism of action of dexmedetomidine in treatment of ischemia/reperfusion injury. Mol Med Rep., 9(5): 1542-1548.
5. **Gertler R, Brown C, Mitchell H *et al.* (2001):** Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent), 14(1): 13-18.
6. **Keles S, Kocaturk O (2017):** The effect of oral dexmedetomidine premedication on preoperative cooperation and emergence delirium in children undergoing dental procedures. Biomed Res Int., 9: 110-114.
7. **Abusinna G, Algharabawy S, Mowafi M (2022):** Comparative evaluation of intranasal midazolam, dexmedetomidine, ketamine for their sedative effect and to facilitate venous cannulation in pediatric patients: A prospective randomized study. Egyptian Journal of Anaesthesia, 38(1): 124-126.
8. **Bajwa S, Kaur G, Khanna M (2017):** Ketamine-the confluence of old and recent concepts. Journal of Pain & Relief, 6: 283-288.
9. **Shafa A, Habibzade M, Shetabi H (2019):** Comparing the hemodynamic effects of nebulized dexmedetomidine and nebulized lidocaine in children undergoing fiberoptic bronchoscopy. Journal of Advances in Medical and Biomedical Research, 27: 14-15.
10. **Singariya G, Malhotra N, Kamal M *et al.* (2022):** Comparison of nebulized dexmedetomidine and ketamine for premedication in pediatric patients undergoing hernia repair surgery: a randomized comparative trial. Anesth Pain Med (Seoul), 17(2): 173-178.
11. **Misra S, Behera K, Mitra K *et al.* (2021):** Effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation: a randomized control trial. Korean J Anesthesiol., 74(2): 150-157.
12. **Schnabel A, Reichl U, Poepping M *et al.* (2013):** Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: a meta-analysis of randomized controlled trials. Paediatr Anaesth., 23(2): 170-179.
13. **Abdel-Ghaffar S, Abdel-Wahab H, Roushdy M *et al.* (2019):** Preemptive nebulized ketamine for pain control after tonsillectomy in children: randomized controlled trial. Braz J Anesthesiol., 69(4): 350-357.
14. **Ahmad M, El Gamal N, Elhelw N *et al.* (2020):** Comparison of the use of nebulized dexmedetomidine, ketamine, and a mixture thereof as premedication in pediatric patients undergoing tonsillectomy: a double-blind randomized study. Research and Opinion in Anesthesia and Intensive Care, 7(1): 70-74.
15. **Motamed H, Masoumi K, Moezzi M *et al.* (2021):** Clinical efficacy of dexmedetomidine versus ketamine in shoulder dislocation reduction: a randomized clinical trial study. Med J Islam Repub Iran, 35: 152-154.
16. **Ali R, Mahmoud N (2022):** The effect of nebulized dexmedetomidine as sedative premedication in pediatrics undergoing cochlear implantation. Egyptian Journal of Anaesthesia, 38(1): 317-318.
17. **Kronenberg H (2002):** Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. J Pain Palliat Care Pharmacother., 16(3): 27-28.