ORIGINAL ARTICLE

Comparative Evaluation the Effect of Intraoperative Infusion of Dexmedetomidine Versus Low Dose Ketamine on Pain and Inflammatory Biomarkers in Patients Undergoing Nasal Surgery

Essam A. Moustafa [a], Ibrahim M. B. Ibrahim [b], Mohamed A. A. Aboelsoud [a], Ahmed G. M. Hegazy [a,*]

[a] Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt
[b] Department of Clinical Pathology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Maintaining a steady blood pressure and oxygen saturation level in the patient while achieving optimal surgical results is the main goal of anesthesia. Combining general anesthetics with systemic medicines is the goal of current multimodal balanced anesthesia.***

Aim and objectives: ***The purpose of this study is to compare the effects of dexmedetomidine and low-dose ketamine infusion on intraoperative hemodynamic stability, blood loss, perioperative opioid needs, and stress response evaluation as measured by C-reactive protein, blood glucose, and serum levels of cortisol and IL-6.***

Patients and methods: ***From December 2022 through June 2024, 80 patients were included in a prospective, randomized, double-blind, comparative trial at Al-Azhar University Hospitals. A closed opaque envelope containing the patients' allocation code was used to randomly divide them into two equal groups in a parallel way using computer-generated numbers.***

Results: ***At 4h, 8h, 12h, 16h, 20h, and 24h after PACU, there was no significant difference between the two groups on the visual analogue scale (VAS). While both groups' IL-6 levels were similar at baseline, the dexmedetomidine group had considerably lower levels at 6 and 24 hours compared to the ketamine group.***

Conclusion: ***There is no statistically significant difference between dexmedetomidine and low-dose ketamine infusion in terms of the number of adverse events, total dose of morphine used, or time to first request of rescue analgesia for patients having nasal and paranasal sinus surgery in terms of pain management. Ketamine reduces the levels of cortisol and C-reactive protein (CRP) without significantly altering blood glucose levels.***

Keywords: Intraoperative Infusion; Dexmedetomidine; Ketamine; Nasal Surgery

1. Introduction

With its anxiolytic, sedative, anesthetic, and analgesic effects, dexmedetomidine is a very selective agonist at the alpha2(α2) adrenoreceptor. In terms of depression of the respiratory system, it has a few negative effects. Its useful qualities explain why it finds widespread application in many different types of operations.[1]

The Food and medicine Administration (FDA) authorized the use of dexmedetomidine, a relatively new medicine, for short-term sedation and analgesia (<24-hours) in the intensive care unit (ICU) in humans towards the end of 1999. Analgesic, hemodynamically stable, and capable of restoring respiratory function in patients on mechanical ventilation, dexmedetomidine is a valuable sedative that allows for early weaning.[2]

For almost forty years, doctors have relied on ketamine hydrochloride, a famous anesthetic.[3] Its hypnotic and antinociceptive effects are likely due to its noncompetitive antagonistic action on the central nervous system's N-methyl-D-aspartate (NMDA) receptor.[4]

Accepted 06 February 2025.
Available online 28 February 2025

* Corresponding author at: Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.
E-mail address: ahmedhegazy651@yahoo.com (A. G. M. Hegazy).

https://doi.10.21608/aimj.2025.446448

While administered in large dosages, ketamine acts as an anesthetic and, at lower levels, as an analgesic. When administered alone or in conjunction with other anesthetics, ketamine may keep pain at bay and cut down on opiate consumption after surgery. The ASA, the AAP, and the ORS all endorse ketamine for use during surgery for patients experiencing moderate to severe postoperative pain.[5]

Patients undergoing surgery on the nose or paranasal sinuses will have their intraoperative haemodynamic stability, blood loss, perioperative opioid requirements, and stress response evaluated by serum cortisol, IL-6, blood glucose, and C-reactive protein (CRP) levels compared to low-dose ketamine infusion.

2. Patients and methods

At Al-Azhar University Hospitals, 80 participants were a part of a prospective, randomised, double-blind, comparative experiment that ran from 2022 to 2024. Participants were selected from the patient records of those who visited the pain management, intensive care unit, and anaesthesia outpatient clinics at Al-Azhar University Hospital. A computer-generated randomization sequence was used to collect samples using the systematic random approach. Using computer-generated numbers, we separated the patients into two equal groups and preserved their allocation codes in a sealed opaque envelope in a 1:1 ratio: Level D: (40-participants): Two doses of ketamine were given to the 40-patients in Group-K: an intravenous bolus dosage of 0.3mg/kg slowly, and then a continuous infusion dose of 0.2mg/kg/hr. Prior to administering anaesthesia, this was completed. Over the course of 10 minutes, 100mL of normal saline was used to provide the bolus dosage of dexmedetomidine.

Ethical considerations:

Following a thorough explanation of the treatment, its anticipated outcomes, and any potential risks, the Ethics Committee gave its approval, and each patient signed an informed consent document.

Inclusion criteria:

Patients undergoing surgery on the nose or paranasal sinuses; patients' ages range from 21 to 40; Based on the criteria set by the American Society of Anaesthesiologists, patients are classified as either I or II.

Exclusion criteria:

The study is contingent upon the participant's voluntary participation; refusal to participate in the study, presence of an allergy to any of the study's drugs, history of substance abuse, mental or psychiatric disorders, history of emergency surgery, current or past pregnancy, severe respiratory or cardiac disorders, renal or hepatic insufficiency, an excess of 35kg/m2 in body mass index, use of any drug that could impact immunity, such as hormonal or chemotherapy treatments, liver dysfunction(AST or ALT> twice the upper normal), and so on. The following are examples of normal values: AST 5-40 and ALT 5-40 units/dl, as reported by the National Health Laboratory Services; individuals with hypertension, sBP>160mm Hg, and diabetes mellitus are also included.

Preoperative assessment:

Methods:

All patients were subjected to the following:

Age, sex, ASA classification, and weight were among the sociodemographic variables gathered. History, including examination of the cardio-respiratory state. As part of the physical examination, the doctor listened for heart sounds and felt around the abdomen. Full blood count, electrocardiogram(ECG), coagulation profile, liver and kidney functions, serum electrolytes, and chest X-ray were all part of the investigation. Surgical suite: All hemodynamic parameters were recorded perioperatively, including the following routine parameters: vital signs(heart rate, systolic and diastolic blood pressure, mean arterial pressure, and electrocardiogram).

Levels of interleukin-6(IL-6), cortisol, blood glucose, and C-reactive protein were tested in the laboratory. Both before and after surgery, at 6-and 24-hour intervals, these were measured in peripheral venous blood. Before the study, the plasma was centrifuged to separate it and kept at a temperature of -70°C. The serum was separated and held at -70 ˚C until it was time to measure basal interleukin-6, cortisol, and CRP. The blood sample consisted of 3ml of venous blood in a plain tube, which did not contain any anticoagulant. After letting the blood clot at room temperature for 30 minutes, it was centrifuged at a speed of 3000-4000 RPM.

Operative data:

Each patient received brief instructions on the visual analogue scale(VAS) prior to surgery. Before the procedure, no medicine was given. Prior to inducing anesthesia, all patients underwent preoxygenation for three minutes. After that, they were all given fentanyl at a dosage of 1-2 µg/kg. Two minutes later, propofol was administered at a dose of 2mg/kg over the course of 90 seconds. To facilitate endotracheal intubation, rocuronium was administered intravenously at a dose of 0.45-0.6 εg/kg. Every patient had a gauze throat pack inserted under their laryngoscope vision, and eye lubrication was applied. The TT size was determined to be 7mm for females and 7.5mm for males. The cuff was then inflated with air.

Perioperative assessment:

All haemodynamic data were obtained at the start, every 15 minutes during extubation,

induction, endotracheal intubation, and recovery. Hypotension was defined as SBP<80 mmHg or MAP<60 mmHg(MAP<25% baseline level), hypertension as MAP>25%, tachycardia as HR>25%, and bradycardia as HR<45 beats per minute. Intravenous(15mg/kg) paracetamol for postoperative analgesia and 4mg ondansetron for nausea and vomiting were given 30 minutes before surgery to all patients.

After the procedure, all infusions were terminated. Reversing the neuromuscular blockade required 0.07mg/kg neostigmine with 15µg/kg atropine. Every patient was moved to the PACU(post-anesthesia care unit). The VAS was used to measure postoperative pain, with 0-representing no pain and 10-representing the worst discomfort.

When necessary, a 2mg intravenous morphine dose was given for postoperative analgesia. 30mg of ketorolac and 15mg/kg of intravenous paracetamol were administered as rescue analgesia if VAS pain levels were assessed to be greater than 4. In the PACU, patients were monitored for bradypnea, drowsiness, nausea, and vomiting, as well as any postoperative opioid needs.

Inflammatory markers assessment:

Using the BioTek ELISA reader and the ab108665Cortisol and ELISA Kit, serum cortisol was measured by immunoassay. The Spinreact CRP-Latex slide agglutination test, a semi-quantitative latex agglutination test, was used to measure the CRP level. Range of reference: up to 6mg/L.6 As a baseline, venous blood samples were taken from each patient on the morning of the surgery day. At 6 and 24 hours after surgery, blood samples were taken to test the levels of cortisol, CRP, and IL-6. Prior to examination, the samples were held at -70 °C after being centrifuged to remove cells and debris.

Primary Outcome: Postoperative pain is assessed using the VAS score.

Secondary Outcome:

Hemodynamic stability(SBP, DBP, MAP and HR) and blood loss. Observed postoperative side effects in the PACU. criteria for perioperative opioid dosage. Assessment of the stress response by measuring blood glucose, CRP, IL-6, and cortisol levels. Lastly, patient satisfaction.

Sample Size analysis:

The sample size was calculated utilising Epi-info TM version 7.2.4.0(2020) according to the specified criteria. Utilising a two-sided confidence level of 95%, a test power of 80%, an error margin of 5%, and a minimum sample size of 72 participants, with an additional 10%(about 8 patients) to account for dropout, the study analysed 40 patients in each group to evaluate the hypothesis based on the collected data.[7]

Statistical analysis:

IBM Inc., Chicago, IL, USA, used SPSS v26 to conduct the statistical study. If the data were normal, it was examined using the Shapiro-Wilk and histograms. The groups were compared using an unpaired Student's t-test for quantitative parametric variables, which are given as mean and standard deviation. In order to test for non-parametric variables, the Mann-Whitney U-test was used using the supplied median and interquartile range(IQR). We used Chi-square or Fisher's exact tests to look at the qualitative variables that were given as percentages or frequencies. Statistical significance was indicated by a two-tailed P-value less than 0.05.

3. Results

Table 1. Demographic data and duration of surgery of the studied groups.

		GROUP-D (N=40)	GROUP-K (N=40)	P-VALUE
AGE(YEARS)	Mean±SD	30.95±5.22	32.4±3.4	0.145
	Range	21-40	27-39	
SEX	Male	21(52.5%)	23(57.5%)	0.653
	Female	19(47.5%)	17(42.5%)	
WEIGHT(KG)	Mean±SD	79.98±7.46	80.98±10.6	0.627
	Range	68-94	59-96	
HEIGHT(CM)	Mean±SD	166.55±6.41	165.15±8.32	0.402
	Range	156-176	153-180	
BMI(KG/M^2)	Mean±SD	29±3.87	29.89±4.87	0.366
	Range	22.6-38.63	19.47-38.95	
ASA PHYSICAL STATUS	I	28(70%)	32(80%)	0.302
	II	12(30%)	8(20%)	
DURATION OF SURGERY(MIN)	Mean±SD	88.5±18.02	90.63±14.38	0.562
	Range	65-120	70-110	

BMI:Body mass index, ASA:American society of anesthesiologists.

As regard to age, sex, weight, height, BMI, ASA physical status and duration of surgery there were statistically non-significant difference between two groups (Table 1;Figures1&2).

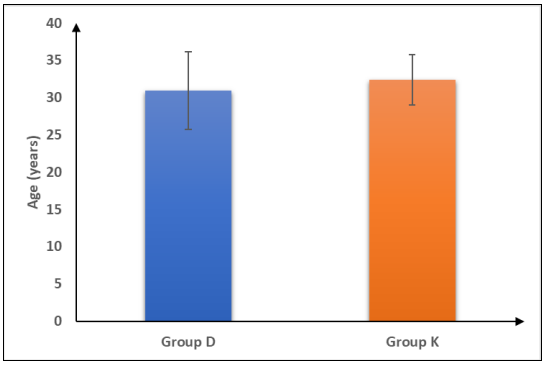

Figure1. Age of the studied groups.

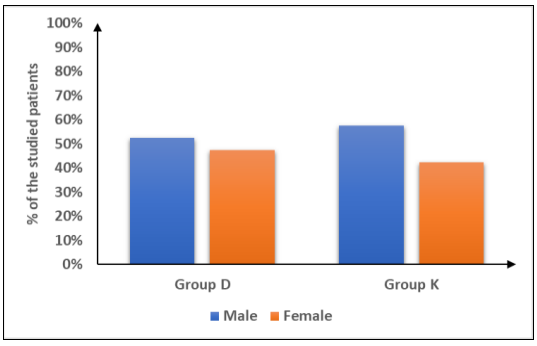

Figure 2. Sex of the studied groups.

Table 2. The participants' heart rates.

	GROUP-D (N=40)	GROUP-K (N=40)	P-VALUE
BASELINE	80.03±8.03	79.83±7.12	0.906
DURING INDUCTION	79.55±8.5	78.35±7.52	0.505
AT BEGINNING OF THE OPERATION	77.55±8.5	77.83±7.18	0.876
15THMIN	74.68±7.9	75.6±7.28	0.588
30THMIN	71.15±8.65	75.13±7.32	0.029*
45THMIN	70.33±7.88	73.85±6.95	0.037*
60THMIN	68.88±7.55	72.7±7.36	0.025*
75THMIN	66.95±8.85	71.25±7.59	0.022*
90THMIN	66.38±7.77	71.23±7.15	0.005*
105THMIN	68.05±8.33	70.15±7.51	0.239
END OF SURGERY	71.9±7.6	73.05±6.91	0.481
DURING EXTUBATING	72.43±7.64	74.1±6.88	0.306
PACU	73.53±7.63	75.05±6.95	0.352

The data is shown as mean±SD, with a significant difference indicated by a P-value of less than 0.05. PACU stands for post-anesthesia care unit.

Regarding heart rate, there was a statistically significant decrease in group D's heart rate at 30-minutes, 45-minutes, 60-minutes, 75-minutes, and 90-minutes compared to group-K(P-value<0.05), but there was no statistically significant difference between both groups at baseline, during induction, at the start of the procedure, at 15-minutes, 105-minutes, at the end of surgery, during extubation, and in the PACU, (Table 2;Figure 3).

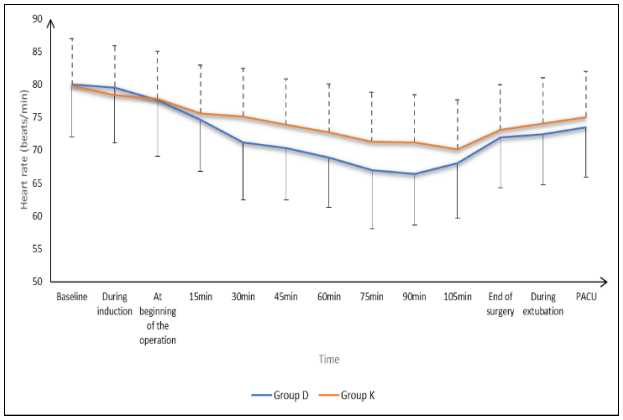

Figure 3. Heart rate of the studied groups.

Table 3. Systolic blood pressure of the groups under study.

	GROUP-D (N=40)	GROUP-K (N=40)	P-VALUE
BASELINE	107.53±5.93	108.2±6.23	0.621
DURING INDUCTION	105.98±6.47	107.03±6.57	0.473
AT BEGINNING OF THE OPERATION	104.08±6.3	106.38±5.98	0.098
15THMIN	102.95±6.98	104.7±6.38	0.245
30THMIN	100.1±6.26	103.78±7.23	0.017*
45THMIN	99.58±6.38	102.8±6.96	0.034*
60THMIN	96.35±6.28	99.28±6.12	0.038*
75THMIN	94.75±5.94	97.6±5.96	0.035*
90THMIN	93.53±5.58	96.63±6.14	0.021*
105THMIN	93.55±5.51	95.95±6.89	0.089
END OF SURGERY	96.45±5.77	97.63±6.29	0.387
DURING EXTUBATING	97.1±5.71	98.65±6.18	0.247
PACU	98.15±5.82	99.05±6.36	0.511

Data presented as mean±SD, *Significantly difference as P-value≤0.05, PACU:Post anesthesia care unit.

There was a statistically significant decrease in systolic blood pressure in group-D compared to group-K at 30-minutes, 45-minutes, 60-minutes, 75-minutes, and 90-minutes, while there was no statistically significant difference between both groups at baseline, during induction, the start of the operation, 15-minutes, 105 minutes, the end of surgery, during extubation, and in the PACU(P-value<0.05), (Table 3;Figure 4).

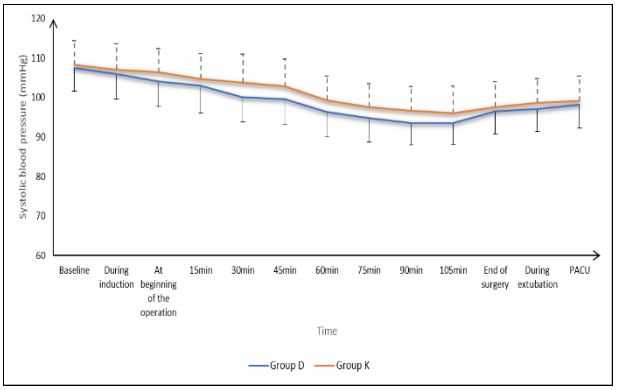

Figure 4.Systolic blood pressure of the groups under investigation.

Table 4. Diastolic blood pressure of the groups under study.

	GROUP-D (N=40)	GROUP-K (N=40)	P-VALUE
BASELINE	70.4±4.65	70.85±4.23	0.652
DURING INDUCTION	69.63±5.31	69.93±4.63	0.788
AT BEGINNING OF THE OPERATION	68.25±5.77	68.6±4.46	0.762
15THMIN	66.68±4.81	66.98±4.6	0.776
30THMIN	64.15±5.38	66.6±4.91	0.036*
45THMIN	63.15±4.53	65.98±4.85	0.009*
60THMIN	60.4±5.02	63.13±4.85	0.016*
75THMIN	59.03±4.94	62.73±4.06	<0.001*
90THMIN	58.85±4.85	62.33±4.02	0.001*
105THMIN	59.15±4.97	60.2±4.05	0.303
END OF SURGERY	62.95±4.75	64.18±4.22	0.227
DURING EXTUBATION	63.58±4.65	64.9±4.17	0.184
PACU	64.05±4.54	65.6±4.34	0.123

The data is shown as mean±SD, with a significant difference indicated by a P-value of less than 0.05. PACU stands for post-anesthesia care unit.

There was a statistically significant decrease in diastolic blood pressure in group-D compared to group-K at 30 minutes, 45-minutes, 60-minutes, and 75-minutes, while there was no statistically significant difference between both groups at baseline, during induction, at the start of the procedure, at 15-minutes, 105-minutes, at the end of surgery, during extubation, and in the PACU(P-value<0.05),(Table 4;Figure 5).

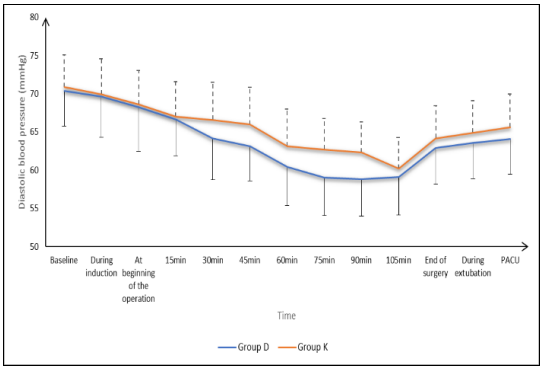

Figure 5.Diastolic blood pressure of the studied groups.

Table 5. Time to request rescue analgesia for the first time and the total amount of morphine consumed by the groups under study.

		GROUP-D (N=40)	GROUP-K (N=40)	P-VALUE
TIME FOR THE INITIAL RESCUE ANALGESIA REQUEST(H)	Mean±SD Range	8.85±2.21 6-12	7.98±1.79 4-10	0.056
TOTAL DOSE OF MORPHINE CONSUMPTION(MG)	Mean±SD Range	1.8±0.76 1-3	2.08±0.97 1-4	0.162

The two groups did not differ statistically in terms of the time it took to request rescue analgesia or the total amount of morphine consumed (Table 5;Figure 6).

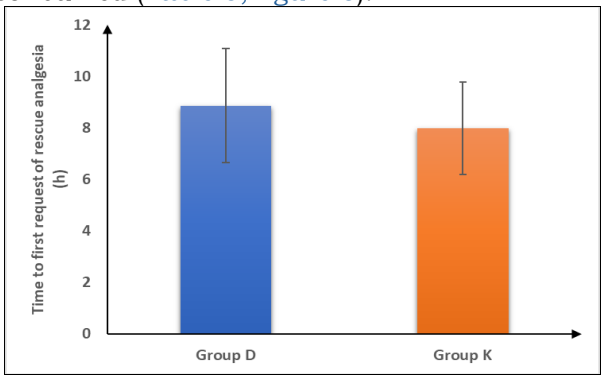

Figure 6. Time to first request of rescue analgesia of the studied groups.

Table 6. VAS of the studied groups.

	GROUP-D (N=40)	GROUP-K (N=40)	P-VALUE
PACU	0(0-0)	0(0-0.25)	0.794
4THHOURS	1(1-2)	1.5(1-3)	0.403
8THHOURS	2(1-3)	2(1-3)	0.357
12THHOURS	2(2-3.25)	3(2-3)	0.718
16THHOURS	3(2-3)	3(2-3)	0.698
20THHOURS	3(2-4)	3(2-4)	0.869
24THHOURS	2(1-3)	3(2-3)	0.112

Data displayed as PACU and median (IQR):The post-anesthesia care unit.

Regarding the VAS, the two groups' differences at PACU, 4th, 8th, 12th, 16th, 20th, and 24th hours were statistically not significant(Table 6;Figure 7).

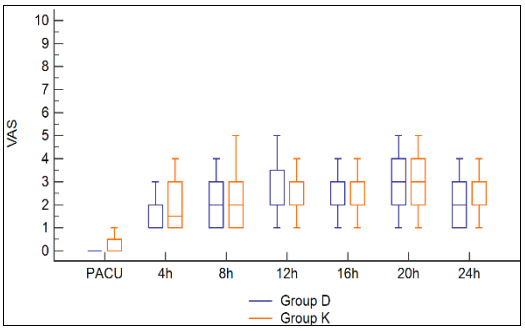

Figure 7. VAS of the studied groups.

4. Discussion

Dexmedetomidine was widely used for induced hypotension. As an α2-adrenergic agonist, it has analgesic, sedative, and sympatholytic effects. Few human investigations showed dexmedetomidine's anti-inflammatory effects. Hemodynamic stability helps optimize the endoscopic sinus surgery operative fields. In in-vitro trials, α2-adrenoceptor therapy reduces endotoxaemia-related cytokine release.[8]

Along with thiopental and propofol, ketamine is an intravenous anesthetic used for general induction. Ketamine exerts its analgesic effects on the spinal cord by acting as an NMDA(N-methyl-D-aspartate) receptor antagonist. Following spinal cord injury, nerve malfunction, or surgery, the NMDA receptors play a crucial role in launching and sustaining nociceptive events.[9]

Dexmedetomidine diminishes sympathetic outflow and noradrenergic activity, leading to a drop in hemodynamic parameters, which may be accounted for by its status as a strong α2-adrenoceptor agonist. Dexmedetomidine also decreases central sympathetic outflow and norepinephrine turnover by activating receptors in the medullary vasomotor region.[10]

In accordance with the findings, Elghamry et al.,[11] 75-women with ASA I–II who were scheduled for elective laparoscopic hysterectomy and were 30-60 years old were included in the

prospective, double-blind, randomized, controlled trial. They were split evenly into three groups: one that received dexmedetomidine, one that received ketamine, and the control group. Compared to the ketamine group, the dexmedetomidine group showed considerably lower heart rates and mean arterial pressures at various time points.

In this trial, neither the overall amount of morphine used nor the time it took to obtain rescue analgesia was significantly different between the two groups.

According to the findings of Mohamed et al.,[12] 90 individuals who were going to get a total abdominal hysterectomy participated in a randomized, double-blind trial. Each of the three groups-control, dexmedetomidine, and ketamine-was randomly assigned a certain number of patients. Both the dexmedetomidine and ketamine groups showed no statistically significant differences in the time to first request of rescue analgesia or total morphine use.

When comparing the two groups at4,8,12,16,20, and 24 hours, there were no statistically significant differences in VAS.

According to the findings, Mohamed et al.,[12] discovered no statistically significant difference in VAS between the ketamine and dexmedetomidine groups at any of the time points studied.

Supporting our results, Youssef et al.,[13] researched the impact of intravenous dexmedetomidine infusion on stress response indicators such as plasma cortisol and interleukin-6 in patients having open heart surgery. Dexmedetomidine inhibits the increase of IL-6 both during and after surgery, as they proved.

In disagreement with our results, Elghamry et al.,[11] discovered no statistically significant variation in IL-6 levels between the two groups. The divergent methods used in the two investigations might explain this discrepancy.

At baseline, neither group's cortisol levels were significantly different from the other; however, at 6 and 24 hours, the dexmedetomidine group demonstrated significantly higher levels than the ketamine group. Both groups showed no statistically significant difference in blood glucose levels 6 or 24 hours post-baseline.

In consistent with our results, Mohamed et al.,[12] 24-hours after surgery, the dexmedetomidine group had a noticeably greater mean serum cortisol level compared to the ketamine group. However, contrary to our findings, they also discovered that the dexmedetomidine group had a noticeably higher mean blood glucose level. The variations in the procedures (abdominal hysterectomy), methods of administration(wound infiltration), and dosages of dexmedetomidine(2μg/kg) and ketamine(2mg/kg) could account for the observed differences.

There was no statistically significant difference in CRP levels across the two groups at baseline in our investigation; however, at 6 and 24 hours, the dexmedetomidine group showed considerably greater levels compared to the ketamine group.

Altiparmak et al.,[14] determined that C-reactive protein levels were noticeably greater in the dexmedetomidine group compared to the ketamine group at the 24-hour mark.

In disagreement with our results, Elghamry et al.,[11] determined that C-reactive protein levels were not significantly different between the two groups.

The present investigation found no statistically significant difference between the two groups with respect to the onset of agitation or vomiting. Neither group's patients reported any symptoms of breath retention, hoarseness of voice, or sore throat.

In accordance with the findings, Elghamry et al.,[11] discovered that in terms of side effects, the dexmedetomidine and ketamine groups were not significantly different from one another.

4. Conclusion

Dexmedetomidine and low-dose ketamine infusion do not differ significantly from one another in terms of pain management for patients undergoing nasal and paranasal sinus surgery, total dose of morphine used, or time to first request of rescue analgesia.

Ketamine reduces the levels of cortisol and C-reactive protein(CRP) without significantly altering blood glucose levels, whereas dexmedetomidine is better at keeping hemodynamic stability and reducing the surgical stress response in relation to IL-6.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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