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Original Research Article

A Comparative Study of Clinical Effects and Recovery Characteristics of Ketamine Versus Fentanyl when used as an Adjuvant along with Dexmedetomidine Infusion Intraoperatively in General Anaesthesia

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Abstract

Background: Reducing postoperative pain enhances the ability to breathe deeply and cough effectively, thereby protecting cardio pulmonary functions. This leads to better oxygenation and probable preservation of positive myocardial oxygen balance, which in turn reduces hospital stay and cost and increases patient satisfaction

Aims: This study compared the clinical effects and recovery characteristics of ketamine versus fentanyl when used as an adjuvant along with dexmedetomidine infusion intraoperatively.

Methods: randomized prospective clinical study in which total of 60 patients of age 18-60 years undergoing major surgeries were divided into two groups: Group (D + K) received an intraoperative infusion of ketamine 0.5 mg/kg/h, while group (D + F) received fentanyl 0.5µg/kg/h along with intravenous dexmedetomidine 0.5 µg/kg/h. Intraoperative heart rate (HR), mean blood pressure, and oxygen saturation were recorded at 0 min, 10 min of induction, and thereafter every 30 min throughout the procedure. Ramsay sedation score (RSS) and visual analogue scale (VAS) score were measured at the end of the surgery, at 2 hours, 4 hours, and 6 hours.

Results: Decreased in HR and mean blood pressure was more with a tendency of developing hypotension in the fentanyl group compared to the ketamine group. Post-anaesthesia care unit (PACU) stay, need for muscle relaxant and VAS score for pain were also significantly lesser in the ketamine group.

Conclusion: Dexmedetomidine with ketamine provided better haemodynamic stability and reduced PACU stay compared to dexmedetomidine with fentanyl.

Keywords: Analgesia; dexmedetomidine; fentanyl; ketamine; sedation.

Introduction

Dexmedetomidine, a highly selective α2 adrenoreceptor agonist, has anxiolytic, sedative, anesthetic, and analgesic properties. It has limited side effects in terms of respiratory depression.[1] Because of these favorable properties, it is commonly used in a wide variety of procedures.[2,3,4]

Ketamine hydrochloride, a well-known anesthetic agent, has been in clinical use for more than four decades. Its antinociceptive-hypnotic effects are most likely the result of the noncompetitive antagonism at the N-methyl-D-aspartate (NMDA) receptor of the central nervous system.[4,5] Ketamine is used as an analgesic in low doses and as an anesthetic in high doses.[6] It is suggested that ketamine maintains analgesia and reduces postoperative opioid use, whether used alone or in combination with other anesthetic agents .[7]

Ketamine and another rarely used α_2 adrenoceptor agonist, clonidine, have been compared for their effects on reducing pain and anesthesia requirements. According to our literature research studies, no similar studies have been found that compare ketamine and fentanyl for the effects [8,9].

One recent study, compared dexmedetomidine and ketamine combination with dexmedetomidine, midazolam and fentanyl combination for procedural sedation in the adult population. [10]This failed to show any significant difference between onset time, recovery time and cardiorespiratory variables. In that study, local anaesthetic was also infiltrated, probably requiring a lesser dose of intravenous drugs. Hence, the cardiorespiratory effects of adjuvants could not have been evident in that study.In our study, this

study compared the clinical effects and recovery characteristics of ketamine versus fentanyl when used as an adjuvant along with dexmedetomidine infusion intraoperatively.

Materials and Methods

It is double-blinded, prospective, randomised controlled trial was conducted from January 2023 to may 2023 at a tertiary care hospital for period of 5 months. Written informed consent was obtained.

Inclusion Criteria

Age between 18 and 60 years with American Society of Anesthesiologists (ASA) physical status I and II patients, undergoing major abdominal or head and neck onco-surgeries were included.

Exclusion criteria: Patients with ASA grade III or more; heart block, arrhythmias, basal heart rate less than 60/min, patients on beta-blockers or calcium channel blockers, known allergy to study drug, lack of consent, known chronic use of analgesics and sedatives, renal and hepatic dysfunction; psychiatric disorders; and respiratory disorder and sleep apnoea .

Baseline demographic and cardiorespiratory parameters were noted in both groups upon arrival of the patient in the operating room. The patients were pre-oxygenated and pre-medicated with intravenous fentanyl 1.5 µg/kg and midazolam 30 µg/kg IV, induced by administering injection propofol (till loss of verbal command) and injection vecuronium 0.1 mg/kg as muscle relaxant. The patient was intubated when there was a disappearance of three (T1) or all twitches (T0) after train of four (TOF) stimuli, and clinical conditions were satisfactory like relaxed jaw, absence of coughing, gagging, swallowing, etc. Maintenance of anaesthesia was done with isoflurane and nitrous oxide in both groups. Immediately after intubation, intraoperative infusion of the following agents was started:

Group **A**: D + K Group – Intraoperative infusion of intravenous (IV) dexmedetomidine 0.5 µg /kg/h in combination with ketamine 0.5 mg/kg/h.

Group **B**: D + F Group - Intraoperative infusion of IV dexmedetomidine 0.5 µg/kg/h in combination with fentanyl 0.5 µg/kg/h.

The primary outcome measured has intraoperative HR, MAP, peripheral capillary oxygen saturation (SpO_2), $EtCO_2$, which were recorded at 0 min, 10 min of induction and thereafter every 30 min throughout the procedure; and also measured after extubation, 5 min after extubation and 2 h in the post-operative period. On arrival at the PACU, RSS was assessed at admission to PACU as well as 60 min later. Secondary outcomes included were pain assessment on 10-point visual analogue scale (VAS) at the end of the surgery, at 2 hours, 4 hours and 6 hours. After arrival in the PACU, oxygen saturation, MAP and HR were noted. Duration of PACU stay, time of administration of first analgesic for each patient, emergence delirium and any adverse events like post-operative nausea and vomiting (PONV), bradycardia, hypotension, hypertension, pain, shivering and delirium were noted.

Qualitative data were analysed with Chi-square test, while quantitative data were presented as mean ± standard deviation (SD), or as the median for skewed data. All statistical analyses were performed with Statistical Package for Social Sciences (SPSS) version 21.0 (International Business Machines, Armonk, NY, USA).

Results

Table 1: Baseline demographic details

	Mean±SD *n*=60		**P**
	Group 1	**Group 2**	
Age (years)	45±11	43±12	0.3
Height (cm)	157±4.0	158±3.8	0.3
Weight (kg)	60±6.2	61±4.	0.2
M: F (ratio)	5:3	2.2:3	0.6
ASA grade 1:2 (ratio)	7:3	2.1:2.0	0.1

Both groups had comparable demographic profiles ie is there is no significance in between them.

Table 2: Preoperative vital paramenters

Vitals	**Group 1**	**Group 2**	P value
Baseline heart rate (beats/min)	73±8	75±6	0.1
Baseline MBP (mmHg)	85±8	83±2	0.1
Baseline SpO_2 (%)	99±1.0	100±1.0	0.2
Baseline $EtCO_2$ (mmHg)	31.6±1.5	32±1.3	0.09

Both groups had comparable vital parameters ie is there is no significance in between them

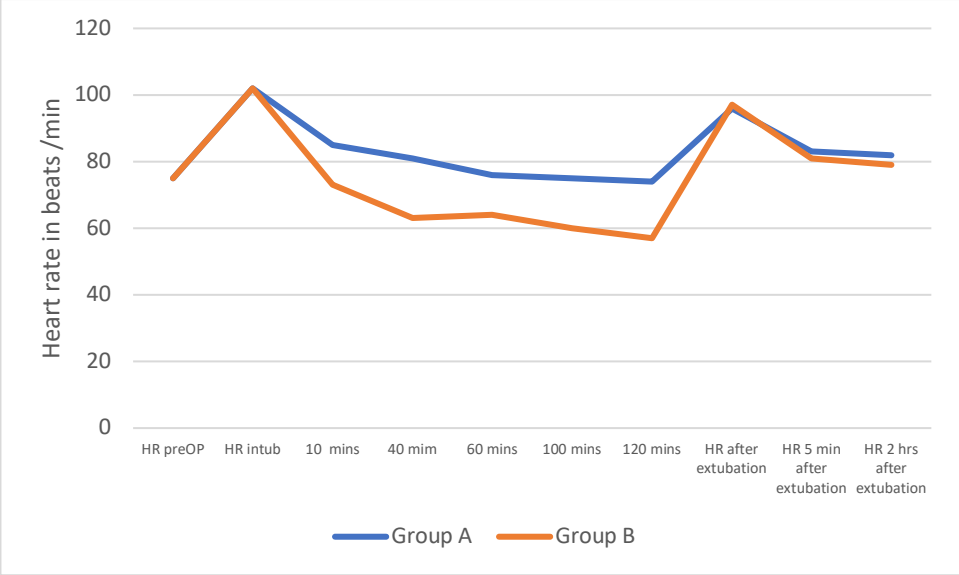

Figure 1: Hear rate at various intervals in the study

HR increased immediately after intubation and then decreased gradually below the baseline value at 10, 40, 60, 100 and 120 minutes. However, there was a greater reduction in HR in the D + F group at all points of time extubation ($P = 0.000$).

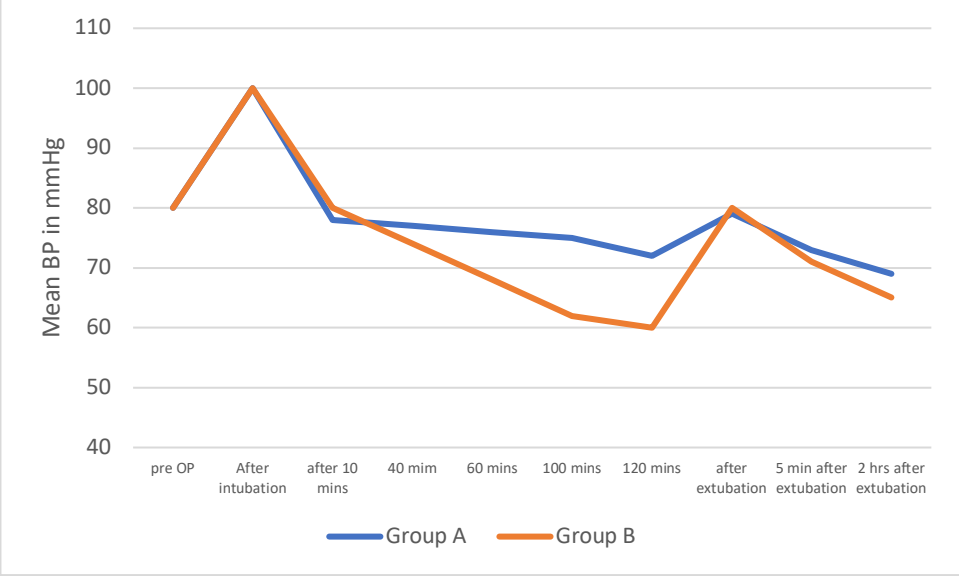

Figure 2: Mean BP at various intervals in the study

After intubation, the mean blood pressure (BP) was 100 ± 10 and 99 ± 8 mm Hg in group A and B, respectively, and both were comparable and statistically insignificant ($P = 0.755$). In both the groups, mean BP increased immediately after intubation, and then it gradually reduced below the baseline value at 10, 40, 60, 100 and 120 min. However, there was a tendency for the development of hypotension in the group B thus giving it a lesser favourable haemodynamic profile as compared to A group. Mean BP showed a significant difference between the two groups ($P < 0.001$) at all points of time post-intubation. Group fentanyl showed statistically significant lower mean BP as compared to ketamine group, and hypotension was observed in four patients in fentanyl group as compared to 1 patient in ketamine group

No differences in the SpO2 or sedation score among the two groups were observed.

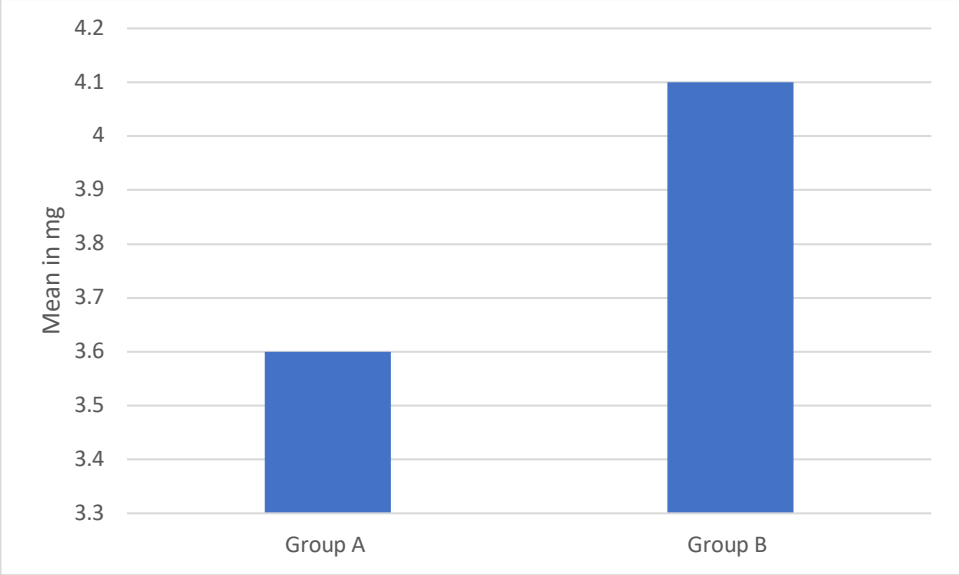

Figure 3: Muscle relaxant requirement in milligrams

The total intraoperative requirement of muscle relaxants in ketamine group (3.6 mg) was significantly lesser than in fentanyl group (4.1 mg) [$P < 0.001$] . There was no significant difference between the analgesic requirements among the two study groups during the first 6 hours in the post-operative period, but the pain score was significantly lesser in ketamine group than fentanyl group at 4 and 6 hours post-operatively [$P < 0.001$].

Extubation time in the ketamine group and fentanyl group which was statistically insignificant.

The mean PACU stay in the ketamine group (1.2 ± 0.20 hours) was significantly lesser than fentanyl group (1.5 ± 0.10 hours) [$P < 0.001$].

Discussion

In our study, there was a decrease in intraoperative HR and BP in both groups, but a greater decrease was seen in the fentanyl group. Haemodynamic variations were easily managed in our study, with IV fluid therapy. One study comparing the haemodynamic effects of ketamine - dexmedetomidine with ketamine -propofol for sedation in post-coronary artery bypass grafting (CABG) patients showed no significant difference in the haemodynamic stability among the two groups, probably because ketamine which antagonises the hypotensive and bradycardic effect of dexmedetomidine, and propofol was common to both the groups.

Dexmedetomidine, a strong 2-adrenergic agonist, has sedative effects that are partially mediated by a rise in parasympathetic outflow and a fall in sympathetic outflow from the locus ceruleus in the brain stem. The medullary vasomotor center's negative feedback receptors are activated, reducing catecholamine release and mediating its sympatholytic effects [11,12]. During the use of dexmedetomidine, bradycardia and hypotension may be noticed due to the decrease in norepinephrine release and potential baroreflex activation.

The cause of the bradycardia in the fentanyl group can be direct stimulation of the central vagal nucleus by fentanyl, as dexmedetomidine was common in both groups. Ketamine prevented bradycardia in the Ketamine Group. Similarly, the fentanyl group had a significant decrease in mean BP compared to the Ketamine group. Fentanyl is also known to cause hypotension indirectly by decreasing central sympathetic outflow, whereas ketamine may antagonise the bradycardia and hypotension, caused by dexmedetomidine. Thus, the dexmedetomidine with ketamine group of patients had better haemodynamic stability with easy arousability.[13]

In our study Group fentanyl showed statistically significant lower mean BP as compared to ketamine group. In a study by Honarmand et al,[14] the largest difference between the Thiopental-Fentanyl and Thiopental-Ketamine groups in any blood pressure parameter was 6.7mmHg (109.2 versus 115.09 SBP) and a heart rate difference of 16.2bpm (69.7 versus 85.9), which was statistically significant. In that study, Thiopental was used at 4.0 mg/kg, Fentanyl at 3.0 µg /kg and Ketamine at 0.1 mg/kg. This corresponds with the results of our study. In our study total intraoperative requirement of muscle relaxants in ketamine group was significantly lesser than in fentanyl group. However, when the add-on effect of ketamine versus fentanyl with dexmedetomidine infusion was compared, the requirement of the muscle relaxant was lesser in the ketamine group. Earlier

cases have been reported where dexmedetomidine and ketamine were used along with inhalational anaesthetic agents without muscle relaxants for surgery.[15] Ketamine allows good intubating conditions without requiring muscle relaxants, and this has been shown in earlier studies also.[16] This finding is contrary to an earlier study where the investigators could not find the difference in muscle relaxation and intubating conditions between the ketamine and alfentanil groups.[17] Dexmedetomidine, ketamine and opioids are known for their analgesic effects.

There was no significant difference between the analgesic requirements among the two study groups during the first 6 hours in the post-operative period, but the pain score was significantly lesser in ketamine group than fentanyl group at 4 and 6 hours post-operatively, fentanyl group, suggesting a better analgesic profile of dexmedetomidine with ketamine. A similar study comparing pain scores in patients undergoing lower limb surgeries under spinal anaesthesia between two groups receiving dexmedetomidine with ketamine (1 mg/kg) or dexmedetomidine with fentanyl (1 μg/kg) found better analgesia in the ketamine group.

Fentanyl provided quicker, better intra-operative and post-operative analgesia. Various studies have used different doses of ketamine intrathecally, and with a similar dose also, different researchers have obtained different results. Unlike fentanyl, has given reasonably consistent results, there was not a consensus on a single dose of ketamine that would produce consistent results with an acceptable safety profile. Hence, it may be better to limit the use of intrathecal ketamine on an individual basis rather than making it a common practice at present.

Although there are some limitations like not being a double-blinded study, with a low number of patients, with different surgeons and different anesthesiologists, this study is very original due to being the first one comparing the effects of dexmedetomidine and ketamine and fentanyl in adult patients.

For better and more reliable results, future studies with double-blinded, with more number of patients, with pediatric or geriatric patients, with a special group of patients, with regional anesthesia, sedation, with different kinds of agents and procedures, with the same surgeon are needed to be done.

Conclusion

Both ketamine and fentanyl, when administered in conjunction with dexmedetomidine, lessen the haemodynamic response to surgical stress, but dexmedetomidine combined with ketamine promotes better haemodynamic stability and quicker post-operative recovery than dexmedetomidine and fentanyl alone. The dexmedetomidine with ketamine group showed a markedly reduced need for muscle relaxants, analgesics, and a shorter stay in the PACU. Therefore, it is advised to utilise ketamine rather than fentanyl as an adjuvant in combination with dexmedetomidine infusion.

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