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# Analgesic Effectiveness Of Intravenous Ketamine Versus Fentanyl In Patients With Proximal Femur Fracture: A Comparative Study

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## ABSTRACT

Introduction: Positioning patients with femur fracture for subarachnoid block (SAB) is associated with excruciating pain. Thus, intravenous (IV) analgesic like ketamine and fentanyl can alleviate pain.

Objective: To compare the analgesic effectiveness of IV ketamine and fentanyl in reducing pain associated with positioning for SAB.

Methodology: This prospective comparative study was conducted in operation theatre of B P Koirala Institute of health sciences from June 2020 to May 2021. We enrolled 60 patients into two groups (allocation ratio 1:1) to receive either 0.3mg/kg ketamine (n=30) or 1.5mcg/kg fentanyl (n=30) using randomized sampling technique. Numeric rating scale for pain (0-10) was used for pain assessment before and after study drug administration.
Data was analysed using Statistical Package for Social Science software. Student's t-test and Mann-Whitney U test were used for normal and non-normal data, respectively, while categorical data was assessed using chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results: The ketamine group showed better analgesia, with lower pain scores at rest 1 [1-2] vs [1-2],(p=0.006) and motion 3 [3-3] vs 3[3-4], (p=0.04). The ketamine group required fewer attempts for successful spinal needle placement (p=0.010) with better anaesthetist satisfaction (p<0.001). Ketamine caused hypertension in 21(35%) and delirium 5(8.3%), while fentanyl caused hypotension 8(13.3%), bradycardia 3(5%), and desaturation 3(5%) patients.

Conclusion: Ketamine provided superior analgesia, with lower pain scores. It also resulted in fewer attempts for successful spinal needle placement and higher anaesthetist satisfaction.

## INTRODUCTION

Femur fracture is common, with incidence of nearly 1.6 million yearly worldwide. It is a painful bone injury which leads to significant morbidity in all age group.[1] Surgical repair of femur fracture is mostly conducted under subarachnoid block (SAB).[2,3] However, positioning these patients for SAB is associated with excruciating pain, even with slight movement of the fracture site. Thus, it is important to provide analgesia to increase patient co-operation.[2] Comfortable position also reduces the number of attempts at spinal needle placement.[4]

Several modalities are available to alleviate such pain. Nerve blocks require a certain level of expertise and availability of ultrasound. So, in a resource limited country like ours, use of intravenous (IV) analgesics still play an important role. Ketamine, N methyl D aspartate receptor antagonist is excellent analgesic at subanesthetic doses. It increases heart rate (HR), blood pressure (BP) which balances the hypotensive effect of SAB. Unlike opioids like fentanyl, it doesn't cause dose dependent respiratory depression. Many studies have been conducted to study the effects of nerve blocks but few studies about IV analgesics. Hence, we aimed to compare the analgesic effectiveness of IV ketamine with fentanyl in reducing pain for positioning in femur fracture patients for SAB.

## METHODOLOGY

This prospective, single-center, comparative study was conducted at B.P. Koirala Institute of Health Sciences(BPKIHS) from June 9th 2020 to May 28th 2021. Ethical approval was obtained from the Institutional Review Committee of BPKIHS (IRC No. IRC/1597/019 on 8th March 2020).

Sample size was calculated with this formula:

$$n = 2SD^2(Z_{\frac{2}{}}^{\alpha} + Z\beta)^2/d^2$$

where, n=sample size for each group; SD= ; Z=1.96 at 95% confidence interval; power=80%; $d^2=(\overline{x_1}-\overline{x_2})^2$ SD= $\frac{SD_1+SD_2}{2}$; $Z_{\frac{2}{}}^{\alpha}=1.96$ where

Based on the study entitled "Preoperative Fasica Iliaca Compartment Block for positioning patients with hip fractures for central nervous blockade."[6] The mean NRS score for pain was 5.5 ± 2.4 for fentanyl in the above article. For ketamine, assuming the NRS to be 1.5 less than intravenous fentanyl based on the study entitled "low dose ketamine for painful orthopedic surgery" and considering equal SD of 2.4 in both group.[7] The study considered 95% confidence interval and 80% power to estimate the sample size. So

SD1=2.4 ; SD2=2.4

$\overline{x_1}= 5.5;$ $\overline{x_2}= 3.5$

$$n = 2SD^2(Z_{\frac{2}{}}^{\alpha} + Z\beta)^2/d^2 = 23$$

Considering 20% drop outs in each group, 28 patients were enrolled in each group with total sample size of 56; however, we enrolled total of 60 patients.

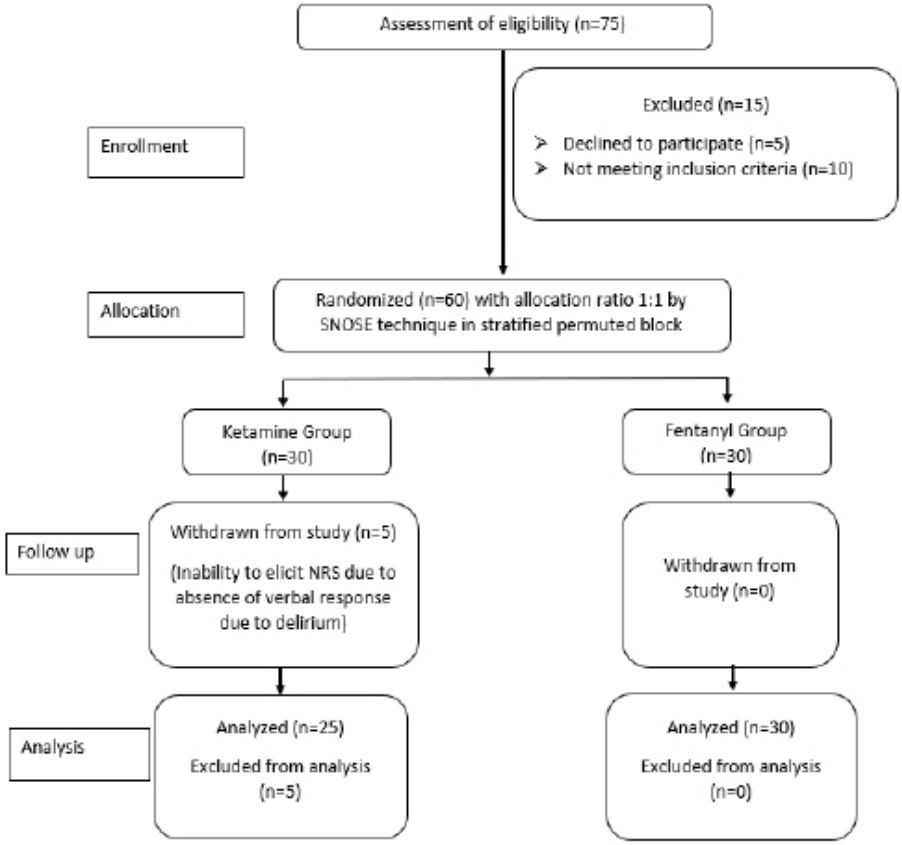


Figure 1: Flow diagram of sampling technique.

All patients over 18 years old with proximal femur fracture, classified as American Society of Anesthesiologist Physical Status (ASA PS) I, II or III and scheduled for surgery under SAB were included. Patients with cardiovascular disease, chronic

painful neuropathy, recent analgesic use (within 8 hours prior to SAB), refusal to consent and contraindicated to SAB or the study drugs were excluded. Out of 75 patients with proximal femur fractures classified as ASA PS I, II, or III, 60 patients were enrolled and randomized equally (1:1) into two groups. In the ketamine group, 5 patients developed delirium, preventing verbal communication for NRS assessment, and were excluded from analysis. All 30 patients in the fentanyl group were included in the analysis. Sampling technique is presented in figure 1, flow diagram.

During pre-operative visit, one day prior to surgery, in the orthopedic in-patient ward, all eligible patients were informed regarding the study and consent was obtained. Patients were instructed to remain nil per oral as per anesthesia protocol. Randomization sequence was generated by the investigator using web based random number generator with a permuted variable block size of 4, 6 and 8 using 1:1 allocation ratio within the blocks.[5] Randomization was stratified based on age (less than 65 and more than 65); 25 patients were <65 years and 30 patients were >65 years of age.

The study group assignments were placed in sequentially numbered, sealed, opaque, stapled (SNOSE) envelopes with the group name enclosed. The investigator forwarded the concealed envelope to the attending anesthetist not involved in the study 30 minutes before SAB. The anesthetist opened the envelope to determine group allocation.

Patient was transferred to the routine operation theatre in trolley maintaining the skeletal traction. All standard monitoring and base line recordings of all vital parameters including heart rate (HR), saturation (sp02), blood pressure (BP) and NRS for pain at rest and movement was assessed (movement is defined at 5 cm active vertical movement of the limb).

An intravenous line was secured and prehydrated with plasmalyte. The attending anesthetist, not involved in the study, calculated and prepared the study drugs. For fentanyl, 2 ml (100 mcg) was diluted with 8 ml normal saline to achieve a concentration of 10 mcg/ml in a 10 ml syringe. For ketamine, 0.4 ml (20 mg) from a 100 mg/2 ml ampule was diluted with 9.6 ml normal saline to achieve a concentration of 2 mg/ml in a 10 ml syringe. Both drugs were prepared in an identical 10 ml sterile syringes as a clear fluid and labelled “study drug”. The ketamine group received a 0.3mg/kg IV bolus dose while the fentanyl group received fentanyl 1.5mcg/kg IV bolus dose.

Five minutes after administering the drug, NRS at rest and during motion was recorded. Patients were assisted into a sitting position by OT assistant. If an NRS of 4 or higher was reported, the procedure was stopped and ketamine 10mg and fentanyl 20 microgram(mcg) was administered intravenously as rescue analgesia before repositioning for ketamine and fentanyl group respectively. Once seated, SAB was performed at the lumbar vertebrae 3-4 interspace using 2.6ml of 0.5% hyperbaric bupivacaine maintaining asepsis. After ascertaining an adequate block height upto T9, patients were transferred to the fracture table, with skeletal traction. The number of attempts needed for successful SAB was documented. The anesthetist performing SAB rated the quality of patient positioning (ease of transitioning from supine to sitting for SAB) as good, satisfactory, or optimal. [6]

Vital parameters and occurrence of any adverse event were monitored throughout the surgery by the primary investigator. Patient satisfaction with analgesia during positioning was evaluated in the PACU using a 5-point Likert scale ranging from ‘strongly satisfied’ to ‘strongly dissatisfied’.[7] The time required for discharge from PACU was noted using Modified Aldrete Score.[8] Hypotension was managed with a rapid infusion of 200 ml Ringer’s lactate (RL) and phenylephrine 50mcg IV bolus. Bradycardia was treated with atropine 0.5mg IV. Nausea and vomiting were managed with ondansetron 4mg IV bolus. Hypoxemia (SpO2 <90 % in room air) was managed with oxygen delivered via face mask at 5L/minute.

The data was initially collected in a proforma then transferred in MS-Excel 2010 and transferred into Statistical Package for Social Science (SPSS software 11.5 version). Normality of the data was tested with histogram, Shapiro Wilk test and Kurtosis skewness test. Normally distributed data was presented as mean and standard deviation (SD) whereas non-normally distributed data as median with interquartile range (IQR). For normally distributed data, student’s t test and for non-normally distributed data, Mann- Whitney U test was applied. For categorical data, chi square test or Fisher’s exact test was applied. P value less than 0.05 was considered significant statistically.

## RESULTS

A total of 55 patients, 25 in ketamine and 30 in fentanyl group, were analyzed. The demographic parameters including age, sex, height, weight, and the baseline hemodynamic parameters were comparable in each group, table 1. Twenty five patients were below 65 years and 30 were above 65 years of age.

**Table 1:** Baseline demographic and hemodynamic parameters of patients in ketamine and fentanyl group

| Parameters | Ketamine group n=25 | Fentanyl group n=30 |
|---|---|---|
| Age (years) | 62 (45- 70) | 65.50 (50 – 72.21) |
| Height(cm) | 160 (150– 170) | 163 (158.75- 165.75) |
| Weight (kg) | 60 (51-68) | 60.0 (53.75- 65.250) |
| BMI (kg/m2) | 22.85 (20.81-23.9) | 22.96 (20.521- 24.034) |
| Gender (Male/female) | 14/11 | 14/16 |
| ASA PS (I/II/III) | 10/14/1 | 8/19/3 |
| **Baseline hemodynamic parameters** | **Mean±S.D** | **Mean±S.D** |
| Heart rate (beats/min) | 79±12.362 | 80±11.961 |
| Systolic blood pressure (mmHg) | 123±16.112 | 126±16.872 |
| Diastolic blood pressure (mmHg) | 72± 9.063 | 77±9,743 |
| Mean Arterial Pressure (mmHg) | 89±10.597 | 93±9.465 |
| Respiratory rate (breaths/min) | 17±1.868 | 17±1.802 |
| SpO2 (%) | 99±0.860 | 98±1.219 |

**Table 2:** Comparison of Numerical Pain Rating Score (NRS) between two groups

| Parameters NRS Score | Ketamine n=25 | | Fentanyl group n=30 | | P value[a] |
|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | |
| Baseline Rest | 3 | 2.5-4 | 3 | 3-4 | 0.665 |
| Baseline Motion | 7 | 6.5-7 | 6 | 5.75-6.25 | 0.06 |
| After medication Rest | 1 | 1-2 | 1 | 1-2 | 0.006* |
| After medication Motion | 3 | 3-3 | 3 | 3-4 | 0.040* |

*Statistically significant; [a]Mann whitney u test; IQR: Interquartile range

Baseline NRS score for pain were statistically comparable between two groups. When comparing ketamine group to fentanyl, the reduction in NRS was significantly more in ketamine group suggesting IV ketamine to be more efficacious than IV fentanyl for reducing pain associated with change is position, table 2.

More number of attempts for successful spinal needle placement were required in fentanyl group (p=0.010). Among 19(35%) patients of ketamine group and in 11(19%) patients off fentanyl group, SAB was successful in the first attempt, whereas in 6(11%) patients of ketamine group and in 16(27%) patients of fentanyl group, 2 attempts were required and 3(5%) in fentanyl group required 3 attempts for successful SAB, figure 2. However, overall satisfaction of patient regarding the anesthetic technique was statistically insignificant (p>0.05), table 2. However, anaesthetist satisfaction level was better with ketamine (p<0.05), figure 3.

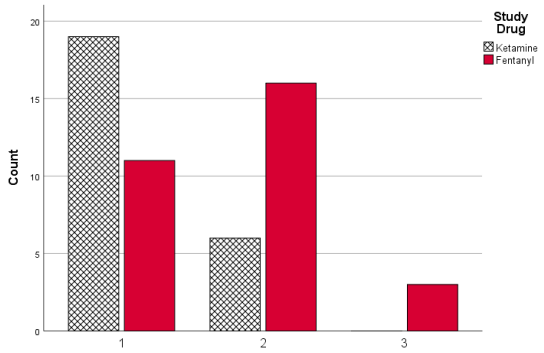


**Figure 2:** Comparison of number of attempts for successful spinal needle placement for SAB

**Table 3:** Level of satisfaction of patients regarding anaesthesia technique

| Level of satisfaction after the procedure | Ketamine group n=25 | Fentanyl group n=30 | P value |
|---|---|---|---|
| Strongly dissatisfied | 0 (0%) | 0 (0%) | 0.102[b] |
| Dissatisfied | 1 (4%) | 3 (10%) | |
| Neutral | 3 (12%) | 10 (33.33%) | |
| Satisfied | 17 (68%) | 16 (53.33%) | |
| Strongly satisfied | 4 (16%) | 1 (3.33%) | |

[b]Chi square test

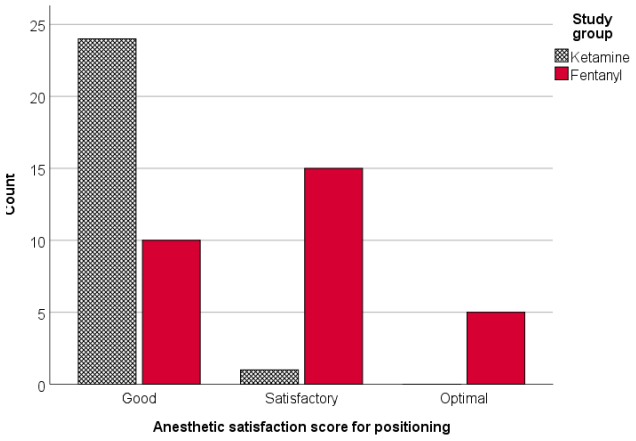


**Figure 3:** Bar diagram showing anaesthetist satisfaction on performing SAB between two groups

**Table 4:** Comparison of adverse effects between two groups

| Adverse events | Ketamine group n=25 | Fentanyl group n=30 | P value |
|---|---|---|---|
| Bradycardia | 0 | 3 (5%) | 0.242[b] |
| Tachycardia | 16 (64%) | 3(5%) | 0.006[b] |
| Hypotension | 0 | 8 (13.33%) | 0.006*[b] |
| Hypertension | 21 (35%) | 0 | <0.001*[b] |
| Nausea/Vomiting | 1 (1.70%) | 6 (10%) | 0.083[b] |
| Desaturation | 0 | 3 (5%) | 0.242[b] |
| Time to discharge from PACU (minutes) | 23.23 ± 8.524 | 26.07 ± 9.223 | 0.154[c] |

*Statistically significant;[b] Fisher's exact test; [c]Independent sample t test

Statistically significant hypertension was observed with ketamine (p<0.001) whereas hypotension was seen with fentanyl (p=0.006), Table 4. Other adverse events like bradycardia, nausea, vomiting and desaturation was statistically insignificant (p>0.05), Table 4. Time to discharge from PACU for both study groups were also comparable (p>0.05), Table 4.

## DISCUSSION

Femur fracture is a debilitating condition that adversely impacts the health of a patient.[8] Surgical repair of such fractures are commonly conducted under SAB.[9] Modalities to decrease movement evoked pain for optimal positioning during SAB is essential. Many techniques have been studied in a hope to eliminate pain with intravenous analgesics, but the best drug has yet to be described.

Both ketamine and fentanyl are good analgesics and have been used to relieve pain due to positioning for delivering SAB in patients with femur fracture. Ketamine has regained popularity for its excellent analgesic effects even in subanaesthetic dose. It increases the release and inhibits the reuptake of catecholamines in circulation, thus helps preserve vascular resistance and BP, which has made it an optimal anesthetic agent in hypotensive patients. Hypotension is a common complication following SAB. Different subanaesthetic doses of ketamine has been studied in an attempt to find the dose which is most effective with the least side effects. We used the dose of 0.3mg/kg, which according to a study conducted by Kumar et al., showed less hemodynamic changes, no delirium and best for procedural sedation.[10,11]

Better alleviation of pain was observed with subanesthetic dose of ketamine than fentanyl. In agreement with our study, Suzuki et al., also reported that ketamine in subanaesthetic doses possesses excellent analgesic properties.[13] Maurset et al. inferred that analgesia induced by 0.3 mg/kg I.V. ketamine was similar to that produced by 0.7 mg/kg pethidine.[15] According to Moataz et al., ketamine 0.3 mg/kg supplemented with midazolam 0.03 mg/kg were best for sedation, pain relief, improved patient comfort, respiratory and cardiovascular stability without emergence reaction when given before establishment of neuraxial anesthesia.[16]

Adequate pain control is needed for optimal positioning for SAB.[16] Optimal positioning is necessary for lesser number of attempts for successful spinal needle placement. Lesser attempts were required in ketamine group, which indirectly indicates better pain control than fentanyl. However, our institution is a teaching hospital and procedures are performed by residents. Variable experience could've caused variable number of attempts which is independent of the pain status of the patient.

Overall satisfaction of patients regarding the anesthetic procedure was statistically insignificant. However, anesthetist satisfaction level for optimal positioning to deliver SAB was better with ketamine than fentanyl.

Patients in ketamine group developed tachycardia. This observation is consistent with previous findings of Diazgranados et al.[13] Moreover, similar to our study, Kumar et al., reported increase in HR following administration of ketamine at 0.3mg/mg and 0.4mg/kg for positioning of patients for SAB in femur fracture.[14] In the line with our observation, Salah et al, reported increase in HR in parturients after ketamine 0.5mg/kg providing good hemodynamic stability during caesarean section under SAB.[15] Similar to our study, Thomas et al. also reported increase in HR with subanaesthetic doses of ketamine.[15] This can be explained by ketamine increasing the release and inhibiting the reuptake of catecholamines in circulation causing sympathetic stimulation leading to increase in myocardial contractility and peripheral vascular resistance, ultimately causing rise in MAP and HR even at subanaesthetic.[16] However, Luiz et al., didn't report increase in HR following ketamine. It may be due to lesser doses (0.25mg/mg and 0.2 mg/kg) of ketamine usage.[8]

Lee et al. also reported no significant increase in HR even with ketamine at 1mg/kg when administered to alleviate pain associated with positioning.[17] This could have been because of concurrent use of dexmeditomidine which acts on presynaptic α2 receptors reducing norepinephrine release, inhibiting central sympathetic outflow causing a decrease in HR.

We observed bradycardia in 5% of fentanyl group which may be a consequence of SAB.[18] Due to sympatholytic effects and vagal predominance in SAB, the compensatory mechanisms of the heart are blunted leading to bradycardia in response to hypotension.[19] Lee et al., reported bradycardia in 66% patients who received fentanyl 1mcg/ kg and dexmeditomidine 1mcg/ kg IV. This high incidence could have been due to alpha 2 receptor agonist action of dexmeditomidine which was used concurrently or due to spinal anesthesia itself. [18] However, in a study conducted by Pakhare et al, no bradycardia was observed despite the use of high dose of fentanyl of 3 mcg/kg before positioning the patients for SAB.[19] Moreover, contrary to our findings, Bantei et al.[20], Madabushi et al.[21], didn't report any bradycardia following the administration of IV fentanyl. This may be due to the use of lower doses of 1mcg/kg and 0.5mcg/ kg, respectively.

In our study, 35% patients developed hypertension with ketamine, but none developed hypotension. In same line with our study result, Luiz et al. also observed increase in BP with ketamine at doses of 0.2mg/kg and 0.25mg/kg which were lesser than doses we used.[20] Similarly, Mohammed et al., also reported hypertension in 40% of patients with subanesthetic dose of 0.25mg/kg of ketamine.[2] Our findings are consistent with Marlow et al who reported increase in MAP with ketamine.[21] Ketamine increases the release and inhibits the reuptake of catecholamines in circulation causing sympathetic stimulation leading to increase in myocardial contractility and peripheral vascular resistance, ultimately causing an increase in MAP and HR even at subanesthetic dose of ketamine.[22] Unlike our observation, Lee et al. reported hypotension with the use of high dose of ketamine (1mg/kg) concomitantly with dexmeditomidine (1mcg/kg).[17] This can be attributed to concurrent use of dexmeditomidine which is alpha 2 receptor agonist that inhibits presynaptic norepinephrine release and sympathetic outflow.

None of our patients in ketamine group developed hypotension. The sympathetic stimulation caused by ketamine may have balanced the hypotensive effects of SAB. Mohhamed et al also noticed hemodynamic stability of patients during SAB after administering ketamine at subanesthetic dose of 0.3mg/ kg used for alleviating pain during positioning and procedural sedation. [2]

However, we observed hypotension in 13.33% from fentanyl group. It can either be because of the sympathetic blockade and parasympathetic stimulation following SAB or due to fentanyl itself. Lee et al. also observed hypotension in 95% patients following the use of fentanyl (1mcg/kg) concomitantly with dexmeditomidine (1mcg/kg) to provide analgesia in femur fracture patients during lateral positioning for SAB.[17] In contrast to the study conducted by Pakhare et al, no hypotension was observed despite the administration of fentanyl at 3mcg/kg to alleviate the positioning related pain in femur fracture patients during SAB. [19] It can be because that study was conducted in patients less than 65 years whereas Lee et al. conducted the study in geriatric patients. Contrary to our findings, Purohit et al. did not observe hypotension in any patients after fentanyl IV administration.[22] This can be attributed to the use of lesser dose of fentanyl.

In our study,5% from the fentanyl group desaturated. Ricardo et al. inferred that fentanyl can cause respiratory depression leading to desaturation especially in geriatric patients.[22] Fentanyl is thought to reduce the response to raised $pCO_2$ and lowered $pO_2$ and thus reduce the drive to breathe. This results in a dose dependent decrease in respiratory rate and thus minute ventilation. In the same line with our findings, desaturation was also reported by Lee et al. in 66 % following administration of fentanyl and dexmeditomidine in femur fracture patients to facilitate positioning for SAB. [17] However, in contrast to our study, Madabushi et al.[22] and Bantie et al.[20] did not observe fall in saturation following IV fentanyl use. It may be due to the use of lesser dose of fentanyl at 1mcg/kg. However, desaturation wasnt observed in ketamine group. In the same line with our study, Moataz et al.[23], Maurset A et al.[24], Oda A et al.[25] and Suzuki M et al[15] did not report desaturation with the use of ketamine at subanesthetic doses. Ketamine minimally affects ventilator drive even at induction doses. It maintains upper airway skeletal muscle tone and upper airway reflexes. However, it may cause apnea occasionally if administered concurrently with opioids. [24]

One patient in ketamine group and 6 patients in fentanyl group complained of nausea/vomiting. Contrary to our study, Lee et al. Madabushi et al.[17] Diakomi et al.[5] Kumar et al.[10] didn't observe such complaints. Luiz et al. reported nausea in 2 patients who received ketamine at 0.25mg/kg.[8]

Delirium was observed in 5 patients in ketamine. Moataz et al studied the analgesic effectiveness and adverse effects of three different subanaesthetic doses of ketamine. Ketamine at 0.3mg/kg didn't cause delirium in any patient in their study.[8] But this can be due to the use of ketamine concurrently with midazolam. Mohammed et al. also studied the analgesic effectiveness of ketamine at dose 0.15mg/kg in patients older than 70 years and 0.25mg/kg in patients younger than 70 years.[2] No emergence reaction was seen. This may be due to lesser dose of ketamine than in our study. In contrary, Luiz et al, also studied 4 different subanaesthetic doses of ketamine.[8] Even at a dose of 0.25mg/kg, 15% of patients were delirious. In a study by Hemant et al. using three groups at doses of 0.3, 0.4 and 0.5 mg/kg, the authors have shown that ketamine produced dose dependent sedation. In another study by Luiz et al., four different subanesthetic doses of ketamine, obtained almost the same results.[8] Although ketamine is known to cause hypertension, delirium and tachycardia, the incidence of these events noted in our study has to be interpreted with caution as our study wasn't powered enough to compare these adverse effects between two groups.

## CONCLUSION

Intravenous ketamine is better than fentanyl in reducing the pain associated with positioning patients with proximal femur fractures for SAB.

## LIMITATION

Our study was single centred. The anaesthesiologists performing SAB had variable degree of experiences which may have affected the number of attempts for successful SAB, patient and anesthetist satisfaction. Five of our patients were delirious and we couldn't attain the NRS. The study was conducted only on patients older than 18 years with proximal femur fracture so we cannot generalize our findings for younger patients with fracture of other sites.

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## CONFLICT OF INTEREST: None

## FINANCIAL DISCLOSURE: None

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