Comparative Evaluation Of Dexmedetomidine, Ketamine And Their Combination For Epidural Analgesia In Lower Limb Orthopedic Surgeries

Dr. Deeksha Mishra[1]*, Dr. Vivek Chakole[2]

Abstract

The pursuit of perioperative pain relief, has led many anaesthesiologists to advocate various methods to counter intraoperative pain that can be extended into the postoperative period much to the satisfaction of the patients. Regional anaesthesia in the form of central neuraxial blocks, owing to its advantages over general anaesthesia, are widely used in for surgeries involving the lower body as well as for postoperative pain management. The desire for efficient block, early postoperative rehabilitation with minimal pain and discomfort makes epidural anaesthesia the procedure of choice amongst other central neuraxial blockade.

Our study aims at evaluating and comparing the efficacy and safety of epidurally injected dexmedetomidine, ketamine and their combination as adjuvants to bupivacaine for intraoperative anaesthesia and analgesia in patients posted for lower limb orthopedic surgeries.

The patients were randomly allocated into groups of two of 30 patients each; Group D: Patients received injection Dexmedetomidine in a dose of 1µg/kg as an adjuvant to 0.375% bupivacaine (7ml diluted till 10ml with sterile water) epidurally, Group K: Patient received injection Ketamine in a dose of 0.5mg/kg as an adjuvant to 0.375% bupivacaine (7ml diluted till 10ml with sterile water) epidurally, Group KD: Patient received injection Ketamine in a dose of 0.3mg/kg & injection Dexmedetomidine a dose of 0.5µg/kg as an adjuvant to 0.375% bupivacaine (7ml diluted till 10ml with sterile water) epidurally.

Sedation scores, haemodynamic parameters like HR, SBP, DBP, MAP and RR and associated side effects were monitored intra-operatively. All the quantitative and qualitative data were analysed using fisher test and ANOVA and p values < 0.05 was considered statistically significant.

Based on the results of our study, we conclude that the combination of Dexmedetomidine and Ketamine is a better and safer adjuvant when administered epidurally with Bupivacaine as it produced a significantly prolonged duration sensory blockade than Dexmedetomidine or Ketamine administered individually as an adjuvant to Bupivacaine for epidural anaesthesia and analgesia. Their combination had an early onset and longer duration of both sensory motor blockade, with the additional benefits of minimal intraoperative sedation, haemodynamic stability and nominal side effects. It was also better in terms of prolonged duration and better quality of postoperative analgesia with the need of lesser number of doses of rescue analgesics and fewer adverse effects.

Keywords: - Dexmedetomidine, ketamine, Epidural analgesia, Lower limb

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INTRODUCTION

Being purely subjective, pain and its intensity vary widely among patients and its varying threshold is majorly because of its emotional component. The pain experienced during surgery is often underestimated and under-treated and that of the postoperative period, largely neglected. In pursuit of this pain relief, many anaesthesiologists using the experience they acquired in the field have

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advocated various methods to counter intra-operative pain that can be extended into the postoperative period much to the satisfaction of the patients.

General anaesthesia or central neuraxial blockade maybe considered for intraoperative anaesthesia, however, the administration of general anaesthesia demands skill and specialized equipment and provides analgesia that cannot be extended into the postoperative period. Central neuraxial blocks are at an advantage over general anaesthesia as it allows the patient to be awake during the procedure, avoids polypharmacy, involves lesser airway manipulation and stress response, decreased incidence of postoperative nausea and vomiting and shorter postoperative fasting period whilst providing adequate sensory and motor blockade. [1]

Numerous techniques and drug regimens have been tried with variable success to produce effective regional anaesthesia that provides an efficient block with minimal time of onset and that which can be prolonged into the postoperative period with minimal complications.[4] Modern-day surgeries also desire early postoperative mobilization and rehabilitation which in turn decreases the incidence of thromboembolic events making epidural anaesthesia the procedure of choice amongst other central neuraxial blockades.[2,3,4] Its versatility lies in its ability to be placed at any desired level of the vertebrae to provide both anaesthesia and analgesia, to supplement and decrease the need for deep levels of general anaesthesia and therefore provide haemodynamically stable intraoperative course.

The most popular method for administering both post-operative analgesia and peri-operative surgical anaesthesia during lower abdomen and limb operations is epidural anaesthesia.[5]To reduce anxiety and help patients relax during regional anaesthesia, numerous methods and medication regimens have occasionally been tried, with varying degrees of success.[6,7,8] The innovative objective of regional anaesthesia is frequently defeated by the impulsive use of huge dosages of sedative or even general anaesthesia to achieve the desired effect, which can have harmful side effects.[9] There is a constant search for a superior adjuvant in regional anaesthesia to address these issues.

Various adjuvants that can be added to local anaesthetics in a central neuraxial block are ketamine, opioids (fentanyl, sufentanil), benzodiazepines (midazolam), dexamethasone and α2 adrenoreceptor agonists (dexmedetomidine, clonidine). Because of its calming, analgesic, peri-operative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing effects, alpha 2-adrenergic receptor agonists have gained interest in them.[10] Dexmedetomidine has an affinity for alpha-2 adrenergic receptors that is eight times higher than that of clonidine. It is a highly selective agonist.[11] It has been demonstrated that ketamine has analgesic effects via inhibiting the N-methyl-D-aspartate receptor, hence preventing and decreasing central sensitization brought on by peripheral nociceptive stimulation. They have been found to extend the duration and intensity of nerve block along with associated anaesthetic sparing and neuroprotective properties. Given the limited studies and paucity of data comparing the effect of epidurally administered dexmedetomidine and ketamine with bupivacaine, this study was conducted to test and re-emphasise the known presumed advantage of the same.[12]

MATERIALS AND METHODS

Our study aims at evaluating and comparing the efficacy and safety of epidurally injected dexmedetomidine, ketamine and their combination as adjuvants to bupivacaine for intraoperative anaesthesia and analgesia in patients posted for lower limb orthopedic surgeries.

This prospective, comparative, observational study on a total of 90 adult patients was conducted in the Department of Anaesthesiology at the "Acharya Vinoba Bhave Rural Hospital," a part of Jawaharlal Nehru Medical College, Sawangi, between December 2020 and August 2022 with approval from the Institutional Ethics Committee and with the patients' written informed consent.

INCLUSION CRITERIA

1. ASA physical status: I and II
2. Age: 18 to 60 years of either sex

EXCLUSION CRITERIA

1. Patients not willing to participate in the study
2. Known sensitivity to any of the drugs under the study
3. Local site infection
4. High abnormal prothrombin time or activated partial thromboplastin time
5. Congenital or acquired coagulopathy
6. Patients with spinal deformity/previous spine surgery

The study involved 90 patients who met all of the study's inclusion and exclusion criteria.
All the patients underwent a pre-anaesthetic evaluation a day before the procedure. The patients were explained about the study purpose, its merits and demerits. They were counselled regarding the procedure and informed written consent was obtained from each patient. When the patients arrived in the operating room, a multipara monitor was connected to them, and vital signs like the heart rate, blood pressure, oxygen saturation percentage, respiratory rate, and electrocardiogram (ECG) were recorded as baseline values and subsequently monitored throughout the procedure. Using a 20 G or 18 G intravenous cannula, an appropriate peripheral intravenous access was established in the upper limb. Intravenous infusion of crystalloids like RL/ NS was started at the rate of 10 ml/kg initially to preload the patient and to correct the deficit followed by maintenance of 2 ml/kg.

With the patient in a Sitting position, under all aseptic precautions, local infiltration with 2 ml of 2% Lignocaine was done in the L2-L3 intervertebral space. The epidural space was then identified with an 18G Tuohy needle by "loss of resistance to air" technique. Space was confirmed using the hanging drop technique. An 18 G epidural catheter was threaded through the needle into the epidural space in the cephalad direction until 3-4cms was within the space. After negative aspiration for blood and CSF, 3 ml of 2% lignocaine with 15 µg injection adrenaline was given as a test dose to exclude the presence of the catheter in an epidural vein or subarachnoid space.

The patient was then given a supine position. After 5mins, if no adverse reactions or haemodynamic changes were noted for the test dose, the study drug dose was administered through the epidural catheter according to the group that the patient belongs.

1. Group D: Patients received injection Dexmedetomidine in a dose of 1µg/kg as an adjuvant to 0.375% bupivacaine (7ml diluted till 10ml with sterile water) epidurally.

2. Group K: Patient received injection Ketamine in a dose of 0.5mg/kg as an adjuvant to 0.375% bupivacaine (7ml diluted till 10ml with sterile water) epidurally.

3. Group KD: Patient received injection Ketamine in a dose of 0.3mg/kg & injection Dexmedetomidine a dose of 0.5µg/kg as an adjuvant to 0.375% bupivacaine (7ml diluted till 10ml with sterile water) epidurally.

The block characteristics were noted in terms of onset and duration of sensory and motor block, peak sensory block and time to achieve it and duration of analgesia (request for the first dose of rescue analgesic at VAS >3). Sedation scores, haemodynamic parameters like HR, SBP, DBP, MAP and RR and associated side effects were monitored intra-operatively. All the quantitative and qualitative data were analysed using fisher test and ANOVA and p values < 0.05 was considered statistically significant.
The demographic data in both the groups were comparable in factors like age, gender, weight, ASA class and the duration of surgery.

STATISTICAL ANALYSIS

Qualitative data was presented with the help of percentage table, association among the study groups was assessed with the help of Chi-square test. Quantitative data was presented as mean and standard deviation, comparison among the study groups was done with the help of student t-test. Software used in the analysis were SPSS (Statistical Package for the Social Sciences) 20.0 version and $p < 0.05$ was

considered statistically significant.

RESULTS AND DISCUSSION

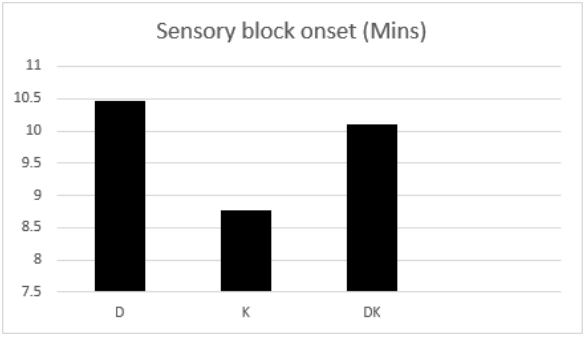
We selected 0.5mcg/kg of epidural Dexmedetomidine and 0.3mg/kg of epidural ketamine for our combination group in a bid to determine if the combination's potency is higher and at lowered doses than either drug administered alone, referring to a clinical trial by Shereen Mamdouh et al., approved by the National Institution of Heath, U.S.A department of health and human services, which investigated the effect of dexmedetomidine, ketamine or their combination as adjuvants to bupivacaine in thoracic epidural analgesia on acute postoperative pain after breast cancer surgery.

Given the advantages of ketamine and dexmedetomidine when added to bupivacaine as adjuvants and the limited studies comparing the effects of the two drugs epidurally led us to conduct a comparative, observational study on 90 ASA I and II patients posted for lower limb orthopaedic surgeries under epidural anaesthesia, to evaluate their efficacy in terms of block characteristics, cardiorespiratory stability and side effects.

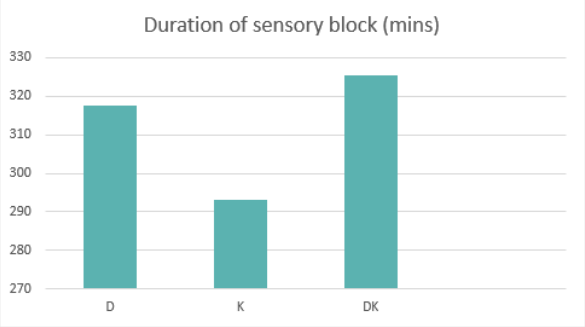
Patients were monitored from the immediate postoperative period until 48 hours. In group D, sensory block began in an average of 10.47 ± 3.66 minutes, in group K, it began in an average of 8.77 ± 2.74 minutes, and in group DK, it began in an average of 10.1 ± 4.13 minutes. However, the p value was calculated to be p = 0.156 which was not statistically significant. In a collateral study by Pandya et al., where epidural ketamine and dexmedetomidine were compared, the time taken for sensory block onset was 10.20 ± 4.80 in group D and 11.23 ± 1.66 in group K. Both the groups had earlier onset of action than their placebo group and the difference was non-significant. In the study conducted by Bajwa et al.wherein dexmedetomidine as an adjuvant to ropivacaine as an adjuvant resulted in an earlier onset (8.52 ± 2.36 min) of sensory analgesia at T10 in comparison to the addition of clonidine (9.72 ± 3.44 min). Our study is consistent with previous reports suggesting faster onset and prolonged duration of caudal analgesia with caudal ketamine in association with bupivacaine and ropivacaine such as in study by Negri et al. who compared ketamine and clonidine in caudal epidural anaesthesia in prolongation of analgesia in children.[14]

Table 1– Comparison of Sensory block onset, time to achieve peak sensory level and Duration of sensory block among the study participants in between the groups

	D	K	DK	p-value
Sensory Block Onset (Mins)	10.47 ± 3.66	8.77 ± 2.74	10.1 ± 4.13	0.156 NS
Time To Achieve Peak Sensory Level (Mins)	20.8 ± 5.90	19.7 ± 5.75	19.9 ± 5.56	0.996 NS
Duration Of Sensory Block (Mins)	317.73 ± 23.28	293.2 ± 21.07	325.43 ± 30.59	< 0.001 S

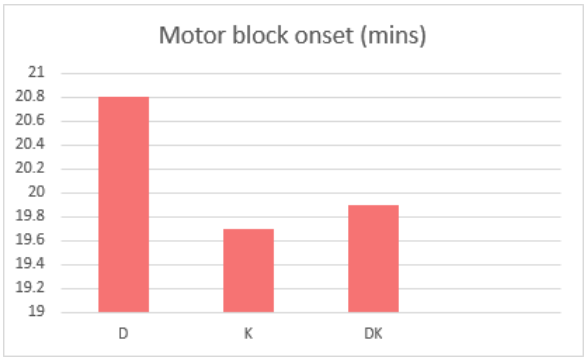


In group DK, patients had a mean total duration of sensory block between 325.43 ± 30.59 minutes which was found to be the highest amongst the three groups. Patients in group D had a mean total duration of sensory block between 317.73 ± 23.28 minutes followed by group K in which the patients had the mean total duration of sensory block between 293.2 ± 21.07 minutes. Hence the mean duration of sensory block was significantly prolonged in group DK as compared to group D and group K with statistically significant difference (p value < 0.001). Our results were concomitant to the study conducted by Pandya et al., where the mean duration of sensory block in dexmedetomidine group was 594 ± 63.04 and that of ketamine was 362.4 ± 45.76 minutes making dexmedetomidine a better alternative to ketamine.

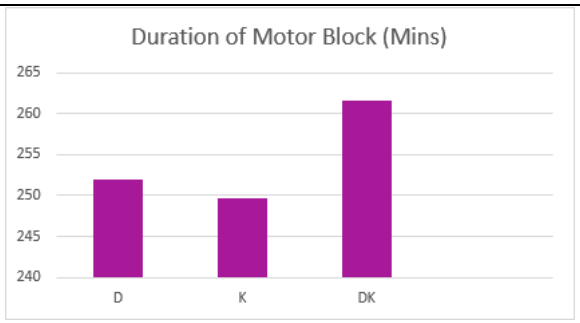


Onset of motor blockade is the time taken from the injection of the drug into the epidural space to attainment of Bromage grade 3 block (complete motor block). The mean time taken for onset of motor block in group D was 20.8 ± 4.24 minutes, in group K was 19.7 ± 3.09 minutes and in group DK was 19.9 ± 3.82 minutes.

	D	K	DK	p-value
Motor Block Onset (Mins)	20.8 ± 4.24	19.7 ± 3.09	19.9 ± 3.82	0.483 NS
Duration Of Motor Block (Mins)	251.9 ± 24.05	249.7 ± 28.63	261.63 ± 21.74	0.15 NS



The duration of motor block was taken from the time of injection to complete regression of motor block (Bromage grade 1). In group DK, patients had a mean total duration of Motor block between 261.63 ± 21.74 minutes which was found to be the highest amongst the three groups. Maximum patients in group D had a mean total duration of Motor block between 251.9 ± 24.05 minutes followed by group K in which the patients had the mean total duration of Motor block between 249.7 ± 28.63 minutes. Hence the mean duration of of Motor block was prolonged in group DK as compared to group D and group K with no statistically significant difference (p value = 0.15).

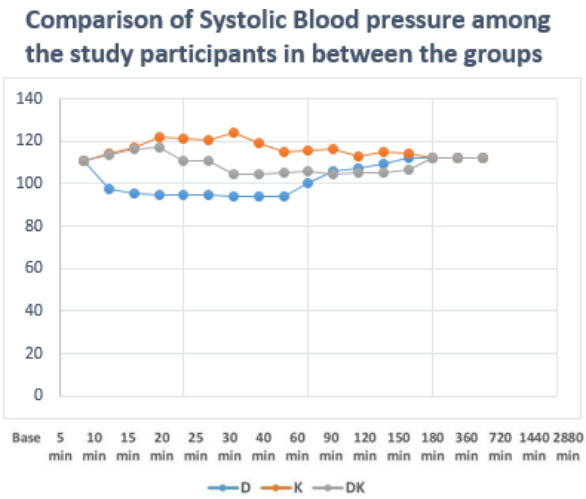


In the study by Pandya et al., the mean duration of motor block was 488.4 ± 42.88 in group D and that of group K was 303.6 ± 36.04, establishing the fact that duration of motor block is prolonged in both the groups but dexmedetomidine has an increased duration of motor block than epidural Ketamine; and the findings of this study we parallel to ours, except that we have a third group of DK where it has proven to be better than both the drugs administered individually as adjuvants to epidural anaesthesia.

After 5 minutes of induction, the mean systolic blood pressure in group D dropped down to 97.5 ± 6.4 from the base value of 110.87± 5.91 and continued in the range of 94.37 ± 7.13 up until 90minutes post induction from where the SBP was in the range of 100.17 ± 6.27 until 360minutes post induction, where the mean SBP started increasing with respect to the previous values, which can be attributed to pain. In group K, the mean systolic blood pressure in group K had a slight increase in mean SBP to 114.1 ± 4.54 from the base value of 111 ± 5.75 and continued to be in an increasing trend and the peak mean SBP being 123.83 ± 6.01 at 30minutes post induction from where the SBP was in the range of 115.63 ± 7.34 until 360minutes post induction. From 720 to 2880 minutes, the mean SBP is seen to be closer to the baseline SBP among the participants, with no statistically significant difference in between the three groups.

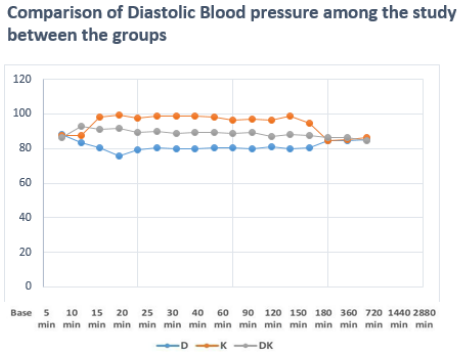
The mean systolic blood pressure in group DK was in the range of 113.37 ± 2.79 from the base value of 110.93 ± 5.56 and continued in the range of 116.86 ± 4.61 up until 30minutes post induction from where the SBP was in the range of 104.3 ± 5.77 until 2880 minutes, where the mean SBP is seen to be closer to the baseline

SBP among the participants. Group DK wasn't anywhere near the extremes of decreasing the mean SBP neither increasing it, on the contrary to the other two groups and maintained a balanced SBP which was closer to the baseline.



While in group D, the mean diastolic pressure saw a slight drop from the baseline value, it was maintained in the range of 80.37 ± 5.87 to 79.77 ± 6.18 throughout, on the contrary group K saw a slight increase in the mean DBP which ranged from 87.57 ± 4.61 to 99.13 ± 4.30. Group DK stuck to the middle ground and the mean DBP was closer to the baseline compared to the other two groups and was maintained in the range of 87.27 ± 3.7 to 91.53 ± 4.58 with statistical significance of p = < 0.001.

Towards the end of our monitoring, from 720 to 2880 minutes, there was no significant difference in between the three groups with respect to their diastolic pressures.



While MAP in group D was in maintained in the range of 88.26 ± 3.66 starting at 5 minutes, to 94.39 ± 3.83 at 1440 minutes, MAP in group K was towards the higher side starting form 96.41 ± 3.51 at 5 minutes to 101.28 ± 3.65 at 360 minutes. In group DK the MAP values were closer to the baseline compared to the other two groups and was maintained in the range of 99.57 ± 2.85 till 360minutes post induction.

There is a significant fall seen in the mean heart rates of patients in group D from baseline after administration of the drug. This fall, however, was not more than 15% from baseline. None of the patients recorded bradycardia. Group K on the other hand lead to an increase in mean heart rate amongst the patients but this increase was not more than 15% of the baseline value. Group DK didn't cause a significant change in the baseline value of mean heart rate till 90mins after the drug was administered after which it was noted to be slightly towards the higher side till 360 minutes postoperatively. However, considering the baseline value of 85.03 ± 10.36, the increase was not more than 15% of the baseline value. The difference in the three groups was statistically significant with p=<0.001.In a study by Ganesh Ram et al., the mean heart rate in group D was 114.73±26.08, while in group K was 111.00±23.18, with the difference being non-significant with p = 0.079; while the mean arterial pressure was 73.33±7.65 in group D, 75.03±6.52 in group K and 72.23±7.15 in group with plain levobupivacaine with p = 0.321. The findings of this study were consistent with ours showing a decrease in hemodynamic parameters with group D and an increase in the same with group K.The above described cardio-respiratory parameters show that none of the patients in our study of dexmedetomidine group experienced hypotension or bradycardia at any point during the study period. This reaffirms the already established effects of α2 agonists in providing a haemodynamically stable perioperative period, as discussed in the study by Taittonen et al. [15] On the other hand, in group Ketamine, two patients developed intraoperative hypertension which continued in postoperative period too. In group DK, the hemodynamics were much stable than the other two groups, causing neither increase nor decrease in hemodynamic parameters, making it the preferred adjuvant among the three

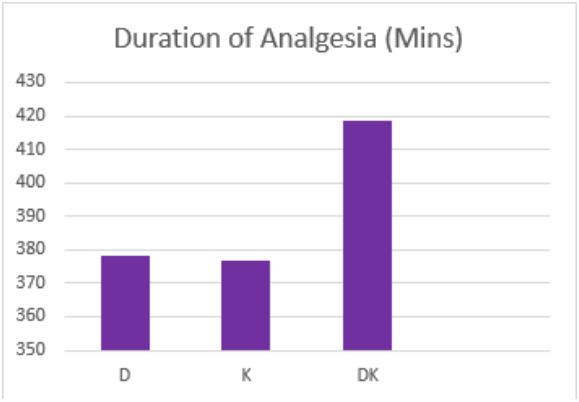
groups as portrayed in the study by Gupta et al. who designed the study to to evaluate the clinical efficacy and safety of dexmedetomidine premedication for balancing the ketamine induced hemodynamic pressor response and psychomimetic effects. [16]

The time of first rescue analgesic requirement was noted. This period was defined as the total duration of analgesia. In our study, patients with VAS score ≥ 3 were treated with Inj. Paracetamol 1gram IV.

In our study, the mean duration of analgesia or in other words, is mean time for the requirement of first rescue analgesic which in group K was 376.57 ± 31.53 minutes whereas in group D and DK were 378.23 ± 33.41 and 418.37 ± 15.49 minutes respectively. The mean duration of postoperative analgesia was significantly prolonged in group DK as compared to group D and group K with statistically significant difference (p value < 0.001). Also, we observed prolonged duration of post operative pain free period in the adjuvant group which used both dexmedetomidine and ketamine as compared to the group which used only dexmedetomidine or ketamine.

Table 2- Comparison of Duration of Analgesia among the study participants in between the groups

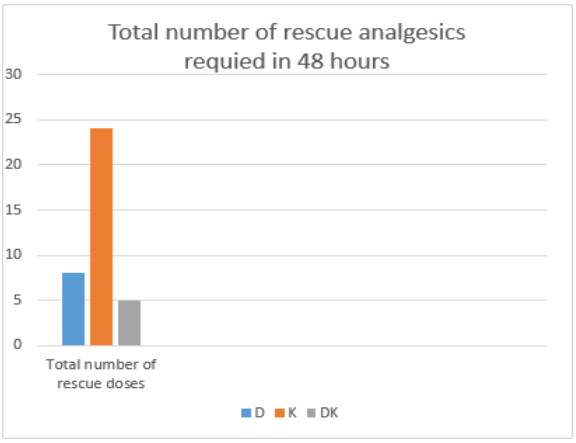
	D	K	DK	
Duration of Analgesia (Mins)	378.23 ± 33.41	376.57 ± 31.53	418.37 ± 15.49	< 0.001 S



There was notable difference in the number of rescue analgesic dose requirement during the postoperative study period among the study groups. Group K had to take higher number of patients requiring doses of rescue analgesics than group D and DK during the 48hour post operative period. In group D, total of 2 participants (6.66%) required a single dose of rescue analgesic, while 3 (10%) required a total of two doses of rescue analgesic during the 48hours postoperative period. In group K, total 8(26.66%) patients required three doses of rescue analgesic and in group DK, 3 (10%) required a single dose of rescue analgesic while 1(3.33%) required two doses of rescue analgesic. P value was 0.398 with the inference of them being non-significant with respect to each other.

Table 3 Number of rescue analgesic doses

Number of rescue analgesic doses	Group D	Group K	Group DK	p value
One	2 (6.66%)	0	3 (10%)	
Two	3 (10%)	0	1 (3.33%)	
Three	0	8 (26.66%)	0	0.398 NS
Total	5 (16.66%)	8 (26.66%)	4 (13.33%)	



In group D, the incidence of dry mouth was present for 1 patient (3.33%) and headache was encountered by 1 patient (3.33%). Shivering occurred in 2 patients (6.7%) and nausea & vomiting in 1 (3.33%). None of the cases reported any episode of respiratory depression, hypotension, bradycardia in our study. With respect to group K, we didn't report any incidence of neurological effects like hallucination or delirium. In group K, total 4 (13.3%) patients experienced nausea and none experienced vomiting and in group DK total 6 (20%) patients encountered nausea and vomiting with 4 experiencing only nausea and two vomitting. The difference was statistically insignificant with p = 0.917. None of the participants experienced complications such as dura puncture, loss of bladder control, post

dural puncture headache, local infection, epidural hematoma, systemic local anaesthetic toxicity or post-operative neurological deficits.

Table 4 Side effects

Side Effects	GROUP			Total	X^2& p-value
	D	DK	K		
Dry Mouth	1	0	0	1	X^2 = 15.811 & p-value = 0.063 NS
	3.3%	0.0%	0.0%	1.1%	
Headache	1	0	0	1	
	3.3%	0.0%	0.0%	1.1%	
Hypertension	0	0	2	2	
	0.0%	0.0%	6.7%	2.2%	
Nausea & Vomitting	1	4	6	11	
	3.3%	13.3%	20.0%	12.2%	
Shivering	2	0	0	2	
	6.7%	0.0%	0.0%	2.2%	
Nil	25	26	22	73	
	83.3%	86.7%	73.3%	81.1%	
Total	30	30	30	90	
	100.0%	100.0%	100.0%	100.0%	

CONCLUSION

Based on the results of our study, we conclude that the combination of Dexmedetomidine (0.5mcg/kg) and Ketamine (0.3mg/kg) is a better and safer adjuvant when administered epidurally with Bupivacaine 0.375% as it produced a significantly prolonged duration sensory blockade than Dexmedetomidine (1mcg/kg) or Ketamine (0.5mg/kg) administered individually as an adjuvant to Bupivacaine for epidural anaesthesia and analgesia. Their combination had an early onset and longer duration of both sensory motor blockade, with the additional benefits of minimal intraoperative sedation, haemodynamic stability and nominal side effects. It was also better in terms of prolonged duration and better quality of postoperative analgesia with the need of lesser number of doses of rescue analgesics and fewer adverse effects. Our experience with epidural dexmedetomidine plus ketamine was satisfactory as compared to both the drugs instilled individually as an adjuvant in lower limb orthopaedic surgeries.

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