Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 06, 2023

EPIDURAL ANALGESIA - A comparative study for postoperative pain relief with 0.125% Bupivacaine plain v/s 0.125% Bupivacaine and Ketamine combination in infra-umbilical surgeries

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Received Date: 20/04/2023 Acceptance Date: 20/06/2023

Abstract

Background: Epidural anesthesia is a widely used technique for perioperative analgesia in different kinds of surgeries. This study was designed to compare plain bupivacaine with bupivacaine and ketamine combination with respect to potency of anaesthesia and post operative analgesia in patients undergoing infra umbilical surgeries, with side effects of both groups. **Methods:** A total of 50 American Society of Anesthesiologists 1 and 2 patients, aged 20–60 years, undergoing elective lower abdominal surgeries, were randomized into two groups. Group B received epidural 0.125% 6 ml Inj bupivacaine Group BK received epidural 0.125% 6 ml inj bupivacaine with inj ketamine (0.5mg/kg). Safety and efficacy of ketamine in epidural analgesia, haemodynamic changes, quality of postoperative analgesia and any untoward effects of ketamine were compared. **Results:** The demographic and hemodynamic parameters were comparable between the two groups. There was prolonged duration of anesthesia and better postoperative pain management with bupivacaine and ketamine group as compared to bupivacaine only group. **Conclusions:** With new developments in medical science and surgery, it is necessary to bring into practice a new pharmacological approach to manage post-operative pain.[49] Ketamine is one such effective analgesic adjuvant which can be used in epidural blocks in combination with local anaesthetics, considering the positive results we received during our study and magnitude of side effects was acceptable and easily treatable.

Keywords: bupivacaine, ketamine, epidural anaesthesia.

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Introduction

Epidural block provides surgical anesthesia as well as post-operative analgesia in patients undergoing lower abdominal surgeries. Post-surgical pain management is an important part of post-surgical care. Post-surgical care also involves necessary medication to prevent negative outcomes such as tachycardia, hypertension, myocardial ischemia, decrease in alveolar ventilation, and poor wound healing. Epidural anesthesia is most commonly provided using a

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combination of local anesthetic and an opioid or non-opioid analgesic, depending on the risk: benefit ratio and severity of the injury.
With the recent advances in the knowledge of molecular mechanisms, the development of multimodal analgesia and new pharmaceutical products to treat postoperative pain are being practiced. [49] The use of adjuvants such as morphine, buprenorphine, and fentanyl, clonidine, ketamine in anaesthetic practice for the improvement of peri-operative analgesia following spinal anaesthesia is common. [51] Ketamine is a rapid-acting cyclohexanone derivative, non-competitive N-Methyl-D-aspartate (NMDA) and glutamate receptor antagonist which blocks hyperpolarization-activated nonselective cation (HCN)1 receptor, producing profound anesthesia and analgesia. [47]

Materials And Methods

This prospective randomized control study to compare postoperative pain relief among different drug combination vs plain drug was done in our institute from patients posted for lower abdominal surgeries in department of anaesthesiology, where patients were divided into two groups using computer generated randomization tables, group B (n=25)- control group receiving epidural 0.125% bupivacaine 6 ml only and group BK (n=25)- group receiving 0.125% bupivacaine 6ml with ketamine (0.5 mg/kg).
Informed written consents were obtained from patients between ages 20- and 60-years undergoing elective infra umbilical surgeries. After their detailed pre anesthetic check-up and required lab investigations were done, those who were given fitness under American society of anesthesiologist grade one and two were divided into two randomized groups, viz. group B and group BK. Patients coming under American society of association grade three and four, with known contraindications for epidural anesthesia, those with hemodynamic instability or cardio- respiratory compromise or who were known allergic to amide group of local anesthetic agents, were excluded from the study.

In the preoperative room, venous access achieved with the 18/20-gauge intracath. After taking the patient into the operative room, minimal standard monitors were attached and baseline values of Heart rate (HR), non-invasive blood pressure (NIBP), pulse oximetry (SpO2), respiratory rate noted. All the patients were preloaded with 500 ml of lactated Ringer solution. After taking all aseptic precautions, the lumbar epidural block induced using 18 gauge Tuohy's needle, in sitting position. After skin infiltration with 2% lignocaine in the L2-L3 intervertebral space, the epidural needle inserted, and epidural space identified by loss of resistance to air technique and hanging drop technique. An epidural catheter was inserted and kept 5 cm in the epidural space and then fixed on the back of the patient. Test dose of 3ml 2% lignocaine with adrenaline given through the catheter after changing to supine position. After ruling out intra-Dural and intravascular placement of the catheter, sub arachnoid block was given with inj bupivacaine 0.5% hyperbaric, 3.5 ml using 23 Gauge Quincke's needle and T8 level was achieved. The study drug was given epidurally 2 hours after sub arachnoid block, prepared by an anesthesiologist aware of the study design.

Observation And Result

Table 1: Comparison of Mean Age, Sex and ASA grading, pre operative heart rate, systolic BP, diastolic BP between two groups.

	Group B	**Group B+K**	**t-Value**	**p- Value**
Age (In Years)	42.0±7.90	45.20±9.04	1.33	0.189 Not Sig. p>0.05
Sex	Male – 4	Male – 4	-	-

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	Female – 21	Female – 21		
ASA Grading	I – 13 II – 12	I – 6 II – 19	**χ2-Value** 0.440	0.507 Not Sig. p>0.05
Heart Rate	79.40±7.16	79.92 ±6.67	0.266	p=0.792 Not Sig. p>0.05
Systolic BP	120.08±10.64	126.80 ±7.35	1.052	p=0.298 Not Sig. p>0.05
Diastolic BP	76.32±7.25	78.64 ±3.55	1.437	p=0.157 Not Sig. p>0.05

Table 2: Comparisons between mean Heart rate per minute and at different time (Min.) in two Groups after giving epidural top-up

Heart rate at (min.)	**Group B**	**Group B+K**	**t-value**	**P-value**
	Mean±SD	**Mean±SD**		
20	64.28±8.42	69.80±9.08	2.229	**0.031 p<0.05 S**
25	67.16±6.14	73.00±10.76	2.356	**0.023 p<0.05 S**

The mean heart rate after giving epidural dose at 5-minute interval between two groups was comparable at time intervals from five minutes (every 5 minutes till 30 minutes) and every 30 minutes thereafter till 180 minutes duration. Significant difference was found in two groups at 20- and 25-minutes duration respectively, but it is not consistent with other time intervals. Hence it does not make any difference.

Table 3: Comparisons between mean Systolic Blood Pressure per minute and at different time (Min.) in two Groups after giving epidural top-up

Systolic blood pressure at	**Group B**	**Group B+K**	**t-value**	**P-value**
	Mean±SD	**Mean±SD**	2.906	**0.006 p<0.05 S**
120	126.64±6.18	120.48±8.61		

The statistical difference between B and B+K group if mean systolic blood pressure after giving epidural dose is not significant as *p* value is more than 0.05 except at 120 minute which is significant as *p* value is less than 0.05. But one significant finding not consistent with other observations which are not significant, can be easily ignored.

Similarly, no significant difference was found between two groups when mean diastolic blood pressure was compared.

Table 4: Comparison of Duration of Analgesia between two groups

Duration of Analgesia	**Group B**	**Group B+K**	**t-value**	**p-Value**
N	25	25	44.371	**p=0.000** **Sig.** **p<0.05**
Mean±SD	193.98±15.01	270.0 ±0.0		

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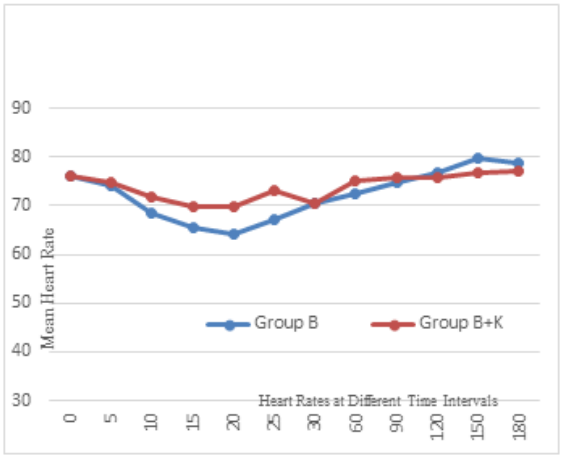

Chart 1: Comparisons between mean Heart rate per minute and at different time (Min.) in two Groups after giving epidural top-up

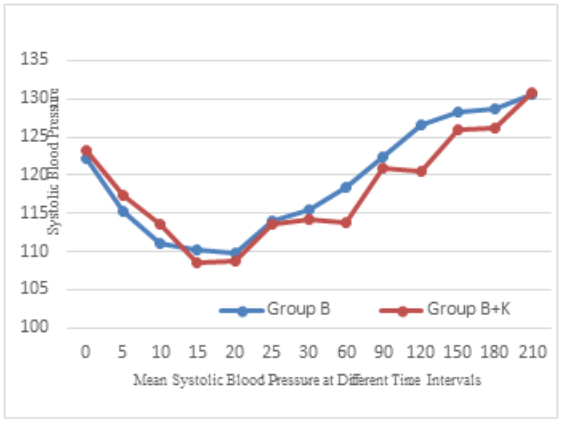

Chart 2: Comparisons between mean Systolic Blood Pressure per minute at different time (Min.) in two Groups after giving epidural top-up

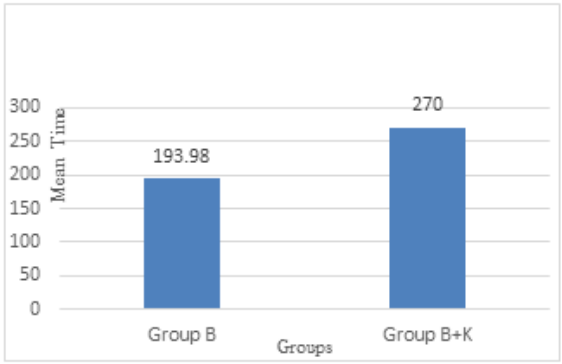

Chart 3: Comparison of Duration of Analgesia between two groups

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Table 5: Comparison of Mean Heart rate in the duration of analgesia after giving epidural dose between Two Groups

Mean Post -op Pulse rate	Group B	Group B+K	t-value	p-Value
N	25	25	0.86	p=0.402 Not Sig. p>0.05
Heart rate	72.41±5.15	73.85 ±2.70		
Systolic Blood Pressure	119.44±7.44	118.25 ±6.96	0.42	p=0.678 Not Sig. p>0.05
Diastolic Blood Pressure	74.93±5.99	74.0 ±4.88	0.44	p=0.667 Not Sig. p>0.05

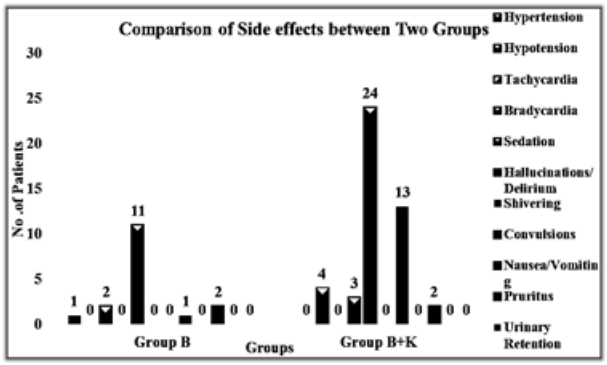

Chart 4: Comparison of Side effects between Two Groups

Discussion

The present study was a randomized control study to compare between postoperative pain relief with 0.125% Bupivacaine plain and 0.125% Bupivacaine and Ketamine combination in infra-umbilical surgeries with sides effects of both group in single top up. Mechanism of action of ketamine is by acting on N-Methyl-D-aspartate (NMDA) receptors, opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive Ca ion channels [(48)].

Ketamine interacts with sodium channels in a local anaesthetic-like fashion, including sharing a binding site with commonly used clinical local anaesthetics.[48] The need for analgesia during the postoperative period is common. In a study by A.H. Chaudhari et al [52], they concluded that caudally administered 0.5 ml/kg bupivacaine 0.25% plus ketamine or bupivacaine 0.25% plus tramadol 1 mg/kg provided a significantly longer duration of analgesia without an increase in the adverse effects when compared to bupivacaine alone.[52]

Shreshtha et al have compared the effect of hyperbaric bupivacaine mixed with intra thecal ketamine to fentanyl in combination with hyperbaric bupivacaine. The results showed that the addition of free ketamine increased the onset of sensory and motor blockade. [54] Many patients who received both ketamine and bupivacaine reported several adverse events such as sedation, dizziness, nystagmus, strange feelings and postoperative nausea and vomiting. Although the addition of intrathecal

preservative free ketamine to spinal bupivacaine had local anaesthetic sparing effects, it did not provide extended postoperative analgesia or decrease the postoperative analgesic requirements. Overall, the study concluded that the high incidences of adverse events and poor patient satisfaction limit the clinical use of spinal racemic ketamine 25mg as an adjunct

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to spinal bupivacaine, although intrathecal racemic ketamine has local anaesthetic-sparing effects.[55]

Togal et al in 2004 carried out a study to evaluate the effects of intrathecal S (+) ketamine added to a small dose of spinal bupivacaine in elderly patients undergoing transurethral prostate surgery. The study thus concluded that Intrathecal S (+) ketamine administered with a low dose of bupivacaine provides shorter motor and sensory block onset time, shorter duration of action and less motor blockade in elderly males.[56] We also referred to a study which showed that Intraarticular injection of 0.5 mg/kg and 1 mg/kg ketamine for postoperative pain management provided similar analgesic efficacy. However, high dose ketamine more noticeably decreased opioid requirement in the early postoperative period.[58]

Some researchers have also studied ketamine with bupivacaine to manage post operative pain in total knee arthroscopy. The combination group that received ketamine and bupivacaine showed reduction in pain scores and thus the study concluded that multimodal analgesic regimen of ketamine and bupivacaine is useful in mitigating postoperative pain in total knee arthroscopy.[60]

We also referred to a study with the aim to increase the natural duration of analgesia which concluded that in the epidural anaesthesia cases adding ketamine and dexmedetomidine as adjuvants to the solution of bupivacaine 0.25%, could increase the duration of analgesia and reduce the consumption of analgesics in patients who had elected for femoral surgeries.

To evaluate efficacy and safety of perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anaesthesia, Brinck et al [70] performed a study which concluded that perioperative intravenous ketamine probably reduces postoperative analgesic consumption and pain intensity.

A systematic review and Meta-analysis by Endeshaw et al [71] surround the practice of adding ketamine to local anaesthetics used for causing a caudal block in children undergoing sub-umbilical surgeries. The main effect of mixing. Preservative-free ketamine at a dosage of 0.5 mg/kg with bupivacaine/levobupivacaine for a caudal block is that the analgesia produced is prolonged compared to local anaesthetics administered alone. Ketamine can thus be considered a good alternative additive for effective caudal block.[71]

The main findings in the review suggested that Study carried out and reported by Abd Al Rahman et al concluded that postoperative morphine consumption can be significantly reduced if ketamine 0.1 mg/kg is added to Morphine 0.3 mg and used with Bupivacaine in comparison to using it alone [73] , for postoperative analgesia in abdominal cancer surgeries.[73]

We referred to a paper that aimed at investigating the effect of ketamine- bupivacaine in TPVB on acute and chronic postoperative pain management, that concluded the combination of drugs controlled post-operative pain in a dose-dependent manner and decreased DN4 scores one month after breast cancer surgery.[74]

The findings of our present study were as follows-

In our study Among Bupivacaine Group, age as compared with among Bupivacaine + Ketamine group, The p value is more than 0.05, there was no significant difference between two groups. In a study done by Sethi, Mamta, et al, [76] among Bupivacaine Group, there was no significant difference between two groups. In a study done by Radbin, et al. [61], Among Bupivacaine Group, sex as compared with Among Bupivacaine + Ketamine Group, Female patients were more in the study of Sağır, Ö. [58], Zhang, J[60] and Radbin, et al.[61] which is similar with our study.

In our study, Among Bupivacaine group and Among bupivacaine + ketamine group patients were allocated ASA grading, for which statistically, the p value is >0.05, there was no significant difference between two groups with respect to demographic data. In a study done

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by Sağır, Ö. [58], Among Bupivacaine group patients and Among bupivacaine + ketamine group patients, findings regarding sex in both groups were similar to our study. In our study, Among Bupivacaine Group pre-operative Mean Heart Rate post epidural top up Mean Heart Rate, Among Bupivacaine + Ketamine group pre-operative Mean Heart Rate and post epidural top up Mean Heart Rate were assessed. There was no significant difference between two groups as in pre-operatively and post epidural top-up.

In our study Among Bupivacaine Group and among bupivacaine + ketamine group, Pre-Operative Mean Systolic BP and Mean Diastolic BP and post epidural top up in the duration of analgesia were compared. There was no significant difference between two groups in pre-operatively and post epidural top-up in the duration of analgesia with Systolic BP and Diastolic BP.

In our study Among Bupivacaine Group Mean Duration of Analgesia and Mean time for First rescue analgesia was 193.98 min. with a SD of 15.01. Among Bupivacaine + Ketamine group Mean Duration of Analgesia and Mean time for First rescue analgesia was 270 min. with a SD of 0. The p value is <0.05, there was a significant difference between two groups only in regards to Duration of Analgesia and first rescue of analgesia time. This prolongation of duration of anesthesia must be the result of addition of intrathecal ketamine to bupivacaine. The increased time for first rescue analgesia would decrease the use of opioids systemically.

In a study done by Radbin, et al. [61], Among Bupivacaine Group Mean Duration of Analgesia was 1.7 hours with a SD of 1.1. Among Bupivacaine + Ketamine group Mean Duration of Analgesia was 2.1 Hours with a SD of 2.4. As they have used only epidural anaesthesia in their study and we have used single shot epidural anaesthesia. The findings in our study were consistent with Duration of Analgesia with the study findings of Radbin, et al. [61]. In a study done by A. Hom Choudhuri, P. Dharmani et al [51] Among Bupivacaine Group Mean Duration of Analgesia, although they have used general anaesthesia and post operatively single shot caudal anaesthesia in paediatric patients. The findings in our study were consistent with Duration of Analgesia and not with the time for First rescue analgesia with the study findings of A. Hom Choudhuri, P. Dharmani et al [51]. The difference may be because cases were done under General Anaesthesia in their study, many drugs used under General Anaesthesia can interfere with the side effects of epidural drug. In a study done by Sağır, Ö.[58], Among The findings in our study were not consistent with study findings of Sağır, Ö.[58] as they have used intra-articular ketamine combined with peri-articular bupivacaine on postoperative pain. Its means that epidural analgesia is more potent than that of intra-articular.

In our study Among Bupivacaine Group Hypotension 02(08%), Nausea/Vomiting 02(08%), Pruritus 00(00). Among Bupivacaine + Ketamine group Hypotension 04(16%), Nausea/Vomiting 02(08%), Pruritus 00(00). The p value is >0.05, there was no significant difference between two groups.

Among Bupivacaine Group Bradycardia 11(44%), Sedation 00(00), Shivering 01(04%). Among Bupivacaine + Ketamine group Bradycardia 03(12%), Sedation 24(96%), Shivering 13(52%). The p value is <0.05, there was significant difference between two groups. This suggests effect of epidural ketamine.

The bradycardia among bupivacaine group was due to its myocardial suppression property which was not seen among bupivacaine + ketamine group which is due to sympathomimetic property of ketamine. Among Bupivacaine + ketamine group sedation may be due to ketamine's property of unique dissociative action and partial agonism on opiate mu-receptors causes state of sedation. The incidence of side effects in bupivacaine +ketamine group in our study and study done by Radbin, et al. [61] were consistent and comparable. Even though study done by a. Hom choudhuri, p. Dharmani et al [52] was General anaesthesia with single shot

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caudal anaesthesia in paediatric age group, the incidence of side effects in both groups were consistent with our study.

Although study done by Sağır Ö[58] is General anaesthesia with intra-articular injection of Bupivacaine and Bupivacaine + Ketamine, the incidence of side effects is much less in our study. Although study done by Zhang J[60] is general anesthesia with intra articular injection of bupivacaine and bupivacaine + ketamine with continuous femoral nerve block with ropivacaine 0.5% 0.1 ml/kg/h, the incidence of side effects is much less in our study, which maybe explained on the basis that we did not use Ropivacaine.

Epidural analgesia is most commonly provided using a combination of local anaesthetic and an opioid. Compared with opioids or local anaesthetics alone, a local anaesthetic–opioid combination provides superior postoperative analgesia with lower local anaesthetic doses and less opioid-related side-effects. To provide sedation, stable hemodynamic and prolonged postoperative analgesia are the main desirable qualities of adjuvant used in epidural anaesthesia. Lower doses of Ketamine were preferred as higher doses results in more side effects such as bradycardia, hypotension nausea, vomiting and dizziness.

The combination of low-dose epidural ketamine results in effective postoperative analgesia and also reduces the post-operative opioid/analgesic requirement, thereby decreasing opioid/analgesic related side-effects in low doses. These findings in our study were consistent with study findings done by Sethi, Mamta, et al. [76]

Summary and Conclusion

The present study was a randomized control study to compare between postoperative pain relief with 0.125% Bupivacaine plain and 0.125% Bupivacaine and Ketamine combination in infra-umbilical surgeries with sides effects of both groups.

In our study Among B and B+K Group, Majority were Females. And patients were allocated as ASA Grade I and ASA Grade II according to their status as there was no significant difference in demographic data of two groups.

In our study Among B and B+K Group pre-operative Mean Heart Rate, Mean Systolic and Diastolic BP and post epidural top up in the duration of analgesia Mean Heart Rate, Mean Systolic and Diastolic BP were indexed and there was no significant difference in the hemodynamical parameters between two groups.

In our study Among B and B+K Group the Mean Duration of Analgesia and Mean time for First rescue analgesia were calculated and there was a significant difference between two groups. It indicates that Bupivacaine and ketamine combination provides sufficient analgesia in post – operative period for adequate duration.

In our study incidence of Hypotension and Nausea/Vomiting seen Among B and B+K Group were comparable. There was no significant difference between two groups.

B+K showed prolonged duration of analgesia with minimal side effects which were acceptable and easily treatable. Hence epidural ketamine can be safely and effectively used.

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