

COMPARISON OF ANALGESIC EFFICACY OF INTRATHECAL KETOROLAC, MORPHINE AND ITS COMBINATION AS AN ADJUVANT TO BUPIVACAINE FOR LOWER LIMB SURGERIES- A PROSPECTIVE RANDOMISED STUDY

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ABSTRACT

BACKGROUND

Ketorolac is a non-steroidal anti-inflammatory agent with strong analgesic activity, when added as an adjuvant to intrathecal bupivacaine acts on the COX receptors at the spinal level and inhibits the synthesis of prostaglandins.

Aims- To evaluate the analgesic efficacy of intrathecal ketorolac, morphine and its combination when added as an adjunct to bupivacaine and, onset of sensory and motor blockade, quality of analgesia, side effects of the adjuvants used intrathecally.

MATERIALS AND METHODS

A prospective, randomised, double blind, placebo controlled study was conducted on 100 adult patients undergoing elective lower limb orthopaedic and general surgeries. Patients were randomly allocated into 4 groups (n=25) by using computer generated random numbers. Each group received 15 mg (3 mL) of hyperbaric bupivacaine along with either 0.5 mL normal saline in group P, ketorolac 2 mg (0.5 mL) in group K, morphine 200 mcg (0.5 mL) in group M, and ketorolac-morphine combination 2 mg + 200 mcg (0.5 mL) in group KM. Statistical analysis of data was done by using statistical package for social science (SPSS) evaluation version 22. One way ANOVA, Kruskal-Wallis tests were used for multiple group comparison and categorical data analysed by chi-square test.

RESULTS

The mean visual analogue scale score in group P was 5.4 ± 1.8 and in groups M, K, KM were 5.3 ± 1.5 , 5.1 ± 1.7 , 5.3 ± 1.6 respectively. The duration of analgesia in group P was 136 ± 16 min. and in groups M, K, and KM were 695 ± 62 min., 590 ± 56 min., and 1188 ± 93 min respectively. The quality of analgesia was excellent at 92% in combination group compared to other groups.

CONCLUSION

Ketorolac-morphine combination as an adjunct to intrathecal bupivacaine provides prolonged post-operative analgesia compared to ketorolac or morphine alone that is up to 15 hours in lower limb surgeries with significant inflammation.

KEYWORDS

Bupivacaine, Ketorolac, Morphine, Anaesthesia, Spinal, Postoperative Pain, Inflammation.

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BACKGROUND

Ketorolac is a potent non-steroidal anti-inflammatory drug, has been shown to have antinociceptive effects when administered intrathecally both in laboratory animals and humans.^[1] Preclinical studies suggest major site of action of ketorolac is the spinal cord and is not neurotoxic.^[2] Intrathecal ketorolac responds better in pain conditions associated with significant inflammation.^[3] Post-operative analgesia is important in perioperative care. A method of post-operative analgesia, which requires minimum technical intervention and expertise and gives good quality analgesia which is safe and easily available is very valuable.

Drugs which are cost effective with least side effects and with good patient and surgeon acceptance is the need of the hour today. Spinal anaesthesia with bupivacaine is a common analgesic technique in lower abdomen and lower limb surgeries. A single intrathecal injection of bupivacaine provides analgesia only for 2.5 hours to 3 hours. Various adjuvants to intrathecal local anaesthetics such as opioids, clonidine, ketamine, neostigmine^[4] have been used to prolong postoperative analgesia. Intrathecal ketorolac does not produce serious adverse events.^[2] This study was conducted to evaluate and compare the analgesic efficacy and side effects between intrathecal ketorolac, intrathecal morphine and combination of ketorolac and morphine when added as an adjunct to bupivacaine for post-operative pain relief in lower limb inflammatory orthopaedic and general surgeries. Our primary objective was to determine the duration of analgesia, secondary objective was to evaluate the onset of sensory and motor blockade, quality of analgesia, s adjuvants used intrathecally.

MATERIALS AND METHODS

A prospective, double blind, placebo controlled randomised clinical study was conducted for a period of 1 year (January

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2014- December 2014) on 100 adult patients, undergoing various elective lower limb procedures (orthopaedic and general surgery) under subarachnoid block at our hospital. The approval of institutional ethical committee was obtained. Age group of 18-60 yrs., patient who gave informed consent, American Society of Anesthesiologists (ASA) physical status I and II, were included in the study. Patients with medical complications like coagulopathies, disease and deformity of spine, with contraindication for non-steroidal anti-inflammatory drugs (NSAIDS) or opioids, history of hypersensitivity to the study drugs were excluded from the study. Sample size was calculated for one way ANOVA design, to analyse duration of analgesia in four groups (P, K, M, KM) as the primary outcome measure is based on the findings from Gabriela et al study, the effect size considered was 0.4 and with alpha error of 5%, power of 80%, the minimum sample size required in each group is 19 and the total sample size is 76. So sample size was rounded off to 25 in each group, making a total of 100. The sample size was calculated using G power software version 3.1.5.^[5,6]

Pre-anaesthetic evaluation was done to all patients under inclusion criteria. Premedicated with tablet diazepam 10 mg orally night before surgery. Basic laboratory investigations were done. Electrocardiogram (ECG) was advised in patients more than 40 years of age and chest x-ray when indicated. Patient's height and weight was noted. The entire procedure of spinal anaesthesia was explained to the patient. Patients were explained about visual analogue scale (VAS) and were taught how to express the degree of pain on the scale.

Patients were randomly allocated into four groups, by computer generated random numbers. Each group consists of 25 patients. All patients received total drug volume of 3.5 mL with any one of the drug solution as shown in Table 1.

The study drug solution was prepared in coded syringes by anaesthesiologist not taking part in the study and was given by another anaesthetist who is also not taking part in the study. Thus, the patient and observer were blinded in the study. Ampoule containing preservative free ketorolac tromethamine 30 mg in 1 mL (Intas pharmaceuticals limited) or preservative free morphine 10 mg in 1 mL (Troikaa pharmaceuticals) was used along with 0.5% hyperbaric bupivacaine (Neon laboratories limited). The dose of intrathecal ketorolac and morphine was measured by using insulin syringe.

In the operating room (OR), routine monitors like non-invasive blood pressure (NIBP), pulse oximetry, ECG were connected. Baseline vital parameters were noted. Peripheral intravenous (IV) line was secured with 18G cannula. Ringer lactate solution 10 mL/kg infused IV before initiation of spinal anaesthesia. Under aseptic preparation, lumbar puncture was performed at L3-L4 position in sitting or lateral position by midline approach after the local infiltration with 2% lignocaine, 3.5 mL of solution prepared (Table 1) was injected into the subarachnoid space and patient was made to lie in the supine position.

Time of intrathecal injection noted. Loss of sensation noted with light touch using cotton swabs and degree of motor block assessed by modified Bromage Scale. Inj. ephedrine 5 mg or inj. mephentermine 6 mg intravenously given to treat arterial hypotension [fall of systolic blood pressure (SBP) >20% from the baseline] and inj. Atropine

(0.6 mg) administered intravenously to treat pulse rate below 55 beats per minute (bpm). Respiratory depression (respiratory rate <10 breaths per minute) noted. Pulse rate, blood pressure, respiratory rate were monitored every 5 min for the first 15 min, then every 15 min for 1 hr, 30 min for the next 2nd hr, 3rd hr, every 1 hr from 4th, 5th, 6th hr after which at 12th and 24th hr throughout intra operative and post-operative period. Side effects like pruritus, nausea, vomiting, urinary retention (non-catheterised patients) and sedation were monitored throughout procedure and post operatively for 24 hrs.

The following Parameters were noted-

- Time of intrathecal injection
- Time of onset of sensory block [i.e. time taken from intrathecal injection of drug to time to complete loss of sensation to light touch with cotton swabs to T10].
- Incidence of hypotension, bradycardia and sedation level was assessed.
- Duration of analgesia [measured from the time of intrathecal injection to the first request of analgesia with VAS>4] was monitored.
- Pain intensity was assessed by visual analogue scale.
- Incidence of side effects like epigastric pain, nausea, vomiting, urinary retention, itching were monitored
- Sedation was monitored by Campbell scoring.^[7]
1-Wide awake, 2-Sedated but easily arousable, 3-Drowsy and difficult to arouse, 4-Unarousable.

Nausea & Vomiting

0-No symptom, 1-Symptom present but treatment not required, 2- Symptoms present & treatment given.

Pruritis - Four-point ordinal scale.

0-None, 1-Mild, 2-Moderate, 3-Severe.

Pain was assessed by visual analogue scale (VAS) at the time of first pain medication, patient was given a scale marked from 0-10 and was asked to mark on a scale the degree of pain he or she experienced ranging from "No" pain at 0 to "Maximum" pain at 10. In patients with VAS>4, rescue analgesic was given with Inj. Diclofenac 75 mg intramuscular (IM) and study concluded. At the end of the study, the patient was asked about the effectiveness of intrathecal drug with respect to pain relief. Depending on the subjective response, quality of analgesia was assessed, noted and compared according to Table 2. All the observations and particulars of each patient were recorded in a proforma and the patient belonging to the study group was disclosed after 24 hours postoperatively.

Statistical analysis of data was done by using statistical package for social science (SPSS) evaluation version 22. Results were expressed as mean, standard deviation. Frequencies expressed as number and percentage. One way ANOVA, Kruskal-Wallis test used for multiple group comparison and categorical data analysed by chi-square test. P - value of 0.05 or less is considered for statistical significance. The characteristics of the four groups were comparable in terms of age, height, weight, ASA classification, gender, and duration of surgery (Table 3). The mean onset of sensory block at T10 in groups K, M, KM and P were 3.12 ± 1.24 min, 2.36 ± 0.81 min, 2.12 ± 0.67 min, and 3.68 ± 1.11 min. respectively. The time of onset of sensory block in KM

and M group was shorter than K and P group. The groups K versus KM, K versus M, KM versus P, and M versus P were statistically significant with earlier onset of sensory block compared to K versus P and KM versus M. (Table 4 & Graph 1). The mean onset of motor block in groups K, M, KM and P were 2.92 ± 0.70 min, 3.36 ± 0.71 min, 3.48 ± 0.65 min., and 3.96 ± 0.61 min. respectively. In the study, the duration of analgesia was considered from the time of intrathecal injection to time of first rescue analgesia. The statistical analysis showed that the duration to first request of analgesia in group K, KM, M is significantly longer when compared to group P. Between groups KM versus K, KM versus M, KM versus P duration of analgesia was significantly longer in KM group. Wherein K versus P, K versus M, and M versus P, the difference in duration of analgesia was statistically significant. In our study, the pain intensity was measured by visual analogue score at first pain medication. Statistical analysis shows that there is no significant difference in VAS score between all the groups and results are comparable. (Table 4 & Graph 1).

With respect to quality of analgesia, statistical analysis showed that patients in group KM, M and K had good-to-excellent quality of pain relief when compared to group P who had poor to satisfactory pain relief. (Graph 4).

Incidence of headache was more with K group 16%, nausea and vomiting was seen in 12% of patients in M group. Bradycardia (4%), shivering (8%) was seen in group P and group M respectively. There was no incidence of pruritus or respiratory depression in any of the four groups. (Graph 5) However, sedation never exceeded grade 2 (drowsy). (Graph 2).

Group Drugs
GROUP-K (ketorolac) 3 mL of 15 mg of heavy bupivacaine + 0.5 mL of 2 mg ketorolac
GROUP-M (morphine) 3 mL of 15 mg of heavy bupivacaine + 0.5 mL of 200 µg morphine
GROUP-KM (ketorolac + morphine) 3 mL of 15 mg of heavy bupivacaine + 0.25 mL of 2 mg of ketorolac and 0.25 mL of 200 µg of morphine
GROUP-P (placebo) 3 mL of 15 mg of heavy bupivacaine + 0.5 mL 0.9% normal saline
*K- Ketorolac, †M- Morphine, ‡KM- Ketorolac and Morphine, §P- Placebo

Table 1. Group Distribution

Pain Score	Pain Relief
1	Excellent
2	Good
3	Satisfactory
4	Poor

Table 2. Quality of Analgesia

Variables	Group K (n=25)	Group M (n=25)	Group KM (n=25)	Group P (n=25)
Age (years)	40.24±16.12	34.56±10.69	38.64±15.53	36.96±10.59
Weight (kg)	57.96±6.79	58.00±5.62	60.04±6.74	57.36±5.66
Height (cm)	164.52±6.80	163.6±5.33	162.12±5.37	163.28±5.68
ASA grade I/II	11/14	14/11	15/10	9/16
Male/female	15/10	16/9	15/10	14/11

Duration of surgery (min.)	74.40±29.68	77.72±27.25	76.68±24.70	76.20±24.54
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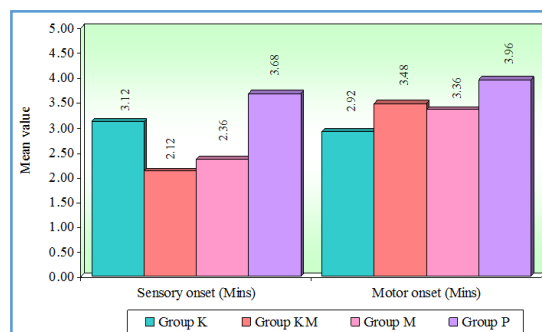
Values in the table are mean ± SD or absolute numbers. SD = Standard deviation, *ASA - American society of Anesthesiologists, †Yrs- years, ‡ Kg- Kilograms, § Cm- Centimetres, † Min.- Minutes.

Table 3. Demographic Chart

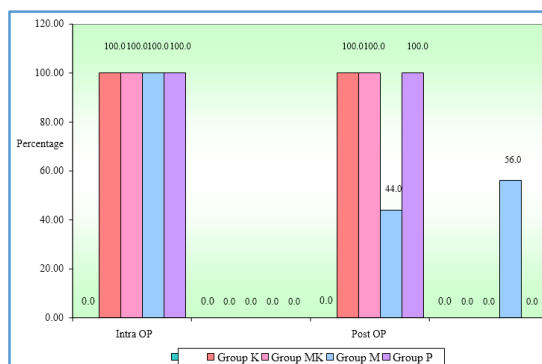
Variables	Group K (n=25)	Group M (n=25)	Group KM (n=25)	Group P (n=25)
Time of onset of sensory block (min.)	3.12±1.24	2.36±0.81	2.12±0.67	3.68±1.11
Time of onset of motor block (min.)	2.92±0.70	3.36±0.71	3.48±0.65	3.96±0.61
Highest dermatome level of sensory block	T10	T10	T10	T10
Time of first analgesic request (min.)	590.20±56.87	695.40±6.2.21	1188.40±9.3.58	136.60±16.85

Values in the table are mean ± standard deviation or absolute numbers (percentage). All times are calculated from time of intrathecal injection. *T- thoracic dermatome, †min.- minutes.

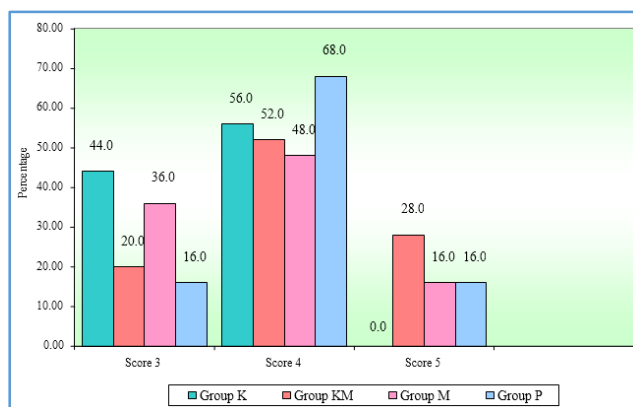
Table 4. The Mean onset of Sensory Block at T10 Level in Groups K, M, KM and P



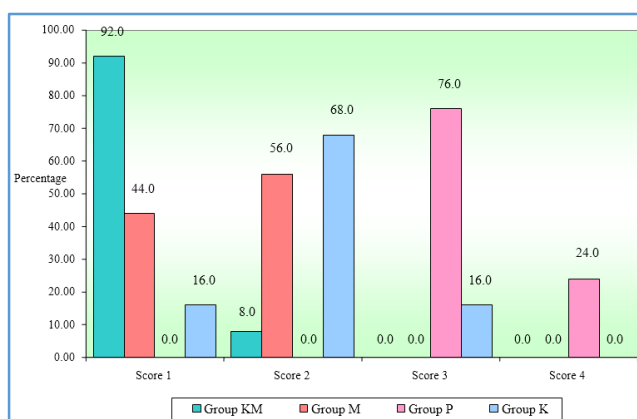
Graph 1: Comparison of Four Groups (K, KM, M, P) with Respect to Sensory and Motor Onset (minutes)



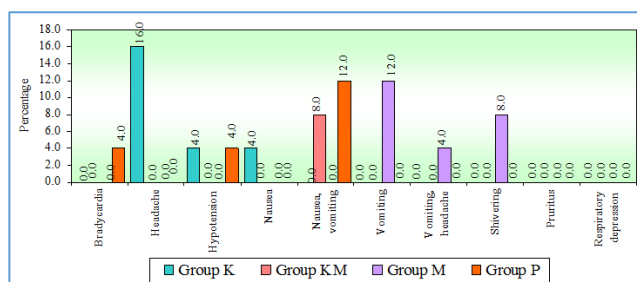
Graph 2. Comparison of Four Groups (K, KM, M, P) with Respect to Intraoperative and Postoperative Sedation Score



Graph 3. Comparison of Four Groups (K, MK, M, P) with Respect to VAS Score (at Time of Rescue Analgesia)



Graph 4. Comparison of Four Groups (K, MK, M, P) with Respect to Quality of Analgesia Score.



Graph 5. Side Effects of Four Groups

DISCUSSION

Ketorolac is a potent nonsteroidal anti-inflammatory drug that has been shown to have antinociceptive effects when administered intrathecally both in laboratory animals and humans.^[1] The dose of ketorolac used in the present study corresponds to that of James C. Eisenach et al.^[2]

Spinal morphine analgesia is mediated by μ 2-opioid receptors. Morphine, which is a hydrophilic opioid, has a longer residence time in the cerebrospinal fluid and therefore has long-lasting analgesia with intrathecal injection.^[4,8] In our study, we compared efficacy and adverse effects of intrathecal ketorolac, intrathecal morphine, combination of both and normal saline with bupivacaine in lower limb inflammatory orthopaedic and general surgeries. The patients studied across the group did not vary much with respect to age, sex, weight, height and ASA grading. The

types of surgeries performed and the duration were almost comparable in the four groups.

In our study, the mean onset time of motor blockade is rapid in K group compared to other groups and rest of the three groups are comparable to each other (Graph 1). Whereas the study conducted by Lauretti et al.^[1] did not show any significant difference in the onset of the motor block between the groups.

The four groups did not show any statistical difference in the level of sensory blockade, $\chi^2 = 15.85$ with a p value > 0.05. (Graph 1). A study conducted by Lauretti et al.^[1] also did not show any difference in the level of sensory blockade between the four groups. In our study, there was no significant haemodynamic and respiratory parameter changes^[3] correlating well with studies conducted by Lauretti et al.^[1] James C. Eisenach et al.^[2,9] Patients who received bupivacaine with ketorolac-morphine combination had significantly longer duration for first request of analgesia almost double when compared to ketorolac and morphine alone groups with p value <0.001 which is statistically highly significant. Similar corroborative results were obtained by Lauretti et al.^[1] in 80 patients undergoing orthopaedic knee surgery with similar four groups, where the mean duration of postoperative analgesia in M group was 440 ± 38 min., K group was 381 ± 44 min., MK group was 926 ± 222 min. compared to control group C was 170 ± 13 min. The results confirm the analgesic efficacy of intrathecal ketorolac, morphine, and its combination as an adjunct in prolonging the postoperative analgesia.

Pain intensity was assessed by visual analogue scale. In the present study, VAS score of 4 is most commonly seen in all four groups with the highest frequency in control group P. As the p value is 0.0594 (>0.05), there was no statistical significance among the four groups. Comparable results to this were also found in the study conducted by Lauretti et al.^[1], where the mean VAS scores (in cm) at first rescue analgesic 5.4 ± 1.8 , 5.3 ± 1.5 , 5.1 ± 1.7 , 5.3 ± 1.6 in groups C, M, K and MK respectively. (Graph 3).

Quality of analgesia in our study- group P had poor to satisfactory pain relief, Groups K, M, KM had good-to-excellent pain relief. Statistical analysis showed that there is significant increase in quality of pain relief with ketorolac, morphine, and combination groups when compared to control group P. Thus, to conclude, the quality of analgesia was best in the combination group and worse in control group. (Graph 4).

Nausea alone was seen in 1 patient in group K and Nausea and vomiting was seen in 2 patients in KM group and 3 patients in group P. None of the patients had either nausea or nausea with vomiting in other groups. Vomiting was noted in 3 (12%) patients in group M and no other groups had vomiting. Shivering was noted in 2 (8%) patients in group M and no other group had shivering. Headache was noted in 4 (16%) patients in group K. Patients in no other groups had headache. Bradycardia was noted in 1 (4%) patient in group P which was transient and reverted back to normal without any intervention. Patients in no other groups had bradycardia. Hypotension was noted in 1 (4%) patient in each group K and P and it necessitated administration of fluid and vasopressors for a variable period for maintenance of BP. (Graph 5). None of the patient had grade 3rd or 4th level sedation. (Graph 2). None of the

patients had urinary retention, pruritus, respiratory depression, epigastric pain, or neurological deficits. All side effects noted were minimal.

Similar results were seen in the study conducted by Lauretti et al,^[1] where there were minimal side effects and no significant complications.

Limitations of our study: The reason for enhancement of onset of sensory blockade and motor blockade in ketorolac-morphine combination group and ketorolac group respectively is not known and there are no supporting literatures available. More studies are required on intrathecal ketorolac as an adjuvant to bupivacaine in humans for evaluation of analgesic efficacy in different surgical procedures.

CONCLUSION

Intrathecal ketorolac-morphine combination as an adjunct to bupivacaine provides prolonged analgesia, superior pain relief and good haemodynamic stability with minimal side effects in patients with significant inflammatory limb procedures when compared to ketorolac or morphine alone as an adjuvant to intrathecal bupivacaine.

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