



A COMPARATIVE STUDY OF CLONIDINE VERSUS TRAMADOL AS ADDITIVE TO BUPIVACAINE IN EPIDURAL ANAESTHESIA

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ABSTRACT

Introduction: Pain is unpleasant sensory-emotional experience and one of the most feared symptoms experienced. Epidural anesthesia is safe, well practiced and inexpensive neuraxial block technique. Bupivacaine is commonly used for epidural anaesthesia. Researches have been conducted to identify different techniques and drugs that improve the quality of surgical anaesthesia, prolong the effect of bupivacaine and duration of postoperative analgesia.

Objectives: To evaluate efficacy of epidural tramadol and clonidine used as adjuvant to bupivacaine.

To compare onset and duration of sensory and motor blockade, quality of anaesthesia and duration of postoperative analgesia.

Methods: A prospective, randomized placebo control study was undertaken, involving 90 patients from SMIMER hospital, Surat. Three groups were allotted 30 patients each and were given, bupivacaine+saline (Group A)/ Bupivacaine+tramadol (Group B)/ bupivacaine+clonidine (Group C). Results were recorded and analyzed.

Results: The onset of sensory block was fastest in Group C. Total duration of sensory blockade was longest in Group B. Total duration of analgesia was longest in Group B, followed by Group C based upon Visual Analogue Scale. Both tramadol (Group B) and clonidine (Group C) prolong duration of analgesia and decrease requirement of post-operative analgesic doses and amongst them tramadol (Group B) is superior.

Conclusion: Tramadol and clonidine both are used as adjuvant to bupivacaine for epidural anaesthesia and post-operative analgesia. Tramadol provides longer duration of post-operative analgesia without sedation and requirement of analgesic is less within 24 hours. Tramadol is useful because of its cost effectiveness and easy availability.

Key Words: Pain, Pre-emptive anesthesia, Sensory blockade, Motor blockade

INTRODUCTION

Pain is “an unpleasant sensory and emotional experience associated with actual/potential tissue damage”. Intraoperative and postoperative noxious inputs cause central sensitization leading pain. Analgesic given before noxious stimulus can attenuate/block sensitization[1].

Pre-emptive analgesia is “an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain”. Pre-emptive analgesia is given to decrease acute pain after tissue injury, to prevent pain-related pathologic modulation of the central nervous system, to inhibit persistent postoperative pain and development of chronic pain[2].

Epidural anaesthesia is safe, inexpensive neuraxial block technique which provides surgical anaesthesia and postoperative pain control. Nowadays anaesthesiologists use poly-pharmacy approach to provide the best possible surgical anaesthesia and post-operative pain relief with minimal side effects[3].

Bupivacaine is amide local anaesthetic, commonly used for epidural anaesthesia. Studies are being conducted to evaluate different techniques and add-on drugs (fentanyl, tramadol etc.) to improve the quality of surgical anaesthesia, prolong the effect of bupivacaine and duration of postoperative analgesia[4].

Clonidine is centrally acting partial α_2 -adrenergic agonist which inhibits voltage gated Na^+ channels and prevents

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action potential generation in dorsal horn cells causing analgesia. It also decreases activity of second-order neurons and weakens the input from peripheral nociceptive A δ and C fibres. When given epidurally, 2 μ g/kg of body weight, it increases the duration of analgesia without side effects like bradycardia, hypotension, respiratory depression and fall in oxygen saturation[5].

Tramadol is synthetic codeine analogue, acting by weak μ -opioid receptor agonism and reuptake inhibition of serotonin and noradrenaline, resulting in antinociceptive effect. Reports show that epidural tramadol can provide post-operative analgesia safely[6].

The purpose of this study was to evaluate efficacy of epidural tramadol and clonidine used as adjuvant to bupivacaine, to compare onset and duration of sensory and motor blockade, quality of anaesthesia and duration of postoperative analgesia.

MATERIALS AND METHOD

After approval from institutional ethical committee and written informed consent, a prospective, randomized placebo controlled, parallel group clinical study was conducted on 90 patients.

Preanaesthetic evaluation was done on the previous day of surgery & procedure was explained.

Study duration: From November 2011 to January 2014.

Inclusion Criteria:

Patients of either sex belonging to ASA (American Society of Anaesthesiologists) I or II between age group of 20 to 60 years.

Exclusion Criteria:

- History of cardiac or renal diseases and taking antihypertensive medications.
- History of analgesic use.
- Chronic pain syndrome.
- Patients with communication difficulties.
- History of any adverse reaction to study drugs.

Methodology:

- Preloading was done with injection Ringer's lactate 15 ml/kg intravenously.
- Injection glycopyrrolate 0.004 mg/kg and injection midazolam 0.08 mg/kg was given intramuscularly as premedication 30 minutes before surgery.
- Epidural space was located by using loss of resistance

technique into the space between L₂-L₃ or L₃-L₄ spine and 20G epidural catheter was inserted through 18G Touhy needle. Placement of epidural catheter in epidural space was confirmed by 3cc injection of lignocaine with adrenaline.

The patients were randomly divided into 3 groups using a computer generated random numbers (30 patients in each). Blinding was not done.

Study groups:

Group-A: 19ml of 0.5% bupivacaine + 2ml 0.9% saline

Group-B: 19ml of 0.5% bupivacaine +2ml tramadol (2 mg/kg)

Group-C: 19ml of 0.5% bupivacaine + 2ml clonidine (2 μ g/kg)

Volume of bupivacaine (0.5%) was kept constant 19ml. Total volume was 21ml.

Sensory blockade: was assessed by using pinprick with hypodermic needle.

0= No sensation

1= Pin sensed as dull pressure

2= Sharp

Motor blockade: Assessed by modified Bromage scale.

0= No block

1= Inability to raise extended leg

2= Inability to flex knee

3= Inability to flex ankle and foot

Sedation: Assessed by five point scale.

1= alert and awake,

2= arousable to verbal command

3= arousable with gentle tactile stimulation

4= arousable with vigorous shaking

5= unarousable

Observations: were recorded as following:

- Measurement, time of onset and total duration of sensory blockade:
- Effective analgesia:
- Measurement, time of onset and total duration of motor blockade:
- Time to achieve T6 level:
- Time from epidural medication to two segment regression:
- Visual analogue scale (VAS) for postoperative pain assessment.
0= no pain, 2= annoying, 4= uncomfortable, 6= dreadful, 8= horrible, 10= worst pain.

- Top up dose given when VAS ≥ 4

Group-A: 0.125% bupivacaine 8ml + 2ml 0.9% NS

Group-B: 0.125% bupivacaine 8ml+ 2ml tramadol (1mg/kg)

Group-C: 0.125% bupivacaine 8ml+2ml clonidine (1 μ g/kg)

- Time of 1st top up dose.

Definitions:

- Onset of sensory blockade - Time from injection of study drugs to complete ablation of pin prick (score 0).
- Effective analgesia - Time between complete sensory block to the return of pain sensation which is tolerable (VAS <4).
- Complete analgesia - Time from onset of sensory blockade to return of pinprick, touch and temperature sensation (VAS >4).
- Onset of motor blockade - Time from injection of study to the time till complete paralysis (Modified Bromage scale 3).
- Duration of motor blockade- Time of onset of complete motor block to the restoration of normal musculature force (Modified Bromage scale 0).

Statistical analysis:

Results were presented as mean \pm SD (standard deviation). ANOVA test was applied for quantitative data and chi-square test for qualitative data.

Significance of p value was suggested as follows:

'p' Value was >0.05 insignificant.

'p' Value was <0.05 significant.

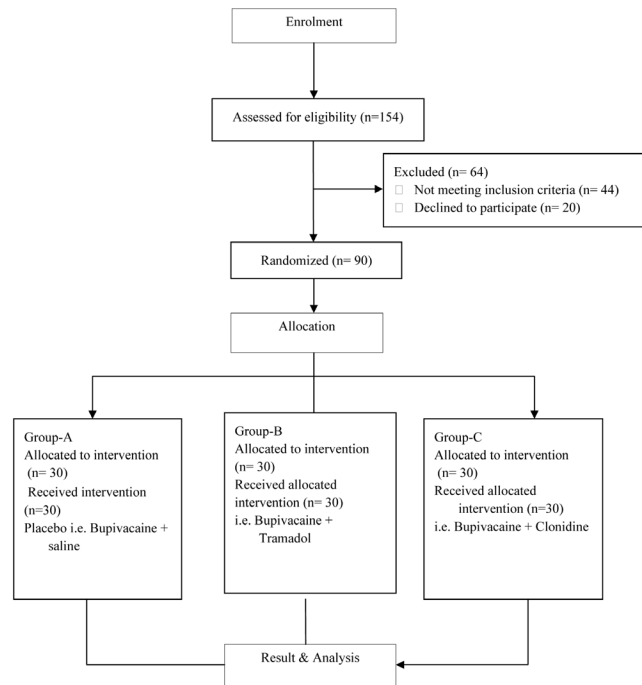
'p' Value was <0.001 highly significant.

RESULTS

This study was conducted on 90 patients of either sex belonging to ASA I and II in age group of 20 to 60 years. Patients undergoing lower abdominal and lower limb surgeries under epidural anaesthesia were selected for the study at SMIMER (Surat Municipal Institute of Medical Education and Research), Surat.

Total 154 patients were sought for this study, 44 patients were excluded as per eligibility criteria, while 20 were not willing to participate. Patients were randomly divided into three groups.

Demographic data of the patients are mentioned in Table 1. Patients were comparable in all groups according to age, weight and height distribution ($p > 0.05$).



Mean duration of surgery in Group-A (101.16 \pm 28.24 minutes), Group-B (99.66 \pm 28.76 minutes) and Group-C (94.5 \pm 21.26 minutes) were comparable among all groups ($p > 0.05$).

Out of 90 patients, 45 patients underwent lower limb and 45 patients underwent lower abdominal surgery. Patients were comparable as per type of surgery.

The onset of sensory block in both Group-C (10.06 \pm 2.03 minutes) and Group-B (12.6 \pm 2.01 minutes) were faster than the Group-A (13.83 \pm 1.96 minutes), with that in Group-C being faster ($p < 0.001$) (Table 2).

Total duration of sensory blockade was longer in Group-B (251.33 \pm 58.5 minute) and Group-C (160 \pm 46.46 minutes) as compared to Group-A (143.33 \pm 53.5 minutes) ($p < 0.001$) (Table 2).

The time to achieve T6 sensory block was shorter in Group-C (15.12 \pm 2.96 minutes) and Group-B (17.38 \pm 4.19 minutes) than Group-A (19.82 \pm 2.33 minutes) ($p < 0.001$) (Table 3).

Time from epidural medication to two segment regression was 140.26 \pm 32.5 minutes, 142.23 \pm 17.1 minutes and 141.83 \pm 11 minutes in Group-A, B and C respectively ($p > 0.05$) (Table 3).

Time of onset of motor blockade was comparable in Group-A (14.7 \pm 2.24 minutes), Group-B (13.93 \pm 2.74 min) and Group-C (13.2 \pm 4.30 min) ($p > 0.05$) (Table 4).

Total duration of motor block were, 136.33 \pm 27.47 minutes, 139.33 \pm 35.03 minutes and 141 \pm 38.26 minutes in Group-A, B and C respectively ($p > 0.05$) (Table 4).

In Group-A, patients had VAS ≥ 4 at an average duration of 170.66 \pm 51.44 minutes after giving epidural anaesthesia when 1st rescue analgesic dose was supplemented. In Group-B, analgesia lasted longer and VAS exceeded 4 after an average of 354.33 \pm 90.19 min. In Group-C, patients were comfortable till 220.33 \pm 96.34 minutes, when first rescue analgesic was required (Table 5).

The total duration of analgesia was longest in Group-B, followed by Group-C.

Time required for first rescue analgesic was longer in Group-B (354.33 \pm 90.19 minutes) than Group-C (218 \pm 30.10 minutes) and minimum in Group-A (168.33 \pm 26.40 minutes) ($p < 0.001$) (Table 6).

Requirement of total number of analgesic doses in 24 hours were higher in Group-A (3.73 \pm 0.5) than in Group-C (2.9 \pm 0.5) and minimum in Group-B (2.4 \pm 0.5) ($p < 0.001$) (Table 6).

Duration of effective analgesia was maximum in Group-B (314.47 \pm 50.88 minutes) and minimum in Group-A (152.67 \pm 58.7 minutes) ($p < 0.001$).

DISCUSSION

In the postoperative period effective pain control must be ensured. However, despite advances in the knowledge of pathophysiology of pain, pharmacology of analgesics and development of more effective techniques, patients continue to experience considerable post-operative pain.

Better postoperative analgesia and faster recovery of gut function were observed when epidural anaesthesia is used as compared to use of systemic opioids. Also, general anaesthesia alone is associated with higher chances of perioperative mortality and morbidity, while epidural anaesthesia can reduce both [7].

Both epidural and parenteral clonidine has been used to relieve postoperative pain. As clonidine induced analgesia is mediated by activation of α_2 -adrenoceptors on the dorsal horn of the spinal cord, its intrathecal or epidural administration close to its site of action seems logical. Clonidine is rapidly and widely absorbed into systemic circulation and reaches to target sites [8].

Tramadol may act by; a weak μ -opioid receptor agonistic action and/or serotonin-noradrenaline reuptake inhibition, leading to antinociceptive effect [9].

After ethical permissions from institutional ethics committee, this study was undertaken to evaluate the effect of tramadol and clonidine as an adjuvant to epidural bupivacaine in patients undergoing lower abdominal and lower limb surger-

ies. Study was conducted on 90 patients of either sex belonging to ASA I & II between age group of 20 to 60 years.

In this study, patients' demographical data in all groups and duration of surgery were comparable ($p > 0.05$).

In present study, the onset of sensory block when clonidine administered was faster as compared to tramadol and control group. Differences in onset of sensory block among the groups were highly significant ($p < 0.001$).

We observed that, tramadol group had longest total duration of sensory block, followed by clonidine group, while shortest in control group. The differences in total duration of sensory blockage between the groups were highly significant ($p < 0.001$).

We noted that, time to achieve T6 sensory block was 17.38 \pm 4.19 minutes, 15.12 \pm 2.96 minutes and 19.82 \pm 2.33 minutes in tramadol, clonidine and control group respectively. These differences between groups were highly significant ($p < 0.001$).

In the present study, two segment regression was 142.23 \pm 17.1 minutes, 141.83 \pm 11 minutes and 140.26 \pm 32.5 minutes in Group-B, C and A respectively. Differences between the groups were insignificant ($p > 0.05$).

Tanmoy Ghatak et al [3] conducted similar study using clonidine or magnesium sulphate as adjuvant to epidural bupivacaine in lower abdominal and lower limb surgery. They observed that onset of anaesthesia was significantly ($p < 0.001$) rapid in magnesium group, 11.80 \pm 3.21 minutes, whereas it was 16.93 \pm 3.43 minutes in clonidine group and 18.73 \pm 2.79 minutes in control group. Time to achieve T6 block was 11.80 \pm 3.21 minutes, 16.93 \pm 3.43 minutes and 18.73 \pm 2.79 minutes in magnesium, clonidine and control group respectively. The difference between the groups was significant ($p < 0.05$). Also the time from epidural medication to two segment regression among groups was statistically insignificant ($p > 0.05$).

Shobhana Gupta et al [10] evaluated the analgesic effect of combination of epidural clonidine with bupivacaine versus epidural bupivacaine alone. In their study the mean time for onset of sensory anaesthesia was significantly faster (493.8 \pm 31.66 seconds) in clonidine group than control group (686.4 \pm 47.42 seconds).

Yaun-Shiou Huang et al [11] conducted a dose-response study of epidural clonidine for postoperative pain after total knee arthroplasty. They divided patients in 4 groups (20 of each). After surgery, groups C0, C1, C2, C4 received patient control epidural analgesia (PCEA) with clonidine 0, 1.0, 2.0, 4.0 μ g/ml respectively and morphine 0.1 mg/ml in 0.2% ropivacaine. They observed that five patients in group C4

and one patient in group C2 suffered from prolonged sensory blockade (longer than 24 h). They concluded that the highest concentration of clonidine (4.0 µg/mL; group C4) produced the best analgesia, but the degree of sedation, sensory and motor blockade were more severe and longer lasting than with lower concentrations of clonidine, and required careful monitoring of patients.

Noha Sayed Hussien [12] compared magnesium sulphate and clonidine as an adjuvant to epidural anaesthesia. They noted that onset of anaesthesia was significantly rapid in magnesium group, 11.80 ±3.24 minutes, compared to 13.83 ±3.72 minutes in clonidine group and 17.71 ±2.66 minutes in control group. Time to reach T6 sensory level were 17.71 ±2.66 minutes, 10.80 ±3.24 minutes and 13.63 ±3.72 minutes in control, magnesium and clonidine group respectively. These differences between the groups were highly significant ($p < 0.001$). Times from epidural medication to two segment regression among groups were insignificant ($p > 0.05$).

The results of all the studies above were consistent with the present study. Administration of clonidine with local anaesthetic accelerates onset and increases duration of sensory block. The probable mechanisms are – (1) Interference with vascular resorption of local anaesthetic by producing vasoconstriction. (2) Direct action on neural tissue especially at the spinal level reducing the release of substance P from primary afferent neurons [13].

Addition of tramadol and clonidine to epidural bupivacaine produce rapid onset and prolong duration of sensory block without affecting two segment regression times.

In present study the onset and total duration of motor block wasn't significantly ($p > 0.05$) affected by either tramadol or clonidine.

Noha Sayed Hussien [12] and Tanmoy Ghatak et al [3] observed no difference in the quality of motor blocks between the groups.

Yaun-Shiou Huang et al [11] observed that higher concentration of clonidine produce prolonged motor block.

The results of above studies were consistent with the present study.

The onset and duration of motor blockade remained statistically insignificant in present study ($p > 0.05$).

In the present study, time required for first rescue analgesic were 354.33 ±90.19 minutes, 218 ±30.10 minutes and 168.33 ±26.40 minutes in Group-B, C and A respectively. The differences were statistically highly significant ($p < 0.001$) among the groups.

We observed that, requirement of total number of analge-

sic doses in 24 hours were higher in Group-A (3.73 ±0.5) than Group-C (2.9 ±0.5) and was minimum in Group-B (2.4 ±0.5), the difference was statistically highly significant ($p < 0.001$).

Tanmoy Ghatak et al [3] noted that, in clonidine group, time taken for first epidural top up dose after epidural anaesthesia, was highest in clonidine group as compared to magnesium group (161.67 ±30.10 minutes) and lowest in control group (150.67 ±35.80 minutes). They suggested that clonidine prolongs duration of anaesthesia with lower VAS score.

Noha Sayed Hussien [12] observed that, in clonidine group, time taken for first epidural top up dose after epidural anaesthesia, was highest (162.22 ±26.66 minutes) as compared to magnesium group (158.62 ±28.11 minutes) and lowest (150.48 ±28.7 minutes) in control group of patients. They said that clonidine prolongs duration of anaesthesia and sedation with lower VAS score.

Shahid Khan et al [14] conducted a randomized controlled trial to compare the effects after caudal bupivacaine alone and bupivacaine-tramadol in children with hypospadias repair. They observed that duration of analgesia was significantly higher in tramadol group (10.40 ±1.69 h) than control group (7.93 ±1.52 h).

Y. Demiraran et al [15] studied a comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children undergoing urological surgery. A single dose of morphine 0.1 mg/kg in isotonic saline 0.2 ml/kg (morphine group) and tramadol 2 mg/kg in isotonic saline 0.2 ml/kg (tramadol group) was administered epidurally. They observed that supplementary analgesia wasn't needed for 16 hours in the tramadol group and for 18 hour in the morphine group, thus pain score and average time for analgesia required were similar in both groups.

S. Prakash, R. Tyagi et al [16] evaluated the analgesic efficacy of three doses of tramadol, administered caudally with bupivacaine, in providing postoperative pain relief in children. Eighty patients were randomized into four groups to receive bupivacaine (0.25%) 0.75 ml/kg (Group B), bupivacaine (0.25%) 0.75 ml/kg with tramadol 1 mg/kg (Group BT1), bupivacaine (0.25%) 0.75 ml/kg with tramadol 1.5 mg/kg (Group BT1.5), or bupivacaine (0.25%) 0.75 ml/kg with tramadol 2 mg/kg (Group BT2) by caudal route. They observed that duration of analgesia was longer in Group BT2 (12 ±0.9 h) compared with Group B (4 ±1 h), Group BT1 (8 ±0.9 h), or Group BT1.5 (11 ±1 h).

Results of the above studies were in accordance with present study.

Administration of clonidine with local anaesthetic increases duration of post-operative analgesia. The probable mecha-

nism for prolong duration of analgesia are – (1) Clonidine may interfere with vascular resorption of local anaesthetic by producing vasoconstriction. (2) Clonidine may induce analgesia by direct distribution to brainstem after vascular resorption [13].

Tramadol inhibits noradrenaline uptake and stimulate serotonin release, and these are transmitter in the descending pathways which enhance analgesia [6].

Thus from the present study we can state that both tramadol and clonidine prolongs duration of analgesia and decreases the requirement of postoperative analgesic doses, however tramadol as an adjuvant to epidural anaesthesia is superior.

Limitations of the current study were: a.) it was a non-blind study which might have lead to observer bias. b.) a larger sample size might have more impact.

CONCLUSION

From this study we concluded that both tramadol and clonidine can be used as an adjuvant to bupivacaine for epidural anaesthesia and post operative analgesia. However tramadol provides comparatively longer duration of post operative analgesia without sedation and less requirement of analgesic within 24 hours. We conclude that tramadol can be a used as an alternative add-on drug to epidural bupivacaine because of its cost effectiveness, easy availability and lesser side effects.

Compliance with ethical standards:

Funding source: None.

Conflict of interest: Dr. Mahesh Sutariya, Dr Anand Amin and Ms Archana Behl declare that they have no conflict of interest.

Statement of human rights:

Ethical approval: “All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

Informed consent:

“Informed consent were obtained from all individual participants included in the study.”

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Table 1: Demographic data

Particulars	Group A	Group B	Group C	p value
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
Age (years)	37.36 \pm 11.59	35.33 \pm 8.72	39.2 \pm 11.74	p > 0.05
Weight (kg)	51.1 \pm 6.22	52.7 \pm 6.35	51.8 \pm 6.8	p > 0.05
Height (cms)	157.83 \pm 5.33	158.66 \pm 5.16	155.7 \pm 5.06	p > 0.05

Table 2: Sensory block

Particulars (minutes)	Group A (Mean \pm SD)	Group B (Mean \pm SD)	Group C (Mean \pm SD)	p value
Time of onset of sensory blockage	13.83 \pm 1.96	12.6 \pm 2.01	10.06 \pm 2.03	p < 0.001
Total duration of sensory blockage	143.33 \pm 53.5	251.33 \pm 58.5	160 \pm 46.46	p < 0.001

Table 3: Time taken to achieve T6 and 2 segment regression

Particulars (minutes)	Group A (Mean \pm SD)	Group B (Mean \pm SD)	Group C (Mean \pm SD)	p value
Time taken to achieve T6	19.82 \pm 2.33	17.38 \pm 4.19	15.12 \pm 2.96	p < 0.001
Time of 2 segment regression	140.26 \pm 32.57	142.23 \pm 17.17	141.83 \pm 11.02	p > 0.05

Table 4: Motor block

Particulars (minute)	Group A (Mean \pm SD)	Group B (Mean \pm SD)	Group C (Mean \pm SD)	p value
Time of onset of motor blockage	14.7 \pm 2.24	13.93 \pm 2.74	13.2 \pm 4.30	p > 0.05
Total duration of motor blockage	136.33 \pm 27.47	139.33 \pm 5.03	141 \pm 38.26	p > 0.05

Table 5: Visual analogue score (VAS) SCORE

Time	Group A (Mean ± SD)	Group B (Mean ± SD)	Group C (Mean ± SD)	p value
Immediate	0	0	0	-
1 hr	0.2 ± 0.406	0.066 ± 0.253	0.03 ± 0.182	p > 0.05
2 hr	1.566 ± 1.813	0.5 ± 1.306	1.0 ± 0.547	p < 0.05
3 hr	1.133 ± 1.776	0.2 ± 0.761	2.133 ± 0.7303	p < 0.05
4 hr	0.333 ± 1.028	0.3 ± 0.836	0.166 ± 0.379	p > 0.05
5 hr	0.4 ± 0.674	1.1 ± 1.322	0.733 ± 0.784	p < 0.05
6 hr	1.366 ± 1.496	1.933 ± 1.760	1.133 ± 1.502	p > 0.05
8 hr	2.3 ± 1.744	1.733 ± 1.910	2.033 ± 1.751	p > 0.05
10 hr	1.033 ± 1.564	0.366 ± 0.964	1.2 ± 1.769	p > 0.05
12 hr	1.2 ± 1.864	1.5 ± 2.012	0.566 ± 1.381	p > 0.05
16 hr	0.9 ± 1.470	0.733 ± 1.362	1.166 ± 1.599	p > 0.05
20 hr	2.333 ± 1.953	2.7 ± 1.878	2.633 ± 1.902	p > 0.05
24 hr	0.3 ± 1.022	0.166 ± 0.746	0.6 ± 1.404	p > 0.05

Table 6: Time for first rescue analgesic and total number of analgesic doses within 24 hours

Particulars (minutes)	Group A (Mean ± SD)	Group B (Mean ± SD)	Group C (Mean ± SD)	p value
Time for 1 st rescue analgesic	168.33±26.40	354.33±90.19	218 ± 30.10	p < 0.001
Total number of analgesic doses within 24 hours	3.73 ± 0.5	2.4 ± 0.5	2.9 ± 0.5	p < 0.001