

Tramadol and its combination with piroxicam in post-cesarean pain management: a comparative study

Banapura Ambika^{1*}, Mamatha K. R.¹, Prabha P.²

¹Department of Pharmacology,

²Department of Anaesthesia,
Bangalore Medical College and
Research Institute, Bengaluru,
Karnataka, India

Received: 08 December 2016

Accepted: 30 December 2016

***Correspondence to:**

Dr. Banapura Ambika,

Email:

ambikabanapura101@gmail.com

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ABSTRACT

Background: Cesarean delivery is a major surgical procedure, requiring high quality pain relief to facilitate early ambulation, infant care and prevention of post-operative morbidity. There is no gold standard for post-cesarean pain management.

Methods: Cases were randomly assigned to 2 groups of 30 cases each. One group received Tramadol 100mg and another, Tramadol 100mg+ Piroxicam 20mg. Injections were given intramuscularly, postoperatively after skin closure. Diclofenac 75mg was the rescue analgesia. Primary outcome measure was control of pain, assessed by visual analogue scale (VAS). Secondary outcomes were sedation and time to rescue analgesia. Safety of the drugs was assessed by adverse drug reactions. Data was analysed by student's t test, analysis of variance and post-hoc test.

Results: Multimodal group showed better analgesia compared to unimodal group ($p < 0.001$). Drowsiness was the main adverse effect in both treatment groups.

Conclusions: Multimodal analgesic combination of tramadol and piroxicam showed superior analgesic effect with better pain control and longer duration of action compared to tramadol alone.

Keywords: Tramadol, Piroxicam, Post-cesarean pain

INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.^{1,2} The World Health Organization and International Association for the Study of Pain have recognized pain relief as a fundamental human right.³ Caesarean section (CS) rates are inexorably rising which has led to the possibility of negative impact on maternal and neonatal health.⁴ CS induces moderate to severe pain for 48 hours.⁵ Postoperative pain leads to patient discomfort, decreased level of satisfaction, prolonged recovery, and higher health costs. Adequate post operative analgesia hastens ambulation, decreases maternal morbidity, improves patient outcome, and

facilitates care of the newborn. These therefore improve the overall quality of life in post cesarean cases.⁶

Postoperative pain management of CS cases has become a major medical and nursing challenge. Although advances have been made in the understanding of pathophysiology of postoperative pain and development of new analgesics and delivery techniques, many patients still suffer from moderate to severe postoperative pain.⁷ CS patients have additional compelling reasons to receive adequate pain relief as they are expected to be alert and energetic enough to take care for, interact with, and breastfeed their newborn.

Early mobilization is a key factor to prevent the risk of thrombo-embolic disease.

Pain has a multifactorial origin, hence it may be difficult to achieve effective pain control with a single drug.⁸ Various agents, routes, modes exist for the treatment of postoperative pain. Historically opioids are most commonly administered analgesia. Pain, pruritus, nausea/vomiting, sedation and respiratory depression are concerning issues that complicate postoperative opioid usage.^{9, 10} These limitations have led to the introduction of use of multimodal analgesia, which is achieved by combining different analgesics that act by different mechanisms of action and at different sites in nervous systems resulting in additive or synergistic analgesia with lowered adverse effects.¹¹

Tramadol is an atypical, centrally acting analgesic, acts as a weak opioid agonist, and also as a serotonin and noradrenaline reuptake inhibitor and is an effective postoperative analgesic.¹²⁻¹⁴

Non-steroidal anti-inflammatory drugs (NSAIDs) have beneficial effect on postoperative analgesia; addition of NSAIDs has been shown to potentiate opioid effect, decrease opioid consumption and also, is devoid of adverse effects of opioids.^{10,15} Piroxicam, NSAID, has long half-life, extensive protein binding which allows for its once a day dosing.¹⁶

μ -Opioidergic and monoaminergic (5-hydroxytryptamine and noradrenaline) pathways and prostaglandin-dependent mechanisms are individually important in the modulation of pain.¹⁷

The combination of several analgesics with different modes of action, also termed “balanced analgesia” may be more effective in reducing nociceptive input and side effects and thereby optimizing pain control.^{18,19}

We explored multimodal approach to pain relief after cesarean section using single dose tramadol and its combination with piroxicam in the management of post cesarean pain.

METHODS

This study was a prospective, hospital-based, open label, parallel group, comparative study approved by the Institutional Ethics Committee of Bangalore Medical College and Research Institute. Sixty patients of ASA (American Society of Anesthesiologists’ Classification) I and II status undergoing elective caesarean section were recruited and written informed consent were obtained.

Exclusion criteria included refusal to participate in the study, hypersensitivity to study medications, any systemic contraindications to the use of study medications, history of peptic ulcer disease or gastro intestinal bleeding, opioid use for the past month, history of selective serotonin reuptake inhibitors use, cases of eclampsia/ pre-eclampsia, significant pulmonary or cardiovascular disease, and those with any intraoperative

complications. All patients had cesarean section under spinal anaesthesia. The spinal was performed using a 25-gauge Quincke needle with hyperbaric bupivacaine 5mg/ml. No other intraoperative analgesia was given. The patients were allocated into two groups with 30 cases in each group. One group received tramadol 100 mg and another group received tramadol 100mg and piroxicam 20 mg. The study drug was administered immediately after surgery, intramuscularly on the operating table, after the skin closure by the attending anaesthetist. Diclofenac 75mg given intramuscularly was the rescue analgesic. Their demographic data, history, clinical and obstetrical examination findings were recorded. This study employed a random allocation design to compare the effectiveness of tramadol as single analgesic agent (unimodal analgesia) and in combination with piroxicam (multimodal analgesia) for the management of post-cesarean pain.

Assessment tools

The primary outcome measure was the control of postoperative pain, which was assessed every 2 hours for a period of 12 hours after surgery by visual analogue scale (VAS) (Figure 1). Secondary outcomes were sedation assessed by Ramsay sedation score (Table 1) and duration of action assessed indirectly by time to first rescue analgesia. The assessment of safety was done by monitoring the adverse drug reactions i.e., maternal and neonatal adverse outcomes.

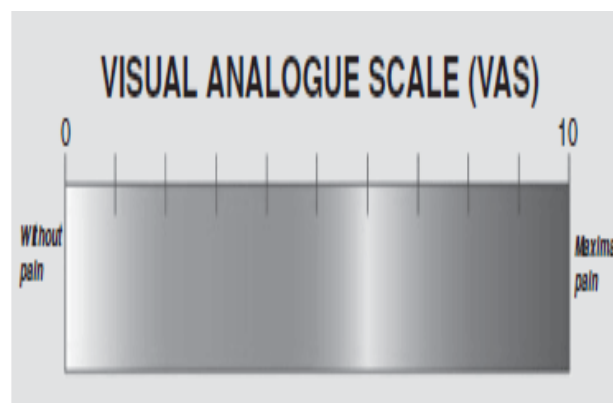


Figure 1: Visual analogue pain scale.

Table 1: Ramsay sedation score.

Points	Level of activity
1	Anxious and agitated or restless, or both
2	Cooperative, oriented, and calm
3	Responsive to commands only
4	Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5	Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6	Unresponsive

Statistical analysis

The sample size was 30 in each arm. The statistical comparison of different parameters between the two treatment groups was done using student's independent sample t test. And, within each treatment group the comparison between mean VAS scores at different points was done by analysis of variance (ANOVA) followed by post hoc test.

RESULTS

The baseline characteristics like age, weight, mean BP, pulse rate, type of spinal anesthesia used (hyperbaric bupivacaine) were similar in both the unimodal and multimodal study groups (Table 2). This eliminated the possible confounding influence of these factors.

Table 2: Baseline characteristics.

	Tramadol	Tramadol +Piroxicam	p value
Age in years Mean (SD)	25.41 (3.94)	24.41 (3.4)	0.2
Weight in Kg Mean (SD)	59.3 (5.75)	60 (5.14)	0.6
Systolic BP (mm of Hg)	116 (3.2)	118 (4.9)	0.07
Diastolic BP (mm of Hg)	74 (2.2)	72.9 (4.2)	0.2
Pulse rate Mean (SD)	92.6 (15.1)	93 (14.3)	0.9
Respiratory rate Mean (SD)	14.65 (1.16)	14.19 (0.6)	0.06

VAS pain scores over 12 hours duration, reduced in both the treatment groups and the reduction was statistically significant ($p < 0.0001$ by repeated measure ANOVA).

Mean VAS scores between the multimodal group (tramadol + piroxicam) and unimodal group showed statistically significant difference ($p < 0.001$). Tramadol + piroxicam showed better reduction in pain compared to tramadol.

Time to first rescue analgesia in tramadol group was 2.5 hours and in tramadol+piroxicam group it was 4 hours (Table 3). Multimodal group (tramadol + piroxicam) showed a longer time to rescue analgesia compared to

unimodal group (tramadol alone) and the difference was statistically significant ($p < 0.001$).

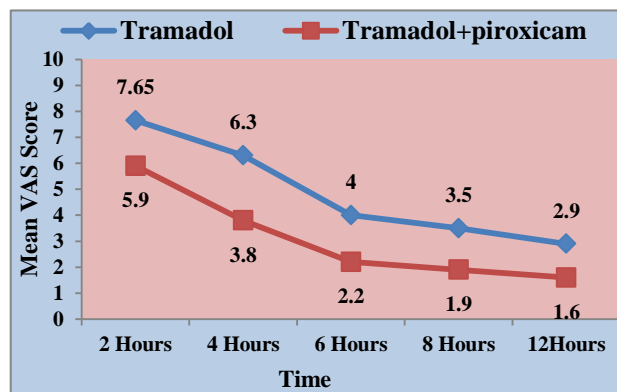


Figure 2: VAS scores in Tramadol and Tramadol+Piroxicam.

Table 3: Comparison of Tramadol versus Tramadol+piroxicam.

	Tramadol	Tramadol +Piroxicam	p value
Mean VAS score Mean (SD)	4.87 (0.67)	3.8 (1.23)	0.0001*
Time to first rescue analgesia in hours Mean (SD)	2.5 (0.3)	4 (0.6)	<0.001*
Mean sedation score Mean (SD)	3 (1.04)	2.9 (1.3)	0.32

Sedation score with tramadol was 3 and that with tramadol+piroxicam was 2.9, mean sedation score was comparable in both the groups.

When VAS scores were compared between the two groups at 2 hours, 4 hours, 6 hours, 8 hours and 10 hours, there was significant difference in the pain scores at all time points.

In tramadol and tramadol + piroxicam group when pain scores were compared within the groups, there was significant decrease in pain score over 12 hours duration (by repeated measures ANOVA). In both the groups, when any of the mean VAS scores was compared with the corresponding VAS score at 2 hours, significant difference was noted (Table 5).

Table 4: Comparison of pain scores over different time points.

	2 Hours Mean (SD)	4 Hours Mean (SD)	6Hours Mean(SD)	8 Hours Mean (SD)	12 Hours Mean (SD)	p value ANOVA
Tramadol	7.65(0.48)	6.3(0.7)	4(0.6)	3.5(0.5)	2.9(0.7)	<0.001
Tramadol + Piroxicam	5.9(0.9)	3.8(0.8)	2.2(0.5)	1.9(0.5)	1.6(0.4)	<0.001
't'	9.45	12.529	13.458	10.59	8.44	
p value (t test)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

Table 5: Results of post-hoc test (applied to mean VAS scores).

	2 Hours Mean (SD)	4 Hours Mean (SD)	6 Hours Mean (SD)	8 Hours Mean (SD)	12 Hours Mean (SD)	p value
Tramadol	7.65(0.48)	6.3*(0.7)	4*(0.6)	3.5*(0.5)	2.9*(0.7)	<0.001
Tramadol + Piroxicam	5.9(0.9)	3.8*(0.8)	2.2*(0.5)	1.9*(0.5)	1.6*(0.4)	<0.001

* In both the groups there was significant difference when any of the VAS scores was compared with the corresponding 2hours VAS score by post-hoc test.

The most common adverse drug reactions in the study were drowsiness and nausea. Number of cases reporting nausea was more with multimodal group.

Table 6: Adverse drug reactions.

Adverse drug reaction	Tramadol	Tramadol + piroxicam
Nausea	3.33%	10%
Drowsiness	13.3%	13.3%
Abdominal pain	3.33%	3.3%
Cough	3.33%	0%
Edema foot	0%	3.33%
No ADR	76.6%	70%

DISCUSSION

Postoperative pain is an acute traumatic pain resulting from surgical tissue injury. Although usually self-limiting and amenable to treatment, it remains the most common and probably, the most distressing and frequently undertreated sequelae of major surgical operations.²⁰

According to the WHO ladder, the combination of paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) with opioids was considered as the second step in the treatment of pain, based on increasing pain severity.²¹

This concept of multimodal analgesia is a technique to improve the analgesia and reduce the incidence of opioid related adverse events may provide for shorter hospitalization times, improved recovery and functions and possibly decreased health care costs.²²

In this study, after parenteral administration of the drugs mean VAS scores with tramadol and tramadol+piroxicam groups were 4.8 and 3.8 respectively, the average VAS score was lesser in the multimodal group compared to unimodal group and hence, multimodal analgesic combination showed superior analgesic property. Combination of opioid and NSAID might have led to the synergistic action in pain reduction as these two analgesics act by different mechanisms of action and at different sites in nervous systems resulting in additive or synergistic analgesia with lowered adverse effects.

In addition it was observed that the multimodal combination showed longer time to rescue analgesia compared to tramadol alone (4 hours vs. 2.5 hours) and hence the total dose of rescue analgesic diclofenac, was lesser in multimodal group. Combination of NSAID i.e., piroxicam with tramadol showed longer time to rescue analgesia compared to the tramadol given alone.

This study also showed that there was no difference in sedation between the groups.

Both the groups showed reduction in pain score over 12 hours; however combination of tramadol and piroxicam group showed significant difference in pain reduction at all time points compared to the unimodal group i.e., tramadol alone.

Similar results were seen in a previous study by Adeniji and Atanda, to compare the effectiveness of intramuscular pentazocine (60 mg) and tramadol (100 mg) as single analgesic agents and combinations of tramadol or pentazocine with intramuscular piroxicam 20 mg, for the management of post-cesarean section pain. The author concluded that the multimodal approach was better than the unimodal approach.²³

However, it is noteworthy that most reports in the literature have not extended the comparison of the efficacy of these drugs beyond the first 6-hour postoperative period whereas in our study, the VAS scores were recorded every 2 hours up to 12 hours after giving the drug and, comparison of VAS scores between different study groups was done at all time points i.e., 2,4,6,8 and 12 hours.

Tramadol proved to have better analgesic effect when combined with piroxicam. Previous study has established that the multimodal approach, reduces the total dose of opioids required in the postoperative phase, as well as its cumulative side effects.²⁴ Some of these studies have compared the use of opioids alone (unimodal) with combinations of opioids and NSAIDs (multimodal) and found that the multimodal approach was more effective; following are some studies.

NSAID (diclofenac) alone and in combination with tramadol, administered parenterally after cesarean section showed that tramadol + diclofenac showed significantly

superior analgesic effects compared with tramadol or diclofenac alone, in study by Wilder smith CH et al.¹⁰

Combination of tramadol + diclofenac versus tramadol + paracetamol was compared in study by Chandanwale et al in patients with acute musculoskeletal conditions, postoperative pain, and acute flare of osteoarthritis and rheumatoid arthritis, showed a significantly greater reduction in pain intensity with a fixed dose combination of tramadol + diclofenac.²⁵

In literature, studies comparing opioids with their combination with piroxicam are limited. A comparative trial by Khalili G et al, evaluating the efficiency of a combination of paracetamol + piroxicam versus each drug alone and also placebo in the management of postoperative pain showed that combination of piroxicam + paracetamol was more effective than piroxicam alone.²⁶

When a single dose piroxicam 20mg was compared with single dose tramadol 100mg in post operative pain after cesarean surgery in study done by Farshchi A et al, piroxicam could relieve postoperative pain after cesarean section as well as tramadol and it could reduce opioid analgesic requirements with less adverse side effects during the first postoperative 24 hours.²⁷

Analgesic efficacy of diclofenac-acetaminophen combination was compared with diclofenac-tramadol combination to optimize multimodal post-operative analgesia in women undergoing caesarean section in randomised trial by Mitra et al, in which both diclofenac + tramadol and diclofenac + acetaminophen combinations could achieve satisfactory post-operative pain control in women undergoing caesarean section. The diclofenac + tramadol combination was overall more efficacious but associated with higher incidence of post-operative nausea.²⁸ In our study the incidence of nausea was 3% in tramadol group but increased to 10% in the tramadol + NSAID group (tramadol + piroxicam).

These findings are similar to our study with respect to analgesic efficacy, time to rescue analgesia as the combination of NSAID (piroxicam) with opioid (tramadol) showed better analgesia, longer time to rescue analgesia and hence support that the multimodal approach was better than the unimodal approach. In our study, piroxicam also showed a synergistic effect on the efficacy of tramadol. It might be possible that in combination with piroxicam's anti-inflammatory action, the tissue swellings from handling at surgery and resultant nerve-endings stimulation were reduced. Further, the improvement in the efficacy was evident in prolongation of the duration of action.

Both the drugs used in the study were safe and there were no serious adverse drug events with any of the drugs. Overall, the most common adverse drug reactions encountered in our study were drowsiness and nausea. Drowsiness was the main adverse drug reaction in both

the groups, with 13% of cases in tramadol as well as in tramadol + piroxicam group. Nausea was reported in 10% of cases who received tramadol + piroxicam whereas in tramadol group, it was seen in 3% of cases. These findings with respect to safety of the drugs are similar to the previous studies.^{23,29}

The limitation of this study is the possible confounding influence of the spinal analgesia agent (bupivacaine) on the observed analgesic effects of all agents studied; however, we reason that since all the patients had the same drug and dosage for the spinal analgesia, except for individual patient peculiarity, this effect should balance out. Long term adverse effects with the drugs could not be assessed as adverse drug reactions were recorded only for 12 hours after giving the single dose of the study drug. Opioid analgesic sparing action of NSAID could not be assessed as the dose of tramadol was same both in unimodal group and in combination group.

CONCLUSION

Multimodal analgesia is safe and effective mode of analgesia for post-cesarean pain management.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Gajanan babu, post graduate student from the Department of Anaesthesia, Bangalore Medical College and Research Institute, Bengaluru for his support in conducting the study.

Funding: No funding sources

Conflict of interest: None

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Banapura A, Mamatha KR, Prabha P. Tramadol and its combination with piroxicam in post-cesarean pain management: a comparative study. *Int J Basic Clin Pharmacol* 2017;6:404-9.