

## SAFETY AND EFFICACY OF TRAMADOL COMPARED TO DICLOFENAC IN RELIEVING POSTOPERATIVE PAIN

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**ABSTRACT: BACKGROUND:** Effective postoperative pain control is an essential component of the care of the surgical patient. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality. Opioids have been the mainstay of treatment for post-operative pain but their side effects such as respiratory depression, sedation, constipation, urinary retention, nausea, vomiting, hypotension, bradycardia, and itching limit their use. Tramadol is a semi-synthetic opiate which has the advantage of less respiratory depression (<1%) besides its good analgesic effect. Non-steroidal anti-inflammatory drugs (NSAIDs) have recently gained wide spread popularity in postoperative pain management. Most NSAIDs have been used for treatment of postoperative pain. However, associated side effects include peptic ulcer disease, gastrointestinal hemorrhage, renal dysfunction, altered liver function, and platelet dysfunction. **OBJECTIVE:** The objective of this study was to compare the efficacy and safety of Tramadol and Diclofenac in relieving postoperative pain. **MATERIALS AND METHODS:** A randomized, open labelled, prospective, comparative clinical study was conducted in 80 post-operative patients, to compare the efficacy and safety of Diclofenac and Tramadol. Diclofenac was prescribed to 40 post-operative patients and Tramadol to another 40 post-operative patients for treatment of pain. Patients were assessed for pain score only once in a day. They were asked to report the average pain intensity over the past 24 hours. Pain was assessed from the time of shifting of the patient to post-operative ward till discharge of the patient from the hospital or number of days the study drugs was given, whichever was earlier. **RESULTS:** The mean pain score on post op day 0 in Diclofenac group was 9.25 and that in Tramadol group was 8.97 (P =0.16). The mean pain score on post-operative day 7 in Diclofenac group was 2.50 and that in Tramadol group was 3.00 (P =0.67.5). The overall incidence of adverse effects was 2.5% in Diclofenac group and 7.5% in Tramadol group (p=0.31) **CONCLUSION:** Both, Tramadol and Diclofenac were equally effective in reducing post-operative pain. The difference in requirement of rescue analgesia and incidence of adverse effects was statistically insignificant in both the groups.

**KEYWORDS:** Post-operative analgesia, Tramadol Diclofenac, Safety, Efficacy.

**INTRODUCTION:** Pain is one of the primary concerns of the surgeon because it is closely associated with the clinical outcome and acute postoperative well-being of the patient. Studies have indicated negative clinical impact of pain on a variety of physiological systems of the body. For example, decrease in vital capacity and alveolar ventilation, pneumonia, tachycardia, hypertension, myocardial ischemia, myocardial infarction, transition to chronic pain, poor wound healing, and insomnia have all been reported.<sup>[1,2,3]</sup>

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Pain has been found to be one of the three most common medical causes of delayed discharge after ambulatory surgery, the other two being drowsiness and nausea/vomiting. Despite an increased focus on pain management programs and the development of new standards for pain management, many patients continue to experience intense pain after surgery.

Effective postoperative pain control is an essential component of the care of the surgical patient. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality<sup>[4,5]</sup> Evidence suggests that surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery.<sup>[6,7]</sup> Good analgesia can reduce this deleterious effect.

Postoperative pain is invariably associated with any type of surgery. Although the severity of pain is related to type of surgery, yet it has been observed that generally 20–40% patients experience pain of moderate intensity and another 50–70% experience severe pain.<sup>[8]</sup>

The advantages of effective postoperative pain management include patient comfort and therefore satisfaction, earlier mobilization, fewer pulmonary and cardiac complications, a reduced risk of deep vein thrombosis, faster recovery with less likelihood of the development of neuropathic pain, and reduced cost of care. The failure to provide good postoperative analgesia is multifactorial. Insufficient education, fear of complications associated with analgesic drugs, poor pain assessment, and inadequate staffing are among its causes.

There have been many advances in the management of postoperative pain through different modalities like peripheral nerve blocks, epidural local anesthetics and/or opioids.<sup>[9]</sup> Opioids have been the mainstay of the treatment for postoperative pain but their side effects such as respiratory depression, sedation, constipation, urinary retention, nausea, vomiting, hypotension, bradycardia, and itching limit their use.<sup>[10]</sup> However, Tramadol is a semi-synthetic opiate which has the advantage of less respiratory depression (<1%) besides its good analgesic effect.<sup>[11,12]</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) have recently gained wide spread popularity in postoperative pain management. Almost all NSAIDs have been used for the treatment of postoperative pain including non-selective (conventional) cyclooxygenase (COX) inhibitors. Their peripheral and central analgesic effect, anti-inflammatory properties and relatively more tolerability than opioids have made them the drugs of choice in postoperative analgesia. Diclofenac (COX-1 & COX-2 inhibitor) is being used conventionally for many years for postoperative pain relief. It is an extremely potent cyclooxygenase inhibitor and it is known to accumulate in the inflamed tissue where its concentration is maintained much higher than in plasma for many hours. It also has active metabolites that act as analgesic. However, the associated side effects of NSAIDs include peptic ulcer disease, gastrointestinal hemorrhage, renal dysfunction, altered liver function, and platelet dysfunction. These side effects limit the use of these agents in many patients during the perioperative period. Since Tramadol and Diclofenac have dissimilar profiles, especially the fact that one of them may be indicated for use when the other is not indicated necessitates that the safety and efficacy of Diclofenac and Tramadol are evaluated in comparison to one another. The present study is therefore, conducted to compare the safety and efficacy of Diclofenac versus Tramadol in the treatment of postoperative pain.

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## OBJECTIVES:

**Primary objective:** To compare the efficacy of Diclofenac and Tramadol in the treatment of post-operative pain in terms of quantitative reduction in the Numeric Rating Scale Score for pain at rest and comparing number of patients in both the groups requiring rescue analgesia.

**Secondary objective:** To assess the tolerability of Diclofenac and Tramadol by comparing the incidence of adverse effects reported by the postoperative patients.

**MATERIALS AND METHODS:** The study was conducted on 80 patients (29 males and 11 females in each group between the age group of 18-75, inclusive of both) in post-operative wards (OBGY, Surgery, Orthopedics and Urology departments) of MediCiti Institute of Medical Sciences, Hyderabad from November 2011 to June 2013. The study was approved by the institutional ethics committee. Informed consent was taken from all the patients who participated in the study.

**SAMPLE SIZE:** Based on one of the previous studies <sup>[13]</sup> done assuming at least 2 units difference in mean pain score between the Diclofenac group and Tramadol group with an alpha of 0.05 (two-sided) and power 80% the estimated sample size in each group was 37. Hence, to round off, 40 patients were taken in each group. Sample size of 40 patients in each group was taken for this study. The 80 patients were divided into two groups:

**Diclofenac group:** 40 patients were included in this group who received 50 mg tablet or 75 mg intramuscular injection twice daily as an analgesic for pain relief in the postoperative period.

**Tramadol group:** 40 patients were included in this group who received 50-100 mg tablet or i.m/ i.v injection twice daily as an analgesic for pain relief in the postoperative period. The following inclusion and exclusion criteria were used to select study participants.

## INCLUSION CRITERIA:

- Male and female patients who were between the age group of 18-75 years (both inclusive).
- Postoperative patients from the departments of Obstetrics and Gynaecology(OBG), Orthopaedics and Surgery.
- Patients with normal haematological parameters and with normal renal and hepatic function tests.
- Subjects able to communicate effectively and provide informed consent.

## EXCLUSION CRITERIA:

- History of allergy or hypersensitivity to Diclofenac or Tramadol.
- Positive test result for hepatitis B surface antigen (HBs Ag), hepatitis C virus antibody (HCV Ab) or HIV-1 antibody or HIV type 2 (HIV-2) antibody (HIV Ab) or VDRL/ syphilis.
- Any history or presence of cancer.
- History of seizures or a recognized risk of seizures.

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The 80 patients who participated in the present study were divided into two groups (40 patients in each group) after systematic randomization. Randomization was done by computer generated random numbers. All patients were visited a day prior to surgery. The general physical as well as systemic examination was carried out. As per the surgeon's advice, routine investigations like complete blood picture, bleeding time, clotting time, complete urine examination, blood sugar, chest x-ray, ECG were carried out along with blood urea and serum creatinine. A linear Numeric Rating Scale (NRS) with scores ranging from 0-10 (where 0 stands for no pain and 10 for worst possible pain) was explained to each patient and consent to participate in the study was obtained (Study Proforma attached as annexure). The patients were then randomly allocated to one of the two groups. Patients were assessed for pain score only once in a day. They were asked to report the average pain intensity over the past 24 hours. Pain was assessed from the time of shifting of the patient to post-operative ward till discharge of the patient from the hospital or number of days the study drugs was given, whichever is earlier. Tramadol was compared with Diclofenac which was more commonly prescribed as standard medication for post-operative pain in our hospital. Hence, Diclofenac was considered as a comparator/ reference drug in our study.

**EFFICACY ASSESSMENT:** Pain intensity was assessed using the NUMERIC RATING SCALE (NRS) FOR PAIN<sup>[14]</sup> The NRS for pain is a unidimensional measure of pain intensity in adults.<sup>[15,16]</sup>

In addition to reduction in pain scores, another parameter for efficacy assessment that was considered was number of subjects in both the groups requiring rescue analgesia. Patients, who complained of pain in spite of giving the study drugs, were given other analgesics as per the surgeon's advice.

**TOLERABILITY/SAFETY ASSESSMENT:** Safety and tolerability were assessed on the basis of the adverse events reported, or changes in vital signs, and physical examination findings recorded before and after the end of treatment. Renal function tests were done at the end of the treatment, only if advised by the surgeon who has done the operation. All reported adverse drug reactions were assessed for causality and severity using Naranjo's causality scale and Hartwig and Siegel severity assessment scale respectively and compared between the groups.

**STATISTICAL ANALYSIS:** Data were entered in Microsoft excel version 2007 and exported to STATA version 10 for analysis. Interval data have been expressed as Mean  $\pm$  SE and categorical data in percentage. P value < 0.05 was considered statistically significant. Comparison for significance in difference of in mean pain scores between the two drug groups was done using unpaired t-test. Comparison of proportions for significance in difference was done by using and Chi-square test.

**RESULTS:** There were no significant differences between the subjects in the Tramadol group and Diclofenac group with regard to demographic variables. The characteristics of study participants are presented in TABLE 1.

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Parameters	Diclofenac group (n=40)	Tramadol group (n=40)	P value	Significance of P value
Age (years) Mean ± SE,	39.900 ± 2.317	41.725 ± 2.227	0.281	Not significant
Males (%)	29 (72.5)	29 (72.5)	1.000	Not significant
Females (%)	11(27.5)	11(27.5)	1.000	Not significant

Table 1: Demographic data of 80 patients who participated in the study

Parameter	Diclofenac group	Tramadol group	Ψ P value	Significance of P value
Pain score post-operative day 0	9.250±0.133	8.975±0.145	0.16	Not significant
Pain score post-operative day 1	7.150±0.222	6.667±0.297	0.19	Not significant
Pain score post-operative day 2	5.722±0.260	5.531±0.314	0.63	Not significant
Pain score post-operative day 3	4.929±0.230	4.800±0.265	0.71	Not significant
Pain score post-operative day 4	4.389±0.231	4.563±0.302	0.64	Not significant
Pain score post-operative day 5	3.615±0.241	3.800±0.327	0.64	Not significant
Pain score post-operative day 6	3.000±0.309	3.000±0.258	1.00	Not significant
Pain score post-operative day 7	2.500±0.500	3.000±0.632	0.66	Not significant

Table 2: Pain score on various post-operative days

Data are in Mean ± SE, Ψ Unpaired t-test.

Further, comparing the post-operative pain score on each post-operative day with pain on post-operative day 0 showed a significant decrease till the seventh day both in the Tramadol group and the Diclofenac group ( $p < 0.001$ ). 5 patients (12.5%) from Diclofenac group and 3 patients (7.5%) from Tramadol group were given rescue analgesic due to insufficient control of pain. Statistically this was not significant ( $p = 0.31$ ).

**TOLERABILITY:** In Diclofenac group, only one patient experienced adverse effect of epigastric pain, whereas in Tramadol group, two patients complained of vomiting and one patient complained of vomiting associated with headache. Causality assessment was done using Naranjo's scale and severity assessment was done using Hartwig and Siegel scale.<sup>[17]</sup> All the

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adverse events were found to fit in the category of "Possible" as per Naranjo's scale. All the adverse events were of "Mild" in severity as assessed from the Hartwig and Siegel scale.

**DISCUSSION:** The mean pain score at baseline was comparable in both the drug groups. The pain score decreased significantly in both the study groups over the post-operative period up to 7<sup>th</sup> post-operative day. However, there was no difference in terms of efficacy of Tramadol and Diclofenac in the treatment of postoperative pain. The need for rescue analgesia and incidence of adverse events reported by the patients were also statistically insignificant. Similar findings were reported by Courtney, et al [2001].<sup>[18]</sup> They compared analgesic efficacy of oral Diclofenac and oral Tramadol for post tonsillectomy pain management and found that both the drugs can deliver same analgesic efficacy. Similar findings were reported by Courtney, et al [2001]. They compared analgesic efficacy of oral Diclofenac and oral Tramadol for post tonsillectomy pain management and found that both the drugs can deliver same analgesic efficacy. They further suggested that oral tramadol can deliver the same analgesic efficacy as oral diclofenac for posttonsillectomy pain relief, which might be beneficial for avoiding the adverse effects of non-steroidal anti-inflammatory drug therapy. Beaulieu, et al [2008]<sup>[19]</sup> performed a randomized controlled trial of controlled-release (CR) tramadol vs. sustained-release (SR) diclofenac in relieving chronic pain due to osteoarthritis of hips and knees. They concluded that CR tramadol is as effective as SR diclofenac in the treatment of pain due to knee or hip osteoarthritis. Shaden Salameh, et al [2011]<sup>[20]</sup> compared single shot of intramuscular diclofenac vs. single shot of intramuscular tramadol in treatment of renal colic. They found that diclofenac was more effective than tramadol in reducing the severity of pain at 30 minutes. Also the need for rescue analgesia was more in tramadol group. No significant side effects were noted in either group. Similarly Pagliara, et al [1997]<sup>[21]</sup> conducted multicentric randomized controlled trial of diclofenac vs. tramadol in patients with moderate to strong musculoskeletal pain caused by trauma. They found that analgesic activity of tramadol was higher than that of diclofenac. Renal colic and osteoarthritis were not included in our study hence the results of Salameh et.al and Pagliara et al. are at variance from the findings of our study. Another study was carried out by Manoharan et al<sup>[22]</sup> to compare tramadol and diclofenac suppository for their analgesic efficacy and side effects after LSCS. Here they found rectal tramadol to be more superior compared to rectal diclofenac in terms of efficacy and side effects. In our study also, LSCS condition was included, but results might be different because of difference in route of administration of the drug. Also the method of assessing pain score was different. Here, duration of analgesia after rectal diclofenac or tramadol was compared. In our study, efficacy was measured in terms of reduction in pain score.

As far as tolerability is concerned, several studies mentioned that diclofenac and Tramadol are equally well tolerated when administered for postoperative pain relief.<sup>[18,21]</sup> Evidence suggests that both Diclofenac and Tramadol are equally effective and well tolerated for relieving postoperative pain. These findings need to be confirmed in large scale studies and explore the possibility of using Tramadol and Diclofenac as alternative to one another depending on patient's medical condition. This may facilitate better options to choose analgesic medication in the post-operative period in case of patient medical condition being unsuitable for the use of any specific type of analgesic.

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**CONCLUSION:** Both, Diclofenac and Tramadol were found to be equally effective in decreasing the post-operative pain. On comparison, the incidence of adverse events and the need for rescue analgesia in both the groups was found to be statistically insignificant. Both the drugs were well tolerated by the patients. Hence, Tramadol can be an alternative when contraindications preclude the use of Diclofenac and vice-versa.

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