

# Triple Blind Randomised Control Trial of Two Different Treatment Analgesic Regimens Following Open Reduction and Internal Fixation of Mandibular Fractures

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## ABSTRACT

**Aim:** This study aims to compare two different analgesic drug regimens following open reduction and internal fixation of mandibular fractures and to study the efficacy of the two drug regimens in post operative pain control.

**Material and method:** This study was performed on 50 patients who were treated for mandibular fractures by open reduction and internal fixation under general anaesthesia at the Department of Oral and Maxillofacial surgery in SDM Craniofacial surgery and Research centre, Dharwad. The period of study was from November 2015 to July 2017. Subjects were divided into two groups i.e. Group 1 (received Piroxicam) and Group 2 (received Tramadol+Acetaminophen). The anaesthetist was in-charge and aware of the drugs prescribed to the patient post-operatively. The Operating surgeon, the observer and statistician were blinded.

**Results:** On the 1st and 2nd post operative days, reduction in pain was assessed by means of "Faces pain scale" a form of visual analog scale. When comparing pain reduction in both the groups, it was found to be more significant in patients belonging to Group 2 as compared to Group 1, i.e. a combination of Tramadol and Acetaminophen was found to be more efficacious.

**Keywords:** Mandibular fractures, Postoperative pain, Analgesics

## INTRODUCTION

Pain in trauma has a dual role. On one hand, pain is a good indicator to establish the severity and type of injury whereas, on the other hand, pain can bring about severe complications and it may lead to further worsening of the patient. Therefore, knowing how to control pain in patients is an important part of systemic approach to trauma.<sup>1</sup>

Pain after any surgical procedure is anticipated and it is controlled by administration of analgesics in most of the cases. Causes of postoperative pain comprise surgical trauma, application of thermal and chemical stimuli to the wound, and often traction and manipulation of soft tissues.<sup>1</sup>

Acute pain occurs as a consequence of tissue damage either accidentally due to an injury or as an outcome of surgery.<sup>2</sup> Greater than 80% of patients who go through surgical procedures experience acute postoperative pain and approximately 75% of the same describe the pain as mild, moderate, severe, or extreme<sup>3</sup>.

Postoperative pain is an essential outcome in assessing overall treatment success and patient contentment. High levels of acute postoperative pain have been reported to be associated with slower recovery of function, increased hospital

stay, and perioperative complications<sup>4</sup>. The management of postoperative pain and inflammation is a crucial component of patient care and are important for cost-effective use of healthcare resources.

This triple blind randomized control study highlights the importance of management of postoperative pain using two analgesics belonging to different groups after open reduction and internal fixation in patients with mandibular fractures.

## MATERIALS AND METHODS

This study was performed on 50 patients who were admitted to the Department of Oral and Maxillofacial surgery in SDM Craniofacial surgery and Research centre, Dharwad for treatment of mandibular fractures by open reduction and internal fixation under general anaesthesia. The period of study was from November 2015 to July 2017, on patients who were diagnosed with unilateral mandibular fractures and treated with ORIF using intraoral approach.

**Ethical approval:** Clearance obtained from Institutional Review Board.

**IRB Number** – 2015/P/OS/37

**CTRI TRAIL REGISTRATION NO.-** CTRI/2018/02/012260

### Sample Size Estimation

**Analysis:** A priori: Compute required sample size

**Input:** Tail(s) = Two  
Effect size d = 0.80 [Ankesh Dilip Jain et al, 2017]

$\alpha$  err prob = 0.05  
Power (1- $\beta$  err prob) = 0.80  
Allocation ratio N2/N1 = 1

**Output:** Noncentrality parameter  $\delta$  = 2.8844410  
Critical t = 2.0085591  
Df = 48  
Sample size group 1 = 25  
Sample size group 2 = 25  
Total sample size = 50  
Actual power = 0.8074866

The sample size has been estimated using the software GPower v. 3.1.9.4

Considering the effect size to be measured (d) at 80% for Two tailed hypothesis [Based on the results of previous study done by Ankesh Dilip Jain et al, 2017], power of the study at 80% and the margin of the error at 5%, the total sample size needed was 50. So, each study group was comprised of 25 samples. [25 samples x 2 = 50 samples]

**Inclusion criteria:** ASA I, unilateral mandibular fractures not associated with any acute infection treated by intraoral approach.

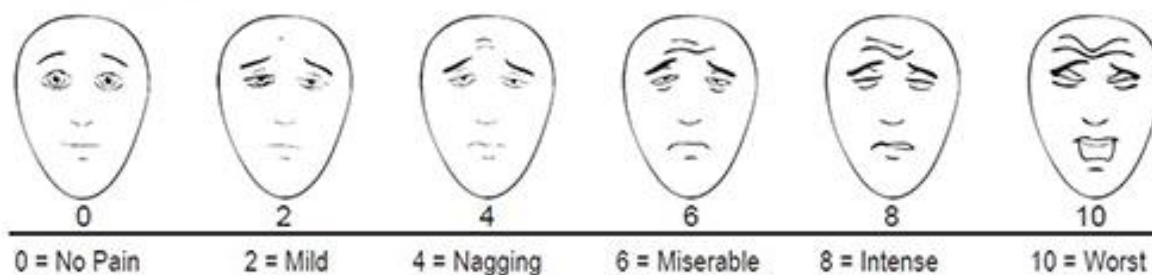
**Exclusion criteria:** Patient with any systemic illness like cardiologic and neurologic disorders, patient with pathologic fractures, osteoradionecrosis, strictly non-operable cases and other facial fractures, paediatric mandibular fractures.

Subjects were divided into two groups i.e. Group 1 (received Piroxicam: 20mg) and Group 2: received Tramadol+ Acetaminophen (Tramadol 37.5mg + Acetaminophen 325mg). Both the drugs were administered orally.

The study was Triple-blinded as in-

- The Participant - The Patient
- The Investigator – Postgraduate trainee
- The Administerer – The Nursing staff under the supervision of a constant Anaesthetist
- The Operating surgeon was blinded as in, he was the person who only performed the ORIF procedure, but not aware of the drugs prescribed.

A constant anaesthetist was in-charge of selecting the drug by randomisation that is, by means of a 'Lottery dip method' to eliminate any bias during administration of the analgesics prescribed to the patient post-operatively. On the 1st and 2nd post operative days, reduction in pain was assessed by means of "FACES PAIN SCALE".



### FACES PAIN SCALE- REVISED

**Statistical analysis:** Data was collected and analysed using SPSS version 24.

### RESULTS

Table 1 shows the age and gender incidence of 50 patients in both Group 1 & Group 2. After Mann Whitney test, the mean age group was found to range between 20-55 years. After Chi square test, it was seen that male population was on the higher side in both the groups.

Table 2 compares the mean VAS scores between the 2 study groups at different time intervals using Mann Whitney test. Significant pain reduction was noted in patients belonging to Group 2 on both POD1 & POD2. Patients belonging to Group 2 showed significant pain reduction

on Day 1 with a mean of 2.88 and also on Day 2 with a mean of 0.16, ( p value= < 0.001).

The pain reduction in each group has been explained separately in Table 3(Piroxicam group) and Table 4,4a (Tramadol+ Acetaminophen group) by comparison of mean VAS scores at different time intervals in both the groups separately using Friedman’s test and Multiple comparison of mean difference in vas scores between time intervals in both the groups, respectively.

The statistical analysis concludes that there is significant pain reduction in both the groups, but the patients belonging to group 2 had a significant pain relief on POD 1 & POD 2 as compared to the patients in group 1.

**Table 1: Age & Gender distribution among the 2 study groups**

Variables	Category	Piroxicam		Tramazac		P-Value
		Mean	SD	Mean	SD	
Age	Mean & SD	32.4	9.1	31.2	8.8	0.65 <sup>a</sup>
	Range	21 - 52		20 - 55		
		n	%	n	%	
Gender	Males	20	80%	22	88%	0.44 <sup>b</sup>
	Females	5	20%	3	12%	

a. Mann Whitney Test, b. Chi Square Test

**Table 2: Comparison of mean VAS scores between 2 groups at different time intervals using Mann Whitney Test**

Time	Groups	N	Mean	SD	Mean Diff	P-Value
Baseline	Piroxicam	25	5.44	0.92	-0.16	0.51
	Tramazac	25	5.60	0.82		
POD1	Piroxicam	25	4.16	1.14	1.28	0.001*
	Tramazac	25	2.88	1.30		
POD2	Piroxicam	25	1.92	0.91	1.76	<0.001*
	Tramazac	25	0.16	0.55		

\* - Statistically Significant, POD1 - Post Operative Day 1; POD2 - Post Operative Day 2

**Table 3: Comparison of mean VAS scores between different time intervals in Piroxicam Group using Friedman's Test**

Time	N	Mean	SD	Min	Max	P-Value
Baseline	25	5.44	0.92	4	6	<0.001*
POD1	25	4.16	1.14	2	6	
POD2	25	1.92	0.91	0	4	

\* - Statistically Significant, POD1 - Post Operative Day 1; POD2 - Post Operative Day 2

**Table 3a: Multiple comparison of mean difference in VAS scores b/w time intervals in Piroxicam group using Wilcoxon Signed Rank Post hoc Analysis**

(I) Time	(J) Time	Mean Diff. (I-J)	95% CI for the Diff.		P-Value
			Lower	Bound	
Baseline	POD1	1.28	0.78	1.78	<0.001*
	POD2	3.52	2.98	4.06	<0.001*
POD1	POD2	2.24	1.79	2.69	<0.001*

\* - Statistically Significant

**Table 4: Comparison of mean VAS scores between different time intervals in Tramadol+ Acetaminophen Group using Friedman's Test**

Time	N	Mean	SD	Min	Max	P-Value
Baseline	25	5.60	0.82	4	6	<0.001*
POD1	25	2.88	1.30	0	6	
POD2	25	0.16	0.55	0	2	

\* - Statistically Significant

**Table 4a: Multiple comparison of mean difference in VAS scores b/w time intervals in Tramadol + Acetaminophen group using Wilcoxon Signed Rank Post hoc Analysis**

(I) Time	(J) Time	Mean Diff. (I-J)	95% CI for the Diff.		P-Value
			Lower	Bound	
Baseline	POD1	2.72	2.14	3.31	<0.001*
	POD2	5.44	4.97	5.91	<0.001*
POD1	POD2	2.72	2.14	3.31	<0.001*

\* - Statistically Significant

## DISCUSSION

The facial region is one of the most commonly injured areas of the body, accounting for 23-97% of all fractures. Mandible is the only mobile bone of the facial skeleton and its fracture has seen a significant increase in the recent years<sup>5</sup>. One of the main post-operative issues in patients after ORIF of mandibular fracture is pain. The various factors which contribute to this are intraoperative multiple local anaesthetic injections, injury to the soft tissues due to interdental wirings, improper reduction and fixation of fracture fragments, postoperative haematoma formation, trismus, malocclusion, infection, dehiscence and conditions like mal-union, non-union or delayed union<sup>6-8</sup>.

Effective postoperative pain control is an essential component of care in a surgical patient. This study assesses postoperative pain control using two analgesic drug regimens in patients treated by ORIF for mandibular fractures and also evaluates the efficacy of these two different analgesics. All the patients received the same amount of sedation (Midazolam and Glycopyrrolate) and anaesthesia (Propofol+ Sevoflurane + Vecuronium). The duration of surgery in all cases was standardised, was less than 3 hours. Patients were kept in the post operative recovery room on the day of

surgery and later shifted to the ward and discharged on second post operative day.

Tramadol is a centrally acting analgesic with a multimode action, used for the management of moderately severe acute and chronic pain. It acts on serotonergic and noradrenergic nociception, while its metabolite O-desmethyltramadol acts on the  $\mu$ -opioid receptor. Its analgesic potency is claimed to be about one tenth that of morphine therefore, is used to treat both acute and chronic pain of moderate to (moderately) severe intensity. Tramadol monotherapy does not usually provide adequate analgesia, its main adverse reactions being nausea, dizziness, and vomiting, particularly at the start of the therapy<sup>9</sup>.

Although non-steroidal anti-inflammatory drugs (NSAIDs) are very effective, their use is associated with a broad spectrum of adverse reactions in the liver, kidney, cardiovascular system, skin and gut. Gastrointestinal (GI) side effects are the most common<sup>10</sup>.

From a global Gastro-intestinal safety point of view, piroxicam was better tolerated than other NSAIDs. A meta-analysis of RCTs supports a similar to more favourable efficacy/safety profile of piroxicam as compared to other NSAIDs<sup>11</sup>. Acetaminophen is one of the traditional,

better tolerated, and active ingredients for short- and fast acting analgesics that act through different pathways from opioids. It is considered that the analgesic effects of Tramadol hydrochloride and Acetaminophen are complementary and that the combination may reduce the risk of dose-dependent adverse drug reactions (ADRs) related to each ingredient without reducing the overall efficacy profile of the single agents. A randomized controlled clinical trial showed clear efficacy and a reliable safety profile of Tramadol and Acetaminophen combination<sup>12</sup>.

In the present study, there is preponderance of males in both the groups, which is quite unique like some of the previous studies by Natu et al<sup>5</sup> in 2012 which showed a ratio of 4.5:1 whereas, Malik et al<sup>6</sup> in 2013 showed a ratio of 2.9:1, another study by Jain et al<sup>1</sup> in 2016 showed a ratio of 5.6:1. Also, Barde et al<sup>7</sup> in 2017 showed a ratio of 3.7:1. A higher overall frequency of mandibular fractures in this study was observed more in men as compared to women which may be explained by the fact that men are more exposed to certain risk situations, such as, more male drivers on the roads, more likely to practice contact sports, prevalence of consumption of alcohol especially in a social setup like pub and bars, which very often may result in brawls and interpersonal violence<sup>13</sup>.

The most common age group of occurrence was found to be around 20-55 years among all the patients in our study. Similar studies done by Natu et al<sup>5</sup> in 2012 and Barde et al<sup>7</sup> in 2017 showed 21- 30 years as the most common age of occurrence, whereas Malik et al<sup>6</sup> in 2013 showed 18 -34 years as the mean age of occurrence.

Valid and dependable assessment of pain is essential intended for both clinical trials and effective pain management. The nature of pain makes objective measurement impossible. Assessment of pain can be an easy and clear-cut task when dealing with acute pain and as a symptom of trauma or

disease. Assessment of location and intensity of pain often suffices in clinical practice. However, other vital aspects of acute pain, in addition to pain intensity at rest, need to be clear and measured when clinical trials of acute pain treatment are considered<sup>14</sup>.

The visual analogue scale for pain has been validated, premeditated extensively, and verified to be a precise and reliable measure of postoperative pain. The application of this scale in trauma and surgical studies from other disciplines attests to its strength.<sup>15</sup>

In our study, the 'FACES PAIN SCALE' a part of the VAS has been used for the assessment of post-operative pain. Cartoon-type faces pain scale, widely used in paediatric patients, has been suggested as the possible options for measuring pain intensity in adults. Validity of faces pain scale is supported by research reporting that people from various cultures identify facial expressions<sup>16</sup>.

On comparing the post operative pain reduction, among the study groups (Group 1 and Group 2) with respect to pain at POD 1 and POD 2, significant pain reduction was seen in Group 2 patients who got a combination of Tramadol+ Acetaminophen as the postoperative analgesic on both the days.

## CONCLUSION

Hence, we come to a conclusion that even though both the drugs were observed to be equally efficient in controlling the post-operative pain, combination of Tramadol+ Acetaminophen was found to be more efficacious than Piroxicam.

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