



## A Comparison of Pre-emptive Analgesic Efficacy of Aceclofenac and Piroxicam for Post-Operative Pain Management after third Molar Surgery: A Prospective, Randomized, Double-blind Study

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### ABSTRACT

The study aimed to compare the analgesic efficacy of Aceclofenac 100 mg and Piroxicam 20 mg as a pre-emptive analgesic for preventing post-operative pain after third molar surgery. Fifty patients with impacted mandibular third molars who required surgical removal were included in the study. These patients were divided into two groups randomly. One group consisted of patients receiving Aceclofenac 100 mg as a pre-emptive analgesic, and the other group consisted of patients receiving Piroxicam 20 mg as a pre-emptive analgesic 1 hour before the procedure. The study findings show both the drugs were equally effective in managing post-operative pain following third molar surgery. On statistical analysis, there was no significant difference in pain experience among both groups A and B in post-operative period who underwent surgery. However, the study observes a highly significant difference in both the groups in terms of pain intensity scores at different times. Results show that there was a significant difference before, 3<sup>rd</sup> day and 5<sup>th</sup> day; Further study shows that the effectiveness of the drug was not confirmed in 24 hours to 3 days. It was observed both the groups shows a significant difference in trismus on the 5<sup>th</sup> and 3<sup>rd</sup> day. This comparative research of pain intensity shows after pre-emptive analgesia with Aceclofenac and Piroxicam in impaction of third molars, a pronounced pre-emptive effect in the group treated with Piroxicam 20mg was seen. Still, there was no statistically significant difference noted in VAS before and 5<sup>th</sup> day of both groups.

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### INTRODUCTION

Pain is the most common symptom bringing patients to the dental office (Schuller *et al.*, 2003). Despite its prevalence, it's very challenging to manage pain in day to day practice. Often the dental treatment alone can provide significant relief from pain, such as immediate reduction of pain following an incision and drainage of an abscess or the relief that can be accomplished by the removal of an affected tooth. So the next step will be towards managing the post-operative pain.

Surgical removal of the third molar is one of the standard procedures done by oral and maxillofacial surgeons. This procedure involves incision and inflammatory injuries that result in pain, swelling,

trismus in the post-operative period (Savin and Ogden, 1997). The first 12 hours following removal of the tooth is considered as the most unpleasant experience. The use of pre-emptive analgesia can reduce this, when started before the beginning of the surgery (Kissin, 2005). It has a significant impact on the patient's pain perception (Katz, 2000; Grape and Tramèr, 2007).

During the perioperative period, there is a flow of nociceptive signals from the operating site. It has a dual-phase character, the initial phase or the first phase results from injuries produced by the surgical procedure, the second phase of nociceptive stimulation is due to the inflammatory responses associated with the tissue injury.

The peripheral tissue injury provokes two kinds of modification in the responsiveness of the nervous system: Peripheral sensitisation, a reduction in the threshold of nociceptor afferent peripheral terminals and Central sensitisation, an active dependant increase in the excitability of spinal neurons. Together these changes contribute to post-injury pain hypersensitivity state found postoperatively. This manifests in an increase in response to noxious stimuli and a decrease in pain threshold at the site of the surrounding uninjured site. The sensory signals generated by the tissue damage during the surgery can produce increased excitability in the central nervous system. The role of Preemptive analgesia is that it blocks the initiation of central sensitisation evoked by incisional and inflammatory injuries occurring during surgery and in the initial post-operative period (González-Darder *et al.*, 1986; McQuay, 1992).

It leads to an effective reduction in the development of Peripheral and Central sensitisation – the reason for primary and secondary hyperalgesia (Kissin, 2000; Kelly *et al.*, 2001). Primary hyperalgesia refers to pain sensitivity at the surgical site, whereas secondary hyperalgesia refers to pain sensitivity in the surrounding tissues.

Thus successful post-operative pain control can be achieved by blocking the beginning of neural cascade which results in increased sensitivity produced by noxious stimuli (Kelly *et al.*, 2001; Chrubasik *et al.*, 2012).

Efficient analgesic agent before the onset of the unpleasant stimulus to prevent central sensitisation and preventing painless sensation from being seen as pain (allodynia) (Kelly *et al.*, 2001; Chrubasik *et al.*, 2012).

The term Pre-emptive analgesia was first introduced by Crile in 1913, which was further developed by

Wall and Woolf. They suggested that simply changing the timing of treatment can have better effects on post-operative pain.

Various Pre-emptive agents including NSAIDs can be used for effective pain management (Ong *et al.*, 2004, 2005). The primary mechanism of action of NSAIDs is inhibition on cyclooxygenase activity; as a result, there is inhibition of prostaglandins which has a pro-inflammatory effect.

We have compared Aceclofenac 100 mg and Piroxicam 20 mg given orally one hour before the surgery among patients undergoing surgical removal of the impacted third molar.

With the help of our prospective randomised, double-blind study, we have compared the efficacy of Aceclofenac and Piroxicam as a pre-emptive analgesic for preventing post-operative pain after third molar surgery. To our knowledge, the comparison perspective of the two compounds like Aceclofenac and Piroxicam was not used in many studies. Hence, the present study attempts to fill the gap by comparing the analgesic effect of two compounds as pre-emptive analgesia for preventing post-operative pain after third molar surgery.

## MATERIALS AND METHODS

The study participants were recruited from the pool of patients in the Department of Oral and Maxillo-facial Surgery at Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, India. Sample size estimation was done, and the minimum sample size of both groups was calculated and arrived at 25 per group. The study was carried for three months.

### Ethical Clearance

Approval was obtained from the Institutional Review Board of Saveetha Institute of Medical and Technical Science, India.

### Study Groups

The study was conducted among 50 subjects, who were randomly grouped into two groups- Aceclofenac group (A) and Piroxicam group (B) as shown in Figure 2.

The Aceclofenac group (A) comprised of 25 individuals, who were given Aceclofenac 100mg preoperatively 1 hour before the procedure.

The Piroxicam group (B) comprised of 25 individuals, who were given Piroxicam 20 mg preoperatively 1 hour before the procedure.

All the subjects were explained about the study in detail and possible complications, and, the patients

had given informed consent.

### Inclusion criteria

1. Healthy subjects without any systemic disease were included in this study.
2. Subjects not under any analgesics or other medications 24 hours before surgery.
3. Subjects not allergic to any medicament.
4. Patients who can report for post-operative review.

### Exclusion criteria

1. Subjects with systemic disease, pregnancy or lactation were excluded.
2. Subjects reported with pericoronitis or pericoronal abscess were excluded from the study.
3. Subjects who had taken any analgesics 24 hours before surgery were excluded.
4. Subjects allergic to any medicament were excluded from the study.

The patient, the operating surgeon, were all blinded during the study process; one principal investigator evaluated all the patients. Each patient was Assessed for pain before the procedure, followed by 24 hours post operatively and on the 3rd and 5th day. Patient's mouth opening was assessed before the procedure, followed by 3<sup>rd</sup> and 5<sup>th</sup> day.

### Criteria for measurement

Pain measurement was done using the Visual Analogue Scale (VAS) on a scale of 0 to 10, as shown in Figure 1.

Trismus recorded as,

Absence of trismus - 0

Mouth opening >76% - 1

Mouth opening >51% - 2

Mouth opening <50% but > 26% - 3

Mouth opening <25% - 4.

### Statistical analysis

The collected data from the patients was analysed by using IBM SPSS statistics software Version 23.0. The obtained data from the VAS was measured by mean & S.D was used, to find the significant difference between the bivariate samples in Paired groups, the Wilcoxon signed-rank test was used. Further to analyse the independent groups of samples, the Mann-Whitney U test was used. For the multivariate analysis in repeated measures, the Friedman test followed by the Wilcoxon signed-rank test was used. For all the statistical analysis, the probability value of .05 is considered as significant.

## RESULTS AND DISCUSSION

VAS evaluated the experience of pain. The mean score VAS before in group A was 1.16, whereas group B it was 1.00 that was not statistically significant. The results are described in Table 1. Likewise, after 24 hours, 3<sup>rd</sup> day and 5<sup>th</sup> day, trismus 3<sup>rd</sup> and 5<sup>th</sup> day showed there was no significant difference in both groups.

The VAS score change at the time of post-operative period was examined by the Wilcoxon Signed Rank Test (two-time points) and Friedman Test (several time points).

The results of the Friedman test in Table 2 represent the highly significant differences of both groups in terms of pain intensity scores at different time points.

The VAS scale was used to measure the pain of patients before and after 24 hours, 3<sup>rd</sup> and 5<sup>th</sup> day of group A patients through Wilcoxon Signed Ranks Test. The paired t-test was utilised, and the results as described in Table 3. Results show that there was a significant difference in Pain before 24 hours, and 3rd day; This reveals that the drug was effective during the post operative period. But in comparison with 24 hours and 3<sup>rd</sup> day, there was no significant difference. This shows that the effectiveness of the drug was not confirmed in 24 hours to 3<sup>rd</sup> day.

The paired t-test was used and tested through VAS among group B patients. Results show that there was a significant difference in 24 hours, before and 3rd day, 24 hours and 5th day, 3rd and 5th day. This reveals that the drug was effective in after post-operative period. But in comparison with 24 hours and 3rd day and before and 5<sup>th</sup> day, there was no significant difference in group B patients, as shown in Table 4.

Through the Wilcoxon Signed Ranks Test, it was observed that both groups shows a significant difference In Trismus in 3<sup>rd</sup> and 5<sup>th</sup> day, as shown in Table 5.

The significant concern for surgeon and anesthesiologist is the efficient post-operative pain management (Kara *et al.*, 2010). Around 80% of patients who underwent surgical procedures experience mild to severe pain during the post-operative period (Hofele *et al.*, 2006).

This study investigated the clinical efficacy of managing post-operative pain using the Aceclofenac and Piroxicam after third molar surgery. The main reason for doing this present study as there are a lot of researchers who have carried out the studies in light of pre and post-treatment, orally or intra-

**Table 1: Comparison of two groups with regards to pain experience at different time points by Mann-WhitneyTest**

Time points	Groups	N	Mean	Std. Deviation	Std. Error Mean	Z value	p-value
VAS Before	A	25	1.16	.800	.160	.791	.429
	B	25	1.00	.707	.141		
VAS 24 hours	A	25	3.56	.507	.101	0.000	1.000
	B	25	3.56	.507	.101		
VAS 3rd day	A	25	3.40	.500	.100	0.000	1.000
	B	25	3.40	.500	.100		
VAS 5th day	A	25	2.04	.889	.178	4.707	.000
	B	25	.68	.627	.125		
Trismus 3rd day	A	25	2.36	.638	.128	1.151	.250
	B	25	2.24	.663	.133		
Trismus 5th day	A	25	1.20	.408	.082	.190	.849
	B	25	1.16	.554	.111		

**Table 2: Friedman test**

	Groups	Mean Rank		
VAS Before	A	1.26		
	B	1.66		
VAS 24 hours	A	3.58		
	B	3.58		
VAS 3rd day	A	3.42		
	B	3.42		
VAS 5th day	A	1.74		
	B	1.34		
<b>Groups</b>	<b>Chi-Square</b>	<b>df</b>		<b>p-value</b>
A	70.364	3		.0005*
B	66.842	3		.0005*

**Table 3: Pain evaluation for VAS before and 24 hours, 3<sup>rd</sup> and 5<sup>th</sup> day for group A patients**

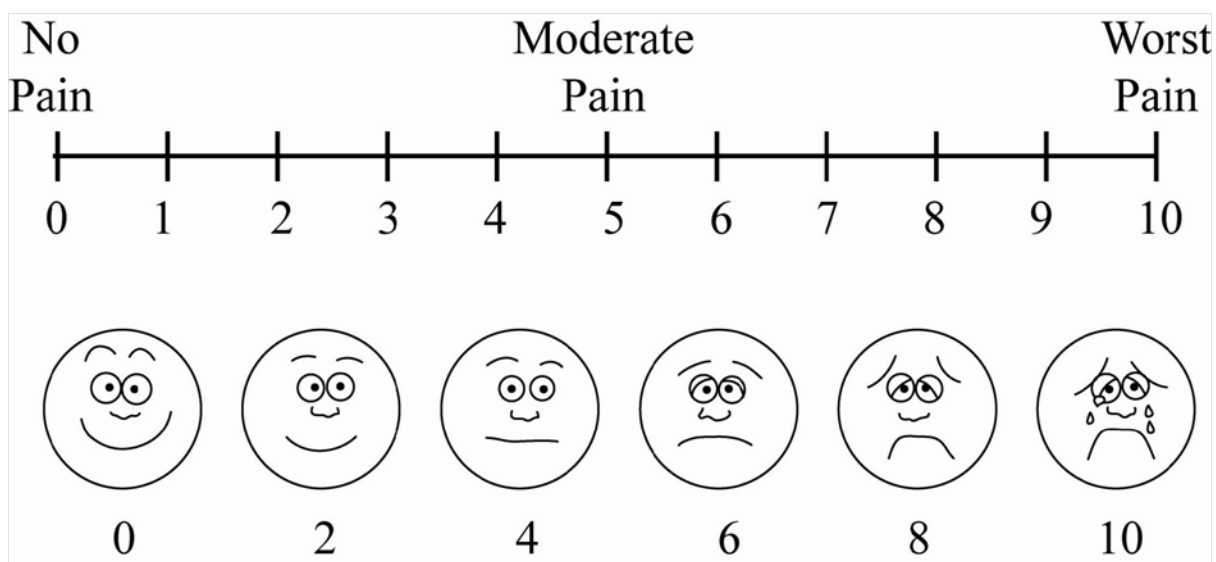
Pain score at different time points of group A	Mean	Std. Deviation	Z value	P value	
Pair 1	VAS Before	1.16	.800	4.425	.0005*
	VAS 24 hours	3.56	.507		
Pair 2	VAS Before	1.16	.800	4.465	.0005*
	VAS 3rd day	3.40	.500		
Pair 3	VAS Before	1.16	.800	2.829	.0005*
	VAS 5 days	2.04	.889		
Pair 4	VAS 24 hours	3.56	.507	1.633	.102
	VAS 3rd day	3.40	.500		
Pair 5	VAS 24 hours	3.56	.507	4.549	.0005*
	VAS 5 days	2.04	.889		
Pair 6	VAS 3rd day	3.40	.500	4.582	.0005*
	VAS 5 days	2.04	.889		

**Table 4: Pain evaluation for VAS before and 24 hours, 3<sup>rd</sup> and 5<sup>th</sup> day for group B Patients**

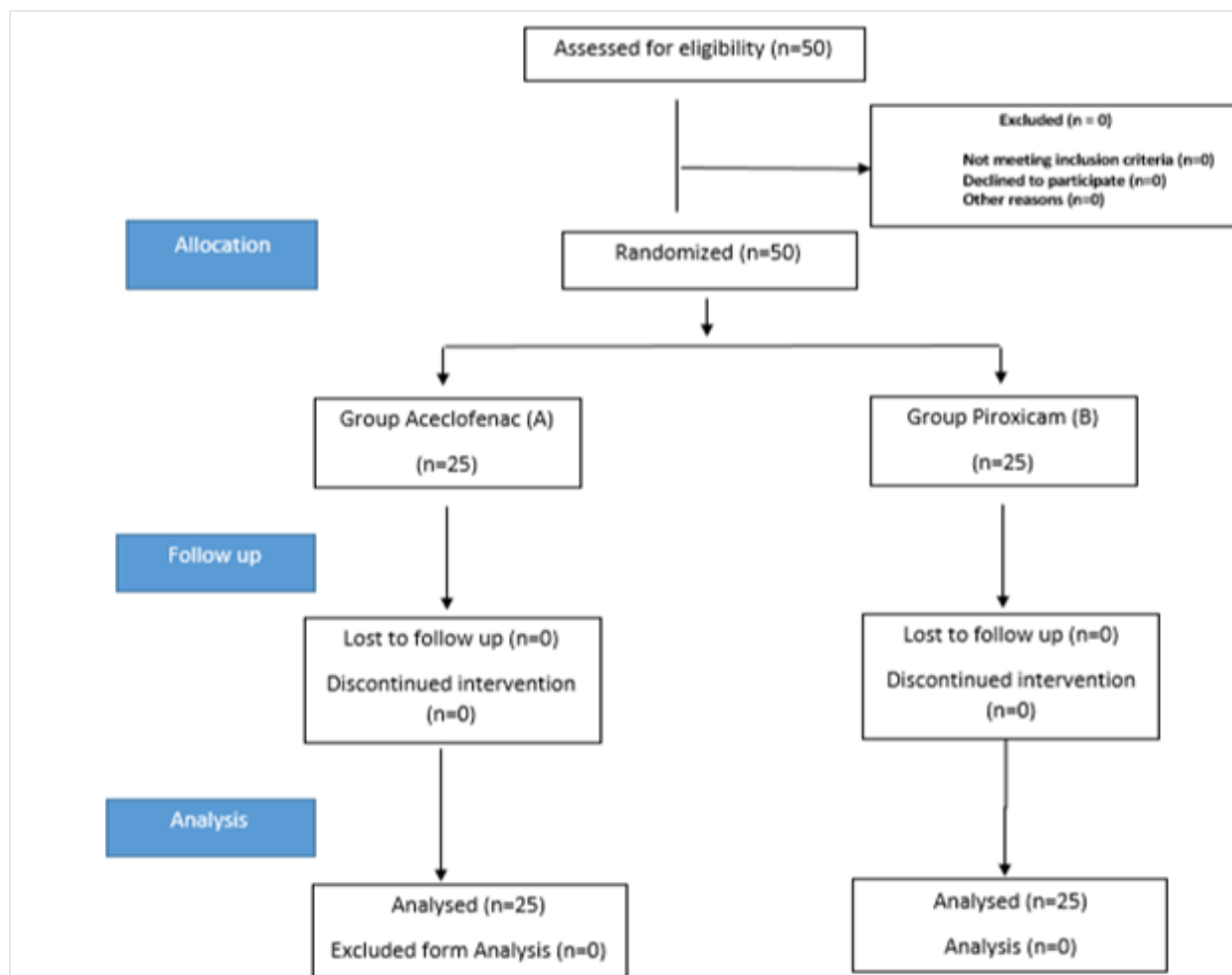
		Mean	Std. Deviation	Z value	P value
Pair 1	VAS Before	1.00	.707	4.483	.0005*
	VAS 24 hours	3.56	.507		
Pair 2	VAS Before	1.00	.707	4.425	.0005*
	VAS 3rd day	3.40	.500		
Pair 3	VAS Before	1.00	.707	1.556	.120
	VAS 5th day	.68	.627		
Pair 4	VAS 24 hours	3.56	.507	1.414	.157
	VAS 3rd day	3.40	.500		
Pair 5	VAS 24 hours	3.56	.507	4.424	.0005*
	VAS 5th day	.68	.627		
Pair 6	VAS 3rd day	3.40	.500	4.465	.0005*
	VAS 5th day	.68	.627		

**Table 5: Evaluation for Trismus 3<sup>rd</sup> and 5<sup>th</sup> day**

		Mean	Std. Deviation	Z	P value
Pair 1	Trismus 3rd day	2.36	.638	4.284	.0005*
Group A	Trismus 5th day	1.20	.408		
Pair 1	Trismus 3rd day	2.24	.663	3.954	.0005*
Group B	Trismus 5th day	1.16	.554		



**Figure 1: Visual Analogue Scale**



**Figure 2: Consort flow chart of patient participation in the study**

venously administered analgesics—however, comparative studies concerning analgesic efficacy for preventing post-operative pain after third molar surgery was limited.

Analgesic treatment is commonly used, and well-accepted procedure for examining anti-inflammatory efficacy (Oncul *et al.*, 2011; Bauer *et al.*, 2013). Aceclofenac and Piroxicam were the commonly prescribed agents for different patients in few European and Asian countries (Lemmel *et al.*, 2002; Kumar *et al.*, 2013). Both compounds are non-steroidal anti-inflammatory drugs (NSAID) which are commonly used for relief of inflammation and pain in ankylosing spondylitis, osteoarthritis and rheumatoid arthritis. However, both the compounds have some side effects, for Aceclofenac has the symptoms of hypotension, fainting, dizziness, occasionally convulsions, respiratory depression and tinnitus. While the side effects of Piroxicam include ringing in ears, headache, skin itching or rash; disorientation, stomach upset etc.

These two compounds act as the non-selective COX inhibitor possessing both antipyretic and analgesic

properties. The biological half-life of Piroxicam is around 50 hours, while for Aceclofenac is 4 hours only.

VAS was used in this study to measure the pain experience of patients who underwent third molar surgery. When patients obtained no medication of analgesics, they reported the pain score of 8 on the VAS scale from 0 to 10, 10 notice the worst pain and 0 represents no pain (Nørholt, 1998).

It is noticed that pain after removal of third molars is of short duration and attains the maximum intensity in the post-operative period (Chitlangia *et al.*, 2013). The experience of pain is useful, especially for examining the single doses of analgesics efficacy. Numerous clinical researches for pre-emptive analgesia value were carried out as per the dosing routes, drug types and administrating times.

The study findings did not receive a significant difference in pain experience among both groups A and B in the post-operative period who underwent surgery via the Mann-Whitney Test. However, the study observes high significant differences in both

groups in terms of pain intensity scores at different time points in the Friedman test. This was in line with the study of Chunduri *et al.* (2013) shows the efficacy of diclofenac and Aceclofenac for the relief of post-operative pain after third molar surgery that shows the epigastric pain and nausea was high in diclofenac group than in Aceclofenac.

Results show that there was a significant difference in before and 24 hours, before and 3<sup>rd</sup> day; before and 5<sup>th</sup> days; 24 hours and 5<sup>th</sup> day and 3<sup>rd</sup> and 5<sup>th</sup> day. Further study shows that the effectiveness of the drug was not shown in 24 hours to 3<sup>rd</sup> day. Besides, the study results indicate that there was a significant difference in before and 24 hours, before and 3<sup>rd</sup> day and 24 hours and 5<sup>th</sup> day, 3<sup>rd</sup> and 5<sup>th</sup> day. It was observed that both the groups shows a significant difference in Trismus 5<sup>th</sup> day and Trismus 3<sup>rd</sup> day. Both the groups experienced pain in their post-operative period operative pain.

Within the limitations of this study, it can be concluded that pre-emptive analgesia with Piroxicam and acetaminophen equally play an essential role in the reduction of post-operative pain following removal of the mandibular third molar.

We recommend that the operating surgeon should have a thorough knowledge of the different drugs used as pre-emptive analgesia in mandibular third molar surgery. Further studies with larger sample size are required to prove this significance. The third molar removal is the most common oral surgical procedure that gives moderate to severe post-operative pain (Schlieve *et al.*, 2013).

## CONCLUSIONS

Better pain management enhances the quality of life after any surgical procedure. However, pre-emptive analgesia may be useful in decreasing pain intensity. This comparative research of pain intensity shows that after pre-emptive analgesia with Aceclofenac and Piroxicam in impaction of third molars demonstrated a pronounced pre-emptive effect was seen in the group that was treated with Piroxicam 20mg. Thus, there was no significant difference noted in the VAS score before the procedure and on the 5<sup>th</sup> day of both the groups.

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## Conflicts of Interest

The authors declare that they have no conflict of interest for this study.

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