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Pre-emptive analgesia before third molar extraction- A prospective study to compare Tramadol and Diclofenac

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ABSTRACT
AIMS AND OBJECTIVES: *To compare the preemptive analgesic effect of Diclofenac Sodium and Tramadol following surgical removal of mandibular third- molars.*
MATERIALS AND METHODS: *The study included patients who were reporting to Department of Oral and Maxillofacial Surgery, SDM dental college for surgical removal of impacted mandibular third-molars. A double-blind clinical study was conducted among 50 patients. Patients were divided into 2 groups. Group I and group II included 25 patients each who were given oral diclofenac sodium 50 mg and tramadol 50mg tablets respectively, 1 hour before the procedure. All the operative procedures were done by a single operator. The 2 groups were compared and data was analysed statistically.*
RESULTS: *In diclofenac group the mean pain score at 2hr was 1.52, which increased at 4 hr and 6 hr with mean score of 2.6 & 3.44 respectively. The pain started reducing from 12hr after surgery, the mean score was 2.24 at 12 hr. In Tramadol group, mean pain score at 2 hr was 1.08, which was less compared to Diclofenac group. But pain score increased subsequently at 4 hr, 6 hr, 12 hr. The mean pain score was more in Tramadol group when compare to the Diclofenac group.*
DISCUSSION AND CONCLUSION: *To conclude 50mg of oral Diclofenac sodium provides a better preemptive analgesia and also reduced post operative edema after surgical extraction of third molars when compare to the same dose of Tramadol. In terms of mouth opening there was no significant changes noted in both the groups.*
KEYWORDS*:- Pain, Diclofenac, Tramadol, Pre-Emptive analgesic, third molar extraction*

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I. Introduction

Effective pain control plays an important role in all aspects of health care. In a dental setup patients often associate dental care with pain; consequently, they may avoid or delay dental treatment, thereby hindering the resolution of dental problems. [1] The word "pain" is derived from Latin word ***poena*** meaning punishment and the treatment was believed to be prayer. Pain is both a symptom and a disease depending on the clinical situation. Pain associated with surgery or dental procedure is acute and is a symptom.[2] Prevention of pain is more proficient than treatment of pain after it has been induced. Preemptive analgesia is the administration of an analgesic before a painful stimulus is given, such as tissue injury during surgery, in an attempt to obtain better pain relief than using the same analgesic after pain stimulus. The idea of preemptive analgesia was first given in the early 1980s, when studies suggested that steps taken to antagonize nociceptive signals prior to surgical stimulus or injury can prevent central hypersensitization, thereby reducing intensity of pain after injury. [1]Preemptive analgesia has three goals. First, to decrease acute pain after tissue injury, both intraoperatively and postoperatively. Second, to prevent pain-related pathologic modulation of the central nervous system (''pain memory''). Third, to inhibit the persistence of postoperative pain and the development of chronic pain.[3]

Tramadol is a synthetic analogue of codeine which belongs to opioids group. It is an analgesic with a low affinity for opioid receptors. Its most of action is due to inhibitory action on the neuronal uptake of norepinephrine and serotonin at synapses in the descending inhibitory pain pathways.

The Diclofenac belongs to NSAIDS group and is an inhibitor of key enzyme cyclo oxygenase, concerned in the metabolism of arachidonic acid into various prostaglandin mediators which are itself potent mediators of inflammation and pain.

The aim of the study was to investigate the efficacy of preemptive analgesia by comparing the analgesic efficacy of Diclofenac Sodium and Tramadol, to compare the pre-emptive analgesic efficacy of oral Diclofenac Sodium versus Tramadol following surgical removal of third- molars and to compare the effect of Diclofenac Sodium and Tramadol on postoperative oedema and trismus.

II. Materials And Methods

The study included out-patients who are reporting to department of Oral and Maxillofacial surgery, SDM college of dental sciences and hospital for surgical removal of impacted mandibular third-molars. A sequential enrolment of 50 patients who reported to Dept. of Oral and Maxillofacial Surgery, for the surgical removal of impacted mandibular third molars was done with an informed/written consent.

Inclusion criteria were patients who required surgical removal of mandibular third-molars for various reasons, systemically healthy patients within the age group of 18 to 50 years of either gender and Impacted teeth with difficulty index of 3 to 6, as per Pederson's scale Tooth inclinations were determined using Winters classification, using only the vertical and mesioangular positions, and by Pell and gregory, using only positions 1 and 2 and classes A and B.

Exclusion criteria were patients under the age of 18 and above 50 years, patients with history of taking analgesics within 24 hours prior to the surgery, patients who are allergic to both Tramadol and Diclofenac sodium , patients with active infection and swelling.

Study design:- This randomized, double-blind clinical study included 50 patients. Patients were randomly divided into 2 groups and the surgeon was unaware of the process. Patients were allocated to each group using sealed envelopes. Approval by the Institutional Review Board was granted. Informed consent was obtained from each subject before each surgical intervention. CONSORT guidelines were followed for the study.

Group I – Included 25 patients, who were given Diclofenac Sodium 50 mg orally 1 hour before the procedure.

Group II – Included 25 patients, who were given Tramadol Hydrochloride 50 mg orally 1 hour before the procedure.

All the operative procedures was done by single operator. The study was double blinded such that both the operator and person assessing pain were not aware of the drug which were administered. Dexamethasone 8mg was administered intravenously just before the procedure in both the groups.

Postoperative pain was measured at 2, 4, 6, 12, 24, 48 and 72 postoperative hours using visual analog scale. Other variables included :-

→Intake of first dose of analgesic post-operatively.

→Total number of tablets consumed in 5 days

→Number of tablets consumed in addition to prescribed regimen

Paracetamol 650mg is given as a rescue analgesia postoperatively in both groups. Total 6 tablets were prescribed per patient and advised to consume only if pain is unbearable.

Swelling:

Swelling measurements were taken with a silk thread and centimetre ruler before surgery and on 5th postoperative day. Linear measurements were made between the angle of the mandible and the following points: Tragus, Outer canthus of eye, Ala of nose, Commissure of mouth and mentus.

Trismus:

Trismus was evaluated by measuring the distance between the incisal edges of the upper and lower central incisors using divider and metallic scale, pre-operatively and on 5th postoperative day.

III. Results

A total of 50 patients were included in the study with no drop outs and 25 patients each in both the group. The age of the patients ranged from 18 years to 39 years with a mean age of 25.96 years and SD is 5.13 in group 1 and age of the patients ranged from 19 years to 43 years in group 2 with a mean age of 27.28 years and SD is 6.74. Out of 25 patients in group 1, 16 were males and 9 were females and out of 25 patients, 18 were males and 7 were females in group 2.

The difference in the pain intensity scores and the total number of analgesics consumed during the 5 post-operative days were analysed using **Mann-Whitney U test** and **Wilcoxon matched pairs test**. The total number of rescue analgesia consumed in 5 days were compared using **Independent t**

test. Facial swelling and trismus scores on pre-operative and 5th postoperative period was compared using **Independent t test.**

a) Statistical analysis of pain scores:- The mean pain score at 12hr in Diclofenac and Tramadol was 2.24 & 3.76 with SD of 1.45 & 1.94 respectively. The P-value was 0.0101 which is statistically significant. The mean pain score at 24hr in Diclofenac and Tramadol was 1.76 & 2.76 with SD of 1.83 & 2.11 respectively. The P-value was 0.0682. The mean pain score at 48hr in Diclofenac and Tramadol was 0.92 & 2.16 with SD of 1.29 & 2.32 respectively. The P-value was 0.0436 which is statistically significant. The mean pain score at 72hr in Diclofenac and Tramadol was 0.32 & 1.32 with SD of 0.95 & 2.27 respectively. The P-value was 0.05 which is statistically significant.(table 1)

b) Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative Angle-Tragus scores by independent(table 2):-

1) The mean difference in pre-op and postop swelling from Angle to tragus in Diclofenac group was 6.20 & 6.25 with SD of 0.87 & 0.87 respectively. The % of change is swelling was 0.77% with P-value of 0.0201 which was statistically significant.

2) The mean difference in pre op and post op swelling from Angle to tragus in Tramadol group was 6.08 & 6.20 with SD of 1.18 & 1.20 respectively. The % of change is swelling was 2.11% with P-value of 0.0017 which was statistically significant.

Variable	Groups	Mean	SD	Sum of rank	U- value	Z-value	P-value
2hrs	Diclofenac	1.52	1.85	679.00			
	Tramadol	1.08	1.80	596.00	271.00	-0.8052	0.4207
4hrs	Diclofenac	2.60	1.41	610.00			
	Tramadol	3.00	2.00	665.00	285.00	-0.5336	0.5936
6hrs	Diclofenac	3.44	1.87	629.50			
	Tramadol	3.72	2.25	645.50	304.50	-0.1552	0.8766
12hrs	Diclofenac	2.24	1.45	505.00			
	Tramadol	3.76	1.94	770.00	180.00	-2.5709	0.0101*
24hrs	Diclofenac	1.76	1.83	543.50			
	Tramadol	2.76	2.11	731.50	218.50	-1.8239	0.0682
48hrs	Diclofenac	0.92	1.29	533.50			
	Tramadol	2.16	2.32	741.50	208.50	-2.0179	0.0436*
72hrs	Diclofenac	0.32	0.95	539.50			
	Tramadol	1.32	2.27	735.50	214.50	-1.9415	0.0500*

Table 1:- Comparison of Diclofenac group and Tramadol group with respect to pain scores at different time points by Mann-Whitney U test

Groups	Pre-operative		Postoperative		Changes from Pre to postoperative	
	Mean	SD	Mean	SD	Mean	SD
Diclofenac group	6.20	0.87	6.25	0.87	0.05	0.10
Tramadol group	6.08	1.18	6.20	1.20	0.13	0.18
% of change in Diclofenac					0.77%#, p=0.0201*	
% of change in Tramadol					2.11%#, p=0.0017*	
t-value	-0.4358		-0.1615		1.9472	
P-value	0.6649		0.8724		0.0574	

Table 2:- Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative Angle-Tragus scores by independent t test

c) Comparison of Diclofenac group and Tramadol group with respect to pre operative and postoperative Angle-Canthus scores by independent t test(table 3):-

1) The mean difference in pre op and post op swelling from Angle to Canthus in Diclofenac group was 10.10 & 10.11 with SD of 0.96 & 1.06 respectively. The % of change is swelling was 0.08% with P-value of 0.9421.
2) The mean difference in pre op and post op swelling from Angle to canthus in Tramadol group was 10.34 & 10.42 with SD of 0.72 & 0.77 respectively. The % of change is swelling was 0.81% with P-value of 0.2084.

d) Comparison of Diclofenac group and Tramadol group with respect to pre-operative and posoperative Angle-Ala of nose scores by independent t test(table 4):-

1) The mean difference in pre-op and postop swelling from Angle to Ala in Diclofenac group was 10.67 & 10.79 with SD of 0.86 & 0.92 respectively. The % of change is swelling was 1.12% with P-value of 0.0394
2) The mean difference in pre op and post op swelling from Angle to Ala in Tramadol group was 10.25 & 10.42 with SD of 1.07 & 1.09 respectively. The % of change is swelling was 1.68% with P-value of 0.0004

Table 3: Comparison of Diclofenac group and Tramadol group with respect to preoperative and Postoperative Angle-Canthus scores by independent t test

Groups	**Pre-operative**		**Postoperative**		**Changes from Pre to postoperative**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Diclofenac group	10.10	0.96	10.11	1.06	0.01	0.55
Tramadol group	10.34	0.72	10.42	0.77	0.08	0.32
% of change in Diclofenac					0.08%#, p=0.9421	
% of change in Tramadol					0.81%#, p=0.2084	
t-value	0.9965		1.2050		0.5986	
P-value	0.3240		0.2341		0.5523	

Groups	**Pre-operative**		**Postoperative**		**Changes from Pre to postoperative**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Diclofenac group	10.67	0.86	10.79	0.92	0.12	0.28
Tramadol group	10.25	1.07	10.42	1.09	0.17	0.21
% of change in Diclofenac					1.12%#, p=0.0394*	
% of change in Tramadol					1.68%#, p=0.0004*	
t-value	1.5323		1.2882		-0.7518	
P-value	0.1320		0.2039		0.4558	

Table 4: Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative Angle-Ala of nose scores by independent t test

e) Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative Angle-Corner of mouth scores by independent t test(table 5):-

1) The mean difference in pre op and post op swelling from Angle to corner of mouth in Diclofenac group was 8.72 & 8.88 with SD of 1.22 & 1.18 respectively. The % of change is swelling was 1.56% with P-value of 0.0497
2) The mean difference in pre op and post op swelling from Angle to corner of mouth in Tramadol group was 8.7 & 8.84 with SD of 0.77 & 0.73 respectively. The % of change is swelling was 1.93% with P-value of 0.0007.

f) Comparison of pre-operative and postoperative Angle-Mentus scores in Diclofenac group and Tramadol group(table 6):-

1) The mean difference in pre op and post op swelling from Angle to mentus in Diclofenac group was 10.23 & 10.29 with SD of 1.64 & 1.61 respectively. The % of change is swelling was 0.59% with P-value of 0.3834.
2) The mean difference in pre op and post op swelling from Angle to mentus in Tramadol group was 10.21 & 10.38 with SD of 1.07 & 1.05 respectively. The % of change is swelling was 1.68% with P-value of 0.0214.

Trismus:

Trismus was expressed as the reduction in the postoperative maximal interincisor distance of each patient compared to the preoperative distance. The interincisal (central incisors) distance was measured pre-operatively and on 5th post-operative day in both Group I and Group II patients.

Pre-operative and postoperative mouth opening scores were compared among the groups by independent t test(table 7):-

1) Group I: Mean pre-operative and postoperative mouth opening was 4.60 & 4.18 respectively. The percentage of changes from pre to postoperative mouth opening was 9.04% with P-value of 0.0143
2) Group II : Mean pre-operative and postoperative mouth opening was 4.16 & 3.96 respectively. The percentage of changes from Pre to postoperative mouth opening was 4.80% with P-value of 0.0097.

Rescue analgesics:

Postoperatively in both the groups Paracetamol 650 mg tablets prescribed as rescue analgesic.

The mean number of rescue analgesics scores in Group I and Group II was compared by independent t test

Group I: Mean number of rescue analgesics score was 3.52 with SD of 1.61

Group II: Mean number of rescue analgesics score was 3.72 with SD of 1.86

Groups	**Pre-operative**		**Postoperative**		**Changes from Pre to postoperative**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Diclofenac group	8.70	1.22	8.84	1.18	0.17	0.22
Tramadol group	8.72	0.77	8.88	0.73	0.14	0.33
% of change in Diclofenac					1.56%#, p=0.0497*	
% of change in Tramadol					1.93%#, p=0.0007*	
t-value	0.0417		0.1590		0.4068	
P-value	0.9669		0.8744		0.6859	

Table 5: Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative Angle-Corner of mouth scores by independent t test

Groups	**Pre-operative**		**Postoperative**		**Changes from Pre to postoperative**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Diclofenac group	10.23	1.64	10.29	1.61	0.06	0.34
Tramadol group	10.21	1.07	10.38	1.05	0.17	0.35
% of change in Diclofenac					0.59%#, p=0.3834	
% of change in Tramadol					1.68%#, p=0.0214*	
t-value	0.0512		-0.2401		-1.1521	
P-value	0.9594		0.8113		0.2550	

Table 6: Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative Angle- Mentus scores by independent t test

Groups	**Pre-operative**		**Postoperative**		**Changes from Pre to postoperative**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Diclofenac group	4.60	0.82	4.18	0.76	0.42	0.79
Tramadol group	4.16	0.71	3.96	0.64	0.20	0.36
% of change in Diclofenac					9.04%#, p=0.0143*	
% of change in Tramadol					4.80%#, p=0.0097*	
t-value	2.0112		1.1057		-1.2494	
P-value	0.0499		0.2743		0.2176	

Table 7: Comparison of Diclofenac group and Tramadol group with respect to pre-operative and postoperative mouth opening scores by independent t test

IV. Discussion

The main aim of the present study was to assess the efficacy of Diclofenac and Tramadol as a pre-emptive analgesia, and their role in post operative edema and trismus prevention. Diclofenac is a NSAID which is available in an oral release potassium salt form and a sodium salt delayed-release and extended-release tablet form. Diclofenac is a strong agent that has inhibitory effect on COX 1 and 2 thereby inhibiting prostaglandin synthesis.[4]It may also inhibit neutrophil aggregation/activation, inhibit chemotaxis, decrease pro-inflammatory cytokine level, and alter lymphocyte activity.

Tramadol is a centrally acting, synthetic analgesic compound that is structurally related to codeine and morphine. It has a dual mechanism of action that involves weak affinity for opioid (mu) receptors and also inhibition of reuptake of serotonin and norepinephrine at synapses in the descending inhibitory pain pathways. Because Tramadol does not affect prostaglandin synthesis, it does not have antipyretic or anti-inflammatory effects.[5]

The evaluation of pain relief is one of the foundation pillars in the outcome assessment of our study. Out of all several aspects of pain, Pain intensity assessment seems to be most reliable. Visual Analog scale (VAS) and Graphic Rating Scale (GRS) are valuable instruments to assess pain intensity and changes due to therapy. Numerical Rating Score (NRS) and Verbal Rating Scale (VRS) are other methods in pain assessment. Although being well understandable and easy to handle (also in telephone interviews), they are not as appropriate to detect changes over time as are VAS and GRS.[6]

In the present study we have used VAS because of convenience and better compliance with patients. A value of 3 or less is generally considered to be indicative of acceptable pain relief. VAS score of more than 3 and 5 are considered to correlate with moderate or severe pain[7]. Disadvantages with the VAS are first, it allots a single value to a multidimensional and complex experience of pain which the patient also often finds difficult to choose. Further, it is not always possible for the patient to imagine what the worst possible pain is. If the patient initially marks 10 to represent his pain and subsequently it worsens further there is no way to show the change. Second, the definition of acceptable pain and moderate and severe pain as less than 3, more than 3 and 5 has been questioned in some studies.[7,8]

Our study reveals that analgesic efficacy of Diclofenac is more as compared to Tramadol in terms of pre-emptive analgesia, similar studies conducted by Mario Alberto et al [9] supported our findings and suggesting that NSAIDS group have superior analgesic properties as compared to Tramadol. Surprisingly we observed in our statistical analysis that Tramadol had given better pain relief in first two hours post-operatively as compared to Diclofenac owing to the fact that Tramadol acts on (mu) receptors. This finding proved the fact that Tramadol provides greater pain relief in first two hours as also suggested by Santos et al [1] and Sinha et al.[10]

Although as we extended our analysis beyond two hours we found that Diclofenac with plasma half life of 1-2 hours was more effective in controlling pain which was in contradictory to many studies done in same aspects before, which suggests that Tramadol with half life of approximately 6.3 hours is better pre-emptive analgesic. The reason behind this difference in present study and other studies is that surgical stimulus is not the only pain promoting factor in third molar extraction, if that would have been the case Tramadol could have shown better results but in contrary in third molar extraction pain is often caused by edema, caused by bone cutting which causes increased release of chemical mediators of inflammation causing local edema which in turn again stimulates pain nerve endings.

As obvious due to knowledge of pharmacodynamics and pharmacokinetics, we know that Tramadol has no effects on inflammatory mediators while Diclofenac is the one with potent action against same mediators, the results of our study also reflected that Diclofenac has superior pre-emptive analgesic properties. While in cases of soft tissue surgeries or any other abdominal surgeries Tramadol was graded superior to Diclofenac as depicted in study by Sinha et al. [10]

Swelling after lower third-molar surgery is difficult to measure accurately, because of three-dimensional morphology of bony contour and overlying soft tissues. Moreover, swelling can involve the skin and mucosa. Methods used to evaluate swelling include photographic analysis, modified face bow, linear measurements, subjective measurements and others. [11] The linear measurements were done using silk thread. To quantify the swelling in this complex area we have used measurements from angle to tragus, Outer canthus of eye, Ala of nose, Commissure of mouth and mentus as used by Santos et al. [1] The measurements were made preoperatively, and on fifth postoperative day. From our results we noted facial swelling was evident in both Diclofenac and Tramadol group but it was less in Diclofenac group when compare to the Tramadol group. The percentage of changes in pre-operative and postoperative facial measurements were statistically significant in both the groups. Again the potent

action of Diclofenac against inflammatory mediators is responsible for this result which is not present in Tramadol.

Swelling and trismus have been considered an inevitable part of the healing process after removal of impacted mandibular third molar teeth, the severity of symptoms being roughly proportional to the amount of trauma, associated with extraction.[12] Degree of trismus was determined by subtracting the postoperative daily measurements of the mouth opening from the measurements before operation. A statistically significant difference in pre-operative and postoperative mouth opening was noted in both Diclofenac and Tramadol group. But when mouth opening is compared within the groups there is no significant difference noted. From the above findings it is evident that both Diclofenac and Tramadol do not have a significant effect on trismus.

The strength of present study is that we have tried to eliminate bias by making the operator blind about the group and the person measuring the variables was not the part of study so as to get accurate results.

One significant weakness of present study was that we have not done the age matching in samples and not analysed for confounding factors. The authors of present study believe that further research should be directed taking in considerations the following points.

V. Conclusion

The third molar extractions are one of the most complicated oral surgical procedures. Post operative pain, swelling and trismus makes the procedure even more complex and difficult to manage. Present study design clearly suggest that Diclofenac with dexamethasone forms a strong combination for pre-emptive analgesic which is in contrast to the previously published studies. We recommend Diclofenac 50mg one hour before the procedure based on findings of our prospective study.

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