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Effect of Pre-Treatment with Ketorolac Tromethamine on Post-operative Pain Following Periodontal Surgery: A Randomized Crossover Clinical Trial

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Abstract

Background: Periodontal surgeries are often followed by post-operative pain and discomfort which is a major concern to both the clinician and the patient. Every effort is being made to reduce the post-operative pain, one amongst them being the pre-operative medication with NSAIDS like ketorolac tromethamine. This type of agent acts peripherally by inhibiting the release of prostaglandins and minimizing the local inflammatory response hence it may be advantageous in reducing post-operative pain and discomfort. Thus, the efficacy of preoperative ketorolac tromethamine administration on periodontal postoperative pain was evaluated. **Material & Methods:** Two groups of 15 patients each were selected for the study. One group received 20 mg ketorolac immediately before periodontal flap surgery, and the other group doesn't received any drug. Combination of Diclofenac sodium 50 mg & Paracetamol 325mg tablets was provided as "rescue analgesic. The visual analog scale modified with using numerical rating scales and Wong-Baker Faces Pain Rating Scale was used to estimate pain. Postoperative pain was assessed hourly for the first 12 h on the day of surgery, and 4 times daily on the 1st and 2nd postsurgical days. Timing and dose of rescue analgesic remedication were also recorded. **Results:** Results indicated that preoperative treatment with ketorolac significantly reduced initial pain intensity and delayed the onset of postoperative pain as compared to no premedication group. Incidence and amount of rescue medication consumption was small in ketorolac groups. No adverse reactions related to preoperative medication were observed. **Conclusion:** The results of this study showed that 20-mg ketorolac administered immediately before periodontal surgery was effective for alleviating the early postoperative painful sequelae, affected delayed pain levels and postoperative rescue analgesic consumption.

Keywords:- Ketorolac, Premedication, Pain Control, Periodontal Surgery.

INTRODUCTION

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[1] It is a distressing feeling often caused by intense or damaging stimuli, periodontal surgery being one among them. Postoperative pain following oral surgical procedures is a common occurrence to

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most patients, the intensity of this pain is related to the surgical procedure itself.[2] Many factors may influence pain intensity, such as the nature, duration, and extent of the surgery, and psychological aspects, such as stress and anxiety.[3] Factors contributing to the occurrence of postoperative dental pain are complex, but many are related to the inflammatory process that is initiated by surgical trauma.[4] Injury to tissue during surgical procedure results in the release of chemical mediators of inflammation (histamine, acetylcholine and bradykinin) and cause hyperalgesia, characterized by decreased pain threshold and increased sensitivity to supra threshold stimuli. Non-steroidal anti-inflammatory drugs (NSAID) inhibit the formation and release of prostaglandins. Although NSAIDs have been shown to be particularly effective in suppressing postoperative dental pain, their use does not prevent the initial pain and discomfort that occur when local anaesthesia wears off.[5] It is proposed that, when NSAIDs are given preoperatively, absorption and distribution of the medication may occur before the initiation of the tissue trauma, the ensuing synthesis of prostaglandins, and the subsequent inflammatory response. Prevention of the inflammatory response may in turn decrease the sequelae of tissue trauma, especially the associated pain experience.[6] Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug with an analgesic potency comparable to morphine, but without the opiate-receptor-associated side effects.[7] The beneficial effects of ketorolac are probably due to drug's ability to block prostaglandin synthesis by preventing the conversion of arachidonic acid to the endoperoxides. The use of ketorolac is suggested by reports describing its efficacy in the symptomatic relief of moderate to severe postoperative pain associated with abdominal, gynaecologic, orthopaedic, urologic and in the treatment of cancer pain.[8] Previous studies have shown that the oral formulation in 10- and 20-mg postoperative doses in an oral surgery model provided the same analgesia as 400-mg ibuprofen, and significantly better analgesia than acetaminophen and acetaminophencodein combinations.[9] With this knowledge in mind, the present research was undertaken to study the effect of pre-treatment with ketorolac tromethamine on post-operative pain so that patient stays with minimal/no discomfort & increase quality of life following periodontal surgery.

Aim & Objectives of the Study

The purpose of present study was to evaluate the efficacy of preoperative administration of oral ketorolac tromethamine, 20 mg on postoperative pain following periodontal surgery with aforementioned aims and objectives:-

To evaluate the efficacy of a preoperative administration of oral ketorolac tromethamine, 20 mg on postoperative pain using VAS Scale during first 12 hr.

To evaluate the efficacy of a preoperative administration of oral ketorolac tromethamine, 20 mg on the time elapsed between the completion of surgery and first analgesic taken.

To evaluate the efficacy of a preoperative administration of oral ketorolac tromethamine, 20 mg on the total analgesic consumption during first 48 hrs after completion of surgery.

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MATERIAL AND METHODS

This study was a randomized, single-dose, single blind clinical trial of crossover study design. This study was conducted in the Department of Periodontics, Government Dental College & Hospital Srinagar. Before the commencement of study an ethical clearance was obtained from institutional Ethical Committee. The study was done on 15 patients with Moderate- Severe Generalised Chronic periodontitis, who gave verbal informed consent to participate in the study. The patients were scheduled for periodontal flap surgery based on the inclusion/exclusion criteria & were divided randomly into two groups, control group (no premedication group n=15) and test group (premedication group n=15). In each patient the mouth was divided & randomly assigned to two experimental segments with each group containing 15 segments. 15 segments were treated with periodontal surgery without preoperative administration of ketorolac tromethamine, 20 mg & 15 segments were treated with periodontal surgery with preoperative administration of ketorolac tromethamine, 20 mg. All examination was carried by a single examiner. 60 minutes prior to the scheduled surgery, each patient received two 10 mg tablets of ketorolac tromethamine according to a randomization list. All interventions were performed under local anaesthesia (2% lignocaine with 1:80,000 epinephrine). Surgical procedure comprised of internally bevelled mucoperiosteal flap elevation, root debridement, and osseous recontouring when positive osseous architecture had to be achieved, flap closure using 3-0 silk sutures. Combination of Diclofenac sodium 50 mg & Paracetamol 325mg tablets were provided as "rescue analgesic" to be taken as required postoperatively to a maximum of 2 tablets per day. The patients were free to take rescue analgesic during the trial period for the relief of persisting pain. The duration of surgery from the time of incision to the placement of the last suture was recorded. At the completion of the surgery, the patients were supplied with printed record forms and were asked to rate their subjective postoperative pain intensity using a visual analog scale (VAS) which consists of a vertical or horizontal line, 10 cm (100mm) in length, with words that convey “no pain” at one end and “worst pain” at the opposite end & modified with using numerical rating scales and Wong-Baker Faces Pain Rating Scale [Figure 1]. On the day of surgery, assessment was made immediately after surgery (baseline score) and then at hourly intervals from 1 to 12 h postoperatively. On the 1st and 2nd postoperative days, VAS-recordings was assessed four times daily (morning, noon, afternoon, and evening). Safety of preoperative medication was assessed by recording any adverse event either reported spontaneously by the patient or elicited by indirect questions posed by the investigator at control visit. The patients were free to take prescribed rescue analgesic during the trial period for the relief of persisting pain, and they were asked to record the dose and the timing of such medication on the daily chart. The time elapsing from initial test drug administration until it became necessary for the patient to take supplemental medication (latency) was recorded. On the day of surgery, the trial was therefore completed after the final assessment, either at 12 hours after the completion of the surgical procedure or when rescue analgesic had to be administered.

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The amount of rescue analgesic was recorded during first 48 hours after the completion of periodontal surgery.

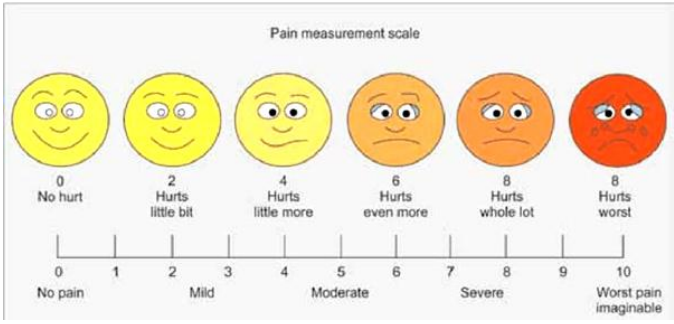

Figure 1: Visual Analog Scale (VAS) modified with using numerical rating scales and Wong-Baker Faces Pain Rating Scale

Inclusion Criteria

- Subjects within the age group of 35-60 years.
- Systemically healthy individuals.
- Subjects maintaining good oral hygiene after completion of scaling and root planing.
- Subjects with radiographic evidence of bone loss.
- Subjects with residual probing pocket depth of > 5mm.

Exclusion Criteria

- Subjects under 18 years of age.
- Pregnant patients, nursing mothers.

Subjects sensitive to salicylates or the trial medication, those receiving treatment with systemic corticosteroids or anticoagulants.

Subjects suffering from active peptic ulceration, gastrointestinal haemorrhage, liver or kidney disease, haemopoietic disorders or any other significant medical problem.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Results on continuous measurement were presented as Mean, SD & Median. Inferential statistics like Mann-Whitney U test and Friedman test were applied. P <0.05 was considered statistically significant.

RESULTS

The study comprised of 15 subjects visiting the OPD of the department of periodontics, Government Dental College & Hospital, Srinagar. The patients were divided into two groups, control group (no ketorolac group n=15) and test group (ketorolac group n=15) based on crossover study design i.e. in each patient the mouth was divided & randomly assigned to two experimental segments with each group containing 15 segments. Surgical factors that could have influenced the subjects' analgesic responses to study medication included duration of surgery, type of periodontal flap surgery, number of teeth involved in the surgical procedure, and amount of local anaesthesia administered. Both groups had these surgical factors common except for the test medication.

[Table 1 & Graph 1] shows the comparison of VAS score of the two groups upto 12 hours after periodontal flap surgery. A Statistically significant difference in VAS score was observed at all time period except at 01 hour i.e. it was higher in No ketorolac group when compared to ketorolac group.

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Table 1: Comparison of VAS Scores at different time period (upto 12 hours) between two groups

Hours	Group	Mean (SD)	Median	P value
1	No Ketorol	0.333(0.488)	0.00	0.017
	Ketorol	0.000(0.000)	0.00	
2	No Ketorol	0.867(0.352)	1.00	0.001*
	Ketorol	0.000(0.000)	0.00	
3	No Ketorol	1.400(0.632)	1.00	0.001*
	Ketorol	0.000(0.000)	0.00	
4	No Ketorol	1.467(0.640)	1.00	0.001*
	Ketorol	0.000(0.000)	0.00	
5	No Ketorol	1.467(0.640)	1.00	0.001*
	Ketorol	0.267(0.458)	0.00	
6	No Ketorol	1.867(0.516)	2.00	0.001*
	Ketorol	0.733(0.799)	1.00	
7	No Ketorol	1.933(0.458)	2.00	0.001*
	Ketorol	0.800(0.676)	1.00	
8	No Ketorol	2.200(0.676)	2.00	0.001*
	Ketorol	1.133(0.640)	1.00	
9	No Ketorol	2.200(0.676)	2.00	0.006*
	Ketorol	1.333(0.816)	1.00	
10	No Ketorol	2.467(0.743)	2.00	0.025*
	Ketorol	1.600(1.056)	1.00	
11	No Ketorol	2.800(0.676)	3.00	0.005*
	Ketorol	1.867(0.990)	2.00	
12	No Ketorol	2.867(0.516)	3.00	0.007*
	Ketorol	2.000(1.000)	2.00	

*Statistically significant ($p<0.05$)

Table 2: Comparison of time elapsed between the completion of surgery and first analgesic taken.

Group	Mean	SD	Median	P value
No Ketorol	4.133	1.767	4.00	0.032*
Ketorol	19.133	18.232	11.00	

*Statistically significant ($p<0.05$)

Table 3: Comparison of number of tablets taken between two groups

Group	Mean	SD	Median	P value
No Ketorol	4.400	1.121	4.00	0.001*
Ketorol	1.400	1.298	2.00	

*Statistically significant ($p<0.05$)

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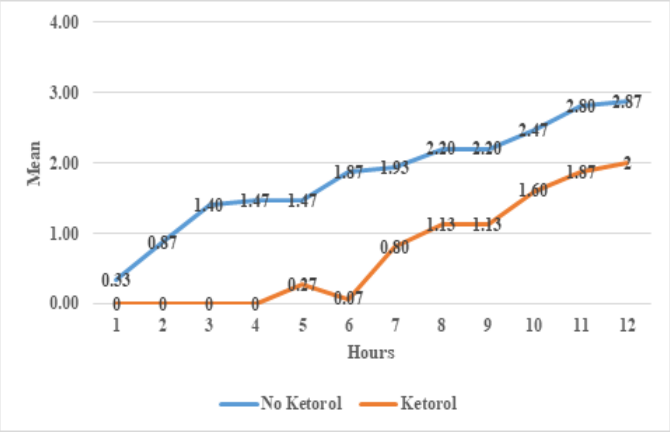
[Table 2] shows the comparison of time elapsed between the completion of surgery and first analgesic taken. A Statistically significant difference was observed on the time elapsed between the completion of surgery and first analgesic taken.

[Table 3] shows the total analgesic consumption (number of tablets taken) during ist 48 hours after completion of periodontal surgery. A Statistically significant differenc in number of tablets taken was observed. It was higher in No ketorolac group when compared to ketorolac group during first 48 hrs after completion of surgery.



Graph 1: Comparison of VAS Scores

DISCUSSION

The present study demonstrated that the pre-treatment with ketorolac immediately before periodontal surgery significantly reduced operative pain, initial post-operative pain intensity and delayed the onset of postoperative pain. Patients receiving the preoperative dose of ketorolac had a significant increase in the amount of time between the presurgical drug administration and the need for postoperative rescue analgesic & the number of rescue analgesic tablets taken postoperatively. The rationale for prophylactic NSAIDs administration is that the presence of the drug in the tissues at the time of surgery results in blocking of both synthesis and direct effects of prostaglandins, and thereby limits postoperative pain and other components of surgically induced inflammation. Oral ketorolac is completely absorbed, with a mean peak plasma concentration occurring an average of 44 min after a single 10-mg dose.[10] Ketorolac is strongly (99%) protein bound, with the degree of binding apparently independent of the plasma concentration of the drug.[11] For this reason, an oral loading approximately twice the maintenance dose was administered to minimize the analgesic delay due to ketorolac's two-compartmental characteristics. Plasma half-life is 4 to 6 h in the normal adult, and analgesia may be maintained 6 to 8h.[12] Since the maximum concentration of prostaglandins in actively injured tissues occurs simultaneously with the peak intensity of postoperative pain, 3 to 4 h after injury,[13] the pharmacokinetic properties of ketorolac may have allowed for achieving therapeutic blood levels of the drug which would have blunt the biochemical processes leading to pain. Among the side effects seen in NSAID therapy, gastrointestinal intolerance and adverse CNS manifestations are the most common with platelet aggregation being the major concern. In this study, low dosage and single-dose administration have excluded the occurrence of adverse side effects. This is in agreement with previous reports where 82% of 115 patients treated with oral single dose of ketorolac registered no complaints during the postoperative observation period.[14]

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CONCLUSIONS

The results of this randomized, single-dose, single blind clinical trial of crossover study design showed that 20-mg ketorolac administered immediately before periodontal surgery was effective for alleviating the early postoperative painful sequelae, affected delayed pain levels and postoperative rescue analgesic consumption. However, no disadvantages related to this method of administration were noted.

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