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Original Article

Dentistry Section

Comparison of Efficacy of Low Dose (25 mg) with High Dose Diclofenac (50 mg) in Management of Postoperative Pain after Periodontal Flap Surgery: A Randomised Clinical Trial

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ABSTRACT

Introduction: The perception of pain is highly subjective and varies substantially among individuals. Diclofenac is powerful NSAID and is associated with adverse effect, like gastric irritability.

Aim: To compare a low dose Diclofenac (25 mg) with Diclofenac (50 mg) in postoperative pain management after periodontal flap surgeries.

Materials and Methods: Study included 20 patients with chronic periodontitis (17-55 years), scheduled for open flap debridement surgery on at least two quadrants >1 week apart. Study group was divided into two groups; one group received low dose Diclofenac (25 mg Diclofenac and 325 mg paracetamol), BID for three days, whereas the other group received Diclofenac (50 mg Diclofenac and 325 mg paracetamol), BID for three days. The pain assessment of the subjects was carried out by VAS and pain assessment questionnaire.

Results: The mean pain scores in both groups were obtained by VAS. After comparing those pain scores of both groups by independent t-test and repeated measures of ANOVA test, statistically significant ($p<0.05$) results were found between both groups at day 1,2 and 3 but less gastric discomfort was observed with Diclofenac 25 mg group.

Conclusion: Diclofenac 25 mg can be used efficiently in controlling postoperative pain after open flap debridement, especially in patients with gastric discomfort.

Keywords: Cyclooxygenase, Drug administration, Post operative pain management

INTRODUCTION

Pain after periodontal surgical procedures is a common manifestation. The perception of pain is highly subjective and varies substantially among individuals [1]. Many factors affect pain perception, such as the nature, duration and extent of the surgery and psychological aspects (e.g., stress and anxiety) [2,3]. Pain after periodontal surgery is an example of acute dental pain of mild to moderate severity [4]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have a significant advantage in the control of pain after periodontal or oral surgical procedures [5-7].

"Diclofenac" is the most commonly prescribed NSAID worldwide and has been available in the United States since 1988 [8]. Diclofenac inhibits the activity of Cyclooxygenase (COX)-1, which has been associated with the gastrointestinal Adverse Effects (AEs) associated with NSAIDs and COX-2, the inhibition of which has been associated with NSAID therapeutic efficacy but is related with an increased risk of cardiovascular adverse effects [9,10]. Diclofenac has been reported to achieve analgesia at concentrations associated with clinically relevant inhibition of the COX-2 enzyme (IC80; the drug concentration that produces 80% inhibition), with a lesser degree of COX-1 inhibition [11]. However, diclofenac products are often dosed supra therapeutically. For example, the commonly used diclofenac dosage of 50 mg Three Times Daily (TID) achieves 90% inhibition of COX- 2 over eight hours after dosing, with only partial inhibition of COX-1 (49.5%). Consequently, lowering the dose would continue to provide analgesia with the potential of a reduced risk for AEs [12]. Large-scale pharmaco epidemiologic studies [13-15] have corroborated findings from clinical studies of toxicity risks with NSAID use. Additional studies have examined the tolerability risks with the use of low versus high doses of NSAIDs and found increased risks in patients receiving high-dose NSAIDs compared with those in patients receiving low doses of these agents [16-21]. Based on the pooled evidence, regulatory agencies around the world, including the US Food and Drug Administration [22], the European Medicines Agency [23], and Health Canada [24], have recommended the use of NSAIDs at the lowest effective dosage and for the shortest duration.

To help physicians and patients to better comply with the recommendation of the use of the lowest effective doses of NSAIDs. Recently a lower-dose submicron version of diclofenac, was created using SoluMatrix Fine Particle Technology (Iroko Pharmaceuticals, Philadelphia, PA). SoluMatrix diclofenac capsules (25 mg) are equivalent to a 50% lower than the normal diclofenac dose. This novel, nonselective NSAID was recently approved by the US Food and Drug Administration for the treatment of acute and chronic pain [22].

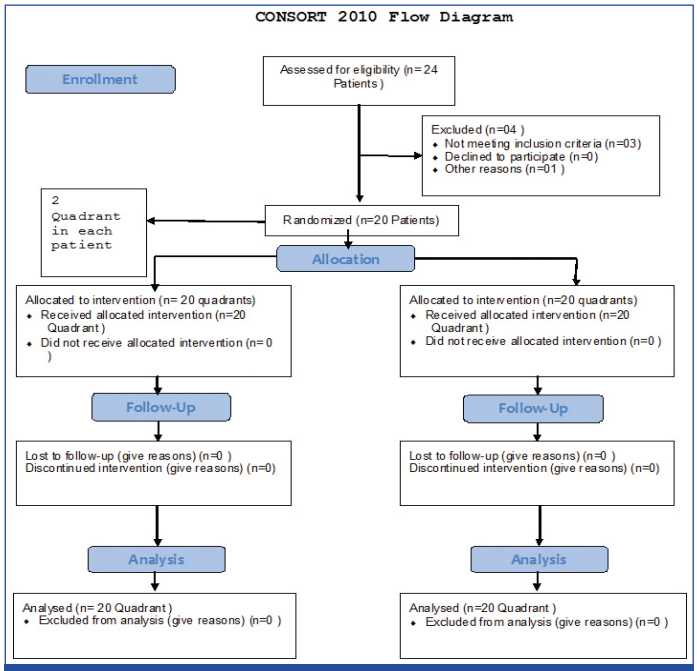
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. Many clinical trials have suggested Diclofenac 50 mg alleviates the postoperative pain, the aim of the present study was to compare a low dose Diclofenac (25 mg) with Diclofenac (50 mg) in postoperative pain management after periodontal flap surgical procedure.

MATERIALS AND METHODS

The present split-mouth, single-blind randomised clinical trial (NCT03519152) was carried out in the Department of

Periodontology and source of the patients was from the outpatient section of Tatyasaheb Kore Dental College and Research Centre, New Pargaon, Maharashtra, India. The ethical clearance was taken from Ethical Committee of the Institute. Patients were enrolled in the study between November 2016 and June 2017. Based on the power of study that was 80% and alpha of 0.05 with SD of ±1.47, authors required 36 quadrants. Considering 10% dropout, sample size was finalised as 20. The study included 20 patients (14 males and 6 females) with generalised chronic periodontitis.

With age ranging from 17-55 years, the selected patient had at least 20 natural teeth, and with no history of previous periodontal therapy preceding six months of study. Medically compromised patients, pregnant and lactating mothers, smokers and alcoholics, those with a history of taking anticoagulant therapy, patient reporting intake of steroidal or non-steroidal anti-inflammatory drugs (previous three months) or antibiotics in previous six month were excluded from the study [Table/Fig-1]. Patient with known hypersensitivity to Diclofenac and gastric diseases were also not considered. The protocol of the study was explained to each patient, and informed consent was obtained after explanation of the study. A split-mouth design was used. A total of 40 quadrants in 20 patients (two quadrants in each patient) were operated. Complete medical evaluations of all the patients were done to rule out any systemic conditions.



[Table/Fig-1]: Flowchart of study design.

All patients were scheduled for open flap debridement surgery on at least two quadrants >1 week apart. Each quadrant was randomly allocated (coin test) a different medication regimen for postoperative pain control and the patient was kept blinded to which medication they received during the treatment in each quadrant. So in one patient two quadrants were operated, one quadrant received low dose Diclofenac tablets {(DYNAPAR LD, TROIKAA PHARMACEUTICALS LTD.,) 25 mg Diclofenac and 325 mg paracetamol}, BID for three days, whereas the other operated quadrant received Diclofenac {(DICLOMOL, WIN- MEDICARE) 50 mg Diclofenac and 325 mg paracetamol}, BID for three days. A flap was raised under local anaesthesia (2% lignocaine with 1:80,000 epinephrine). In both quadrants, same technique of anaesthesia was employed. The location and the extent of surgery, volume of the local anaesthesia given, and time required to perform the surgical procedure were noted in the patient file [Table/Fig-2]. Patients were instructed to complete VAS chart once in the morning and once in evening for three days with the gap of eight hours in between and were recalled

Questionnaire:-

Name of the patient:-

Age/Sex:- Phone number:-

Address:- Surgical Area Involved:-

Extent of surgery:- Volume of local anaesthetics:-

Duration of surgery:-

1] Did you complete the course of medicines prescribed?

O Yes O No

2] Any discomfort experienced between span of taking drugs?

O Yes O No

3] Any other complaint other than pain experienced?

O If yes
what_____

O No

4] Which tablet better relives the pain with less gastric discomfort? (A group or B group)

[Table/Fig-2]: Questionnaire.

on 4th day and asked about any discomfort noted during following postoperative days in the form of questionnaire. For measuring the clinical pain intensity the patients were provided with the Visual Analog Scale (VAS) [Table/Fig-3]. The VAS consists of a 10 cm line anchored by two extremes: no pain and pain that could not be more severe. Patients were asked to make a mark on the line representing their level of perceived pain.

Questionnaire:-

Name of the patient:-

Age/Sex:- Phone number:-

Address:- Surgical Area Involved:-

Extent of surgery:- Volume of local anaesthetics:-

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1] Did you complete the course of medicines prescribed?

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O If yes
what_____

O No

4] Which tablet better relives the pain with less gastric discomfort? (A group or B group)

[Table/Fig-3]: Visual Analoge Scale.

STATISTICAL ANALYSIS

Data were analysed using statistical software. The p-value was set at 0.05 for all tests. The post-surgical pain parameters were presented as mean±SD and were compared using the independent

t-test. For the intra group analysis repeated measures of analysis of variance (ANOVA) test was used.

RESULTS

Twenty acquiescent patients {14 males (70%) and 6 females (30%)} between the ages of 17 and 55 years (mean age 37.9±7.5) completed the study, and data obtained from questionnaire [Table/Fig-2] showed that side effects such as gastric irritation, stomach bloating, stomach burning were reported for diclofenac 50 mg group in eight patients and no side effects were noted in low dose diclofenac group. [Table/Fig-4,5] show the mean and standard deviation of the results obtained using VAS, for Diclofenac 25 mg and Diclofenac 50 mg group respectively. A stastically significant lower pain score was observed in both groups, at all three days (p<0.05).

Diclofenac (25 mg)	N	Mean	Std. Deviation	Std. Error	95% CI		Repeated measures ANOVA
					Lower	Upper	
Day 1	20	5.4	1.47	0.33	4.71	6.09	F=105.7 p<0.005
Day 2	20	4.35	1.39	0.31	3.70	5.00	
Day 3	20	0.75	0.72	0.16	0.42	1.09	

[Table/Fig-4]: Showing the mean pain scores in the Low Dose Diclofenac 25 mg group obtained by using VAS.
*Significant (<0.05)

Diclofenac (50 mg)	N	Mean	Std. Deviation	Std. Error	95% CI		Repeated measures ANOVA
					Lower	Upper	
Day 1	20	5.4	1.79	0.40	4.56	6.24	F=79.2 p<0.005
Day 2	20	3.5	0.83	0.19	3.11	3.89	
Day 3	20	0.35	0.49	0.11	0.12	0.58	

[Table/Fig-5]: Showing the mean pain scores in the Diclofenac 50 mg group obtained by using VAS.
*Significant (<0.05)

[Table/Fig-6] shows comparison of pain scores in two study groups obtained by using VAS, when both the groups were compared with each other by using independent t-test. The results were statically non significant on day 1 vs day 2 (p=0.127), day 1 vs day 3(p=0.507) and day 2 vs day 3 (p=0.292).

Time period	Groups	N	Mean	SD	Mean Difference	Independent t test	
						T	p-value
Day 1 to Day 2	Diclofenac (50 mg)	20	1.05	1.15	-0.85	-1.56	0.127
	Diclofenac (25 mg)	20	1.9	2.15			
Day 1 to Day 3	Diclofenac (50 mg)	20	4.65	1.69	-0.4	-0.67	0.507
	Diclofenac (25 mg)	20	5.05	2.06			
Day 2 to Day 3	Diclofenac (50 mg)	20	3.6	0.99	+0.45	-1.069	0.292
	Diclofenac (25 mg)	20	3.15	1.60			

[Table/Fig-6]: Showing the mean of VAS scores in diclofenac 50 mg and low dose diclofenac 25 mg groups.

DISCUSSION

Although the surgical extraction of impacted third molars is the most widely accepted model to compare the efficacy of analgesics and anti-inflammatory drugs, the prevention and control of pain after periodontal surgery is also of great concern for patients and clinicians. Several studies [25-29] have investigated different NSAIDs for this purpose, but to the authors' knowledge, there was no available study on the use of low dose Diclofenac after periodontal surgery. This unprecedented clinical trial was designed to compare a combination agent (Diclofenac, 25 mg, and paracetamol, 325 mg) to the traditionally used analgesic (Diclofenac 50 mg, and paracetamol 325 mg) the authors have attempted to identify the possibility of using this low dose diclofenac 25 mg as an alternative and taking advantage of the fact that it has fewer side effects than diclofenac 50 mg.

To help physicians and patients to better comply with the recommendation of the use of the lowest effective doses of NSAIDs, a novel, nonselective NSAID was recently approved by the US Food and Drug Administration for use as a treatment for acute and chronic pain [22]. This NSAID, a lower-dose submicron version of diclofenac, was created using SoluMatrix Fine Particle Technology (IrokoPharmaceuticals, Philadelphia, PA) SoluMatrixdiclofenac capsules (35 mg) are equivalent to a 20% lower diclofenac dose compared with diclofenac potassium Immediate-Release (IR) 50 mg and have reported analgesia in clinical trials in patients experiencing acute pain after bunionectomy and pain associated with osteoarthritis [30]. In addition, SoluMatrixdiclofenac capsules were recently approved by the FDA for the management of mild to moderate acute pain and osteoarthritis-related pain [31].

Many studies used a VAS [32-35] or the VRS [36-38] for rating the patient's pain perception during a 3-10-hour period of pain evaluation.

In this study, pain intensity was recorded for the 1st, 2nd and 3rd day after surgery; the pain scale was marked twice a day with a gap of eight hours in between. An eight hour period seems to be appropriate for pain intensity assessment because it covers well the duration of action of drug [39]. The pain threshold level after periodontal surgery is at its peak within the immediate 11-hour postoperative period. It is 25% to 40% same as that being reported after more extensive surgical interventions, such as wisdom teeth surgery and is greatest which explains why pain was rarely being reported on the following days [40,41]. In the present study, low-dose diclofenac 25 mg and diclofenac 50 mg reduced postoperative pain for the first eight hours, albeit with a declining effect. Considerable pain was reported after first eight hours in the low-dose diclofenac group by 9 (45%) patients compared to 20 (100%) patients. These results can be linked to the known pharmacokinetics of each drug. When diclofenac is taken postoperatively, the plasma concentration is expected to be below optimal levels at 5-6 hours after dosing [39]. There was no statistically significant (p>0.005) pain score difference between the two strengths when they were observed on day 1 vs day 3, day 1 vs day 2 and day 2 vs day 3 obtained by VAS scale [Table/Fig-6]. Both strengths when compared of low-dose diclofenac and diclofenac 50 mg, showed statistically significant lower pain scores (p<0.005) on all postoperative days [Table/Fig-4,5]. The early onset of action of the low-dose diclofenac 25 mg may be attributed to a new, proprietary dry milling process that creates submicron drug particles. This process improves absorption properties and enables efficacy at lower doses [42]. The average low-dose diclofenac 25 mg drug particle size achievable using this technology is 200 nm to 800 nm, approximately 10-20 times smaller than the traditionally available diclofenac 50 mg this increased surface area to mass ratio of the smaller drug particles ensuing in rapid dissolution [42]. In a phase 1 study, submicron diclofenac 35 mg (Zorvolexz) administration demonstrated a comparable time to reach peak plasma levels as diclofenac potassium immediate release 50 mg tablets, indicating a similar rate of absorption but with an overall systemic exposure that was 23% lower [16]. The results in the present study are in accordance with the results of previous studies in which low dose diclofenac 25 mg relieved the pain. Gibofsky A et al., performed a double-blind study in which the analgesic activities of low-dose diclofenac (35 mg Twice or Thrice daily) was evaluated, this enrolled patients

>40 years of age with clinically and radiographically confirmed (Kellgren-Lawrence Grade II-III) hip or knee Osteoarthritis (OA). Submicron diclofenac 35 mg significantly improved WOMAC pain subscale scores from baseline at 12-weeks compared with placebo [30].

Gibofsky A et al., performed a study in which submicron diclofenac 18 mg and 35 mg three times daily demonstrated efficacy in a phase three study in patients with acute postoperative pain after bunionectomy surgery. Significant results were noted for these strengths and the preparations are approved in the United States for the treatment of mild to moderate acute pain in adults [43]. In the current study, statistically significant lower pain scores were observed in both groups. Diclofenac 25 mg was effectively able to reduce pain after periodontal flap surgery. This was the lowest possible dose that minimised gastric discomfort along with efficient analgesia. Therefore this low dose diclofenac 25 mg can be used as an alternative to traditional dose of 50 mg for the management of postoperative pain after periodontal flap surgery.

LIMITATION

As the study included VAS the pain measuring criteria is subjective. Pain threshold levels differs in every individual and it is gender subjective.

However, further studies need to be done on larger populations and on medically compromised patients, to provide a rational basis for the use of low-dose diclofenac effectively in postoperative pain relief.

CONCLUSION

The findings from the present study suggest that low dose diclofenac 25 mg can be effectively used as an alternative in reducing post-operative pain after periodontal flap surgery. It is more advantageous since the adverse effects exerted by low dose diclofenac 25 mg are minuscule as compared to the traditional dose of diclofenac 50 mg.

Further studies with larger sample size should be conducted to corroborate the effectiveness of low dose diclofenac.

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