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Effects of ibuprofen and diclofenac potassium on blood coagulation tests after periodontal surgery

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Abstract
Non-steroidal anti-inflammatory drugs are potent analgesics, anti-inflammatory and ant-pyretic agents. These drugs are potent inhibitors of the cyclooxygenase enzymes within the platelets. This inhibition blocks the production of thromboxane (TXA2), which increases the risk of prolonged bleeding. Platelet aggregation by NSAIDs is reversible, but the effect depends on the dosage and duration of therapy, serum levels, half-life, and simultaneous use of anticoagulants or alcohol. This study was therefore done to assess and compare the effects of the most commonly used NSAIDs; ibuprofen and diclofenac potassium on bleeding after periodontal surgery.

Keywords: NSAIDs, ibuprofen, diclofenac potassium, periodontal surgery.

Introduction
Non-steroidal anti-inflammatory drugs have become increasingly popular as an effective analgesic in management of post-operative pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat many rheumatological problems, sprains and strains, dysmennorhea, and other mildly to moderately painful conditions. In general, non-steroidal anti-inflammatory drugs are potent analgesics, anti-inflammatory and anti-pyretic agents [1].
Ibuprofen is phenyl propionic acid derivative and diclofenac is phenylarylacetic acid derivative. Ibuprofen and diclofenac are better tolerated than aspirin. The side effects are milder and their incidence is lower when compared to aspirin. As an anti- inflammatory agent, they are mainly used in treatment of musculo-skeletal disorders such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The interruption of non-steroidal anti-inflammatory drug therapy will result in increased pain associated with inflammation of joints in patients suffering from osteoarthritis and rheumatoid arthritis [1, 2].
Ibuprofen is an active inhibitor of collagen–induced platelet aggregation which plays a role in the formation of the platelet plug during primary haemostasis following injury [3]. However, non-steroidal anti-inflammatory drug induced cyclo-oxygenase inhibition is reversible and lasts only as long as drug is in the circulation. So these drugs need to be stopped for 1-2days, depending on the drugs half-life, for the bleeding to return to normal. Published reports of medical and surgical literature have shown numerous studies correlating the use of NSAIDs and the amount of bleeding during surgeries; whereas studies regarding the effect of NSAIDs during periodontal surgery is meagre [4, 5, 6].
The prevalence of medical conditions such as arthritis and heart disease is steadily increasing in our society. While there are several studies presently under way to assess the relationships between heart disease, arthritis and periodontal disease, little research has addressed the interaction of drug treatment. Many patients who suffer from heart disease or osteoarthritis take some form of analgesic, either aspirin or other non-steroidal anti-inflammatory drugs. Each of these drugs has properties that may affect bleeding during periodontal surgery [7].
Many medical and dental practitioners are prompted to discontinue the use of NSAIDs before any surgical procedure due to the fear of uncontrolled bleeding associated with these drugs. The interruption of NSAID therapy may result in increased pain associated with inflammation, and the interruption of aspirin therapy may cause increased risk of Thromboembolism, myocardial infarction and cerebro vascular accident [3].

It is beneficial to both the patient and the clinician to determine the actual effect of NSAIDs on bleeding. This study was therefore done to assess and compare the effects of the most commonly used NSAIDs; ibuprofen and diclofenac potassium on bleeding after periodontal surgery.

Materials and methods

- A total of forty medically healthy patients were selected for the study.
- The Inclusion criteria of the study was
- Patients with chronic generalized periodontitis, who needs to be subjected to periodontal flap surgery.
- Age group older than 18 years.
- No history of any systemic disease.
- No history of any medication affecting the platelet function.
- No history of gastric or peptic ulcers and known drug allergy for NSAIDs.

The Exclusion criteria was as follows

- Pregnant and lactating women.
- Patients for whom ibuprofen is contraindicated.
- Patients requiring antibiotics.

The subjects were divided into two groups. Group I subjects were prescribed ibuprofen 400mg (®Abbott India Ltd.), and Group II subjects were prescribed diclofenac potassium 50mg (®Novartis India Ltd.); starting 2 hours prior to the surgical procedure and continued for five post-operative days.

The parameters considered were:
1. Bleeding time
2. Prothrombin time
3. Activated partial thromboplastic time
4. Platelet count.

All the patients were subjected to blood investigations prior to the surgical procedure, to record the bleeding time, prothrombin time, activated partial thromboplastin time, and platelet count.5ml of blood was collected from the antecubital vein and stored in a vial containing EDTA as the anticoagulant. An estimation of blood sugar level, haemoglobin concentration, and complete blood picture was also done to rule out any systemic conditions. On obtaining the results and ensuring that all the parameters were within the normal range, the subjects were appointed for open flap debridement for the management of periodontal pockets. The subjects were asked to take one tablet 2 hours prior to the procedure.

After administering local anaesthesia, a quadrant-wise surgery was performed. The flap design was not standardized for the study. Therefore, incisions were placed depending on the objectives of the surgery. A sharp surgical scalpel blade (#15) was used for the incisions. A periosteal elevator was used to separate the muco-periosteum from the bone by moving it mesially, distally, and apically until the desired reflection was accomplished. Degranulation was done with the help of Gracey curettes. An ultrasonic scaler was used when needed. Subgingival calculus was removed and the root surfaces were planned.

After thorough debridement, a solution of betadine and saline was used for irrigating the surgical site. Osseous contouring, if needed, was performed with the help of a bone file. Appropriate sutures were placed to get a good flap approximation. No other haemostatic agents were used. A periodontal dressing was given. Post-surgical instructions were given. Depending on the sampling, the subjects were instructed to take ibuprofen or diclofenac, one tablet every 8 hours, for the next 5 days. Blood investigations were again carried out on the last day of the drug regime; when the subjects returned for suture removal. The pre-operative and post-operative results were compared and statistically analyzed.

Results

A total of 40 patients were selected for this study based on the selection criteria. Simple random sampling was done and the subjects were divided into two groups. Those in Group I was prescribed 400mg ibuprofen every 8 hours, starting 2 hours prior to the surgery and continued for five post-operative days. The subjects in Group II were prescribed 50mg diclofenac potassium, following the same therapeutic regime as the subjects in Group I.

Pre-operative and post-operative blood coagulation test values were compared with Student *t* test. Comparison of same variables between both the groups was also performed with Students *t* test. P value <0.05 was considered statistically significant. Chi-square test was done to assess the statistical significance between the groups, when comparing the post-operative values with the normal range.

The mean values of pre-operative and post-operative bleeding time, prothrombin time, aPTT, and platelet count were calculated for both Group I and Group II and tabulated as paired sample statistics (Table 1) (Graph 1, 2, 3, 4). Subjects in Group I showed a pre-operative mean bleeding time of 1.571 ± 0.351 min, mean prothrombin time of 13.22 ± 0.705 sec, meana PTT of 31.39 ± 3.074 sec, and mean platelet count of 2.792 ± 0.438 lakhs/cu.mm. The mean values of post-operative bleeding time, prothrombin time, aPTT, and platelet count for these subjects were 1.769 ± 0.406 min, 14.17 ± 1.36 sec, 34.815 ± 1.901 sec, and 2.888 ± 0.466 lakhs/cu.mm respectively.

In Group II, the pre-operative mean bleeding time was 1.707 ± 0.691 min, mean prothrombin time was 13.545 ± 0.524 sec, mean aPTT was 32.77 ± 0.904 sec, and mean platelet count was 2.81 ± 0.402 lakhs/cu.mm. The post-operative mean of bleeding time, prothrombin time, aPTT, and platelet count for these subjects were 1.709 ± 0.360 min, 14.31 ± 1.157 sec, 32.88 ± 3.95 sec, and 2.888 ± 0.454 lakhs/cu.mm respectively.

The difference between the pre-operative and post-operative mean values of bleeding time, prothrombin time, aPTT, and platelet count in both the groups showed that, except for the bleeding time in Group II, the mean difference between pre-operative and post-operative values for all the other parameters in both the groups were statistically significant. (Table 2).

When an inter-group comparison of the mean difference of all the parameters was done, no statistically significant results were obtained. This may suggest that both ibuprofen and diclofenac had similar extent of influence on the parameters assessed. (Table 3).

Table 1: Mean values of BT, PT, aPTT and PC in both the groups

Groups	N	Mean	std. deviation	Std. error mean
Group I				
BT pre	20	1.5710	.35181	.07867
BT post	20	1.7690	.40674	.09095
PT pre	20	13.2200	.70532	.15771
PT post	20	14.1700	1.36925	.30617
aPTT pre	20	31.3900	3.07432	.68744
aPTT post	20	34.8150	1.90132	.42515
PC pre	20	2.7925	.43843	.09804
PC post	20	2.8885	.46663	.10434
Group II				
BT pre	20	1.7075	.69116	.15455
BT post	20	1.7095	.36015	.08053
PT pre	20	13.5450	.52463	.11731
PT post	20	14.3100	1.15754	.25883
aPTT pre	20	32.7700	.90488	.20234
aPTT post	20	32.8800	3.95203	.88370
PC pre	20	2.8100	.40269	.09004
PC post	20	2.8895	.45452	.10163

Table 2: Difference between the Mean values of BT, PT, aPTT and PC

groups	Paired difference		t	p
	Mean	standard deviation		
Group I				
BT pre-BT post	-.19800	.24028	-3.685	.002sig
PT pre- PT post	-.95000	1.06153	-4.002	.001sig
aPTT pre-aPTT post	-2.04000	1.87768	-4.859	.000sig
PC pre- PC post	-.09600	.15541	-2.763	.012sig
Group II				
BT pre-BT post	-.00200	.53340	-.017	.987ns
PT pre- PT post	-.76500	.88691	-3.857	.001sig
aPTT pre-aPTT post	-1.49000	1.52208	-4.378	.000sig
PC pre- PC post	-.07950	.13919	-2.554	.019sig

Table 3: Inter-group comparison of mean difference

Groups	N	Mean	Std. deviation	t
BT Group I	20	.1980	.24028	1.49800
Group II	20	.0020	.53340	P=.142ns
PT Group I	20	.9500	1.06153	.59800
Group II	20	.7650	.88691	P=.553ns
aPTT Group I	20	2.0400	1.87768	1.01800
Group II	20	1.4900	1.52208	P=.315ns
PC Group I	20	.0960	.15541	.35400
Group II	20	.0795	.13919	P=.726ns

Table 4: Comparison of BT with the normal range

	Group		Total
	I	II	
BT post normal count	20	20	40
%	100.0%	100.0%	100.0%
Total count	20	20	40
%	100.0%	100.0%	100.0%

Table 5: Comparison of PT with the normal range

	Group		Total
	I	II	
PT post abnormal count	3	1	4
%	15.0%	5.0%	10.0%
Normal count	17	19	36
%	85.0%	95.0%	90.0%
Total count	20	20	40
%	100.0%	100.0%	100.0%

Chi-square tests

	Value	Asymp. sig. (2-sided)
Continuity correction	.278	.598ns

Table 6: Comparison of aPTT with normal range

	Group		Total
	I	II	
aPPT post abnormal count	2	0	2
%	10.0%	0%	5.0%
Normal count	18	20	38
%	90.0%	100.0%	95.0%
Total count	20	20	40
%	100.0%	100.0%	100.0%

Chi-square tests

	Exactsig. (2-sided)
Fisher's Exact Test	.487ns

Table 7: Comparison of PC with the normal range

	Group		Total
	I	II	
PC post normal count	20	20	40
%	100.0%	100.0%	100.0%
Total count	20	20	40
%	100.0%	100.0%	100.0%

Discussion

Ibuprofen and diclofenac, among several NSAIDs, have been used in dentistry for the management of pain and inflammation. Ibuprofen is a propionic acid derivative and diclofenac is a phenyl acetic acid derivative. These drugs are potent inhibitors of the cyclooxygenase enzymes within the platelets. This inhibition blocks the production of TXA2, which increases the risk of prolonged bleeding. Platelet aggregation by NSAIDs is reversible, but the effect depends on the dosage and duration of therapy, serum levels, half-life, and simultaneous use of anticoagulants or alcohol.

Vogel *et al*. (1992) [8], demonstrated that ibuprofen when administered either immediately before or immediately after periodontal surgery significantly delays the onset of pain. The subjects in their study underwent elective periodontal flap procedures and osseous recontouring involving at least three posterior teeth. Patients with uncontrolled systemic conditions, pregnant and lactating women, and patients contraindicated for ibuprofen were excluded. One group of subjects were given ibuprofen 600mg approximately 5-10 minutes prior to delivery of local anaesthesia. A second group of subjects were given ibuprofen 600mg after the surgery. The degree of pain was recorded using a questionnaire. The results demonstrated that dosing with 600mg ibuprofen either immediately before periodontal surgery or immediately after periodontal surgery significantly delayed the onset of pain. The post-surgical administration showed a greater delay in the onset of pain.

In the present study, 400mg ibuprofen and 50mg diclofenac potassium were used as analgesic drugs on patients who underwent periodontal flap procedures for the management of periodontal pockets. Patients took one pre-operative dose; 2 hours prior to the procedure, and continued every 8 hourly for five post-operative days. Even though pain assessment was not a part of this study, none of the patients reported back to the department with complaint of pain.

Naclerio-Homem *et al*. (2009) [9], observed no significant increase in prothrombin time, aPTT, clot retraction, and platelet count when 50mg ketoprofen and 25mg diclofenac potassium were administered prior to surgical removal of third molars and continued for five post-operative days. They suggested that the inhibitory action of NSAIDs on COX-2 enzyme within the platelets would block the production of TXA2, which increases the risk of prolonged bleeding. But, the normal aPTT results suggested that the activity of the intrinsic pathway was not reduced to a level where sufficient factor X would not be activated. Also, the normal range of PT values revealed sufficient production of thrombin.

The mean bleeding time was found to be higher in patients who took ibuprofen pre-operatively. A statistically significant increase in intra-operative bleeding was also observed. This was considered to be due to the active inhibition of collagen-induced platelet aggregation which plays a role in the formation of platelet plug during primary haemostasis following injury. However, the total blood loss was found to be well within the normal range. This was also observed by Shiva Prasad *et al*. (2008) [3] in patients who underwent modified Widman flap surgery.

Hecht *et al*. [10] and Braganza *et al*. [7] measured the amount of blood loss during the periodontal surgical procedures. They observed increase in blood loss when ibuprofen was used. More bleeding occurred in the mandibular arch when compared to maxillary arch [11].

Similar results were also observed by Cardwell *et al*. (2005) [4] in an intervention review on the effect of ketorolac on bleeding in paediatric tonsillectomy patients. Ketorolac is a non-selective COX inhibitor, like ibuprofen and diclofenac. It was observed that ketorolac did not significantly alter the peri-operative bleeding requiring surgical intervention.

The results showed that both ibuprofen and diclofenac did not cause a significant increase in blood parameters which required immediate attention. Healing after surgery in all the patients was uneventful.

Conclusion

A total of forty medically healthy subjects were selected and divided in to two groups. Group I patients were prescribed ibuprofen 400mg, and Group II patients were prescribed diclofenac potassium 50mg, starting 2 hours prior to the surgery and continued every 8 hours for five post-operative days.

Blood samples were collected before the first dose of the drug, and at the end of the drug regime. The values were statistically analyzed. The following conclusions were made;

1. Ibuprofen and diclofenac potassium caused an increase in the values of postoperative blood coagulation parameters when compared to baseline.
2. The increase was higher in the ibuprofen group.
3. The increased values were still within the normal range.
4. Hence, for the clinical conditions established by this study, ibuprofen and diclofenac seem to be safe as far as post-operative bleeding is concerned. The safety of these drugs is comparable to their anticoagulation effect.

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