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EFFECT OF DICLOFENAC SODIUM AT LOW CONCENTRATION LEVEL ON THE RATE OF ORTHODONTIC TOOTH MOVEMENT IN RAT

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ABSTRACT: The purpose was to evaluate the influence of a NSAID, Diclofenac Sodium (DFS) on the tissue reaction related to orthodontic tooth movement (OTM). **Methods**: 27 adult male wistar rats were divided into 3 Groups of 9 each. Orthodontic closed coil spring was placed between rat incisor and molar to produce a 50 gm of force. The experimental Groups1 and 2 received orthodontic force and either DFS of 0.0025mg/0.05ml or 0.05ml of saline, Group 3 received only orthodontic force and served as a control group. At the end of day 5, 10 and 15 the animals were sacrificed and histological examination was performed. **Results:** Student's t test showed a statistically significant difference between the control Groups and experimental Groups. Group 1 showed a statistically significant reduction in osteoclastic cell count at day 5, 10 and15 when compared to Group 2 and Group 3. **Conclusion:** The results indicate that the Diclofenac Sodium even at low concentration level diminishes the number of osteoclasts probably by inhibiting the secretion of prostaglandins there by reducing the OTM.

KEYWORDS: NSAID, Diclofenac Sodium, Orthodontic Tooth Movement (OTM).

INTRODUCTION

Even though the biochemical mediators that initiate orthodontic tooth movement were not fully understood[1], the role of prostaglandins and other mediators like cyclic amp, vitamin D, thromboxanes, cytokines, interleukins, leucotrines have been extensively studied by various authors[2-9]. As a milestone in 1984 Yamasaki etal[10] administered prostaglandin1 locally and showed an increase in rate of tooth movement in human subjects.

In 1991 vane and coworkers[11] made the landmark observation that Aspirin and some NSAIDS blocked prostaglandins synthesis. Chumbley and Tuncay [12] showed a significant reduction in tooth movement in mongrel cats' canine retraction experiment using Indomethacin (an Aspirin like drug).The hypothesis that those drugs which suppress production of prostaglandins should reduce the rate of tooth movement was well proved by previous studies using NSAIDS like aspirin, Acetaminophen,Meloxicam, Celecoxib, Parecoxib, Rofecoxib, Indomethacin, Ibuprofen and Flurbiprofen in miniature pigs,rabbits,beagles and rats.[13-19]

Pain killers especially commonly available NSAIDS have been prescribed by orthodontists to those patients receiving orthodontic treatment. Acetaminophen which acts centrally to block pain sensation rather than those work peripherally remains the only choice of pain relieving medication during orthodontic treatment for decades [20,14]. In one study done by Felix de Carlos etal [21] showed a significant reduction in rate of tooth movement for 50 and 100gms of force using 10mg/kg of body weight of Diclofenac Sodium (DFS). The present study was designed to test the efficacy of local injection of Diclofenac Sodium (DFS) in altering the tissue reaction relation to orthodontic tooth movement in rats at low concentration level

Materials and Methods

Twenty seven male adult albino wistar rats each weighing 250 to 350 gms were received and maintained with 12hr light/dark cycle in central animal house, Annamalai University. The animals were randomly divided into 3 Groups of 9 animals each. They were further divided into 3 sub groups of 3 animals each.

Prior to appliance insertion all animals were color coded according to their groups. The animals body weight were cautiously monitored prior to appliance insertion and then daily till they are sacrificed. The animals were anesthetized using ketamine (44mg/kg bodyweight) and xylazine (2mg/kg bodyweight) [3]. The appliance design of this study follows that used by Leiker etal[22]. A closed coil nickel-titanium spring (Sentalloy, GAC, clr lslip, NY) calibrated to produce a force of 50gms was ligated to the maxillary first molar and incisors **(Fig.1).** To minimize the appliance dislodgement, all animals were fed with finely ground rat lab pellet ad libitum.

The drugs were delivered locally mesial to the maxillary first molar, once daily at the same time point from the day of appliance incersion till they are sacrificed. Group 1(DFS+OF) received Diclofenac Sodium at the low concentration level of 0.0025mg/0.05ml, Group 2 (S+OF) received saline 0.05ml and Group 3 (OF)received only orthodontic force and no injection, served as control.

Table I explains the animal grouping, drug dosage and their sacrifice regime. All animals well tolerated the experimental procedure. There was no gross reduction in body weight and no appliance dislodgement during the experimental period; hence no animal was excluded from the study. At the end of the experiment all the animals were sacrificed by co_2 inhalation

Histopathology

After appliance removal Premaxilla was dissected, the specimens placed in 10% formalin immediately. Decalcification was done using 9% formic acid. After wax block preparation the premaxilla were hemi sectioned at coronal, middle and apical third of the molar root level. Each section was again serially sectioned at 4 to 6 µm in the coronal plane. The sections were mounted on glass microscope slides and stained with hematoxylin and eosin. Multinuclear osteoclasts and osteoblasts on the stained sections were counted by two pathologs twice at different times using light microscope.

Table.1. Animal grouping, drug dosage and sacrifice regime.

Groups	Drug dosage	Number of animals sacrificed			Total
		Day5	Day10	Day15	
G1- Diclofenac Sodium and Orthodontic force* **(DFS+OF)**	0.0025mg/0.05ml	3	3	3	9
G2 -Saline and Orthodontic force* **(S+OF)**	0.05ml	3	3	3	9
G3-Orthodontic force* **(OF)**	---------	3	3	3	9
Total					27

(*.orthodontic force has been standardized for 50gms)

Table .2. The mean and standard deviation of histological osteoclastic cell count at the three levels coronal, middle, apical root surface for three Groups at three time intervals (5,10,15 days) of animal sacrifice

Groups	5 days			10 days			15 days		
	Coronal psi	Middle psi	Apical psi	Coronal psi	Middle psi	Apical psi	Coronal psi	Middle psi	Apical psi
Group 1	1.71± 0.68	1.32± 0.48	1.61± 0.07	2.70± 0.33	1.34± 0.55	1.57± 0.04	1.89± 0.53	1.22± 0.21	2.33± 0.41
Group 2	3.30± 0.74	4.10± 0.78	2.20± 0.02	4.20± 0.12	5.20± 0.22	5.03± 0.36	6.30± 0.11	7.10± 0.22	5.22± 0.85
Group 3	3.60± 0.79	4.40± 0.65	2.20± 0.33	2.10± 0.13	3.90± 0.44	2.54± 0.05	5.20± 0.17	4.33± 0.92	2.50± 0.23

(Mean ± Standard Deviation)

Results

When the rat molar was moved mesial by the orthodontic force the remodeling phase of alveolar bone was markedly changed. The compression of periodontal ligament and appearance of osteoclasts on the mesial side of the molar root in the experimental Group 1(DFS+OF) at day 5 is shown in **Fig. 2**. The appearance of osteoblasts on the distal side of the molar root in the control Group G2(S+OF) is shown in **Fig 3**.

Table III, Table IV and and Table V shows statistically significant reduction in osteoclastic cell count in Group 1(DFS+OF) than Group 2(S+OF) and Group 3 (OF) at day 5, 10, 15 except only at the apical level at day 15 between Group1 (DFS+OF) and Group 3 (OF). But Intra group comparison of Group 1(DFS+OF) coronal, middle and apical root surfaces at day 15 revealed no statistical significance between coronal and apical. Also there was no statistical significant difference between Group 2(S+OF) and Group 3(OF) at day 5.However Group 2(S+OF) showed a significant increase in osteoclastic cell count when compared to Group 3(of) at day 10 and 15.In overall Group 1(DFS+OF) showed statistically significant reduction in cell count throughout the study when compared to Group 2(S+OF) and Group 3(OF).

Statistical method

All the data were subjected to intergroup and intragroup comparison using descriptive statistical analysis and paired student's t- test (SPSS/win-10). Based on the mean value we are able to find out which group is higher. The difference is statistically proved if the t- test is significant. Suppose the "t" value is not significant that indicate there is no difference among groups.($p<0.05$). The mean and standard deviation of histological osteoclastic cell count at the three levels that is coronal middle and apical for three groups at three time intervals (5,10,15 days) of animal sacrifice is shown in **Table II**. Bar chart representation of the above results were given in **Graph I** . The data was then subjected to statistical analysis.

Discussion

Orthodontic tooth movement requires remodeling of the alveolar bone[23]. A patient's bone resorption potential and timely orthodontic treatment outcome depends on recruitment of mature oestoclast and its precursors, oestoclast differentiation and number of functional oestoclast at the bone, periodontal ligament interfaces[24].Interpretation of Tsay etal [25] study results indicates that during prolonged periods of tooth movement the replenishment of osteoclasts in the periodontal membrane depends on the viability of hemopoietic organs

Interestingly early experiments done by Kenichi Yamasaki etal[26,1] suggests a strong local role played by inflammation mediator prostaglandin as a mediator of bone resorption during orthodontic tooth movement, revealing to a possible hypothesis that local administration of active prostaglandin increasing rate of tooth movement and suppression of local prostaglandin by use of such drugs (NSAID) either a reduction in rate of tooth movement or reduced number of osteoclasts at the experimental sites during experimental tooth movement done in animals[2,9,27-30].

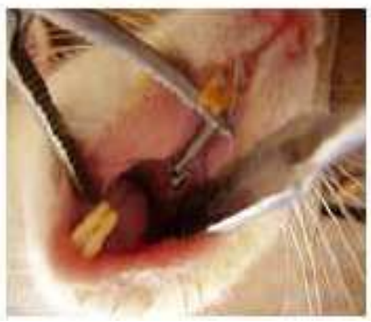

Fig.1 After appliance insertion

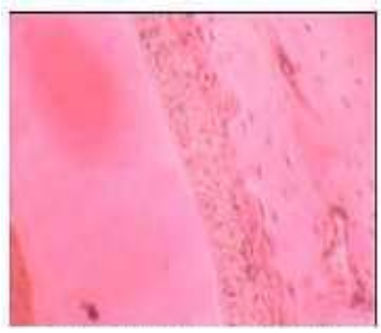

Fig.2 . Appearance of osteoclast on the compression side

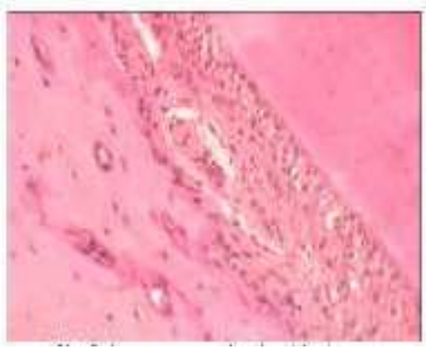

Fig.3 Appearance of osteoblasts on tension side

Table.3 Inter Group comparison for three Groups at day 5

Groups at day 5	Coronal psi		Middle psi		Apical psi	
	Mean	SD	Mean	SD	Mean	SD
Group 1	1.71	0.68	1.32	0.48	1.61	0.07
Group 2	3.30	0.74	4.10	0.78	2.20	0.02
t-value	43.69		7.10		17.30	
P value	0.001^{S}		0.019^{S}		0.003^{S}	
Group 1	1.71	0.68	1.32	0.48	1.61	0.07
Group 3	3.60	0.79	4.40	0.65	2.20	0.33
t-value	4.43		9.08		3.85	
P value	0.047^{S}		0.012^{S}		0.051^{S}	
Group 2	3.30	0.74	4.10	0.78	2.20	0.02
Group 3	3.60	0.79	4.40	0.65	2.20	0.33
t-value	0.68		0.42		0.00	
P value	0.567^{NS}		0.716^{NS}		1.000^{NS}	

S – Significant (p<0.05) NS – Not Significant

Table.4 Inter Group comparison for three Groups at day 10

Groups at day 10	Coronal psi		Middle psi		Apical psi	
	Mean	SD	Mean	SD	Mean	SD
Group 1	2.70	0.33	1.34	0.55	1.57	0.04
Group 2	4.20	0.12	5.20	0.22	5.03	0.36
t-value	12.14		20.20		16.33	
P value	0.007^{S}		0.002^{S}		0.004^{S}	
Group 1	2.70	0.33	1.34	0.55	1.57	0.04
Group 3	2.10	0.13	3.90	0.44	2.54	0.05
t-value	5.14		40.68		211.74	
P value	0.036^{S}		0.001^{S}		0.001^{S}	
Group 2	4.20	0.12	5.20	0.22	5.03	0.36
Group 3	2.10	0.13	3.90	0.44	2.54	0.05
t-value	303.11		10.14		11.64	
P value	0.001^{S}		0.010^{S}		0.007^{S}	

S – Significant (p<0.05) NS – Not Significant

The histopathological results of the present study were subjected to statistical analysis using descriptive statistical analysis and paired student's t- test (SPSS-10) revealed that experimental rats which received daily injection of diclofenac sodium and orthodontic force Group 1 (DFS+OF) showed statistically significant reduction in osteoclastic cells at all three levels that is coronal, middle and apical at three time points (5,10,15 days) when compared to those rats received saline and orthodontic force Group2 (S+OF) and only orthodontic force Group 3(OF).

Diclofenac sodium, a member of aryl acetic acid group of NSAIDs is a potent anti-inflammatory drug routinely given for dental treatments and systemic reasons. It interferes with cyclooxyganase pathway and blocks both cox1 and cox2 metabolites. In one study Felix de Carlos[21] used Diclofenac Sodium 10mg/kg with 50grms or 100gms of force and found significantly inhibited orthodontic tooth movement in rats. In the present study we used local injection of (Group 1) . Diclofenac sodium at 0.0025mg/0.05ml with 50gms of force, which is comparatively very low dose to the previous study, also potently reduced the appearance of osteoclasts. Group 2(S+OF) showed a gradual increase in cell count on 5, 10, 15 days. This might be probably due to the daily injection regime which might have altered the local inflammatory environment. But Group 3(OF) which received only orthodontic force showed an increased cell count at day 5 followed by a slight drop in cell count at day 10 then a sudden or gradual increase in cell count which represents the classical 3 phase orthodontic tooth movement described by Burstone.C [31] in 1962. That is initial phase [displacement of tooth in the periodontal membrane space], lag phase [no or relatively low rate of tooth movement], post lag phase [rate of movement gradually or suddenly increased].

Table.5. Inter Group comparison for three Groups at day 15

Groups at day 15	Coronal psi		Middle psi		Apical psi	
	Mean	SD	Mean	SD	Mean	SD
Group 1	1.89	0.53	1.22	0.21	2.33	0.41
Group 2	6.30	0.11	7.10	0.22	5.22	0.85
t-value	18.38		45.53		6.85	
P value	0.003^{S}		0.001^{S}		0.021^{S}	
Group 1	1.89	0.53	1.22	0.21	2.33	0.41
Group 3	5.20	0.17	4.33	0.92	2.50	0.23
t-value	16.13		4.76		0.84	
P value	0.004^{S}		0.041^{S}		0.491^{NS}	
Group 2	6.30	0.11	7.10	0.22	5.22	0.85
Group 3	5.20	0.17	4.33	0.92	2.50	0.23
t-value	31.75		4.56		4.82	
P value	0.001^{S}		0.045^{S}		0.040^{S}	

S – Significant (p<0.05) NS – Not Significant

In overall Diclofenac Sodium is capable of reducing the number of oestoclast at the compression side even at the low concentration level [0.0025mg/ml] when injected locally. In the present study we were not able to achieve the complete elimination of oestoclast, this further validate that not only the cyclooxyganase metabolites play a vital role in OTM, lipooxygenase pathway also contributes a Role for OTM. Since multiple mediators and signaling molecules are involved during inflammatory reactions evoked by orthodontic force, blocking of all mediators and signaling molecules at molecular level is questionable.

CONCLUSION

The ability of Diclofenac Sodium to interrupt orthodontic tooth movement and reduce the rate of tooth movement was proved in the present study by the expression of reduction in osteoclastic cell numbers .Although systemic administration of these NSAIDS are contraindicated in the sense of impairing the entire orthodontic treatment process by reducing the rate of tooth movement [32,33,34], the daily local injection of Diclofenac Sodium to a particular tooth, especially to the posterior teeth might enhance the anchorage potential. However the present results need to be confirmed in other species including humans. To overcome the daily injection in humans, sustained release transmucosal adhesive strips carrying these drug or the 'IntelliDrug' device[35] representing a revolutionary method for delivering drugs for long-term through the buccal mucosa, according to the patient needs, in periods lasting days, weeks or months will be a promising solution in near future.

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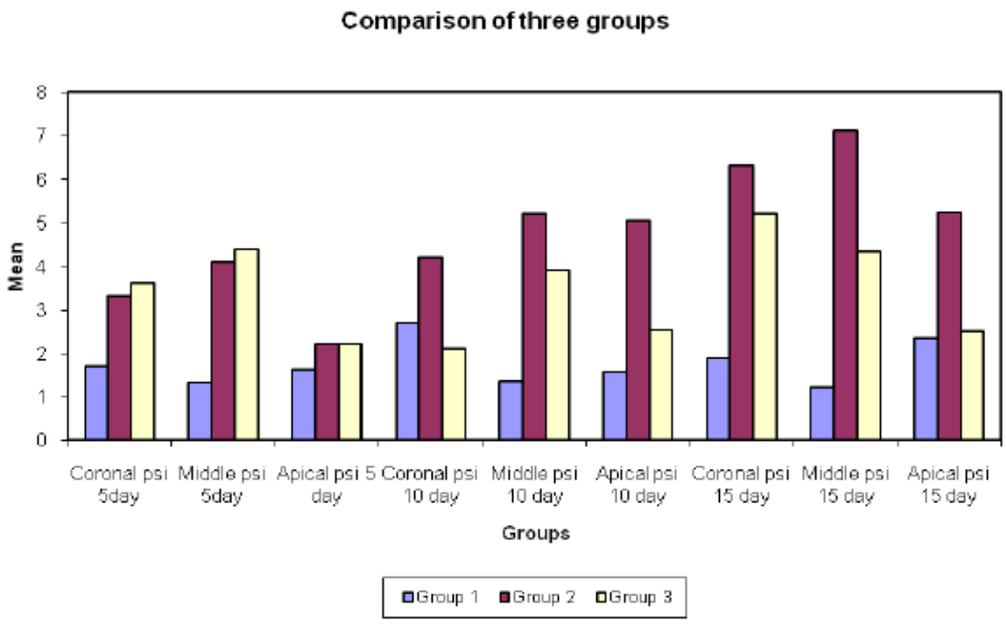

Graph.1 Bar chart comparison of the mean and standard deviation of histological osteoclastic cell count at th three levels coronal, middle, apical root surface for three Groups at three time intervals (5,10,15 days) of anim sacrifice

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