Original Article

Comparison of the Effectiveness Between Preoperative Ibuprofen and Naproxen for Pain Control after Orthodontic Archwire Placement

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Abstract

Background: Orthodontic procedures like separator placement, archwire placement, and activation, application of orthopedic forces, and debonding cause pain in patients. Researchers showed that the administration of preoperative NSAIDs reduces the pain that patients commonly experience during archwire placement.

Purpose: This quasi-experimental study evaluates the efficacy of naproxen and ibuprofen as preoperative analgesics.

Method: Selected 56 cases were divided into two groups. Ibuprofen and Naproxen were administered one hour before archwire placement, and their pain level was recorded in a pre-developed 100 mm visual Analogue Scale for chewing, biting, fitting front teeth, and fitting back teeth together at different time points after archwire placement. A quasi-experimental study was performed.

Result: The patients who took Naproxen (500mg) preoperatively felt significantly less pain than Ibuprofen (400 mg) at 6, 12, 24, 48, and 72 hours in chewing food, only at 24 hours for biting food while for fitting back teeth at 6, 12 hours and seven days and for fitting front teeth at 24 and 72 hours. The pain in chewing and biting was found to be quite similar, except that there were no differences in pain scores between the two experimental groups at two hours. In both treatments, female participants had a lower pain level than men. In addition, it was found that there is an additional need for one or two post-operative analgesics for complete pain relief.

Conclusions: Naproxen (500 mg) is more effective than ibuprofen (400 mg) for decreasing the severity of pain during archwire placement.

Keywords: Preoperative NSAIDs, Ibuprofen, Naproxen, Visual Analogue Scale.

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Introduction

In orthodontic treatment, pain is the most uttered negative effect for clinicians and patients.[1-3] Surveys report that it is the most common cause of treatment abandonment.[2,3] Patients should generally prepare themselves for some level of pain and discomfort during their orthodontic treatment. Unpleasant tactile sensations, a feeling of confinement in the oral cavity, tightening of the soft tissues, stresses on the mucosa, dislocation of the tongue, painful teeth, and pain are all manifestations of discomfort.[4] Research shows that ninety percent of participants experienced pain throughout orthodontic treatment, and the other 30% contemplated stopping treatment early due to the discomfort they felt.[5] From a 203 Chinese orthodontic patients sample, ninety-one percent experienced discomfort during every visit.[6,7] Studies have shown that ninety-five percent of people undergoing orthodontic treatment would feel pain.[8,9] After the periodontal ligament has been compressed, the orthodontic device applies force to the teeth, causing ischemia, inflammation, and edema. After periodontal ligament compression and inflammatory response activation, alogens such as histamine, bradykinin, prostaglandin, serotonin, and substance P are produced.[10,11]

It is believed that one's current emotional state, pressure levels, cultural norms, gender, and chronological age, all have a role in their perception of pain. Cyclic nucleotides and prostaglandin are suggested mediators of bone resorption and tooth movement. Pain control with NSAIDs is the preferred method respecting orthodontic treatment. Surprisingly, no universally accepted drug regimen for this condition has been established as of yet.

NSAIDs work by blocking cyclooxygenase enzymes, which stop prostaglandins from being made and stop inflammation and nerve receptors from becoming more sensitive. Ibuprofen and Naproxen are both made from propionic acid and work to relieve pain.[12,13] However, Ibuprofen works for a shorter amount of time than Naproxen.[13] Both NSAIDs are said to have a peripheral analgesic effect on prostaglandin production causing tooth movement.

In the past ten years, medicine and dentistry have paid a lot of attention to pre-emptive analgesia to prevent or lessen pain after surgery. This method tries to stop pain instead of just covering it up. The idea is that preemptive analgesia stops or reduces the nervous system from remembering the pain stimulus, which makes it less likely that painkillers will be needed later.[14,15] When NSAIDs are taken before surgery, the body has time to absorb them before tissue damage triggers the synthesis of prostaglandins.

No previous study has been reported on "Pre-operative Ibuprofen Versus Naproxen for control of pain after orthodontic archwire placement and activation" at BSMMU till now. Yet no well-accepted way is there to control this pain. So reducing the pain is a necessary aspect for clinicians and patients.

Our study is to test the efficacy of two drugs (Naproxen and Ibuprofen) in managing this pain. We have tried to see in which parameter the patient feels more pain and most minor discomfort. In a previous study, the dose of Naproxen was 550 mg, but here 500 mg of Naproxen is used instead of 550 mg to see whether a little reduction in amount alters the previous result. The last study (Omur Polat *et al*.) found that both NSAIDs could not relieve pain entirely during the treatment period. They found that complete pain relief was achieved by prescribing additional post-operative NSAIDs. In our study, we also observed whether their recommendation regarding other post-operative NSAIDs was significant or not and to find out the effectiveness between Naproxen and Ibuprofen as preoperative analgesics during orthodontic treatment.

Methods

Selection of participants:

The study was conducted in the Orthodontics department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The inclusion criteria were to the patients who were fixed orthodontic therapy administered to the selected patients, and their age was between 20 to 25 years. Patients with preexisting systemic conditions and those who declined participation were excluded from the trial.

Every day, on average 4-5 patients came for archwire placement. We select 4 participants each day and randomly assigned in the Naproxen 500mg or Ibuprofen 400 mg treatment group. Study investigator informed study details to the participants and if the participants willingly agreed to participate and signed to the informed consent form were finally enrolled. Enrollment was ongoing since the last participants had enrolled in the study.

Sample Size Calculation-

$$\frac{(z_\alpha + z_\beta)^2 \times (\delta_1{}^2 + \delta_2{}^2)}{(\mu_1 - \mu_2)^2}$$

$$= \frac{(1.96 + 0.85)^2 \times (2.75^2 + 2.81^2)}{(6.27 - 5.32)^2}$$

$$= \frac{2.8^2 \times (7.56 + 7.89)}{.95^2}$$

$$= \frac{7.896 \times 15.45}{.9025}$$

$$= \frac{121.99}{.9025}$$

$$= 135.17$$

$$n \approx 136$$

From the previous studies:

z_α = z value of standard deviation at 5% significant level

= 1.96

z_β = z value of standard deviation at 80% power

= 0.85

μ_1 = Mean of one group = 6.27

μ_2 = Mean of other group = 5.32

δ_1 = Standard deviation of one group = 2.75

δ_2 = Standard deviation of other group =2.81

Therefore the sample size for each group will be 136.

So total sample size of the two groups is 272, according to the formula.

10-15 patients in the orthodontic department of BSMMU in one month will fulfill the inclusion criteria. The study duration is six months and the sample size was roughly 70 during the study period.

In this case, the final sample size was estimated (nf) using the following formula.

$$n_f = \frac{n}{1+\frac{n}{N}} = \frac{272}{1+\frac{272}{70}} = 55.67 \approx 56$$

Where n = the desired sample size when the population is less than 10,000

n= the desired sample size, when the population is more than 10,000

N= the estimate of population size.

Therefore, the sample size was 56 (estimated sample size).

Sampling technique: Simple random sampling was done. The participants who fulfilled the inclusion criteria were given a notation number. By lottery method, 56 cases were selected for data collection during the study.

Data collection technique:

A total of 56 cases were selected in the orthodontic department and were divided into two groups of 28 each, one was administered Naproxen 500mg, and the other was administered Ibuprofen 400 mg, 1 hour before archwire placement. Using a 100mm pain scale (visual analog scale) for the intensity of discomfort felt during chewing, biting, fitting front teeth, and fitting back teeth, participants reported their levels of activation and pain experiences. The patient reported discomfort occurrence and intensity at 2, 6, 12, 24, 48, 72 hours, and 7 post-archwire days. Patients were instructed to bring the completed survey to their subsequent session.

We purchased all the drugs from the same manufacturer given to the participants. Quasi-Experimental trials were performed where simple randomized sampling was done to prevent bias. The data were submitted for statistical analysis.

A sheet marked for the time of recording with a 100mm visual analgesic scale for recording the pain was given to the patients.

Data management:

After collecting data, the questionnaires were manually checked, and if any discrepancies were found those were solved immediately by participants over the phone. After completion of data collection, all data were entered in Microsoft Excel and later converted to SPSS. Data checking and cleaning were performed in SPSS. Data were screened and chewed for any kind of missing values and discrepancies.

Ethical consideration:

The research protocol was approved by the ethical committee (Local Ethical Committee Institutional review board) of BSMMU, Memo no: BSMMU/2015/1296, dated 16-08-2015. A detailed medical history was taken from the participants to see whether there was any systemic disease. Participants with any type of systemic disease or contraindication to NSAIDs were excluded from the study. So there is no physical risk to the participants throughout the study period. All participants will be provided with a case number to maintain their confidentiality. Participant or legal guardian wrote informed consent was obtained. As a result of the technique, both doctors and patients were better able to make informed decisions on how to handle the situation.

Statistical analysis:

All the quantitative data were expressed as numbers or percent, and quantitative data were expressed as mean and standard deviation. Data analysis was performed using the Statistical Package for Social Science (SPSS) for Windows (version 20) and STATA version 15. Data normality (data distribution patterns) and homogeneity of variances were checked by qq-plot or histogram. A mixed model ANCOVA was used to follow up the pain level as an outcome variable and given medication as an independent variable, to investigate the control of pain between the two treatment groups. The least significant difference (LSD) was used for multiple comparison tests of the severity of pain between the treatment groups. All the patients were repeatedly observed after archwire placement in regular intervals. So to assess the treatment effects on changes in pain levels, the Generalized Estimating Equation (GEE model was analyzed using an exchangeable correlation matrix). We then consider the treatment effects on changes in pain levels adjusted by age, sex, time, and the interaction between the treatment arm and time. A p-value$\leq$0.05 was considered significant.

Results

A total of 56 patients came to BSMMU for orthodontic Archwire replacement in 2016 (April 2016 to September 2016). The mean age of the participants in this study was 22.84±1.45 years, and the period between the two treatments arms was similar (Table 1). The majority of the patients in this study were female, 83.9% (47/56). At hours 24 and 48, most of the patients had reported the highest pain level, but in both the treatment arms, female patients had a lower level of pain than men.

Table 1: Basic characteristics of the study participants.

Variables	Ibuprofen, n=28	Naproxen, n=28
Age (mean±SD)	22.75±1.46	22.93±1.46
Sex		
Male. n(%)	4 (14.30%)	5 (17.90%)
Female, n (%)	24 (85.70%)	23 (82.10%)
The highest level of pain is stratified by Sex (Pain level, hr)		
Chewing food, Pain level (Hour)		
Male	8.00 (24hr)	4.40 (12 hr)
Female	6.43 (24hr)	3.91 (48hr)
Biting food, Pain level (Hour)		
Male	8.25 (24hr)	6.80 (6th hr)
Female	7.21 (24hr)	6.43 (48hr)
Fitting back teeth, Pain level (Hour)		
Male	8.50 (48hr)	6.60 (48hr)
Female	7.13 (24hr)	6.78 (48hr)
Fitting front teeth, Pain level (Hour)		
Male	6.75 (24hr)	4.40 (24hr)
Female	4.71 (24 hr)	3.48 (48hr)

Data are presented as mean ± standard deviation or number with the percentage in parentheses.

ANCOVA model was applied to compare the difference in pain mean level of the two treatment groups at various time intervals. Age and sex were used as the covariates. A significant decreased of mean pain level at Naproxen group compared to ibuprofen group for chewing food at 6th($p=0.002$), 12th($p=0.004$), 24th($p<0.000$), 48th($p<0.000$) and 72 hour ($p<0.000$) respectively (Table 2). Whereas for biting food, pain levels decreased significantly only at the 24th hour (($p<0.000$) in the Naproxen group compared to Ibuprofen. Pain in fitting back teeth was also significantly decreased in the Naproxen group on the 6th ($p=0.005$), 12th ($p<0.000$), and day 7 ($p<0.000$), respectively. While for fitting front teeth, pain levels were also manifestly decreasing at 24th ($p=0.004$) and 72 hours ($p=0.03$) in the Naproxen group compared to the Ibuprofen group (Table 2). But both the fitting back and front teeth pain not significantly decreasing at the same time.

Table 2: Comparison of mean pain level between the two treatment arms during the study period.

	2 hr	p	6 hr	p	12 hr	p	24 hr	p	48 hr	p	72 hr	p	7 days	p
Chewing food														
Ibuprofen	2.12±1.84		3.40±1.73		5.00±2.01		6.41±1.91		5.46±1.77		5.01±2.06	<.000	1.54±1.48	
Naproxen	1.63±1.52	0.28	1.89±1.79	0.002	3.36±2.31	0.004	3.05±1.93	<.000	3.79±1.13	<.000	2.27±1.94		1.43±0.57	0.72
Biting food														
Ibuprofen	2.11±1.84		4.48±1.93		5.12±2.17	0.96	7.19±1.66		6.11±1.73		4.07±2.05	0.46	2.19±1.54	
Naproxen	2.29±1.94	0.72	5.38±2.78	0.14	5.10±1.88		5.10±1.88	<.000	6.42±1.91	0.53	4.47±1.93		1.99±0.82	0.56
Fitting back teeth														
Ibuprofen	2.13±1.84		5.11±1.97		6.42±1.91	<.000	7.29±1.70		7.08±1.74		6.23±1.97	0.71	6.24±1.94	
Naproxen	1.62±1.52	0.26	3.50±2.27	0.005	2.29±1.74		6.43±1.91	0.08	6.75±2.12	0.53	6.42±1.91		2.19±1.54	<.000
Fitting front teeth														
Ibuprofen	1.99±1.39		2.00±1.39		3.31±1.57	0.62	5.00±2.02		3.70±1.21		3.67±1.79	0.03	1.10±1.13	
Naproxen	1.40±1.45	0.13	1.57±1.03	0.20	3.55±1.95		3.35±2.23	0.004	3.33±1.57	0.33	2.54±1.80		0.65±1.06	0.13

Data are presented as mean ± standard deviation. Both groups had the same number (n=28) of patients. Significance p≤0.05.

The generalized estimating equation (GEE) model showed that chewing food teeth pain (Beta coefficient, β=-1.97, 95% confidence interval, CI -2.76, -1.19) and fitting front teeth pain (β =-1.09, 95% CI -1.98, -0.20) was significantly decreasing in the overall period (2nd, 6th, 12th,24th, 48th, 72th and 168 hours) among those patients who got treatment Naproxen group compared to Ibuprofen group (Table 3/Figure 1).

Table 3: Longitudinal change in pain levels in the Naproxen group compared to Ibuprofen.

	Crude		Adjusted	
	β(95% CI)	p-value	β(95% CI)	p-value
Naproxen				
Chewing food	-1.66(-2.40, -0.92)	<0.000	-1.97(-2.76, -1.19)	<0.000
Biting food	-0.10(-0.86, 0.67)	0.81	-0.07(-0.90, 0.77)	0.87
Fitting front teeth	-1.62(-2.43, -0.80)	<0.000	-1.09(-1.98, -0.20)	0.01
Fitting back teeth	-0.64(-1.31, 0.03)	0.06	-0.61(-1.31, 0.10)	0.09

Data is presented as a beta coefficient (β-coefficient) with 95% confidence intervals. The model was adjusted for age, sex, time, and the interaction between the treatment arm and time.

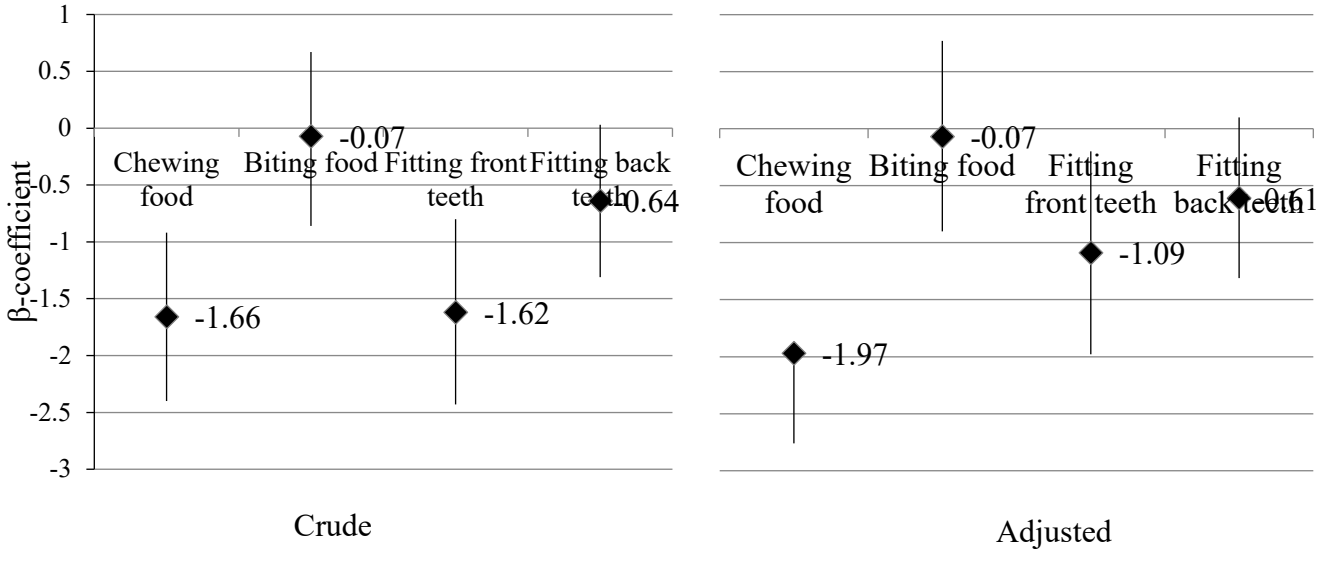
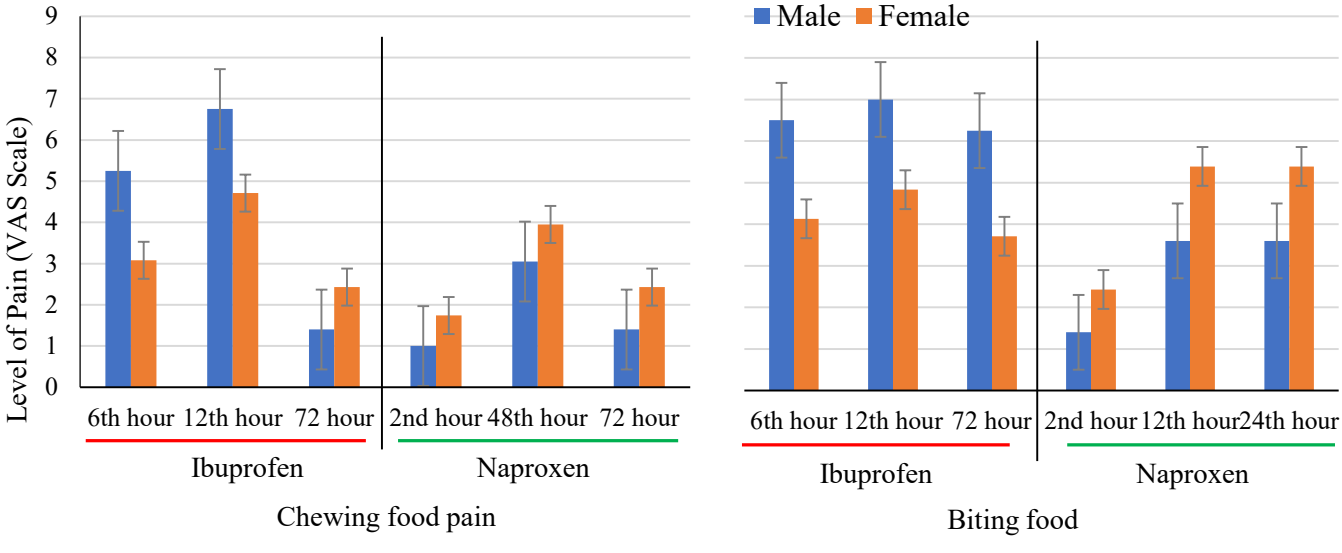


Figure 1: Longitudinal change in pain levels in the Naproxen group compared to Ibuprofen. The model was adjusted for age, sex, time, and the interaction between the treatment arm and time.

The stratified ANCOVA model adjusted by age showed that the pain level in chewing food, biting food pain, fitting back teeth pain, and fitting front teeth pain significantly differed for sex in different time points (Figure 2). The Ibuprofen group significantly decreased female pain levels compared to males in the various time points, whereas the Naproxen group significantly decreased male pain levels compared to females in the different time points.



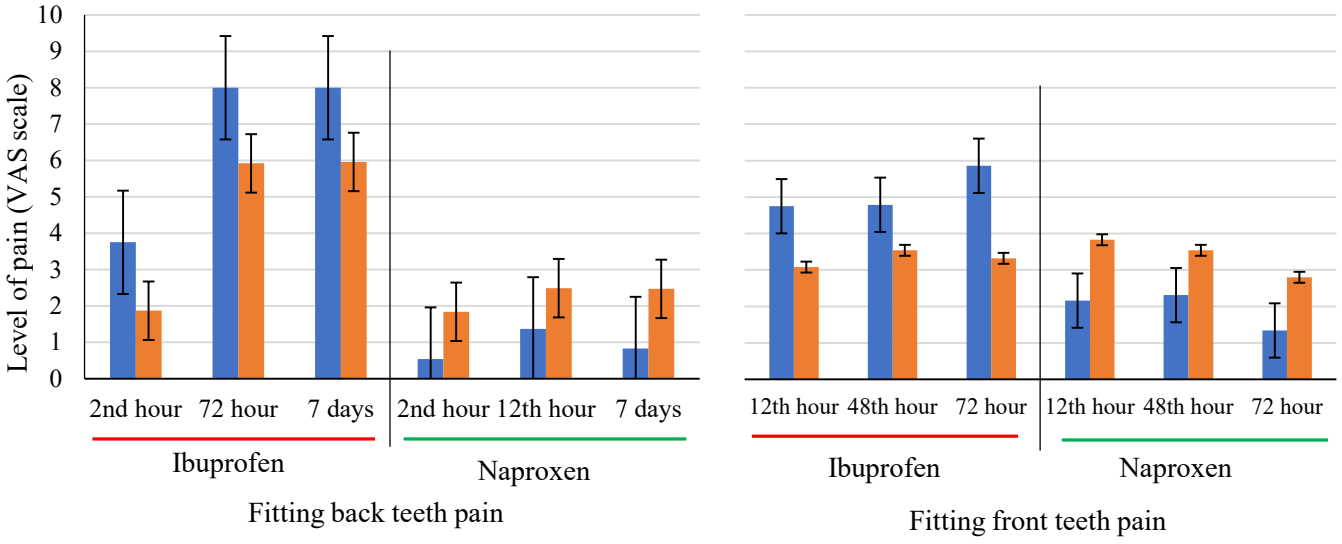


Figure 2: Level of pain in two treatment groups stratified by sex.

Discussion

Mediators such as cyclic nucleotides and prostaglandins have been suggested as mediators of bone resorption and tooth movement.[16,17] One of the primary mediators of this inflammatory response that promotes vascular dilatation and permeability and causes bone resorption via osteoclastic cell activation is a prostaglandin, prostaglandinE2 (PGE2).[18,19] This inflammatory response is liable for pain in patients. As no study was reported on preoperative Ibuprophen versus Naproxen for pain control after orthodontic archwire placement at BSMMU, this study would test the effectiveness of two drugs (Ibuprophen and Naproxen) in the management of this pain and recommend whether a longer-acting and the safer drug is needed for orthodontic pain control.

Naproxen reduces discomfort following archwire insertion in this experiment. We compared Ibuprophen and Naproxen for pain management following archwire implantation and activation. This study included 48 Bangladeshi adults who had archwire placement. The patients who were included in this study got randomly Ibuprofen (400mg) (n=28) or Naproxen (500mg) (n=28). All the patients were given a single oral dosage an hour before the operation.

After the treatment, the patient was given directions and asked to complete a questionnaire. The questionnaire was a seven-page booklet with a 100-mm horizontal VAS where patients could mark how uncomfortable they were. Patients had to keep the pain/discomfort scale every time they chewed, bite, put their front teeth together, or put their back teeth together. After 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, and seven days, the patient wrote down how much pain they were feeling. The questionnaire was due at the final appointment. There was no good way to objectively measure pain response, so we used the PPA 100-mm VAS, which was shown to be a simple and reliable way to measure pain intensity from the patient's perspective.[20]

Various trials pain control trials after archwire placement were administered that Naproxen significantly reduced pain than other treatment.[1] There is no published data on pain control after archwire placement in Bangladesh. There was no difference between the sex and level of pain in the previous studies. But in this study, we found a significant difference in pain levels in sex for two treatment groups. Pain-reducing capability is higher for males in the Naproxen group, while pain-reducing ability is higher in the Ibuprofen group for females. However, we have less number of males compared to females.

The result of the study revealed that those patients who administrated Naproxen (500mg) preoperatively felt significantly lower pain than Ibuprofen at six-hour, twelve hours, twenty-four hours, forty-eight hours, and seventy-two hours in chewing food, only at twenty-four hours for biting food, while for fitting back teeth at six hours, twelve hours and seven days and for fitting front teeth at twenty-four hours and seventy-two hours.

Results for both chewing and biting pain were identical, with except no variations in pain levels were seen here between the two experimental groups two hours after the trial began. Jackson *et al.*, Dionne, and Cooper found before that taking NSAIDs before oral surgery could delay the start of pain and make it less severe. Prostaglandin formation in peripheral tissue is probably stopped, which has an anti-inflammatory effect before surgery. If NSAIDs were taken before the process, the body would take them in before prostaglandins were made. This would make the inflammation response less severe. Based on this study's results, when compared to the Ibuprofen group, the Naproxen sodium group had much less pain 12 and 24 hours after archwire placement compared to the Ibuprofen group.

So far, only ibuprofen has been used in a study as a preoperative analgesic administered one hour before to archwire installation.[21,23] Law *et al.* found that taking ibuprofen or a placebo before surgery reduced pain from chewing much compared to taking it after surgery. Similarly, Bernhart *et al.* found that patients who took pre- or postoperative ibuprofen reported less discomfort than those who took only postoperative ibuprofen.

This study also revealed that the overall change of pain levels for chewing and fitting back teeth significantly decreased during the study period but no significant difference was observed for biting and fitting front teeth. This finding is a big step forward in the search for effective painkillers after archwire placement in orthodontics: the first study shows the overall pain reduction during the study period using the generalized estimating equation (GEE) model, which is minimize the inter co-linearity for each participant. Naproxen sodium one hour before archwire implantation reduced pain. The multidimensional nature of pain may explain why these two studies and this one disagree about ibuprofen's analgesic impact. How a person reacts to pain depends on things like how much pain they've felt before, how old they are, what kind of device they're using, how they're feeling right now, how stressed they are, and what their social status is.[20]

Some of the NSAIDs' most common side effects or duodenal ulcers, gastrointestinal bleeding, renal insufficiency, asthma, allergies, high blood pressure, congestive heart failure, atherosclerosis, and interactions with drugs that treat high blood pressure. Salmassain R. *et al*. found that ibuprofen stopped prostaglandin E (PGE) manufacturing capacity in the periodontal tissues, which slowed the rate at which teeth moved.[24]

In the previous study, we observed that acetaminophen is indeed the best painkiller for relieving braces painthough acetaminophen might have lowered the level of prostaglandin in the periodontal ligament, the percentage of tooth movement was not much different from that of the controls.[25-26] Walker and Buring found that NSAIDs stop the cyclooxygenase pathway from working, which stops PGE from being made.[27] This was thought that NSAIDs might also prevent the osteoclastic activity needed for teeth to move, which would slow the rate at which orthodontic teeth move.[28,29] We take higher anti-inflammatory doses than OTC. After orthodontic procedures, lesser doses of anti-inflammatory medicines are administered for 1-3 days. In healthy people without systemic disorders, our doses are typically removed from the body before orthodontic tooth movement.

Although there is an unavailability of standard care analgesics to relieve pain caused by fixed orthodontic appliances, in our study, we aimed to compare the analgesic effect of ibuprofen and naproxen sodium for better management of tooth archwire placement pain, where we found that Naproxen was superior then Ibuprofen. However, further in-depth studies are needed before concluding to evaluate more effective, safer, and longer-acting NSAIDs.

Limitations

The research has several drawbacks. First, the sample size was relatively small, but the study was strorobustugh based on the expected effect size, and a big more significant able would help get better results. Secondly, the age group could be the more significant issue for this study to conclude for any final decision; in this study, we had only the age group between 20 to 25 years. So, this study provides a strong intimation of the potential for pain control after orthodontic archwire placement. Thirdly, we have a difference in sex for both treatment groups. Importantly, in contradiction to our findings, none of the other trials showed any pain for the sex difference.

Conclusion

When compared with preoperatively given ibuprofen, naproxen sodium (500 mg) taken one hour before archwire installation significantly lowered the degree of discomfort at different time points (400 mg). Because the majority of patients have their worst pain between 12

and 24 hours after having an archwire placed, it has been shown that a single preoperative dose of an analgesic is not enough to treat pain effectively. In this study, we found that females felt less pain than mail at different time points, and Ibuprofen was found more effective in females, whereas naproxen worked more in males.

References

1. Nathalia Jimenez, Gerardo Moreno, Mei Leng, Dedra Buchwald, Leo S Morales. Patient-reported quality of pain treatment and use of interpreters in spanish-speaking patients hospitalized for obstetric and gynecological care. J Gen Intern Med 2012 Dec;27(12):1602-8. doi: 10.1007/s11606-012-2154-x. Epub 2012 Jul 11.
2. G Thomas Kluemper, Douglas G Hiser, Mary Kay Rayens, Michael J Jay. Efficacy of a wax containing benzocaine in the relief of oral mucosal pain caused by orthodontic appliances. Am J Orthod Dentofacial Orthop. 2002 Oct;122(4):359-65. doi: 10.1067/mod.2002.126405.
3. R G Oliver, Y M Knapman. Attitudes to orthodontic treatment. Br J Orthod. 1985 Oct;12(4):179-88. doi: 10.1179/bjo.12.4.179.
4. Aiste Kavaliauskiene 1, Dalia Smailiene, Ieva Buskiene, Daiva Keriene. Pain and discomfort perception among patients undergoing orthodontic treatment: results from one month follow-up study. Stomatologija, 2012;14(4):118-25.
5. Mladen Otasevic, Farhad B Naini, Daljit S Gill, Robert T Lee. Prospective randomized clinical trial comparing the effects of a masticatory bite wafer and avoidance of hard food on pain associated with initial orthodontic tooth movement. Am J Orthod Dentofacial Orthop. 2006 Jul;130(1):6.e9-15. doi: 10.1016/j.ajodo.2005.11.033.
6. Nelli Koritsánszky 1, Melinda Madléna. pain and discomfort in orthodontic treatments. Literature review. Fogorv Sz. 2011 Dec;104(4):117-21.
7. K K Lew. Attitudes and perceptions of adults towards orthodontic treatment in an Asian community. Community Dent Oral Epidemiol, 1993 Feb;21(1):31-5. doi: 10.1111/j.1600-0528.1993.tb00715.x.
8. Sujoy Banerjee, Rajlakshmi Banerjee, Usha Shenoy, Sanket Agarkar, Sangeeta Bhattacharya. Effect of orthodontic pain on quality of life of patients undergoing orthodontic treatment. Indian J Dent Res. 2018 Jan-Feb;29(1):4-9. doi: 10.4103/ijdr.IJDR_113_16.
9. Sergl HG, Klages U, Zentner A. Pain and discomfort during orthodontic treatment: causative factors and effects on compliance. Am J Orthod Dentofacial Orthop. 1998 Dec;114(6):684-91. doi: 10.1016/s0889-5406(98)70201-x.
10. Judit Symmank, Sophie Appel , Jana Asisa Bastian, Isabel Knaup, Jana Marciniak, Christoph-Ludwig Hennig, Annika Döding, Ulrike Schulze-Späte, Collin Jacobs, Michael Wolf. Hyperlipidemic Conditions Impact Force-Induced Inflammatory Response of Human Periodontal Ligament Fibroblasts Concomitantly Challenged with P. gingivalis-LPS. Int J Mol Sci, 2021 Jun 4;22(11):6069. doi: 10.3390/ijms22116069.
11. L Furstman, S Bernick. Clinical considerations of the periodontium. Am J Orthod. 1972 Feb;61(2):138-55. doi: 10.1016/0002-9416(72)90092-9.
12. Tilo Grosser; Emer Smyth; Garret A. FitzGerald. Anti-inflammatory, Antipyretic, and Analgesic Agents; Pharmacotherapy of Gout. The Pharmacological Basis of Therapeutics. https://accessbiomedicalscience.mhmedical.com/book.aspx?bookid=1613
13. Omur Polat, Ali Ihya Karaman, Ercan Durmus. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. Angle Orthod, 2005 Sep;75(5):791-6. doi: 10.1043/0003-3219(2005)75 [791:EOPIAN]2.0.CO;2.
14. Henry McQuay, Dawn Carroll, Andrew Moore. Variation in the placebo effect in randomised controlled trials of analgesics: all is as blind as it seems. Pain, 1996 Feb;64(2):331-335. doi: 10.1016/0304-3959(95)00116-6.
15. P M Roth, W J Thrash. Effect of transcutaneous electrical nerve stimulation for controlling pain associated with orthodontic tooth movement. Am J Orthod Dentofacial Orthop 1986 Aug;90(2):132-8. doi: 10.1016/0889-5406(86)90045-4.
16. Moshabab A Asiry. Biological aspects of orthodontic tooth movement: A review of literature. Saudi J Biol Sci, 2018 Sep;25(6):1027-1032. doi: 10.1016/j.sjbs.2018.03.008. Epub 2018 Mar 14.

17. K Yamasaki. The role of cyclic AMP, calcium, and prostaglandins in the induction of osteoclastic bone resorption associated with experimental tooth movement. J Dent Res, 1983 Aug;62(8):877-81. doi: 10.1177/00220345830620080501.
18. Steven K Juhn 1, Min-Kyo Jung, Mark D Hoffman, Brian R Drew, Diego A Preciado, Nicholas J Sausen. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. Clin Exp Otorhinolaryngol. 2008 Sep;1(3):117-38. doi: 10.3342/ceo.2008.1.3.117. Epub 2008 Sep 30.
19. S Koka, R A Reinhardt. Periodontal pathogen-related stimulation indicates unique phenotype of primary cultured human fibroblasts from gingiva and periodontal ligament: implications for oral health disease. J Prosthet Dent, 1997 Feb;77(2):191-6. doi: 10.1016/s0022-3913(97)70234-8.
20. Marianne Bergius 1, Ulf Berggren, Stavros Kiliaridis. Experience of pain during an orthodontic procedure. Eur J Oral Sci. 2002 Apr;110(2):92-8. doi: 10.1034/j.1600-0722.2002.11193.x.
21. S L Steen Law 1, K A Southard, A S Law, H L Logan, J R Jakobsen. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. Am J Orthod Dentofacial Orthop. 2000 Dec;118(6):629-35. doi: 10.1067/mod.2000.110638.
22. Bird SE, Williams K, Kula K. Preoperative acetaminophen vs ibuprofen for control of pain after orthodontic separator placement. Am J Orthod Dentofacial Orthop. 2007 Oct;132(4):504-10. doi: 10.1016/j.ajodo.2006.11.019.
23. Bernhardt MK, Southard KA, Batterson KD, Logan HL, Baker KA, Jakobsen JR. The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. Am J Orthod Dentofacial Orthop. 2001 Jul;120(1):20-7. doi: 10.1067/mod.2001.115616.
24. Reza Salmassian 1, Larry J Oesterle, W Craig Shellhart, Sheldon M Newman. Comparison of the efficacy of ibuprofen and acetaminophen in controlling pain after orthodontic tooth movement. Am J Orthod Dentofacial Orthop. 2009 Apr;135(4):516-21. doi: 10.1016/j.ajodo.2007.05.020.
25. Oscar R Arias 1, Maria C Marquez-Orozco. Aspirin, acetaminophen, and ibuprofen: their effects on orthodontic tooth movement. Am J Orthod Dentofacial Orthop, 2006; 130(3):364-70. doi: 10.1016/j.ajodo.2004.12.027.
26. Kehoe MJ, Cohen SM, Zarrinnia K, Cowan A. The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin E2 synthesis and the degree and rate of orthodontic tooth movement. Angle Orthod. 1996;66(5):339-49. doi:10.1043/0003-3219(1996)066<0339:TEOAIA>2.3.CO;2.
27. J Bryan Walker, Shauna M Buring. NSAID Impairment of Orthodontic Tooth Movement. SAGE Journal. Volume 35, Issue 1, https://doi.org/10.1345/aph.1018
28. Diravidamani K, Sivalingam SK, Agarwal V. Drugs influencing orthodontic tooth movement: An overall review. J Pharm Bioallied Sci. 2012 Aug;4(Suppl 2):S299-303. doi: 10.4103/0975-7406.100278.
29. Krishnan V, Davidovitch Z. The effect of drugs on orthodontic tooth movement. Orthod Craniofac Res. 2006 Nov;9(4):163-71. doi: 10.1111/j.1601-6343.2006.00372.x.