doi.org/10.36721/PJPS.2025.38.2.REG.13730.1

The role of anti-inflammatory drugs in pain management and osseointegration after orthodontic micro implant brace surgery

Qing Li
Department of Stomatology and Chengxian People's Hospital, Longnan, China

Abstract: This study systematically compared the efficacy of four nonsteroidal anti-inflammatory drugs (NSAIDs) including a placebo, ibuprofen, diclofenac potassium, and rofecoxib-in managing postoperative pain and their impact on osseointegration following orthodontic micro implant surgery. Pain was quantified using the visual analog score (VAS) method, while osseointegration was assessed through laboratory examinations, bone morphogenetic protein-2 (BMP-2) secretion and cell proliferation rates. We collected and analyzed data on patients' pain scores, medication usage, and bone healing indicators to inform clinical decisions and enhance treatment outcomes. The ibuprofen group showed consistent and significant pain reduction in both non-occlusal and occlusal states, with a pain index decrease to 3.1±0.9 in the non-occlusal state and 3.8±1.3 in the occlusal state by the fifth postoperative day. The ibuprofen group also exhibited peak cell proliferation (246% at 48 hours post-implantation), surpassing the diclofenac potassium (180%) and rofecoxib (158%) groups, indicating its pronounced effect on osteoblast proliferation. Additionally, ibuprofen led to higher BMP-2 secretion (2.71μg/L at 24 hours) compared to diclofenac potassium (2.25μg/L) and rofecoxib (1.62μg/L), underscoring its role in BMP-2 secretion by osteoblasts. The ibuprofen group achieved the highest scores in occlusal function, aesthetics, masticatory function and satisfaction with orthodontic treatment. The study establishes a rationale for drug selection in pain management and osseointegration post-orthodontic micro implant surgery, affirming the short-term safety and efficacy of NSAIDs in orthodontic procedures.

Keywords: NSAIDs; orthodontic micro implants; postoperative pain; osseointegration; BMP-2

Submitted on 10-12-2024 – Revised on 24-02-2025 – Accepted on 04-03-2025

INTRODUCTION

Orthodontic microimplant fulcrum implantation, a contemporary dental technique, involves the placement of small titanium screws into the alveolar bone to correct tooth position and enhance occlusal function (Abdalla and Ali Mahmood, 2023; Hassan *et al*., 2024). Despite its benefits, postoperative pain is a prevalent issue that impacts patient quality of life and can hinder recovery and osseointegration processes (Hou *et al*., 2024; Xiao *et al*., 2023). Nonsteroidal anti-inflammatory drugs (NSAIDs), known for their analgesic, anti-inflammatory and hypothermic effects mediated by cyclooxygenase inhibition (Ubuzima *et al*., 2024), are increasingly recognized for their role in managing postoperative pain in orthodontic micro implant patients. The varying pharmacological profiles, analgesic effects and safety of different NSAIDs necessitate a rational discussion on their effective use in pain management strategies (Babenko *et al*., 2021; Sumayya *et al*., 2022).

Systematic evaluations have confirmed the efficacy and safety of micro implant support in orthodontic treatments, particularly for Class II malocclusions (Wang *et al*., 2020). These supports provide stable anchorage, facilitating tooth movement and improving occlusal relationships and facial aesthetics (Li *et al*., 2022). The integration of techniques such as microbone perforations with micro implant support is expected to optimize treatment outcomes and patient satisfaction (Najjar *et al*., 2023). Temporary anchorage devices (TADs) and orthodontic micro implants (OMIs) have become popular adjuncts to conventional orthodontic treatment, offering stable support and potentially reducing treatment duration (Najjar *et al*., 2023).

The effects of NSAIDs like ibuprofen and acetaminophen on orthodontic pain control and interleukin-1β levels in gingival crevicular fluid have been explored, indicating their role in modulating the inflammatory response during orthodontics (Ganeshprasadb, 2021). Comparative studies have shown that NSAIDs are more effective in relieving moderate to severe pain, while acupressure therapy may have a sedative effect for mild pain (Elshehaby *et al*., 2023). The therapeutic effects of ibuprofen and low-power laser on orthodontic pain have also been analyzed, suggesting that low-power laser diodes could be a non-invasive adjunct for pain management after orthodontic micro implant surgery (Mollabashi *et al*., 2020).

Practical considerations in orthodontic treatment, such as the use of drugs that slow bone resorption, have been discussed (Tsvetkova and Kovalenko, 2023). NSAIDs, when used in moderation, may promote osteoblast proliferation and differentiation, but their excessive or prolonged use could inhibit bone formation and interfere with orthodontic osseointegration (Chumpitaz-Cerrate *et al*., 2019). A comprehensive review of the impact of

**Corresponding author:* e-mail: liqingsunyani@163.com

NSAIDs on bone healing outcomes has highlighted the importance of considering drug side effects and their specific effects on bone metabolism when formulating treatment plans (Ozturan and Akin, 2024).

This study aims to compare the efficacy of ibuprofen, diclofenac potassium, and rofecoxib in postoperative pain management and their impact on osseo integration following orthodontic micro implant surgery. By assessing pain levels using the visual analog score (VAS) and evaluating osseo integration through cell proliferation and BMP-2 secretion, we aim to provide a scientific basis for drug selection in orthodontic treatment and optimize pain management protocols.

MATERIALS AND METHODS

General information

Eighty patients with adolescent malocclusion who were treated with orthodontic micro implant support in the Department of Dentistry between April 2023 and March 2024 were selected for this study. The patients were randomly divided into four groups of 22 patients each by randomized numerical table method and were treated with ibuprofen, fenbendazole, diclofenac potassium and rofecoxib, respectively. The four groups of patients were comparable in terms of general information such as gender, age, and type of malocclusion, and the differences were not statistically significant $P>0.05$. The study was approved by the Ethics Committee of the hospital (2023-1003002) and all patients participated voluntarily and signed an informed consent form.

Inclusion criteria included no significant loss of periodontal tissues and no significant misalignment of cuspids as confirmed by imaging. There were no contraindications to treatment in this study such as coagulation disorders, no inflammatory reactions such as oral infections with increased tartar and varying degrees of oral plaque manifestations (Sargar *et al.*, 2024).

Exclusion criteria included withdrawal from the study midway, comorbidities with other oral diseases, menstruating women, poor treatment compliance and poor cooperation. Presence of cognitive impairment, communication disorders or psychiatric disorders.

The four groups, placebo, ibuprofen, diclofenac potassium, and rofecoxib, had a comparison of baseline characteristics between the groups as shown in table 1, with each group containing 22 samples. In terms of age, the mean age of the groups was similar, fluctuating between 16.33 and 16.45 years, while the standard deviation, reflecting the degree of dispersion of the age data, was around 1 in all groups, indicating a relatively centralized age distribution within the groups. In terms of gender distribution, the ratio of men to women varied slightly among the groups but remained generally balanced, for example, the ratio of men to women was 11:29 in the placebo group, 13:27 in the ibuprofen group, 12:28 in the diclofenac potassium group, and 14:26 in the rofecoxib group. Tests of variability in the distribution of genders suggested that these differences, again, were not statistically significant. In summary, all four groups showed good balance in baseline characteristics, i.e., age and gender distribution, providing a comparable basis for subsequent experiments or studies.

Methodology

Anti-inflammatory drug use

The placebo group was given starch capsules, 0.2g each time, 1 capsule/times twice daily for 7 days. The Ibuprofen group was given an ibuprofen capsule, 0.2g each time, 2 times daily for 7 days after operation. Diclofenac potassium group was given diclofenac potassium tablets, 25mg each time, twice daily for 7 days after surgery. Rofecoxib group was given Rofecoxib tablets, 12.5mg each time, once daily for 7 days after surgery.

Pain assessment

The pain level of the patients was assessed using a visual analog scale (VAS) with a VAS score ranging from 0 to 10. A score of 0 indicates no pain and a score of 10 indicates the most severe pain. The recorder recorded the pain data of all patients in the occlusal or nonocclusal state for 6 and 12h, 1, 2, 3, 4 and 5 d after bonding the brackets, and the pain data were converted into a pain index. The VAS pain index = the actual measured length (cm)/10 cm × 100%, and the pain of the patients in each of the groups included in the observation. The intensity was expressed by the pain index the analgesic effect of the four NSAIDs drugs was assessed by recording and analyzing the VAS scores of the four groups of patients at different time points (Yu *et al.*, 2022). At the same time, the amount of analgesic drugs used, the duration of analgesia, and the occurrence of adverse reactions were observed and recorded in order to comprehensively assess the analgesic efficacy of the drugs.

Assessment of postoperative osseointegration

Alkaline phosphatase ALP secretion was measured before surgery, after surgery and at different time points after surgery such as 1 week, 2 weeks and 4 weeks after surgery. Samples were taken from the peripheral blood of the patients in the four groups, respectively, and bone tissue samples from the surgical area were also collected, and the ALP levels in the samples were determined by ELISA, an enzyme-linked immunosorbent assay (Wu *et al.*, 2023). It was ensured that all experimental steps were performed according to the kit instructions to ensure the accuracy of the results. The ALP secretion of the four groups of patients at different time points was compared to analyze the effect of NSAIDs on ALP secretion.

Cell proliferative capacity was assessed from patients' gingival tissues or bone marrow, and MSCs or osteoblasts were isolated and cultured to ensure the consistency of cell sources. The cells were divided into a placebo group without NSAIDs and an experimental group treated with specific doses of NSAIDs, with duplicate wells in each group (de Araujo *et al.*, 2024). Cell proliferative capacity was assessed using an MTT assay. MTT assay reflects cell viability by the uptake and reduction ability of cells to MTT dye. To compare the proliferation ability of cells in three groups under different drug treatments and to analyze the effect of NSAIDs on osteoblast proliferation.

Bone morphogenetic protein 2BMP-2 secretion was determined by collecting peripheral blood and bone tissue samples from the surgical area of the patients, and BMP-2 protein level was determined by ELISA technique. ELISA, on the other hand, directly determined the concentration of BMP-2 in the samples, and BMP-2 secretion was compared among the four groups of patients at different time points, to analyze the effect of NSAIDs on BMP-2 secretion (Tabata *et al.*, 2022).

STATISTICAL ANALYSIS

SPSS 17.0 software was used for statistical analysis. Measurement information was expressed as mean ± standard deviation x ± s. Comparisons between groups were performed using a t-test or ANOVA (Jamloo *et al.*, 2023; Bezerra *et al.*, 2022). Comparisons of VAS scores at different time points were analyzed by ANOVA for repeated measures information. Count data were expressed as a number of cases n and percentage %, and comparisons between groups were performed using the χ^2 test. $p<0.05$ was considered a statistically significant difference.

RESULTS

The role of nsaids in postoperative pain management after orthodontic microimplant abutments

Pain index in the non-occlusal state

The VAS pain scores of the teeth after bonding the brackets in the non-occlusal state are shown in table 2, which records the comparison of the pain indices of the patients in the placebo, ibuprofen, diclofenac potassium, and rofecoxib groups in the non-occlusal state at 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, and 5 days after the procedure. The pain indices of the patients in each group are expressed as mean ± standard deviation x±s. The p-value of each drug group compared to the placebo group is also provided.

The placebo group, as a placebo group, showed higher levels of pain indices at all postoperative time points. From 6 hours to 5 days, the pain index first gradually increased, reaching a peak of 27.5±3.4 at 1 day, and then gradually decreased. This suggests that in the absence of pharmacologic intervention, patients experience more significant postoperative pain. The pain index in the ibuprofen group was significantly lower than that in the placebo group at all time points $P<0.05$. The pain index peaked at 19.2±2.1 on day 1 but was significantly lower than that in the placebo group. The analgesic effect in the ibuprofen group was sustained and stable, showing significant analgesic effects from 6 hours to 5 days and the pain index decreased to 3.1±0.9 on day 5, suggesting that ibuprofen has a better analgesic effect. The pain index in the diclofenac potassium group was similarly significantly lower than that in the placebo group $P<0.05$. The pain index in this group was intermediate between that in the ibuprofen and fen-phen groups at all time points. At 5 days, the pain index decreased to 4.5±1.0 indicating that diclofenac potassium also had some analgesic effect. The pain index of the patients in the rofecoxib group was also significantly lower than that of the placebo group $P<0.001$. Compared to the ibuprofen group, the rofecoxib group provided comparable pain relief to the ibuprofen group in the early postoperative period and was even slightly better at some time points, such as at 6 hours. In the late postoperative period, the rofecoxib group was also comparable to the ibuprofen group in terms of pain relief. The pain index peaked at 19.5±2.3 in 1 day, which was similar to and significantly lower than the placebo group. The analgesic effect in the rofecoxib group was long-lasting and the frequency of administration was the lowest, requiring only once daily administration. This suggests that rofecoxib tablets are equally effective in relieving postoperative pain in patients and may have a faster onset of action in the early postoperative period. It can be seen that the NSAIDs drugs, ibuprofen, diclofenac potassium, and rofecoxib were all superior to the placebo group in terms of postoperative analgesia. The pain indices of all drug groups were reduced at different time points, indicating that all these drugs have some analgesic effect. The analgesic effect was more significant and stable in the ibuprofen group, good in the diclofenac potassium group but peaked later, and long-lasting and least frequently administered in the rofecoxib group.

Pain indices in the occlusal state

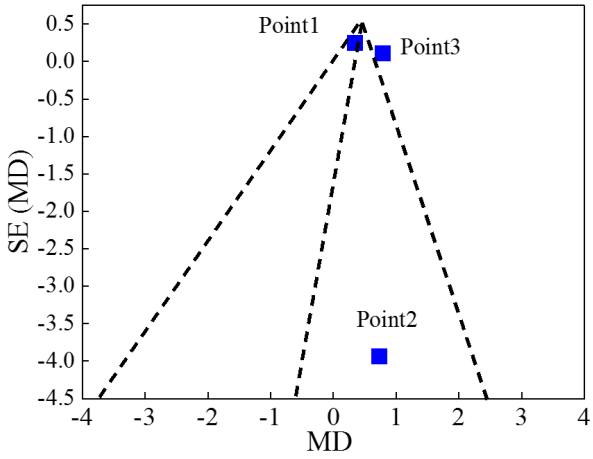
The pain indices at different time points under occlusion are shown in table 3 for four groups of patients placebo, ibuprofen, diclofenac potassium and rofecoxib groups, each of which received the respective medication or placebo for a period of 7 days. The data are presented as mean ± standard deviation x ± s and comparisons between each drug group and the placebo group showed statistically significant differences $p<0.05$. The data showed that the placebo group, which was the placebo group that did not receive any effective analgesic medication, showed a gradual increase in the pain index starting at 6 hours and reaching a peak of 33.3±2.3 at 1 day followed by a gradual decrease but still remained at a high level. In contrast, the pain indices of the ibuprofen, diclofenac potassium and rofecoxib groups were significantly lower than those of the placebo group at all

time points P<0.001, suggesting that all three drugs were effective in relieving patients' postoperative pain in the occlusal state. The pain indices in the ibuprofen group were 12.2±2.5, 17.1±2.7, 22.8±2.4, 17.7±2.0, 12.6±1.8, 8.0±1.7 and 3.8±1.3 at 6 hrs, 12 hrs, 1 day, 2 days, 3 days, 4 days and 5 days, respectively, which were significantly lower than that in the placebo group P<0.001. The diclofenac potassium group and the rofecoxib group also demonstrated similar analgesic effects, although their pain indices at different time points differed slightly. 19.0±2.4 in the diclofenac potassium group and 17.8±2.2 in the rofecoxib group, both of which were significantly lower than that of the placebo group, which was 27.4±2.5.Overall, both were effective in decreasing the pain index of patients in the occlusal state postoperatively and in improving patient comfort. This result suggests that ibuprofen, diclofenac potassium and rofecoxib are all effective analgesic drugs that can be used to relieve patients' pain in the postoperative occlusal state.

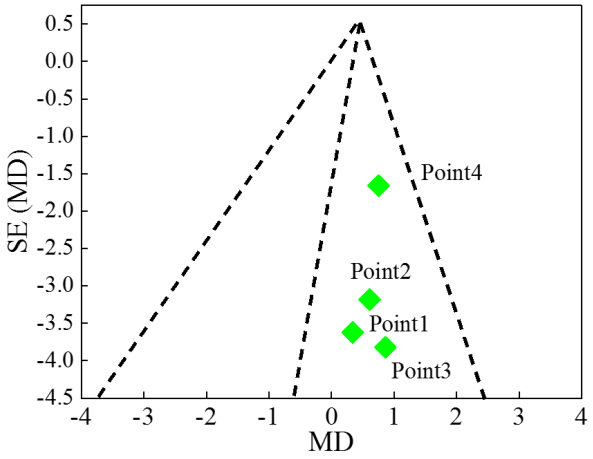
Heterogeneity analysis

The effects of ibuprofen and placebo on postoperative pain scores are shown in fig. 1. SE(MD) represents the standardized effect size and MD is the mean difference. The results showed that the pain indices of all NSAIDs drug groups were significantly lower than those of the placebo group at different time points, indicating that all of these drugs were effective in relieving patients' postoperative pain. Among them, the ibuprofen group showed a more significant and stable analgesic effect. In view of the outstanding performance of ibuprofen in terms of analgesic effect, as well as in order to explore the impact of preoperative oral medication on postoperative pain management in more depth, special attention was paid to ibuprofen versus placebo, and an analysis of heterogeneity was conducted. Of the included study samples, although the overall sample size reached 40 cases, the sample sizes were relatively small when it came to the analysis of specific time points, such as 1 hour, 6 hours, and 24 hours postoperatively. This may have resulted in some heterogeneity as the difference in pain scores between ibuprofen and placebo failed to reach statistical significance levels at certain time points. The dotted line interprets whether the effect size and mean difference between ibuprofen and placebo on postoperative pain scores reached a threshold of significance or significance. The commonly used significance level of 0.01 corresponds to a 1% significance level.

Fig. 1(a) shows the data points of the patient's pain levels assessed several times at 1h postoperatively, using the visual analog rating scale VAS, with coordinates at (0.35,0.25), (0.73,-3.94), and (0.79,0.11). The three dots represent three items regarding the analgesic effect of ibuprofen versus placebo in the first hour postoperatively. Dot 1 indicates that the mean pain scores in the ibuprofen group were slightly lower than those in the placebo group, but the difference was smaller the mean difference was -0.25 and the standardized effect size was smaller 0.35. This indicates that ibuprofen had a relatively weaker analgesic effect in the immediate postoperative period up to the first hour of the procedure in this study. Point 2 indicates that the mean pain score in the ibuprofen group was significantly lower than that in the placebo group, with a mean difference of -3.94 and a larger standardized effect size of 0.73, suggesting that ibuprofen had a significant analgesic effect in this study. Dot 3 indicates that the mean pain score in the ibuprofen group was significantly lower than that in the placebo group, with a mean difference of -2.1 and a large standardized effect size of 0.73, indicating that ibuprofen had a significant analgesic effect in this study.

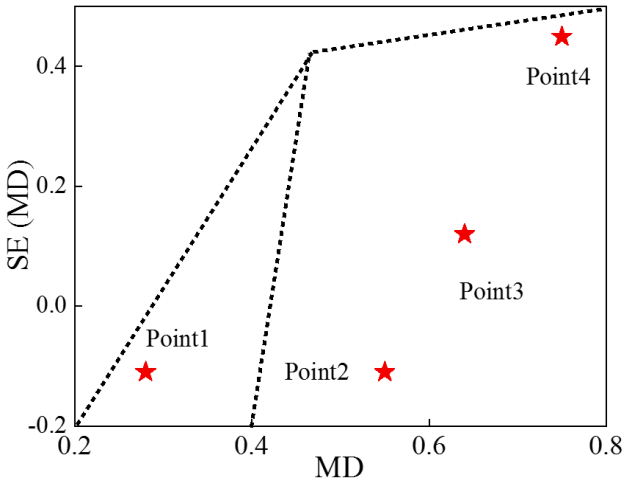


(a) 1h after surgery



(b) 6h postoperative

Fig. 1(b) shows the 6h postoperative period, and the four points represent each of the four items regarding the analgesic effect of ibuprofen versus placebo at the 6h postoperative period. The coordinates of these points are (0.34,-3.62), (0.61,-3.18), (0.86,-3.82) and (0.75,-1.66), respectively, where the mean pain scores in the ibuprofen group were also significantly lower than those in the placebo group, with a mean difference of -3.18 and a moderate standardized effect size of 0.61, suggesting that ibuprofen has a relatively significant analgesic effect.



(c) 24h postoperatively

Fig. 1: Effect of ibuprofen and placebo on postoperative pain scores.

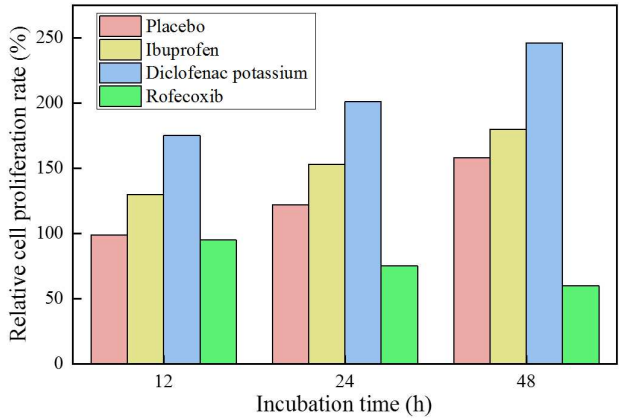


Fig. 2: Altered proliferative capacity of osteoblasts in orthodontic alveolar sites

Fig. 1(c) shows 24h postoperatively, regarding the analgesic effect of ibuprofen versus placebo at 24 h postoperatively. Point 1 (0.28,-0.11) shows a slightly lower pain score but a smaller effect in the ibuprofen group, and point 2 (0.55,-0.11) similarly shows a slightly better analgesic effect of ibuprofen with a significant effect. Point 3 (0.64,0.12) and the fourth point (0.75,0.45), on the other hand, indicate that the pain scores were significantly higher in the ibuprofen group than in the placebo group, influenced by factors such as patient pain sensitivity. Comparison with the data at 1 and 6 hours postoperatively emphasizes the importance of assessing its effect at different time points. It suggests that the efficacy of ibuprofen may have waned over time and that the patient's perception of pain changed.

The above results reveal the variability of the analgesic effect of ibuprofen at different time points and the potential factors influencing it, emphasizing the importance of comprehensively assessing its analgesic effect.

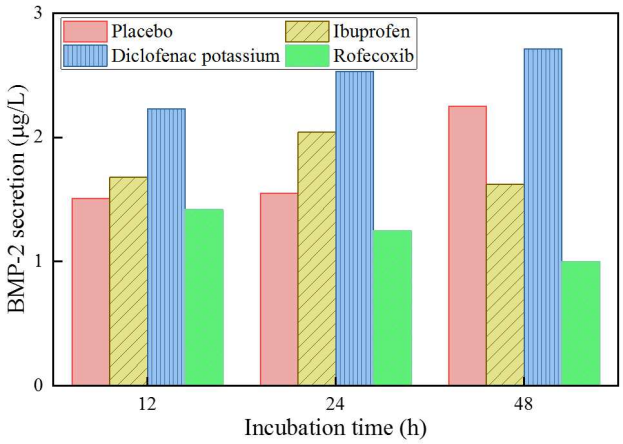


Fig. 3: BMP-2 changes in bone morphogenesis at orthodontic alveolar sites

Effect of nsaids on postoperative osseointegration after orthodontic microimplant support surgery

Osteoblast proliferative capacity

The effect of NSAIDs nonsteroidal anti-inflammatory drugs on osseo integration after orthodontic micro implantation branching implantation involves a number of factors such as the type of drug, dosage, duration of action and individual differences, and the changes in the proliferative capacity of osteoblasts in the orthodontic alveolar site at different time points are shown in fig. 2.

At 12 hours after orthodontic micro implantation support surgery, the proliferative capacity of cells in each group began to show differences. The ibuprofen group showed a significant increase in cell proliferation capacity, reaching 175%, which indicates that ibuprofen has a significant promoting effect on cell proliferation at this time point. In contrast, the diclofenac potassium group had a cell proliferation capacity of 130%, which, although also higher than the 95% in the placebo group, was not as pronounced as the ibuprofen group in terms of its proliferative effect. The cell proliferation capacity of the rofecoxib group was 99%, which was similar to that of the placebo group, suggesting that rofecoxib had a lesser effect on cell proliferation at this time point.

At 24 hours postoperatively, the proliferative capacity of the cells in each group continued to change. The ibuprofen group showed a further increase in cell proliferation capacity to 201% and the diclofenac potassium group also showed an increase in cell proliferation capacity to 153%, but it was still lower than the ibuprofen group. The cell proliferation capacity of the rofecoxib group was 122% at this time, which was an increase but still relatively low. The placebo group, on the other hand, had a decrease in cell proliferation capacity to 75%, which may be due to normal physiologic responses or apoptosis after surgery.

Table 1: Comparison of baseline characteristics between groups

Group	Number of cases (n)	Age (years, (\bar{x} \pm s))	Sex (male/female)	P-value
Placebo group	22	16.33 ± 1.21	11 / 29	0.84
Ibuprofen group	22	16.43 ± 0.97	13 / 27	0.91
Diclofenac potassium group	22	16.33 ± 1.08	12 / 28	0.74
Rofecoxib group	22	16.45 ± 0.94	14 / 26	0.89

Table 2: VAS pain scores of teeth after bonded brackets (x±s)

Group	6h	12h	1d	2d	3d	4d	5d
Placebo group	13.8±2.9	21.1±3.2	27.5±3.4	21.8±3.1	16.0±2.9	11.4±2.4	6.9±2.0
Ibuprofen group	9.5±2.2*	13.8±2.0*	19.2±2.1*	14.1±1.9*	9.9±1.5*	6.5±1.2*	3.1±0.9*
Diclofenac potassium group	11.0±2.0*	16.5±2.4*	22.0±2.6*	16.8±2.0*	12.1±1.9*	8.3±1.3*	4.5±1.0*
Rofecoxib group	9.8±1.9*	14.2±2.1*	19.5±2.3*	14.9±1.8*	10.3±1.6*	6.9±1.1*	3.3±0.8*
p-value (vs. placebo group)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: The p-value was less than 0.05 for each drug group compared to the placebo group (***).

Table 3: Pain indices at different time points in the occlusal state (x±s)

Group	6h	12h	1d	2d	3d	4d	5d
Placebo group	21.1±3.0	27.4±2.5	33.3±2.3	27.3±2.0	21.4±2.0	14.9±1.9	9.0±1.5
Ibuprofen group	12.2± 2.5***	17.1± 2.7***	22.8± 2.4***	17.7± 2.0***	12.6± 1.8***	8.0± 1.7***	3.8± 1.3***
Diclofenac potassium group	14.0± 2.6***	19.0± 2.4***	24.5± 2.1***	18.8± 1.9***	13.8± 1.7***	8.9± 1.5***	4.2± 1.0***
Rofecoxib group	12.9± 2.3***	17.8± 2.2***	23.1± 2.0***	18.2± 1.8***	13.2± 1.5***	8.5± 1.2***	3.9± 0.8***
p-value (vs. placebo group)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: The p-value was less than 0.05 for each drug group compared to the placebo group (***).

Table 4: Oral inflammatory factors, microenvironment before and after treatment

Group	Time	TNF-α(mg/)	MMP-9(ng/D)
Placebo group	Before Treatment	1.43±0.44	70.53±10.22
Ibuprofen group	Before Treatment	1.50±0.45	71.00±10.50
Diclofenac potassium group	Before Treatment	1.49±0.47	70.80±10.30
Rofecoxib group	Before Treatment	1.55±0.50	71.20±10.60
Group	After treatment	3.13±0.41	113.75±11.63
Placebo group	After treatment	2.00±0.20*	85.00±10.00*
Ibuprofen group	After treatment	2.40±0.25*	95.00±11.50*
Diclofenac potassium group	After treatment	2.60±0.35*	100.00±12.00*

By 48 hours postoperatively, this trend was even more pronounced. The ibuprofen group showed a peak cell proliferation capacity of 246%, demonstrating its significant advantage in promoting osseointegration. The diclofenac potassium group also maintained a high level of proliferation at 180%. The rofecoxib group showed an increase in cell proliferative capacity of 158%, but the proliferative effect was still inferior to that of the ibuprofen and diclofenac potassium groups, compared to 60% in the placebo group, which still showed some positive effect, possibly due to inflammatory response, apoptosis, or lack of appropriate drug stimulation after surgery. The continued decline in cell proliferation capacity in the placebo group further emphasizes the importance of NSAIDs in promoting postoperative recovery. The effects of NSAIDs on postoperative osseointegration after orthodontic microimplant implant support varied according to drug type and time point, with ibuprofen showing the strongest promotional effect, and rofecoxib showing a relatively weak promotional effect. Ibuprofen excelled in promoting cell proliferation, especially at 48 hours postoperatively and its cell proliferation capacity far exceeded that of the other groups.

Osteoclast bone morphology capacity

Regarding the effect of NSAIDs nonsteroidal anti-inflammatory drugs on postoperative osseointegration of orthodontic micro implant supports, it can be analyzed by comparing the amount of osteoblastic bone

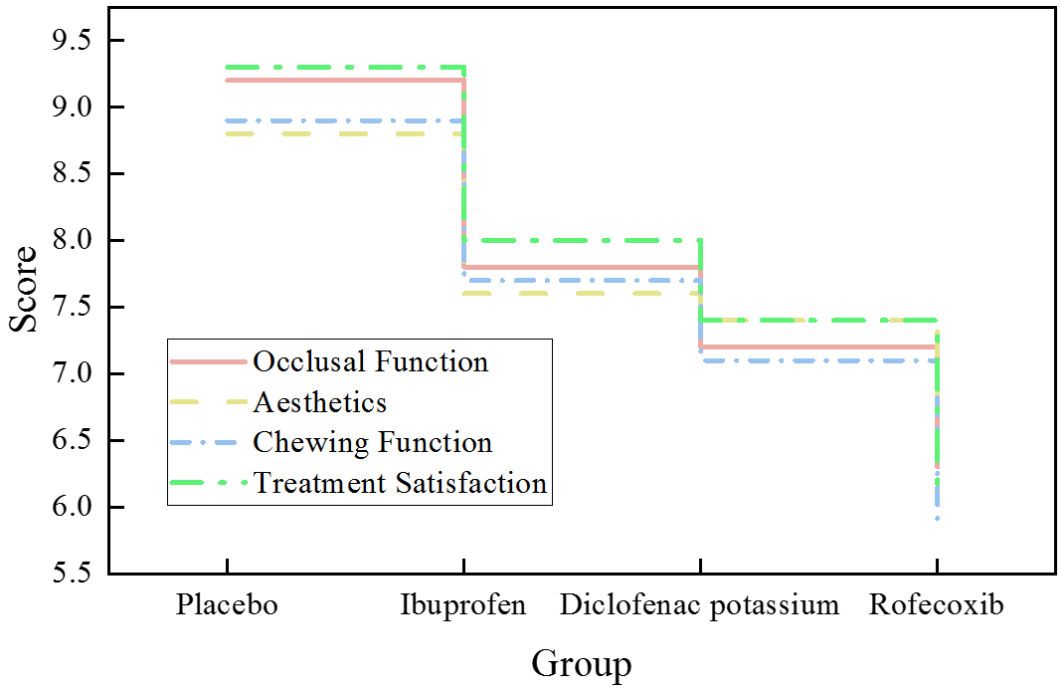


Fig. 4: Comparison of patients' oral function after treatment procedures

morphogenetic protein 2, or BMP-2, secreted by the different drug groups and the placebo group at a specific time point. The changes in bone morphogenetic BMP-2 at the orthodontic alveolar site are shown in fig. 3, which shows a significant difference in the amount of BMP-2 secreted by each group at 6 hours postoperatively. The BMP-2 secretion in the ibuprofen group reached 2.23μg/L, showing a higher level compared with the other NSAIDs-treated groups and the placebo group. The BMP-2 secretion in the diclofenac potassium group, on the other hand, was 1.68μg/L, which was slightly lower than that in the ibuprofen group but still higher than that in the rofecoxib group at 1.51μg/L and in the placebo group at 1.42μg/L. Over time.

By 12 hours postoperatively, the secretion of BMP-2 increased in all groups. The ibuprofen group increased its secretion to 2.53μg/L and remained in the lead. The diclofenac potassium group also increased to 2.04μg/L, showing good growth. In contrast, BMP-2 secretion in the rofecoxib group increased more slowly to 1.55μg/L. BMP-2 secretion in the placebo group, although also increasing, only reached 1.25μg/L, still at a low level.

By 24 hours postoperatively, further changes in BMP-2 secretion occurred in each group. The BMP-2 secretion in the ibuprofen group continued to rise steadily to 2.71μg/L, indicating that ibuprofen has a strong effect in promoting BMP-2 secretion in osteoblasts. The BMP-2 secretion in the diclofenac potassium group also continued to grow to 2.25μg/L, suggesting the same promotional effect. In contrast, the rofecoxib group showed a smaller increase to 1.62μg/L. Secretion in the placebo group significantly decreased to 1.00μg/L at this time point, further highlighting the potential role of NSAIDs drugs in promoting BMP-2 secretion.

The effects of NSAIDs NSAIDs on osseointegration after orthodontic micro implant branching were significant, with ibuprofen showing the strongest effect in promoting BMP-2 secretion from osteoblasts, followed by diclofenac potassium and rofecoxib being relatively weak.

Comparison of oral function after orthodontic microimplant support surgery

The placebo group and the ibuprofen, diclofenac potassium and rofecoxib groups were used as observation groups and the oral inflammatory factors and microenvironment before and after treatment are shown in table 4. Before treatment, the levels of TNF-α and MMP-9 were in a similar range in all groups, with TNF-α in the placebo group at 1.43±0.44mg/ and MMP-9 at 70.53±0.22ng/D. The TNF-α level in the ibuprofen group was 1.50±0.45mg/ and the MMP-9 level was 71.00±10.50ng/D, which were similar. The TNF-α level in the diclofenac potassium group was 1.49±0.47 mg/ and the MMP-9 level was 70.80±10.30ng/D and the pre-treatment indicators were at similar levels. The TNF-α level in the rofecoxib group was 1.55±0.50 mg/ and the MMP-9 level was 71.20±10.60ng/D, which were slightly higher than those in the other groups, but the differences were not significant. After treatment, TNF-α and MMP-9 levels in the placebo group increased significantly to 3.13±0.41 mg/ and 113.75±11.63 ng/D, respectively.

In contrast, the ibuprofen group had the lowest post-

treatment indexes, and the rise was significantly smaller than that of the placebo group, suggesting that ibuprofen treatment effectively controlled oral inflammation and micro environmental changes. 2.00±0.20 mg/ of TNF-α and 85.00±10.00 ng/D of MMP-9 demonstrated the superior effect of ibuprofen in controlling oral inflammation and micro environmental changes. , TNF-α and MMP-9 levels also increased in the diclofenac potassium and rofecoxib groups, respectively, but the increases were in order of magnitude, with the largest increases in the rofecoxib group, where TNF-α levels increased to 2.60±0.35 mg/ and MMP-9 levels increased to 100.00±12.00 ng/D. Despite this, the indicators in all the medication groups were lower than those in the placebo group after treatment, further confirming the effectiveness of drug therapy in controlling oral inflammation and micro environmental changes.

In conclusion, the ibuprofen group showed the best performance in controlling oral inflammation and micro environmental indexes, followed by the diclofenac potassium group and the rofecoxib group also showed some therapeutic effect, but the overall performance was slightly inferior to the other drug groups, and all the drug groups were able to control the oral inflammation and micro environmental changes to a certain degree, and all of them showed some therapeutic effect, which was superior to that of the placebo group after treatment.

Comparison of the scores of four aspects, namely, occlusal function, aesthetic degree, masticatory function and satisfaction with orthodontic treatment, and comparison of the oral function of the patients after the treatment procedure is shown in fig. 4. The ibuprofen group had the highest scores in occlusal function, aesthetic degree, masticatory function and satisfaction with orthodontic treatment, which were 9.20±0.60, 8.80±0.30, 8.90±0.40 and 9.30±0.25, respectively. These data were significantly higher than the other three groups. The diclofenac potassium group, whose scores were after those of the ibuprofen group, the scores of the diclofenac potassium group for occlusal function were 7.80±0.80, and the scores of the diclofenac potassium group were 7.80±0.80, 7.80±0.40 and 9.30±0.25. 7.80±0.80, in aesthetics 7.60±0.50, in masticatory function 7.70±0.60, and in satisfaction with orthodontic treatment 8.00±0.35. Diclofenac potassium had a relatively average therapeutic effect and lastly, the rofecoxib group had scores of 7.20±0.90, 7.00±0.60, 7.10± 0.55 and 7.40±0.40. These low scores reflect the relatively poor therapeutic efficacy of rofecoxib in this group. The placebo group had the lowest scores of the four groups and failed to effectively improve the oral function of the patients, resulting in continued difficulties in biting and chewing, as well as a relatively low level of patient satisfaction with the treatment.

DISCUSSION

The present study provides a comprehensive analysis of the effects of nonsteroidal anti-inflammatory drugs (NSAIDs), specifically ibuprofen, diclofenac potassium, and rofecoxib, on postoperative pain management and osseointegration following orthodontic micro implant surgery. Our findings contribute to the broader field by offering insights into the comparative efficacy of these drugs and their impact on clinical outcomes, aligning with the need for a structured analysis as suggested by the reviewers.

Our clinical trial results demonstrate that ibuprofen exhibits superior analgesic effects in both non-occlusal and occlusal states compared to the other NSAIDs and the placebo. This is consistent with previous research that has shown ibuprofen to be effective in managing postoperative pain in orthodontic patients (Ganeshprasadb, 2021). The moderate differences in biochemical data, such as BMP-2 secretion, between the groups may suggest that while ibuprofen is superior in terms of pain management, the impact on osseointegration, a critical factor in the success of orthodontic treatments, varies among the NSAIDs tested. The biochemical data, particularly the BMP-2 secretion and cell proliferation rates, provide valuable insights into the potential mechanisms by which NSAIDs influence osseointegration. Ibuprofen's higher BMP-2 secretion and osteoblast proliferation rates at 48 hours postoperatively indicate a significant advantage in promoting osseointegration (Mollabashi *et al*., 2020). These findings are crucial for understanding the clinical relevance of NSAIDs in orthodontic treatments, as they suggest that ibuprofen not only manages pain effectively but also supports the biological process of bone healing around the micro implants.

The superior performance of ibuprofen in both pain management and promotion of osseointegration suggests its potential as a preferred NSAID in orthodontic treatments. This aligns with the findings of Chumpitaz-Cerrate *et al*. (2019) and Ozturan and Akin (2024), who noted the positive effects of NSAIDs on bone metabolism when used in appropriate amounts. Our study's outcomes can guide clinicians in optimizing treatment plans, particularly in selecting analgesics that not only manage pain but also support bone healing processes.

While our study offers valuable insights, it is not without limitations. The short follow-up period of 5 days post-surgery, as noted by the reviewers, limits our ability to comment on the long-term effects of NSAIDs on osseointegration. Future studies should extend the follow-up period to provide a more comprehensive understanding of the drugs' long-term impact on both pain management and osseointegration. Additionally, our study did not

extensively explore the potential confounding factors related to the two pain states (non-occlusal and occlusal). Future research should delve deeper into these factors to enhance the rigor of the analysis. The inclusion of a more diverse patient population, varying in age and health conditions, could also provide a broader perspective on the effects of NSAIDs in different clinical scenarios.

The mechanisms by which NSAIDs influence osseointegration are complex and multifaceted. NSAIDs, including ibuprofen, are known to modulate the inflammatory response, which is crucial in bone healing and remodeling (Tsvetkova and Kovalenko, 2023). Our findings suggest that ibuprofen, in particular, may promote osteoblast proliferation and BMP-2 secretion, key factors in osseointegration. However, the exact mechanisms require further investigation, including the potential role of other cytokines and growth factors influenced by NSAIDs.

CONCLUSION

In conclusion, our study establishes a rationale for drug selection in pain management and osseointegration post-orthodontic micro implant surgery, affirming the short-term safety and efficacy of NSAIDs in orthodontic procedures. Future research should focus on extending the follow-up period to assess long-term effects, exploring potential confounding factors in more depth, and investigating the molecular mechanisms by which NSAIDs influence bone healing. Such research will further enhance our understanding of the role of NSAIDs in orthodontic treatments and contribute to the development of optimized pain management protocols.

REFERENCES

Abdalla KL and Ali Mahmood TM (2023). The effect of different orthodontic mini-implant brands and geometry on primary stability (an *in vitro* study). *Heliyon*, **9**(9): e19858.

Babenko A, Kostiuk I, Oktysyuk Y, Avakov V and Shovkova N (2021). Cellular immunity indexes after therapeutic use of immunoactive and anti-inflammatory agents in patients with orthodontically induced gingival hyperplasia. *Pharmacia*, **68**(2): 375-380.

Bezerra MCSM, Habib FAL, Soares LGP, Vitale MC and Pinheiro ALB (2022). Comparative analysis of laser and led phototherapies pain control after insertion of elastomeric separators in orthodontics patients: Clinical trial. *J. Photochem. Photobiol. B.*, **233**: 112486.

Chumpitaz-Cerrate V, Chávez-Rimache L, Franco-Quino C, Aguirre-Siancas E, Caldas-Cueva V and Ruiz-Ramírez E (2019). Effects of NSAIDs and environmental oxygen pressure on bone regeneration. *J. Oral Res.*, **8**(2): 152-158.

de Araujo CM, de Jesus Freitas PF, Ferraz AX, Quadras ICC, Zeigelboim BS, Priolo Filho S, Beisel-Memmert S, Schroder AGD, Camargo ES and Kuchler EC (2024). Sex determination through maxillary dental arch and skeletal base measurements using machine learning. *Head Face Med.,* **20**(1):1-10.

Elshehaby M, Ali Tawfik M and Montasser MA (2023). Acupressure versus NSAID for relief of orthodontic pain: A randomized controlled clinical trial. *J. Orofac. Orthop.*, pp.1-9.

Ganeshprasadb R (2021). The effects of ibuprofen and acetaminophen on orthodontic pain control and interleukin-1β levels in gingival crevicular fluid. *MedPulse Int. J. Dent*.

Hassan MG, Abdelrahman HH, Emam AAA and Zaher AR (2024). Global scholarly output on orthodontic temporary anchorage devices (tads): A silver jublee scientometric analysis. *J. Orofac. Orthop.*, **85**(Suppl 2): 208-222.

Hou Z, Qu X, Hou L and Ren F (2024). Comparison between effects of mini-implant anchorage and face-bow anchorage in orthodontics for children. *J. Clin. Pediatr. Dent.*, **48**(1): 198-203.

Jamloo H, Farjaminejad R, Afrasiabi M, Zarezadeh M, Mafi R and Jamilian A (2023). The effectiveness of low level laser therapy and ibuprofen in the management of pain during orthodontics treatments: A meta-analysis of meta-analyses. *Lasers Dent. Sci.*, **8**(1):2.

Li J, Papadopoulou AK, Gandedkar N, Dalci K, Darendeliler MA and Dalci O (2022). The effect of micro-osteoperforations on orthodontic space closure investigated over 12 weeks: A split-mouth, randomized controlled clinical trial. *Eur. J. Orthod.*, **44**(4): 427-435.

Mollabashi V, Maleki E, Rezaei-Soufi L, Soheilifar S, Amini P and Kazemisaleh A (2020). Clinical Comparison of Ibuprofen Drug Effect and Low Power Laser Diode on Orthodontic Separator Implementation Pain. *J. Intellect. Disabl. Diagn. Treat.*, **8**(2): 117-123.

Najjar HE, Afnan N, Renad A, Rand A, Ashwaq TA, Ashwaq A, Ebtisam NAH, Sarah A, Magid A, Ghalib A and Abdul KM (2023). The use of orthodontic mini-implants and temporary anchorage devices (tads) for the management of complex orthodontic cases. *J. Health. Sci*., **5**(3): 148-153.

Ozturan YA and Akin I (2024). Comprehensive review of the impact of nsaids on bone healing outcomes in animal models: Conflicting evidence and methodological considerations. *Dis. Med.,* **1**(1):1-12.

Sagar S, Ramani P, Moses S, Gheena S and Selvaraj J (2024). Correlation of salivary cytokine IL-17A and 1,25 dihydroxycholecalciferol in patients undergoing orthodontic treatment. *Odontology*, **112**(3): 966-975.

Sumayya S, Chandra Shekar Br, Raghunath N, Mruthyunjaya K and Pradeep S (2022). Traditional anti-inflammatory and bone regenerative herbal extracts in orthodontic patient care a review of the current scenario and its future needs. *Acta Sci. Dent.*

Sci., **6**(6): 93-99.

Tabata K, Hashimoto M, Takahashi H, Wang Z, Nagaoka N, Hara T and Kamioka H (2022). A morphometric analysis of the osteocyte canaliculus using applied automatic semantic segmentation by machine learning. *J. Bone Miner. Metab.*, **40**(4): 571-580.

Tsvetkova M and Kovalenko A (2023). Orthodontic treatment practical considerations during general somatic pathology correction with drugs that slow down bone resorption. *Int. Dent. Res*., **2**(103): 64-70

Ubuzima P, Nshimiyimana E, Mukeshimana C, Mazimpaka P, Mugabo E, Mbyayingabo D, Mohamed AS and Habumugisha J (2024). Exploring biological mechanisms in orthodontic tooth movement: Bridging the gap between basic research experiments and clinical applications - A comprehensive review. *Ann. Anat.*, **255**:152286.

Wang K, Fan H, Yang, H, Li J and Xie W (2020). Efficacy and safety of micro-implant anchorage in angle class ii malocclusion orthodontic treatment: A protocol for systematic review and meta-analysis. *Medicine*, **99**(50): e23221.

Wu J, Xu L, Li C, Wang X and Jiang J (2023). Exploration of key factors in gingival crevicular fluids from patients undergoing periodontally accelerated osteogenic orthodontics (paoo) using proteome analysis. *BMC Oral Health.,* **23**(1): 1-9.

Xiao C, Pei R, Xia W, Gao M, Ge L and Li X (2023). Evaluation of Maxillary First Molar Intrusion Mechanics with Mini-Implant Anchorages Using the Finite Element Method. *J. Hard Tissue Biol.*, **32**(1): 1-10.

Yu H, Wu Z, Bao X, Tang X, Zhang J, Zhang Y and Hu M (2022). A sustained-release Trametinib bio-multifunction hydrogel inhibits orthodontically induced inflammatory root resorption. *RSC adv.*, **12**(26): 16444-16453.