BMC Oral Health

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Evaluating and comparing the effects of paracetamol and ibuprofen on wound healing, MMP-9, and TGF-β1 levels in patients following upper third molar tooth extraction

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Abstract

Background Paracetamol and ibuprofen are commonly prescribed pain relievers used in dental treatments, but their use can delay wound healing and lead to malunion and weaken the strength of newly formed bones. This randomized controlled clinical trial aimed to evaluate the wound healing (WH) and anti-inflammatory effects of paracetamol and ibuprofen on tooth extraction wounds in patients.

Methods This study involved a total of 20 patients who required removal of their fully erupted upper third molar under local anaesthesia at the Oral and Maxillofacial Surgery Clinic, Faculty of Dentistry, Chiang Mai University. The study subjects were divided into two groups of 10 patients each who were prescribed 400 mg of ibuprofen or 500 mg of paracetamol for seven days. Subsequently, WH was evaluated and the resulting proportions were compared using Landry Turnbull and Howley Index (LTHI) scores. Salivary matrix metalloproteinase 9 (MMP-9) and transforming growth factor beta1 (TGF-β1) concentrations were used as proinflammatory indicators. Accordingly, the WH values and the resulting proportions were compared using Fisher's exact test with a confidence interval (CI) of 95% ($P < 0.05$). The concentrations of MMP-9 and TGF-β1 were measured using ELISA and compared using the Mann–Whitney U test at 95% CI ($P < 0.05$). The obtained statistical values were then analysed and interpreted accordingly.

Results LTHI values on days 3 and 7 after tooth extraction were not significantly different between the two treatment groups. Salivary MMP-9 levels were lower in the paracetamol-treated group than in the ibuprofen-treated group ($P < 0.01$) on day 3 only. The LTHI concentration was also negatively correlated ($r = -0.433$) with the MMP-9 concentration ($P < 0.05$) but was positively correlated ($r = 0.369$) with the salivary TGF-β1 concentration ($P < 0.05$). Interestingly, MMP-9 was negatively correlated with TGF-β1 in the ibuprofen treatment group ($r^2 = -0.351$).

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Conclusion Ibuprofen can inhibit the inflammatory process and delay healing in the extraction socket. After discontinuation of medication, no differences were observed in the healing effects between the paracetamol and ibuprofen groups.

Trial registration The clinical trial was retrospectively registered at the Australian New Zealand Clinical Trial Registry (ANZCTR) NHMRC Clinical Trials Centre, Camperdown, Australia (Registry URL: https://www.anzctr.org.au) (Registration number: ACTRN12624000595516 Date: 9/5/2024).

Keywords Dental extraction, Wound healing, Ibuprofen, Paracetamol, MMP-9, TGF-β1

Introduction

Wound healing (WH) is an integral part of any surgical procedure. It is a fundamental physiological process that involves the coordinated interaction of various cells and their products that must function as a system [1]. This process is divided into three phases: (1) the inflammatory phase, (2) the proliferative phase, and (3) the remodelling phase [2–4]. Landry, Turnbull, Howley Index (LTHI) scoring method was used to assess WH in post-surgery patients. The parameters of which included suture, tooth extraction, gingivectomy, and gingivoplasty operations [5–7]. Matrix metalloproteinases (MMPs) were intimately involved in all phases of the WH process. Accordingly, the levels remained low under normal circumstances but could increase markedly upon sudden injury or wound occurrence [8]. Among them, MMP-9 is primarily secreted by neutrophils and macrophages during the inflammatory phase and functions in the WH process through cell signalling and by guiding keratinocytes to the wound edges to aid in wound closure while regulating neovascularization [9]. Transforming growth factor-beta 1 (TGF-β1) is a crucial protein involved in the WH process and is secreted by platelets and macrophages. Importantly, TGF-β1 plays a significant role in granulation tissue formation by attracting fibroblasts and producing collagen fibres during the proliferative phase and stimulating fibroblasts to contract and close wounds [10]. The functions of both MMP-9 and TGF-β1 are interrelated and balanced in terms of both the formation and structural equilibrium of extracellular matrix components [8]. A previous study revealed that an increase in MMP levels, accompanied by a decrease in TGF-β1 levels, can be found in patients with delayed wound healing [11]. Importantly, MMP-9 and TGF-β1 can be found in blood, saliva, and gingival crevicular fluid; therefore, they can serve as indicators of inflammatory events in oral tissue, including during the wound healing processes that occur within the oral cavity [12–17].

The regeneration of periodontal tissue is one of the main goals of periodontal therapy. Accordingly, current drugs are being used to relieve pain, inhibit the cyclooxygenase (COX) pathway, reduce the activity of MMPs, and inhibit destruction of periodontal connective tissue or inactivate bone resorptive cells, but they are also known to interfere with the process of wound healing [18]. Paracetamol and ibuprofen are commonly administered as pain relievers in patients undergoing dental treatments. Paracetamol is an analgesic drug that can alleviate both pain and fever but has been found to be ineffectual in terms of its anti-inflammatory properties [19]. In comparison, ibuprofen is a type of nonsteroidal anti-inflammatory drug (NSAID) that effectively reduces pain by mitigating inflammation [20–23]. A novel NSAID-derived poly(anhydride-ester) is involved in the delayed

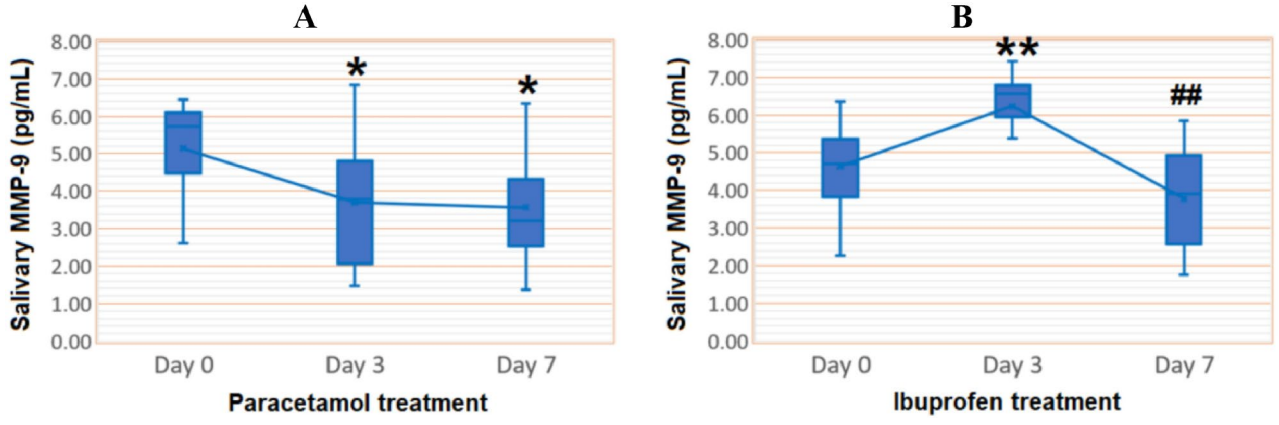

Fig. 1 Salivary MMP-9 concentrations among patients receiving paracetamol (**A**) and ibuprofen (**B**) ($n = 10$ each) for 0, 3, and 7 days. Data are expressed as median±IQR. Using the Mann–Whitney U test, $^{*}P < 0.05$, $^{**}P < 0.01$ when compared with day 0 and $^{\#\#}P < 0.01$ when compared with day 3. Abbreviations: MMP-9 = matrix metalloproteinase 9, IQR = interquartile range

Table 1 The patients enrolled in this study were randomly separated into two groups. Data are expressed as absolute or median±IQR values according to the Mann–Whitney U test. Significant differences were determined using Fisher's exact test

Information	Paracetamol	Ibuprofen	*P* value
Number	10	10	-
Gender	4 male/6 female	4 male/6 female	-
Age (year)	21 ± 3	22 ± 3	0.567
BMI (kg/m^2)	20.48 ± 0.73	20.30 ± 1.38	0.910

Abbreviation BMI = body mass index

wound healing process in bone and periodontal regeneration by inhibiting inflammation [24]. Nonetheless, selective cyclooxygenase 2 (COX-2) inhibitors, which are commonly prescribed in orthopaedic patients, have been acknowledged to not impose a counterproductive effect or interfere with the healing of tendons [25]. Taken together, bone repair may become abnormal, leading to a reduction in the overall strength of the regenerated bone. Hypothetically, ibuprofen could impact the healing and anti-inflammatory effects of tooth extraction wounds. Thus, we undertook this study to evaluate the wound healing and anti-inflammatory properties of ibuprofen and paracetamol after upper third molar extraction.

Results

Patient characteristics

A total of twenty subjects in each of the two treatment groups were enrolled in this study, and their physical information is presented in Table 1. The results were further assessed using the Mann–Whitney test and expressed as absolute numbers or medians ± interquartile range (IQR). Accordingly, group 1 subjects (4 male and 6 female) had a median age of 21 years with an IQR of 3 years and were given paracetamol, while group 2 subjects (4 male and 6 female) had a median age of 22 years with an IQR of 3 years and were given ibuprofen. Importantly, body mass index (BMI) and the age of the two treatment groups were not significantly different.

Evaluation of LTHI values

In terms of the evaluation of wound healing on day 3 after tooth extraction, 6 of the 10 patients who received paracetamol had an LTHI = 3, while 4 of the 10 patients had an LTHI = 2. In comparison, 7 of 10 patients who received ibuprofen had an LTHI = 3, while 3 of 10 patients had an LTHI = 2. No significant differences were observed (P = 0.370) between the two treatment groups. Regarding the evaluation of the wound healing process seven days after tooth extraction, 7 of 10 patients who received paracetamol had an LTHI = 4, while 3 of 10 had an LTHI = 3. In comparison, 5 of 10 patients who had received ibuprofen had an LTHI = 4, while another 5 had an LTHI = 3. Notably, no significant differences were detected (P = 0.370) between the two treatment groups (Table 2).

Salivary MMP-9 and TGF-β1 concentrations

As is shown in Figs. 1 and 2, the salivary MMP-9 and TGF-β1 concentrations before tooth extraction and after NSAID treatment (day 0) were comparable and not significantly different between the paracetamol-treated group and the ibuprofen-treated group. MMP-9 levels were significantly decreased in the paracetamol-treated patients on days 3 and 7 after tooth extraction (Fig. 2A); in contrast, MMP-9 levels were increased in the ibuprofen-treated group on day 3 and subsequently decreased on day 7 (P < 0.01) (Fig. 2B).

In addition, salivary TGF-β1 levels in the paracetamol-treated group were significantly reduced on day 3 and then increased on day 7 after tooth extraction among patients taking the drug (Fig. 2A). However, there were no significant changes in salivary TGF-β1 levels in the ibuprofen-treated group on days 3 and 7 after tooth extraction or after drug administration (Fig. 2B).

Correlation between LTHI and MMP-9 or TGF-β1 concentrations

According to our findings, the LTHI values exhibited a negative correlation (r = -0.433) with MMP-9 concentrations along with a moderate to strong linear relationship (P < 0.05) (Fig. 3A). Conversely, LTHI values showed a positive correlation (r = 0.369) with salivary TGF-β1 concentrations in conjunction with a moderate to strong linear relationship (P < 0.05) (Fig. 3B). Notably, salivary MMP-9 concentrations and salivary TGF-β1 concentrations tended to be negatively correlated in the ibuprofen treatment group (r^2 = -0.351), but they were not correlated with each other in the paracetamol treatment group (r^2 = 0.099), as has been shown in Fig. 3C.

Table 2 LTHI values were assessed in patients receiving Paracetamol and Ibuprofen. Significant differences were determined using Fisher's exact test. According to the Mann–Whitney U test, no significant differences were detected (P = 0.567)

Group	Day 3			Day 7		
	LTHI = 2	LTHI = 3	*P* value	LTHI = 3	LTHI = 4	*P* value
Paracetamol	4 (40%)	6 (60%)	0.370	3 (30%)	7 (70%)	0.650
Ibuprofen	7 (70%)	3 (30%)		5 (50%)	5 (50%)	

Abbreviations LTHI = Landry, Turnbull, Howley Index

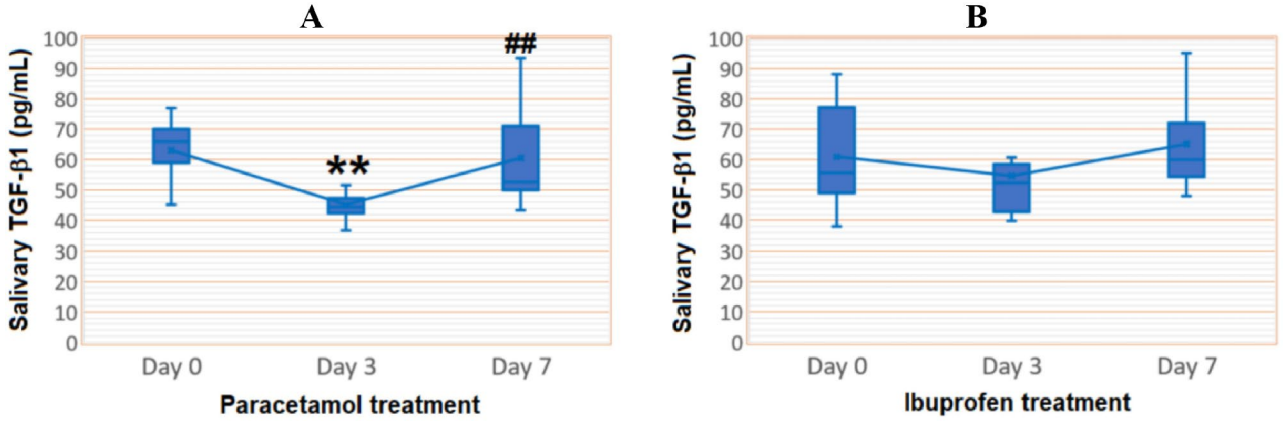

Fig. 2 Salivary TGF-β1 concentrations among patients receiving paracetamol (**A**) and ibuprofen (**B**) ($n = 10$ each) for 0, 3, and 7 days. Data are expressed as median±IQR. According to the Mann–Whitney U test, $^{**}P < 0.01$ when compared with day 0; $^{\#\#}P < 0.01$ when compared with day 3. Abbreviations: IQR = interquartile range, TGF-β1 = transforming growth factor-beta 1

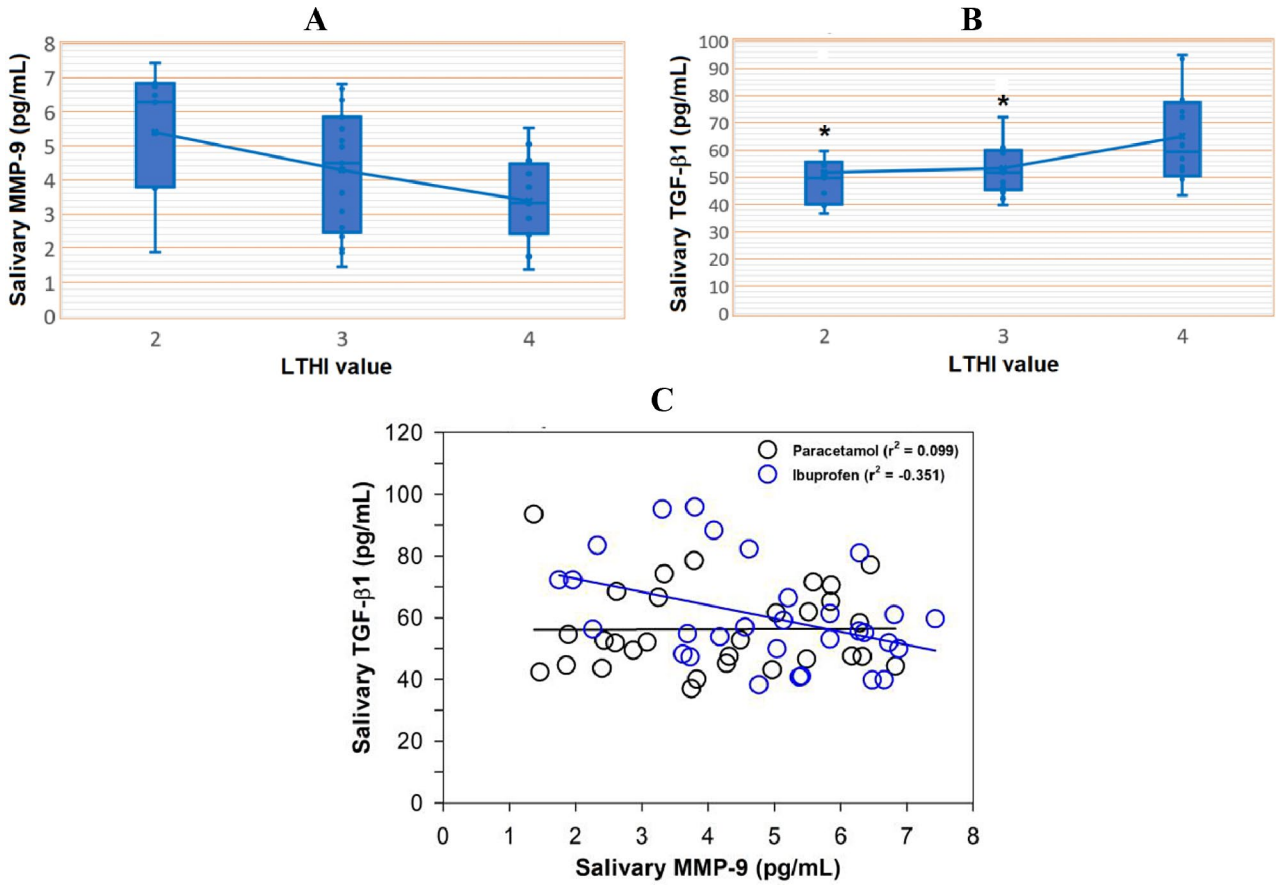

Fig. 3 Relationships between LTHI values and salivary MMP-9 (**A**) or TGF-β1 (**B**) concentrations and between salivary MMP-9 and TGF-β1 (**C**). The indicators were measured in patients receiving paracetamol and ibuprofen ($n = 10$ each) for 0, 3, and 7 days. Data are expressed as median±IQR. According to the Mann–Whitney U test, $^{**}P < 0.01$ when compared with day 0; $^{\#\#}P < 0.01$ when compared with day 3. Abbreviations: LTHI = Landry, Turnbull, Howley Index, MMP-9 = matrix metalloproteinase 9, TGF-β1 = transforming growth factor-beta 1

Methods

Ethical approval declarations and clinical trial registry

Ethical approval for this project was granted by Professor Dr. Anak Iamaroon, D.D.S., Ph.D., who is Chairman of the Institutional Review Board (IRB) of Human Experimentation Committee from the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand, (Certificate Number: 57/2022, Date: October 17th, 2022). All patients

were fully informed about the particulars of the study and provided their signatures on the consent forms before any study procedures were initiated. This study followed the guidelines of the Helsinki Declaration 2008: Ethical Principles for Medical Research Involving Human Subjects. Subjects' rights were protected by an appropriate IRB, and written informed consent was obtained from all subjects. The study was registered retrospectively at the Australian New Zealand Clinical Trial Registry (ANZCTR) NHMRC Clinical Trials Centre, Camperdown, Australia (Registry URL: https://www.anzctr.org.au) and can be referenced under the Registration Number: ACTRN12624000595516 Date: 9/5/2024.

Study design

This was a randomized controlled trial experimental study that compared the effects of paracetamol and Ibuprofen on tooth extraction wounds in patients, wherein paracetamol was used as the reference drug.

Subject selection

This single-centre, single-dose, randomized, double-blind, controlled clinical trial involving outpatients who had undergone upper third molar tooth extraction procedures at the Oral and Maxillofacial Surgery Clinic, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand, was conducted from September 21st, 2022, to February 24th, 2023. The inclusion criteria involved the following: patients who were within an age range of 15–30 years, who were healthy (American Society of Anesthesiologists (ASA) class I and II), and who reported a normal BMI within a range of 18.5–24.5 kg/m^2. In addition, they were free from pathological conditions, denied having any history of chronic illnesses or drug allergies, and had just undergone molar extraction. The study participants included volunteers with fully erupted upper third molars, which was determined by a review of panoramic radiographs. The exclusion criteria were as follows: (1) pregnant, heavy smokers, allergic to paracetamol, ibuprofen, or any anaesthetic medications (e.g., mepivacaine and epinephrine-related drugs). (2) Patients who reported any pre-existing medical conditions such as hypertension, diabetes, liver disease, kidney disease, blood clotting disorders, or gastritis. (3) Patients who had wounds/injuries in various parts of their body prior to initiating the experimental study or those who had severe gingival inflammation (Gingival index>2). 4). Patients who had taken medication or dietary supplements that could impact the wound healing process. 5) Patients who experienced psychological or communication disorders. With regard to potential discontinuation, the criteria were as follows: (1) Patients could give up or withdraw from the study at any time; (2) Patients who experienced difficulties or complexities pertaining to their tooth extractions within 30 min of the procedure; (3) Patients who experienced severe post-extraction pain and who were unable to adequately manage that pain with the provided pain-relief medication alone or who required additional pain-relief medication beyond the prescription; (4) Patients who experienced postoperative complications, such as uncontrolled bleeding, infections, and communication between the oral cavity and nasal cavity, or alveolar osteitis (dry socket). Each subject required surgery with nearly the same magnitude of trauma on the jaw.

Sample size calculation

The sample size was calculated according to the data obtained from a study conducted by Rauten et al. [26] in combination with the data obtained from a study conducted by Yamano et al. [16] using STATA® version 16.0 software (StataCorp, LLC, College Station, TX, USA). Initially, the total sample size was 16 individuals, who were then divided into two groups ($n=8$ each). However, the researchers decided to increase the sample size to a total of twenty individuals, which were then divided into two groups ($n=10$ each), by including additional participants.

Study intervention

By using the block randomization method, participants were divided into two groups. Group 1 patients were instructed to take a paracetamol tablet (500 mg, Foramol-500, Forty-two Medicare, Company Limited, Bangkok, Thailand) after tooth extraction every 6 h for a total of 10 tablets, and Group 2 patients were instructed to take an ibuprofen tablet (400 mg, Probufen-400, Advanced Pharmaceutical Manufacturing Company Limited, Bangkok, Thailand) three times daily after meals for a total of 10 tablets after tooth extraction. Their medical histories were recorded, and a physical examination was conducted prior to the tooth extraction procedure. The step-by-step procedure for tooth extraction, along with the potential risks associated with the treatment, was explained to the subjects. First, a local anaesthetic solution containing 2% mepivacaine hydrochloride with epinephrine (dilution 1:100,000) (Scandonest 2% Special, Septodon Company, Kent, UK) was injected at 0.6 mL into the buccal vestibule and 0.3 mL into the palatal area using the buccal and palatal infiltrate technique. The local anaesthetic was administered, and 10 min were allowed to pass for the action to take place. The tooth was then extracted using forceps. Afterward, patients were instructed to bite down on a gauze pad for one hour, while pain medication was provided to the patients to manage any postoperative discomfort. Herein, all the extracted upper molars were fully erupted, making the

extraction socket difficult to clean and presenting a high risk of decay in the future.

Saliva collection

Before saliva collection, patients were asked to abstain from eating and drinking for one hour. They were then instructed to rinse their mouths with clean water and wait 10 min prior to the collection process. Saliva samples were collected from each patient at three different time points (before tooth extraction, 3 days after tooth extraction, and 7 days after tooth extraction) using a plastic micropipette tip. Samples were then transferred into microtubes (1.5 mL capacity) and kept frozen in a freezer at -20 °C for up to 3 months for analyses of MMP-9 and TGF-β1 (Fig. 1).

Measurement of MMP-9 and TGF-β1 concentrations

Salivary MMP-9 and TGF-β1 concentrations were determined using sandwich-type enzyme-linked immunosorbent assay (ELISA) kits (ABBEXA Company Limited, Bar Hill, Cambridge, UK) according to the manufacturer's instructions. In terms of quality control, the human MMP-9 ELISA kit (catalogue number: abx050165) had a sensitivity of 0.1 ng/mL and a coefficient of variation < 10% for intra-assay and inter-assay analyses, while the human TGF-β1 ELISA kit (catalogue number: abx153266) had a sensitivity of < 5.7 pg/mL and a coefficient of variation of < 10% for intra-assay analysis and < 12% for inter-assay analysis.

Evaluation of tooth extraction wounds

Healing scores reported as LTHI values were evaluated on days 3 and 7 after tooth extraction based on various characteristics, such as residual wound inflammation, granulation tissue quantity, haemorrhage status, the presence of suppuration, and epithelial tissue expansion [27]. The evaluations were classified into five score levels: 5 = excellent, 4 = very good, 3 = good, 2 = poor, and 1 = very poor. In addition, the calibration values were determined through both intra-rater reliability (κ = 0.916) and inter-rater reliability (κ = 0.874) analyses, and the degree of agreement was determined using kappa statistics.

Primary outcome

The primary outcome is the assessment of tooth extraction wound healing that was determined based on LTHI values and concentration values of salivary MMP-9 and TGF-β1 to indicate the degree of wound healing. In cases where the wound heals well, there should be a low concentration of MMP-9 and a high concentration of TGF-β1. Conversely, if wound healing is poor, there would be a high concentration of MMP-9 and a low concentration of TGF-β1.

Secondary outcome

The secondary outcome of this study was to examine the relationship between the MMP-9 and TGF-β1 concentrations in conjunction with the LTHI, value and evaluate the possibility to be used as wound healing biomarkers.

Statistical analysis

The results were analysed and are expressed as mean±IQR using STATA version 16.0. The median concentrations of MMP-9 and TGF-β1 in the saliva samples collected at different time points from patients who received paracetamol and ibuprofen were determined and compared using the Mann-Whitney U test at a 95% confidence level. The proportions of LTHI values between patients who received paracetamol and those who received ibuprofen were determined and compared using Fisher's exact test at a 95% confidence level. The relationships between LTHI values, MMP-9 concentrations, and TGF-β1 concentrations were determined and compared using Spearman's correlation coefficient at a 95% confidence level. Accordingly, $P < 0.05$ was considered to indicate a significant difference. We have complied with the appropriate guidelines/checklist of the Strengthening the Reporting of Observational (STROBE) protocol. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is presented in Fig. 4.

Discussion

Paracetamol (analgesic drug) and ibuprofen (NSAID) are commonly prescribed pain relievers for patients undergoing dental treatments [28]. In fact, patients undergoing tooth extraction often experience moderate to severe pain within the first 24 h, for which the pain gradually subsides within 72 h. However, the short-term administration of ibuprofen to dental patients can delay the healing of bone fractures and wounds over a brief period [29]. Similarly, Voulteenaho and colleagues have reported that NSAIDs delayed wound and bone repair in mice [30]. A randomized controlled clinical study demonstrated that ibuprofen, which is an NSAID, can delay wound healing, cause abnormal bone regeneration, and reduce the strength of regenerated bones [31]. In contrast, one clinical study revealed that ibuprofen treatment did not affect radiological migration, range of motion, wrist motion improvement, or pain scores in patients with displaced Colles' fractures when compared with those in the placebo group [32]. Herein, we have hypothesized that ibuprofen could inhibit the inflammatory process, and this results in a temporary delay in the wound healing process. However, after discontinuing the medication, wound healing characteristics did not significantly differ between the two treatment groups on day 7 after tooth extraction. Thus, the present study evaluated the

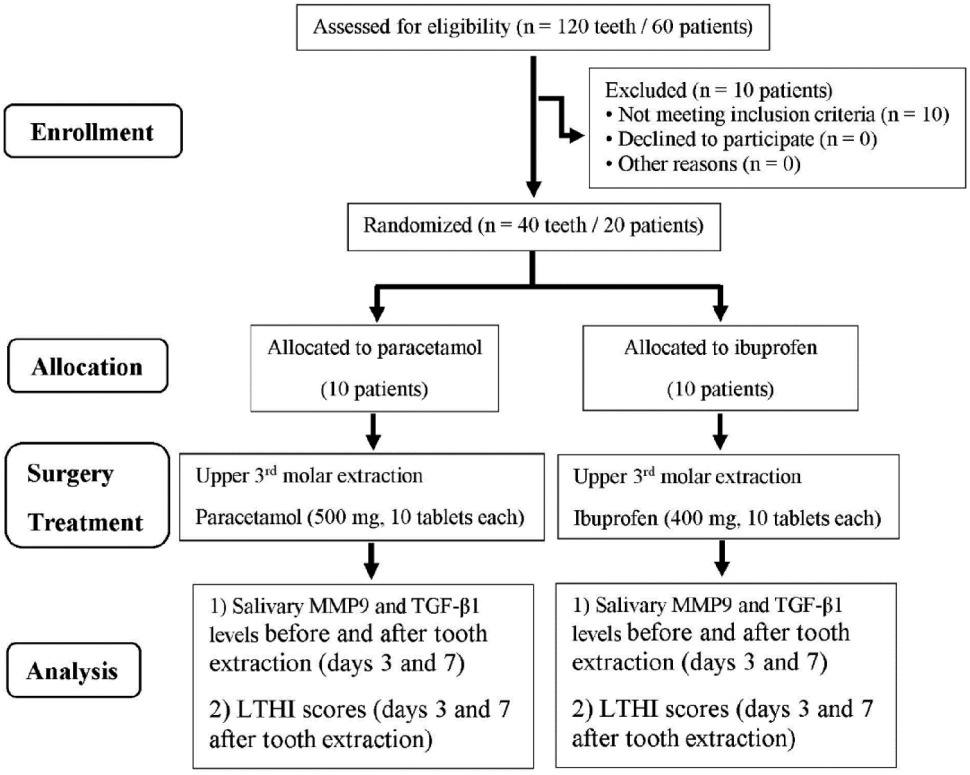

Fig. 4 CONSORT flow diagram of the study design

effectiveness of ibuprofen and paracetamol on wound healing status, as well as MMP-9 and TGF-β1 levels, in saliva collected from patients after upper third molar extraction. According to our findings, following tooth extraction, patients receiving paracetamol exhibited better wound healing results (LTHI=3) than did those receiving ibuprofen; however, there were no significant differences between the two treatment groups. Notably, treatment with NSAID or selective COX-2 inhibitors at standard doses for a period not exceeding two weeks had no impact on wound healing [21]. Gallaher et al. revealed that wound healing status was not significantly different between the group receiving NSAID and the group that received the placebo for two weeks, while healing was significantly delayed after subjects had taken the drugs for eight weeks [33]. In addition, our results revealed a negative correlation between LTHI values and salivary MMP-9 concentrations in post-extraction patients, suggesting that high levels of salivary MMP-9 would indicate poor wound healing characteristics or vice versa.

Regarding pro- and anti-inflammatory cytokines, patients receiving ibuprofen had significantly greater salivary MMP-9 concentrations on day 3 post-extraction than those receiving paracetamol, suggesting a slower wound healing process in the ibuprofen group. Moreover, the levels of MMP-9 and TGF-β1 in the saliva did not significantly differ between the two treatment groups on day 7 following tooth extraction. Consistently, Caley and colleagues observed an increase in MMP-9 concentrations in cases of wound formation, whether in new wounds or chronic wounds [9]. Additionally, Sabino et al. reported that slow-healing or chronic wounds are characterized by increased levels and activity of MMP-9 [8].

After a wound occurs, cytokine TGF-β1 is converted to its active form to promote growth, repair, and inflammation. Additionally, there is an upregulation in the tissue inhibitor of metalloproteinase 1 (TIMP-1) expression in human articular cartilage [34]. Accordingly, TGF-β1 serves as a potent regulator of proinflammatory responses and defensive reactions in the dentin-pulp complex and has pleiotropic effects on the healing of pulp and odontoblasts [35]. Similarly, there is a positive correlation between LTHI values and TGF-β1 activity, suggesting that high TGF-β1 activity indicates good wound healing characteristics or vice versa, while a low concentration of TGF-β1 suggests poor wound healing characteristics. Consistently, the results from an animal study revealed that the levels of TGF-β1 activity and TGF-β1 receptor gene expression significantly decreased in a delayed WH process [10]. Indeed, the WH of human gingival tissue after tooth extraction could be attributed to the primary role of TGF-β1 and MMPs (e.g., MMP-8 and MMP-9) in the proliferative phase, which involves cell proliferation and collagen fibre synthesis in granulation

tissue [36, 37]. This process typically starts approximately 48 h after injury and can continue for up to 14 days.

In terms of limitations, there were some difficulties associated with collecting saliva specimens from the mouth cavities of subjects and the stability of MMP-9 and TGF-β1 in saliva samples that were kept frozen in a freezer at -20 °C. In addition, the limited number of participants may have hindered the use of follow-up procedures in terms of treatment outcomes. Hence, we investigated the WH characteristics and monitored the levels of MMP-9 and TGF-β1 for up to seven days after tooth extraction. In terms of these challenges, scheduling patient appointments for wound assessment and saliva collection should be extended for up to two weeks after tooth extraction. Taken together, the resulting data support the use of ibuprofen treatment to improve tooth post-extraction repair and healing and suggest that modulation of the TGF-β1 signalling pathway could reduce inflammation while maintaining the strength of the wound. This would allow for the administration of pain relief medication and longer-term patient follow-up appointments. This approach enables the collection of data over an extended timeframe and encourages greater patient cooperation in evaluating treatment outcomes. Longer-term studies on the effects of NSAID on oral wound healing may require different case studies to ensure prolonged pain relief prescriptions and extended patient follow-ups. For example, studies involving volunteers undergoing jaw surgery, tumor removal, or other major surgeries could provide opportunities for long-term data collection and better patient compliance for follow-up appointments.

Conclusion

Ibuprofen inhibits the inflammatory process, and this results in a temporary delay in the wound healing process. However, after discontinuing medication, wound healing characteristics did not significantly differ between the two treatment groups on day 7 after tooth extraction. Importantly, salivary MMP-9 concentrations were negatively correlated with salivary TGF-β1 concentrations and LTHI values, while salivary TGF-β1 seemed to be positively correlated with LTHI. In future studies, it may be necessary to explore additional scenarios in which the objective is to study the effects of NSAID on WH status in the oral cavity over extended periods of time.

Abbreviations

ANZCTR	Australian New Zealand Clinical Trial Registry
ASA	American Society of Anaesthesiologists
BMI	Body mass index
CONSORT	Consolidated Standards of Reporting Trials
COX	Cyclooxygenase
COX-2	Cyclooxygenase 2
ELISA	Enzyme-linked immunosorbent assay
IQR	Interquartile range
IRB	Institutional Review Board
LTHI	Landry, Turnbull, Howley Index
MMPs	Matrix metalloproteinases
MMP-9	Matrix metalloproteinase 9
NSAID	Nonsteroidal anti-inflammatory drug
STROBE	Strengthening the Reporting of Observational
TGF-β1	Transforming growth factor-beta 1
TIMP-1	Tissue inhibitor of metalloproteinase 1
WH	Wound healing

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-024-04916-0.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We wish to thank all the patients who participated in the study. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

Author contributions

S.Y., P.C., O.K., P.S., S.S. and V.C. contributed to the study conception and design. S.Y., O.K., P.S., S.S. and V.C. contributed to the data acquisition and interpretation. S.Y. and O.K. contributed to the data analysis and interpretation. S.Y., P.C., P.S., S.S. and V.C. contributed to the drafting and critical revision of the manuscript.

Funding

This research was supported by the Residency Training Program in Oral and Maxillofacial, Surgery, Faculty of Dentistry, Chiang Mai University, Thailand (ID: 62010303). Consumable reagents were supported by Royal Project Foundation, Thailand (Grant number: 3055-A205).

Data availability

Data is provided within the manuscript or supplementary information files.

Code availability

Not applicable.

Materials availability

Not applicable.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by Professor Dr. Anak Iamaroon, D.D.S., Ph.D., Chairman of the IRB of Human Experimentation Committee from the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand, (Certificate Number: 57/2022, Date: October 17th, 2022). The study was registered retrospectively at the ANZCTR Centre, Camperdown, Australia (Registration Number: ACTRN12624000595516 Date 9/5/2024). The informed consent to participate was obtained from all of the participants in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 16 May 2024 / Accepted: 16 September 2024
Published online: 03 April 2025

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