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Research Article

The Effect of Systemic Proteolytic Enzymes on Postoperative Inflammatory Response and Quality of Life after Surgical Extraction of Impacted Mandibular Third Molar

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Abstract

Background: The surgical extraction of impacted third molar usually results in postoperative inflammation manifested as pain, facial swelling and trismus which may cause deterioration in the patient's quality of life. ***Methods***: This randomized controlled study included 56 patients indicated for surgical extraction of IMTM under local anesthesia. These patients were randomly assigned into two groups: a study group that included patients who received Tibrolin® postoperatively and a control group that did not. The predictor variable was whether to use SET or not. Pain measured by the pain numerical rating scale (NRS), facial swelling, and the degree of trismus were the outcome variables. The Arabic version of the Oral Health Impact Profile 5 (OHIP5-Ar) questionnaire was used to measure quality of life (QoL) on the day of surgery (day 1) and on days 3, 7, and 13. ***Results***: The study group demonstrated significantly lower pain scores postoperatively on day 1 and a lesser degree of facial swelling on day 3 compared to the control group, while no significant differences were observed regarding the other time intervals. There were no significant differences in the degree of trismus or QoL between the two groups. ***Conclusions***: Tibrolin® administration following the surgical extraction of IMTM might reduce post-operative complaints in patients with surgical extraction of IMTM.

Keywords: Bromelain, Health care, Pain, Quality of life, Third molar, Tibrolin.

تأثير الإنزيمات المحللة للبروتين الجهازية على الاستجابة الالتهابية بعد العملية الجراحية ونوعية الحياة بعد الاستخراج الجراحي للضرس الثالث للفك السفلي المتأثر

الخلاصة

الخلفية: عاده ما يؤدي قلع الضرس الثالث جراحيا الى التهاب مابعد الجراحه الذي يتمثل بالالم وتورم الوجه و عدم القدره على فتح الفم وتدهور نوعيه حياة المريض. **الأهداف**: تقييم تأثير تيبرولين® كعلاج إنزيمي جهازي (SET) على الاستجابة الالتهابية بعد العملية الجراحية ونوعية الحياة بعد الاستئصال الجراحي للأضراس الثالثة المتأثرة بالفك السفلي(IMTM) . **الطرق**: شملت هذه الدراسة المعشاة ذات الشواهد 56 مريضا يشار إليهم للاستخراج الجراحي ل IMTM تحت التخدير الموضعي. تم تعيين هؤلاء المرضى بشكل عشوائي في مجموعتين: مجموعة دراسة شملت المرضى الذين تلقوا تيبرولين® بعد الجراحة ومجموعة مراقبة لم تتلق. كان متغير التنبؤ هو ما إذا كان يجب استخدام SET أم لا. كان الألم الذي يقاس بمقياس التصنيف العددي للألم[NRS] ، وتورم الوجه، ودرجة التشنج هي متغيرات النتيجة. تم استخدام النسخة العربية من استبيان ملف تأثير صحة الفم 5 (OHIP5-Ar) لقياس جودة الحياة (QoL) في يوم الجراحة (اليوم 1) وفي الأيام 3 و 7 و 13. **النتائج**: أظهرت مجموعة الدراسة درجات ألم أقل بكثير بعد الجراحة في اليوم 1 ودرجة أقل من تورم الوجه في اليوم 3 مقارنة بالمجموعة الضابطة ، في حين لم تلاحظ فروق ذات دلالة إحصائية فيما يتعلق بالفترات الزمنية الأخرى. لم تكن هناك فروق ذات دلالة إحصائية في درجة trismus أو QoL بين المجموعتين. **الاستنتاجات**: قد يقلل إعطاء تيبرولين® بعد الاستخراج الجراحي ل IMTMمن شكاوى ما بعد الجراحة لدى المرضى الذين يعانون من الاستخراج الجراحي لIMTM .

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INTRODUCTION

Tooth impaction occurs when a tooth does not fully erupt into its final functional position within the anticipated time frame [1]. Mandibular third molars are known to have the highest rate of impaction among all teeth [2,3]. The most frequent operation in oral and maxillofacial surgery is the surgical extraction of impacted third molars [4]. It entails soft tissue incision and reflection with or without bone removal and tooth sectioning; this usually results in postoperative inflammation manifested as pain, facial swelling, and trismus, which may cause a deterioration in the patient's quality of life (QoL) for up to one week

postoperatively [5,6]. The complexity of surgically removing third molars ranges from ordinary to challenging, and surgical time is one of the key factors for assessing surgical difficulty [7]. A longer recovery time following third molar extraction is reported to be associated with increased surgical complexity [8]. Additionally, as the level of surgical difficulty rises, complications become more frequent [9,10]. To guarantee patient comfort and uncomplicated healing, postoperative inflammation must be controlled [11]. Conventionally, anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and opioids are used to control the postoperative inflammatory response following third-molar surgery [12]. Natural ingredients with anti-inflammatory properties have been used as cures for inflammatory disorders including pain, fever, migraine, and arthritis for a long time [13]. In systemic enzyme therapy (SET), exogenous hydrolytic enzymes from plant or animal origins are administered orally in enteric-coated tablets to mitigate the postoperative inflammatory response [14]. Both of these enzymes, bromelain and trypsin, are endopeptidases that hydrolyze peptide bonds in specific positions of the peptide chain. In numerous clinical investigations, it has been shown that the efficacy of such enzymes is similar to that of corticosteroids, NSAIDs, and other anti-inflammatory treatments [15,16]. Bromelain is notably useful for treating inflammation, soft tissue injuries, especially when edema is present, and postoperative tissue reactions [17]. Bromelain 90 mg, Trypsin 48 mg, and a bioflavonoid (Rutoside 100 mg) are combined in a fixed dose in Tibrolin® (Tibrolin®, Zuventus Healthcare Ltd., Maharashtra, India). This combination has been demonstrated to have strong anti-inflammatory benefits and promote wound healing in some clinical studies [18,19]. A small number of clinical studies have looked at how Tibrolin® as SET affects the inflammatory response after surgery to remove impacted mandibular third molars (IMTM). This aims to evaluate how well Tibrolin® affected pain, swelling, trismus, and quality of life after surgery to remove IMTMs. The null hypothesis stated that there is no difference in the outcome of interest between the two groups, while the alternative hypothesis stated that there is a significant difference between the two groups.

METHODS

Study design and setting

This randomized controlled study was conducted during the period from December 2022 to September 2023 at the Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Baghdad.

Ethical consideration

The Institutional Research Ethics Committee approved the protocol of this study (protocol- 673122), and all patients enrolled in this study were informed about the aim and nature of the study and they signed an informed consent. The study was guided by Consolidated Standards of Reporting Trials (CONSORT) guidelines and was registered at ClinicalsTrial.gov (NCT05681312).

Patient selection and randomization

This study included patients indicated for surgical extraction of IMTM under local anesthesia who met the eligibility criteria. The patients were randomly assigned into two groups using an online randomization tool provided by https://www.graphpad.com: a study group that included the patients who received Tibrolin® postoperatively and a control group that did not.

Inclusion criteria

The inclusion criteria were healthy patients over 18 years old with American Society of Anesthesiologists (ASA) category I (healthy, non-smoking, no or minimal alcohol use) presenting with IMTM classified as class I and II, positions A and B according to Pell and Gregory's classification.

Exclusion criteria

Patients with uncontrolled systemic diseases, acute infection at the surgical site at the time of operation, cysts or tumors associated with the impacted teeth, and class III and position C according to Pell and Gregory's classification were excluded from the study.

Intervention and outcome measurements

A priori sample size calculation was performed using G Power 3.1.9.7 for Windows (Heinrich-Heine University, Dusseldorf, Germany). The following parameters were used: alpha error of 0.05, power of 0.80, and effect size of 0.8. The estimated sample size was 52 patients; therefore, the study included 63 patients to account for potential dropouts. A panoramic radiograph was taken for each patient to determine the angulation of the impacted tooth according to the Winter classification and the depth and position of the impacted tooth according to the Pell and Gregory classification, in addition to the relationship of the roots with the inferior alveolar canal. Facial measurements were done preoperatively as a baseline record by measuring the distance between six predetermined points preoperatively on the day of surgery (day 1). The first measurement was the distance between the lateral canthus (Cn) and gonion (Go); the second measurement was the distance between the corner of the mouth (Cm) and the tragus of the ear (Tr); and the third measurement was the distance between the pogonion (Pg) and Tr (Figure 1).

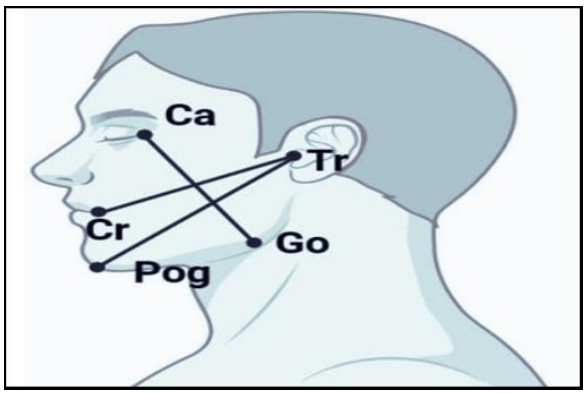

Figure 1: Facial measurement. Ca: Canthus, Cr: Corner of the mouth, Tr: Tragus, Go: gonion, Pog: pogonion.

The mean of three measurements was recorded in mm as a baseline facial measurement [10]. The maximum mouth opening (MMO) was determined by measuring the distance in mm between the upper and lower incisors preoperatively with a Vernier caliper. The QoL was measured preoperatively as a baseline record by using the Arabic version of the oral health impact profile 5 (OHIP5-Ar) questionnaire on the day of surgery (day 1), which was filled out by the patients. It consists of 5 questions representing the four suggested dimensions: oral function, orofacial pain, orofacial appearance, and psychosocial impact. Responses to the OHIP5-Ar questions were made on a 5-point Likert scale (0 = never; 1 = hardly ever; 2 = occasionally; 3 = fairly often; and 4 = very often). All the surgical procedures were scheduled to start at 10:00 a.m. and were performed by the same operator under local anesthesia through inferior alveolar nerve block (IANB) using lidocaine hydrochloride, a 2% local anesthetic agent, with adrenalin 1:80000. A standardized surgical technique was used for all patients in a sterile environment. A two-sided flap was used and a mucoperiosteal flap was reflected. Bone cutting with or without tooth sectioning proceeded under continuous irrigation with normal saline and the tooth was extracted. The duration of the operation was recorded in minutes from the first incision to the last suture as a determinant of operative difficulty. Postoperatively, the pain was assessed by using a 0–10 pain numerical rating scale (NRS), where 0 equals no pain and 10 equals the worst pain possible. This assessment was performed on the day of surgery (day 1), 6 hours after the surgery, and on days 3 and 7 postoperatively. Facial measurements were performed in the same manner described preoperatively on days 3 and 7 postoperatively to assess the degree of postoperative swelling. The degree of trismus was determined by measuring the MMO postoperatively on days 3 and 7. The QoL was measured by completing the questionnaire on days 3 and 7.

Statistical analysis

The statistical analysis was performed using GraphPad Prism version 6 for Windows (GraphPad Software). For the descriptive analysis, frequencies and percentages of the categorical variables were recorded, whereas for the continuous variables, the mean (standard deviation, SD) and median (interquartile range, IQR) were calculated. The normality of the distribution of the continuous variables was examined using the Shapiro-Wilk test. The Mann-Whitney U test, unpaired t-test, Friedman test with Dunn's multiple comparisons test, Fisher's exact test, and Chi-square test were used in the inferential statistical analysis. The differences were considered significant at $p < 0.05$.

RESULTS

During the study period, 63 patients indicated for surgical extraction of IMTM who met the eligibility criteria were enrolled in the study and were randomly assigned into two groups: 32 in the study group and 31 in the control group. Seven patients were lost to follow-up—four in the study group and three in the control group—and were excluded; the remaining 56 patients who were assigned to both groups, 28 each, were included in the statistical analysis (Figure 2). The mean (SD) and median (IQR) ages of the patients were 25.1 (4.67%) and 24 (6.5%), respectively.

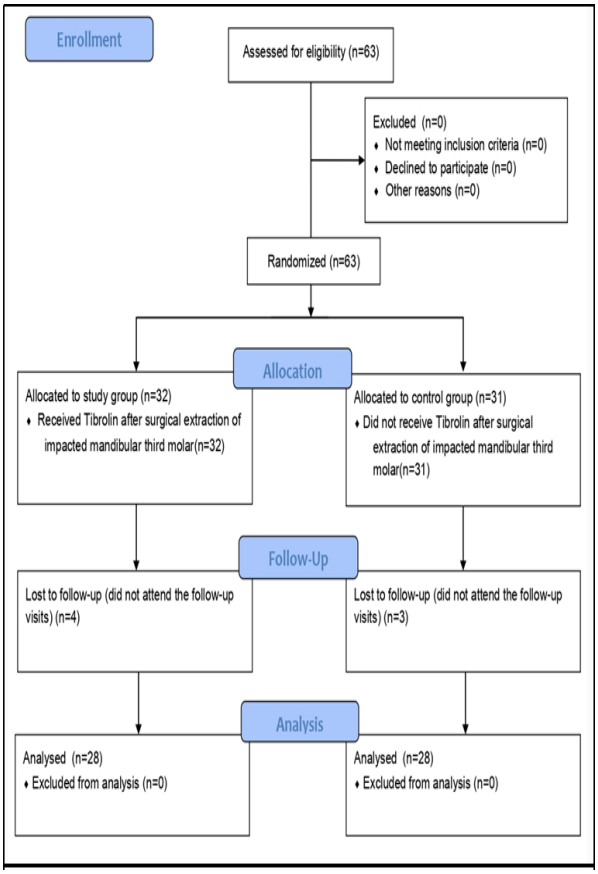

Figure 2: Flow chart of the study.

The patients consisted of 33 (59%) males and 23 (41% females). The differences between the groups in terms of age, gender, indications for extraction, Pell and Gregory categorization, angulation of impacted teeth, and extraction time are demonstrated in Table 1.

Table 1: Comparison of the covariates between the two groups

Variables	Study group	Control group	*p*-value
Age (year)			
Mean (SD)	25.18(4.93)	25.04(4.48)	0.958[a]
Median (IQR)	24(7)	23(4)	
Gender n(%)			
Male	15(53.6)	18(64.3)	0.5875[b]
Female	13(46.4)	10(35.7)	
Indications for extraction n(%)			
Pain	13(46.4)	11(39.3)	0.767[c]
Caries	2(7.1)	5(17.9)	
Pericoronitis	5(17.9)	6(21.4)	
Resorption	4(14.3)	3(10.7)	
Orthodontic treatment	4(14.3)	3(10.7)	
Pell and Gregory classification n(%)			
Class			
I	15(53.6)	17(60.7)	0.788[b]
II	13 (46.4)	11(39.3)	
Position			
A	12(42.9)	14(50)	0.789[b]
B	16(57.1)	14(50)	
Angulation n(%)			
Mesioangular	9(32.15)	12(42.9)	0.598[c]
Vertical	9(32.15)	6(21.4)	
Horizontal	10(35.7)	10 (35.7)	
Duration (min)			
Mean (SD)	30.85(15.65)	29.62(17.23)	0.628[a]
Median (IQR)	29.0(20)	22.65(25)	

SD: Standard deviation; IQR: Interquartile range; [a] Mann Whitney test; [b] Fisher's exact test.

Generally, the pain scores recorded by the patients in both groups on day 1 (6 hours postoperatively) were higher and gradually decreased on days 3 and 7. The difference between the groups was significant only on day 1, where patients in the study group recorded significantly lower pain scores than the control group, while on days 3 and 7, the differences were not significant, as shown in Table 2.

Table 2: The differences in pain scores between the study and control groups

Pain score		Study group	Control group	*p*-value
Day 1 (6 hours postoperatively)	Mean (SD)	4.214(3.63)	6.696(2.83)	0.013[a]
	Median (IQR)	4.50(6.75)	7.50(5.5)	
Day 3	Mean (SD)	3.250(3.44)	3.071(2.96)	0.891[a]
	Median (IQR)	2.50 (6)	2.00(6.75)	
Day 7	Mean (SD)	1.286 (2.43)	1.107(1.85)	0.916[a]
	Median (IQR)	0.0(1.75)	0.0(1.75)	

SD; Standard deviation, IQR; Interquartile range, [a] Mann Whitney test

The comparison of the differences in facial measurements between the two groups demonstrated that patients in the study group had a significantly lesser degree of swelling on day 3 compared to the control group and this was also evident when comparing the facial measurements on day 7 to the preoperative baseline measurements, while the differences in facial measurements recorded between days 3 and 7 showed a non-significant difference between the two groups, as shown in Table 3.

Table 3: The differences in facial measurements between the two groups

Facial measurement (mm)	Study group		Control group		*p*-value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Preoperative vs Day 3	-2.89(4.11)	-2.00(2.83)	-5.4(3.62)	-5.60(5.13)	0.002[a]
Day 3 vs Day 7	2.72(2.94)	2.000(4)	3.20(2.53)	2.65(3.23)	0.511[b]
Preoperative vs Day 7	-0.17(5.85)	0.0(2.55)	-2.19(4.23)	-1.700(3)	0.008[a]

SD: Standard deviation: IQR; Interquartile range; [a] Mann Whitney test; [b] Unpaired *t*-test.

The differences in mouth opening and QoL between the two groups did not reveal significant changes during the study period, as shown in Figures 4, 5, and 6.

DISCUSSION

Several studies have used bromelain as a proteolytic enzyme to mitigate the postoperative inflammatory reaction following third-molar surgery. Mendes *et al*. (2019), in a systematic review and meta-analysis, assessed the effects of bromelain on health outcomes in third-molar surgery patients [20]. Their review included six randomized clinical studies and they reported that bromelain showed a moderate effect size on reducing postoperative pain, which was limited to the first 24 hours and 7 days after surgery.

Table 4: The differences in maximum mouth opening between the two groups

Facial measurement (mm)	Study group		Control group		*p*-value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Preoperative vs Day 3	13.36(8.98)	10.50(13.75)	14.18(8.31)	15.50(13.5)	0.724[a]
Day 3 vs Day 7	-6.29(5.72)	-5.00(8.5)	-7.82(6.89)	-7.50 (8)	0.368[a]
Preoperative vs Day 7	7.07(8.06)	4.50(10.5)	6.36(6.52)	4.50(8.25)	0.964[b]

SD; Standard deviation, IQR; Interquartile range, [a] Unpaired t-test, [b] Mann Whitney test.

Table 5: The difference in QoL between the baseline vs day 3 between the groups

Groups	Baseline		Day 3		Difference		*p*-value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Study	1.5(3.27)	0(0.75)	4.14(3.30)	3.5(3)	2.64(4.18)	3(3)	0.816[a]
Control	2.11(2.99)	1.5(3.75)	5.29(3.55)	4.5(4)	3.18(4.57)	3(6.75)	

SD: Standard deviation; IQR: Interquartile range, [a] Mann Whitney test.

Table 6: The difference in QoL of baseline vs day 7 between the groups

Groups	Baseline		Day 7		Difference		*p*-value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Study	1.5(3.27)	0(0.75)	1.93(2.29)	2(2)	0.429(3.73)	1.5(2)	0.257[a]
Control	2.11(2.99)	1.5(3.75)	2.04(2.50)	1(3.75)	-0.07(4.04)	0(2.75)	

SD: Standard deviation; IQR: Interquartile range; [a] Mann Whitney test.

Bromelain is reported to have analgesic properties, which are thought to be the result of its direct influence on pain mediators such as bradykinin [21] and the reduction of prostaglandin E2 and substance P concentration [22]. SET is reported to reduce the postoperative inflammatory response; therefore, this study aimed to investigate the effect of SET in the form of Tibrolin® on postoperative pain, swelling, trismus, and the QoL following surgical extraction of IMTM. Patients in both groups reported pain scores that were higher on day 1 (6 hours postoperatively) and gradually decreased in the third and seventh days postoperatively, which agrees with the general pattern reported by studies that pain intensity peaks at 6–8 hours after third molar surgery [18,19]. The only difference between the two groups was evident on day 1, when patients in the study group (the Tibrolin® group) reported significantly lower pain scores than patients in the control group. Studies that investigated the effects of SET on the postoperative inflammatory response following third-molar surgery have reported a variety of methods and results. Concerning postoperative pain, this study is in line with Wala *et al*. [23], who used the same combination of bromelain, trypsin, and rutoside administered three times daily for three days and compared it with ibuprofen and the trypsin-chymotrypsin combination. The authors reported that the bromelain, trypsin, and rutoside combination was significantly better at reducing postoperative pain than the ibuprofen and trypsin-chymotrypsin combination and that the difference was discernible on the first, third, and seventh postoperative days. The same combination was also used, although in higher doses, along with standard anti-inflammatory drugs and analgesics for five days postoperatively in another study [24] that reported a significant reduction in the mean pain scores on the third, fifth, and seventh days following surgery. Abhinav and Kumar in 2023 [25], on the other hand, in a double-blinded prospective randomized clinical trial, used the same combination of bromelain, trypsin, and rutoside with 500 mg paracetamol and compared them with oral serratiopeptidase and 500 mg paracetamol. They found that the reduction of postoperative edema, pain, and trismus following lower third molar surgery was comparable in both groups. Also, Gandhewar *et al*. 2020 [12] used Tibrolin® in patients who underwent surgical removal of mandibular third molars with different timings of administration: before, on the day of surgery, and immediately after surgery, and they compared the postoperative inflammatory sequelae with a control group of patients who received NSAID (diclofenac) postoperatively for 5 days. The authors reported that administration of Tibrolin® had a comparable reduction in pain and swelling to the control group. The facial measurements, as an indicator of swelling after surgery, increased in both groups on the third day and subsided on the seventh. Swelling usually reaches its peak after 12–48 hours after third molar surgery and resolves by the 5th–7th day [26]. When compared to the control group, patients in the study group demonstrated significantly lower levels of swelling on day 3 compared to the control group, and this was also evident when comparing the facial measurements on day 7 to the baseline measurements. This suggests that Tibrolin® was effective in reducing the swelling in patients in the study group compared to the control group and that the reduction in swelling was maintained over time. These results, however, disagree with other studies that observed no effect of the combination of bromelain, trypsin, and rutoside on the postoperative swelling following third molar surgery compared to a control group or a group of patients that received a combination of ibuprofen and trypsin-chymotrypsin [27], as well as serratiopeptidase and paracetamol [25]. One study, however, reported a significant reduction in postoperative swelling on the third, fifth, and seventh postoperative days after third molar surgery in patients who used bromelain, trypsin, and rutoside with higher doses along with standard

anti-inflammatory drugs and analgesics compared to a control group [24]. It is suggested that bromelain favors the re-entry of interstitial fluid and inflammatory component cells into the bloodstream, thus reducing the swelling in the area [28]. It also exhibits fibrinolytic activity, which aids in the reabsorption of edema fluid [29]. Trypsin was reported to serve as a thrombolytic and fibrinolytic agent, thereby breaking down the fibrin mantle and promoting adequate blood flow during the process of wound healing [30]. Additionally, in conjunction with bromelain, they decrease the levels of pro-inflammatory cytokines [31]. However, Mendes *et al*. [20] did not find any clinical evidence supporting the effectiveness of bromelain in reducing facial swelling after third molar surgery. Concerning the MMO as an indicator for postoperative trismus, this study showed that it decreased on the 3rd day postoperatively compared to the preoperative baseline measurement and improved on the 7th day with non-significant differences between the two groups. This observation has been reported in other studies that evaluated the effect of the same SET combination used in Tibrolin® on the postoperative trismus after third molar surgery and found that no significant favorable effect was detected [24,27]. Moreover, many studies that evaluated the effect of bromelain on postoperative trismus reported no significant effect on reducing the degree of trismus following third molar surgery [16,20]. Trismus after the surgical extraction of IMTM results from several factors, such as pain, hematoma, edema, tendon, and muscle injuries. This condition could arise from the traumatic handling of tissues during the extraction process. Furthermore, the decrease in muscular activity at the site of intervention has been regarded as an inherent protective mechanism to alleviate pain [32,33]. This could explain the non-significant difference in the degree of trismus between the two groups in this study. The patients' QoL is becoming increasingly recognized as an important outcome that can be measured to evaluate new drugs or procedures that may improve different aspects of their daily lives [34]. Moreover, third molar surgery stands as one of the most frequently conducted surgical procedures worldwide, exerting a notable influence on QoL throughout the postoperative phase, and it serves as one of the most widely employed interventional study models [6]. In the present study, the Arabic version of oral health impact profile 5 (OHIP5-Ar) was used to evaluate the QoL perception of the patients. Alhajj *et al*. [35] maintained that this version is a reliable instrument to assess oral health-related QoL in an Arabic-speaking population and they recommended it be used in dental practice and for research purposes as well due to its sufficient psychometric properties, low burdens, and easy applicability. In this study, the participants in both groups reported deterioration in their QoL on day 3 postoperatively when compared to their preoperative baseline status. On day 7, however, there was a significant improvement to nearly that of the baseline record. This pattern of alteration in the QoL following third molar surgery is in line with McGrath *et al*. [36], who observed a substantial decline in QoL following third molar surgery during the immediate postoperative phase, using two distinct oral health-related quality of life measures: OHIP-14 and OHQoLUK. This is, to the best of our knowledge, the first study to investigate the effect of the proteolytic enzyme combination in Tibrolin® on QoL after third molar surgery. Majid and Al-Mashhadani [16] evaluated the effect of oral bromelain on QoL along with pain and swelling following mandibular third molar surgery. The authors compared the effect of bromelain 250 mg 4 times daily for 4 days with diclofenac and placebo, and they reported significant improvement in QoL comparable to that of diclofenac compared to the placebo group. The questionnaire that these authors used was a modification of another questionnaire reported by Savin and Ogden (1997) [37] that was translated into the Arabic language. It consisted of 5 domains: social isolation, eating, speech, sleep, and appearance, with a total of 14 questions and 42 scores. This difference in QoL between the current study and that of Majid and Al-Mashhadani [16] may be related to the dose of bromelain used in the latter study: 250 mg four times daily compared to the dose of bromelain in Tibrolin®, which is 90 mg. Also, the different questionnaires used might have caused this difference in the results obtained, as they may have captured different aspects of QoL. The results of this study demonstrate that three areas, namely, discomfort about appearance, less flavor in food, and difficulty doing usual jobs, were not much affected in both groups since the most important issues and problems were difficulty chewing and painful aching, which is in agreement with Sato *et al*. (2009) [29], who identified that mouth opening and chewing were the primary limitations for patients during the initial three postoperative days, with the highest pain intensity reported on the first day postoperatively.

Limitations of the study

The primary study limitation stems from the principal researcher's lack of blinding regarding the patient assignment to both groups and the postoperative outcome assessment, potentially leading to an assessment bias. Also, the technical limitations inherent to the contact linear method of assessing facial swelling may have resulted in some inaccurate facial measurements.

Conclusion

Tibrolin® administration following the surgical extraction of IMTM decreases postoperative pain and swelling. However, there were no significant changes in MMO or QoL. These findings suggest that Tibrolin® may have benefits during the postoperative period.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

REFERENCES

1. Lateef TA, Bede SYH, Mohammed JA. The influence of prophylactic Dexamethasone on postoperative swelling and trismus following impacted mandibular third molar surgical extraction. *J Bagh Coll Dent*. 2010;22(4):85-90.
2. Bede SY. Factors affecting the duration of surgical extraction of impacted mandibular third molars. *World J Dent*. 2018;9(1):8–12. doi: 10.5005/jp-journals-10015-1498.
3. Veronez B, Matos FP de, Monnazzi MS, Sverzut AT, Sverzut CE, Trivellato AE. Maxillofacial infection. A retrospective evaluation of eight years. *Brazilian J Oral Sci*. 2014;2(13):98–103. doi: 10.1590/1677-3225v13n2a04.
4. Shabat MA, Bede SY. Effect of the local application of bupivacaine in early pain control following impacted mandibular third molar surgery: A randomized controlled study. *Dent Med Probl.* 2021;58(4):483–488. doi: 10.17219/dmp/133664.
5. Kareem ASA, Al Hussaini AH. Effect of platelet rich-fibrin on alveolar osteitis incidence following surgical removal of impacted mandibular third molars: A comparative study. *J Bagh Coll Dent.* 2019;31(4):63-70.doi:10.26477//jbcd.v31i4.2723.
6. O'Sullivan L, Ríordáin RN. Variations in reporting of clinician-reported outcome measures in third molar surgery: A focused review. Surg. 2022;20(3):43–50. doi: 10.1016/j.surge.2021.03.008.
7. Shin YS. How to improve the national health insurance fee-for-service schedule*? Health Welfare Forum.* 2019;20(6):39–52.
8. Lago-Méndez L, Diniz-Freitas M, Senra-Rivera C, Gude-Sampedro F, Gándara Rey JM, García-García A. Relationships between surgical difficulty and postoperative pain in lower third molar extractions. *J Oral Maxillofac Surg*. 2007;65(5):979-983. doi: 10.1016/j.joms.2006.06.281.
9. Jerjes W, El-Maaytah M, Swinson B, Upile T, Thompson G, Gittelmon S, et al. Inferior alveolar nerve injury and surgical difficulty prediction in third molar surgery: the role of dental panoramic tomography. *J Clin Dent*. 2006;17(5):122-130. PMID: 17240930.
10. Contar CM, de Oliveira P, Kanegusuku K, Berticelli RD, Azevedo-Alanis LR, Machado MA. Complications in third molar removal: a retrospective study of 588 patients. *Med Oral Patol Oral Cir Bucal*. 2010;15(1):e74-78. doi: 10.4317/medoral.15.e74.
11. Abhinandan U, Arvind R, Srikant N. Comparison of anti-inflammatory efficacy of three different therapeutic modalities after mandibular third molar impaction surgery-a cross sectional study. *J Int Dent Med Res*. 2022;15(4):1684–1689.
12. Gandhewar T, Andrade NN, Aggarwal N, Choradia S, Mathai PC, Nerurkar S. The effects of systemic proteolytic enzyme therapy on pain and swelling in third molar surgery equal to diclofenac therapy: a prospective randomized double blinded clinical trial. *Oral Maxillofac Surg*. 2020;24(4):461-468. doi: 10.1007/s10006-020-00854-7.
13. Yuan G, Wahlqvist ML, He G, Yang M, Li D. Natural products and anti-inflammatory activity. *Asia Pac J Clin Nutr*. 2006;15(2):143-152. PMID: 16672197.
14. Maurer HH, Tauvel FX, Kraemer T. Screening procedure for detection of non-steroidal anti-inflammatory drugs and their metabolites in urine as part of a systematic toxicological analysis procedure for acidic drugs and poisons by gas chromatography-mass spectrometry after extractive methyl. *J Anal Toxicol.* 2001;25(4):237–244. doi: 10.1093/jat/25.4.237. PMID: 11386636.
15. Inchingolo F, Tatullo M, Marrelli M, Inchingolo AM, Picciariello V, Inchingolo AD, et al. Clinical trial with bromelain in third molar exodontia. *Eur Rev Med Pharmacol Sci*. 2010;14(9):771–774. PMID: 21061836.
16. Majid OW, Al-Mashhadani BA. Perioperative bromelain reduces pain and swelling and improves quality of life measures after mandibular third molar surgery: a randomized, double-blind, placebo-controlled clinical trial. *J Oral Maxillofac Surg*. 2014;72(6):1043–1048. doi: 10.1016/j.joms.2013.12.035.
17. Mameli A, Natoli V, Casu C. Bromelain: An Overview of Applications in Medicine and Dentistry. *Biointerface Res Appl Chem.* 2020;11(1):8165–8170.doi: 10.33263/BRIAC111.81658170.
18. Kaur R, Abmwani S, Mehta B. Trypsin, rutoside and bromelain alone and fixed dose combination: a natural, safer and effective anti-inflammatory agent. *J Drug Deliv Ther*. 2014;4(1):108–110.
19. A, Langade D, Sonawane D, Gavai P. A randomized, clinical trial to evaluate efficacy and tolerability of trypsin: chymotrypsin as compared to serratiopeptidase and trypsin: bromelain: rutoside in wound management. *Adv Ther.* 2017;34(1):180–198. doi: 10.1007/s12325-016-0444-0.
20. Mendes ML, do Nascimento-Júnior EM, Reinheimer DM, Martins-Filho PR. Efficacy of proteolytic enzyme bromelain on health outcomes after third molar surgery. Systematic review and meta-analysis of randomized clinical trials. *Med Oral Patol Oral Cir Bucal*. 2019;24(1):e61-e69. doi: 10.4317/medoral.22731.
21. Kwatra B. A review on potential properties and therapeutic applications of bromelain. *World J Pharm Pharm Sci.* 2019;8(11):488–500. doi: 10.20959/wjpps201911-14941.
22. Kumar ST, Prasanna RA, Kirubanandan JR, Elaveyini U, Devi SP, Balasubramaniam M. Postoperative healing after surgical removal of mandibular third molar: A comparative study between two proteolytic enzymes. *J Pharm Bioallied Sci*. 2020;12(1):289-294. doi: 10.4103/jpbs.JPBS_87_20.
23. Wala LJ. Clinical evaluation of anti-Inflammatory properties of combination of bromelain trypsin and rutoside with combination of ibuprofen trypsin and chymotrypsin following third molar extraction–A comparative study. *Rajiv Gandhi Univ Health Sci (India)*. 2017;8(2):468-468.
24. Vishal KT, Priya S, Sinha DK, Kumar C. Effect of bromelain, rutoside and trypsin combination on postoperative pain, swelling and trismus after surgical third Mmolar extraction. *J West Bengal Univ Heal Sci.* 2021;1(3):18–25.
25. Abhinav RP. Systemic enzymes and their role in the reduction of post-operative edema after surgical removal of lower third molars: A randomized controlled double-blind study. *J Popul Ther Clin Pharmacol.* 2023;30(6):200–206. doi: 10.47750/jptcp.2023.30.06.027.
26. Thorat SD, Nilesh K. Efficacy of low-level laser therapy in the management of postoperative surgical sequelae after surgical removal of impacted mandibular third molars. *Natl J Maxillofac Surg.* 2022;13(1):52-56. doi: 10.4103/njms.NJMS_52_20.
27. Wala LJ, Choudhary A, Reddy BC. Clinical evaluation of anti-inflammatory properties of combination of bromelain, trypsin and rutoside with combination of ibuprofen, trypsin and chymotrypsin following third molar extraction–A comparative study. *J Med Sci Clin Res.* 2020;8(2):464-468.
28. Liu S, Zhao H, Wang Y, Zhao H, Ma C. Oral bromelain for the control of facial swelling, trismus, and pain after mandibular third molar surgery: a systematic review and meta-analysis. *J Oral Maxillofac Surg*. 2019;77(8):1566-1574. doi: 10.1016/j.joms.2019.02.044.
29. Sato FRL, Asprino L, de Araújo DES, de Moraes M. Short-term outcome of postoperative patient recovery perception after surgical removal of third molars. *J Oral Maxillofac Surg*. 2009;67(5):1083–1091. doi: 10.1016/j.joms.2008.09.032.
30. De la Barrera-Núñez MC, Yáñ ez-Vico RM, Batista-Cruzado A, Heurtebise-Saavedra JM, Castillo-de Oyagüe R, Torres-Lagares D. Prospective double-blind clinical trial evaluating the effectiveness of Bromelain in the third molar extraction postoperative period. *Med Oral Patol Oral Cir Bucal.* 2014;19(2):157-162. doi: 10.4317/medoral.19105.
31. Daftary GV, Shah AP, Divekar GH, John J, Patil NN. Systemic

therapy with bromelain-trypsin-rutoside combination in inflammation: A narrative review of the pharmacodynamics. *Natl J Physiol Pharm Pharmacol*. 2022;12(10):1521-1528. doi: 10.5445/njpp.2022.12.1037420212502202.

32. De Marco G, Lanza A, Cristache CM, Capcha EB, Espinoza KI, Rullo R, et al. The influence of flap design on patients' experiencing pain, swelling, and trismus after mandibular third molar surgery: a scoping systematic review. *J Appl Oral Sci*. 2021;29:e20200932. doi: 10.1590/1678-7757-2020-0932.
33. Villela GA, Mariano RC, de Menezes PHM, Saraiva MCP, Antoniali C. Does etoricoxib or Ddexamethasone control inflammatory pain, edema, and trismus after impacted third molar surgery? A double-blind, split-mouth randomized clinical trial. *J Anesth Clin Res*. 2023;14:1106. doi: 10.35248/2155-6148.23.14.1106.
34. Majid OW. Submucosal dexamethasone injection improves quality of life measures after third molar surgery: a comparative study. *J Oral Maxillofac Surg*. 2011;69(9):2289–2297. doi: 10.1016/j.joms.2011.01.037.
35. Alhajj MN, Halboub E, Khalifa N, Amran AG, Reissmann DR, Abdullah AG, et al. Translation and validation of the Arabic version of the 5-item Oral health impact profile: OHIP5-Ar. *Health Qual Life Outcomes*. 2018;16:218. doi: 10.1186/s12955-018-1046-0.
36. McGrath C, Comfort MB, Lo ECM, Luo Y. Changes in life quality following third molar surgery–the immediate postoperative period. *Br Dent J*. 2003;194(5):265–268. doi: 10.1038/sj.bdj.4809930.
37. Savin J, Ogden GR. Third molar surgery—a preliminary report on aspects affecting quality of life in the early postoperative period. *Br J Oral Maxillofac Surg*. 1997;35(4):246–253. doi: 10.1016/s0266-4356(97)90042-5.