Can Topical Agents (Arnica and Mucopolysaccharide Polysulfate) Reduce Postoperative Pain, Edema and Trismus Following Mandibular Third Molar Surgery?

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Background: Postoperative supplemental maintenance following mandibular third molar surgery remains an area of interest.

Purpose: Topical agents can modulate inflammatory processes. The aim of the present study was to determine if topical application of arnica or mucopolysaccharide polysulfate (MPSP) reduces pain, trismus, and edema following the removal of impacted mandibular third molars.

Materials and Methods: A single center randomized controlled clinical trial was conducted. The patients were randomized into three groups: the control group (standard therapy [ST]: antibiotic + nonsteroidal anti-inflammatory drugs twice a day), the arnica group (arnica + ST), and the MPSP group (MPSP + ST). The patients' pain, trismus, and edema values were measured preoperatively and on postoperative days 1, 3, 5, and 10. Sex, age, and operation time were also included. Analyses included descriptive statistics, analysis of variance, post hoc tests, and determinations of intraclass correlation coefficients. Statistical significance was set at $P < .05$.

Results: Sixty patients with a mean age of 26.98 ± 10.88 years were included in the study; 55% were females and 45% were males. The mean operation time was 23.8 ± 3.27 minutes. According to the visual analogue scale scores (in centimeter units), the arnica and MPSP groups felt less pain than the control group until day 5 (0.6 ± 0.88, 3.75 ± 1.16, 4.75 ± 1.29, and 1.05 ± 1.10, respectively, for the arnica group; 0.35 ± 0.59, 3.25 ± 1.62, 5.0 ± 1.65, and 1.50 ± 1.32 for the MPSP group; and 1.30 ± 1.17, 5.75 ± 1.37, 7.05 ± 1.10, and 3.15 ± 1.53 for the control group; $P < .05$). The trismus was lower on days 1, 3, and 5 in the arnica group (−8.05 ± 2.82, −12.15 ± 3.1, and −2.15 ± 1.81, respectively) than in the control group (−12 ± 3.82, −15.65 ± 4.81, and −4±2.81, respectively) ($P < .05$). The edema was lower on days 1 and 3 in the MPSP group (0.95 ± 2.2 and 1.75 ± 3.7, respectively) than in the control group (2.45 ± 0.9 and 3.6 ± 0.8, respectively) ($P < .05$). Arnica and MPSP had similar pain-relieving action, but arnica was more effective at reducing trismus, while MPSP was more effective at reducing edema.

Conclusions: Topical application of arnica or MPSP may have a beneficial effect on relieving pain 5 days after surgery, but arnica was also effective at reducing trismus, while MPSP was also effective at reducing edema. Both arnica and MPSP reduced postoperative sequelae.

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The removal of an impacted mandibular third molar usually causes some degree of pain, swelling, and trismus. This is because the procedure involves surgical trauma in a highly vascularized area, thereby leading to predictable inflammatory complications, also termed "sequelae."[1] Pharmacological treatment of the inflammatory response is the most commonly applied method for relieving postoperative sequelae.[2,3] Inflammatory mediators (eg, prostaglandins, bradykinin, leukotrienes, and platelet-activating factor) are discharged into the surrounding tissues following surgical intervention. The resulting irritation leads to increases in vascular dilatation and permeability, which trigger subsequent edema and interstitial tissue responses.[4,5] Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) is one way of enhancing the patient's post-surgical comfort.[6] Topical creams, such as arnica and mucopolysaccharide polysulfate (MPSP), are agents that can be used for this treatment.[7]

Arnica (also known as mountain arnica, mountain tobacco, wolf's bane, and leopard's bane) has traditionally been used as a topical agent for the treatment of inflammation-related symptoms, such as edema, pain, and malfunction.[8,9] A number of studies have shown its positive effect on the inflammation[10,11]; similar to the effects on the inflammatory cascade[12] achieved with topical glucocorticoids.[10,13] Arnica's content may cause allergic reactions and may also prove toxic to healthy tissues[14]; however, arnica is generally used only topically due to side effects that have been observed following oral administration.[11] Besides, MPSP is a semi-synthetic molecule produced through the sulfation of a mixture of glycosaminoglycans derived from mammalian cartilage. It has different therapeutic effects on blood coagulation, the anti-inflammatory reaction, and fibrinolysis.[7,15,16] It can also be used to suppress edema following orthognathic surgery.[17]

Discomfort following oral surgery is a primary concern for both patients and clinicians. Synthetic glucocorticoids can be used following the removal of an impacted mandibular third molar as an alternative to nonsteroidal treatment, although some undesirable side effects are associated with their use. The topical application of arnica or MPSP may be considered an alternative treatment approach due to the minimal side effects of these two topical agents. However, information is lacking concerning their effectiveness as treatments for postoperative edema, pain, and trismus after oral surgery.

The purpose of the present study was to determine if topical application of arnica or MPSP reduces pain, trismus, and edema following the removal of impacted mandibular third molars. The following null hypotheses were established: the use of the topical agents would not influence i) pain, ii) maximal mouth opening (MMO), and iii) edema values on postoperative days 1, 3, 5, and 10 following impacted mandibular third molar surgery. The specific aims of the study were: 1) to measure pain, edema, and trismus on postoperative days 1, 3, 5, and 10, and 2) to compare the effectiveness of arnica and MPSP on relieving postoperative pain, edema, and trismus.

Materials and Methods

STUDY DESIGN/SAMPLE

The study population consisted of all patients admitted to the Department of Oral & Maxillofacial Surgery between December 2018 and December 2019 for assessment, management, and removal of an impacted mandibular third molar under local anesthesia. The study protocol was registered at ClinicalTrials.gov (NCT04534426) in August 2020. All patients were informed about the surgery, the postoperative period, and the possible complications. The study complied with the Declaration of Helsinki in terms of medical protocol and ethics. The regional Ethical Review Board of Abant Izzet Baysal University Local Ethical Committee (2018/284) approved the study, and each patient provided informed consent to participate in the study.

The present randomized controlled trial was designed in accordance with the CONSORT guidelines.[18] A parallel-group and single-blinded design was preferred to attain the aims of the study. The patients included in the study had no systemic disease (diabetes, hypertension, hyperthyroidism, hypothyroidism, any cardiac disease, autoimmune disorder, etc), good oral hygiene, Parant level II surgical difficulty,[19] no pericoronitis, no drug allergy, and no need for preoperative drugs, and all were older than 16 years of age. The Parant Classification[19] levels were as follows: level I, extraction with forceps; level II, extraction through osteotomy only; level III, requiring crown sectioning; and level IV, requiring root section. The exclusion criteria were pregnancy, lactation, smoking, refusal to give informed consent, patients with any missing data or recall visits, and the use of any non-prescribed medicines during the follow-up period.

The patients who met all the inclusion criteria were randomized through a simple randomization method, the closed-envelope approach, and were divided into three groups. The arnica group was treated post-surgically with topical arnica, in addition to undergoing the standard therapy (ST) (use of antibiotic + NSAIDs twice a day). The MPSP group was treated post-surgically with topical MPSP, in addition to undergoing the ST. The control group was treated post-surgically only with the ST. After the surgery, all patients were instructed to bite on gauze for

30 min, clean the region that had been operated on, and refrain from engaging in any form of physical exertion. The patients were also given verbal and written recommendations about soft diets, the use of medications, and oral hygiene. The patients were advised not to apply cooling packs to their cheeks or to engage in mouth-opening exercises to ensure that the effects of the topical agents they were to apply could be evaluated. A systemic antibiotic (1000 mg amoxicillin/clavulanic acid, twice a day; Augmentin, GlaxoSmithKline, Brentford, UK) and a NSAID (50 mg diclofenac potassium, twice a day; Cataflam, Novartis, Stein, Switzerland) were prescribed for all the patients as the standard treatment protocol.

VARIABLES

All patients underwent surgery between 09:00 AM and 11:30 AM. All surgeries were performed under local anesthesia by the same (experienced and blinded) oral and maxillofacial surgeon and an assistant. Articaine with 1:200,000 epinephrine (Ultracain-DS, Hoechst Marion Roussel, Turkey) was used for the inferior alveolar and buccal nerve blocks. An incision was made on the buccal side through a triangular flap. A surgical round tungsten carbide bur on a straight handpiece was used for bone removal under copious irrigation with an isotonic 0.9% NaCl solution. Following the mandibular third molar extraction, the socket was inspected and copiously irrigated, and then the flap was sutured with 4-0 silk sutures (Dogsan, Trabzon, Turkey). The operation time (the time interval between the initial incision and the suture closure) was recorded using a digital watch. A small gauze pack was applied to the surgical site, and the patient was given postoperative instructions. Postoperatively, amoxicillin/clavulanic acid (1000 mg orally every 12 h) and diclofenac potassium (50 mg orally every 12 h) were prescribed for 5 days following the surgery. The patients were examined on days 1, 3, 5, and 10 after surgery. During each visit, the patients' pain, MMO, and edema were measured. The sutures were removed on the seventh day. Only 1 impacted mandibular third molar extraction was performed on each patient.

Predictor Variables

The predictor variables in the present study were the two different experimental groups and the control group. The patients were randomly distributed into three groups: the arnica, MPSP, and control groups. In the arnica and MPSP groups, the patients were given an unlabeled tube containing cream (arnica cream [Arnika Krem, MediTech, Istanbul] for the arnica group and MPSP cream [Hirudoid Fort Krem 445 mg/100g; Santa Farma, Istanbul] for the MPSP group) that was to be applied topically to the skin surface of the masseteric and submandibular regions (2 cm in length) every 8 h, starting immediately after the surgery and continuing for the following 10 days. The exact compositions of the creams are provided in Table 1. The arnica and MPSP groups also received the standard therapy. In the control group, only the standard therapy was applied following surgery.

Outcome Variables

In the present research, the primary outcome variables were the pain, MMO, and edema values.

Covariates

Covariates, such as sex, age, and operation time, were included.

DATA COLLECTION METHODS

Analysis of the Visual Analogue Scale (VAS) Scores

The patients' postoperative pain was assessed using a 10-centimeter VAS-anchored scale divided into centimeter blocks (ranging from 0 for no pain to 10 for the worst possible pain). The patients' preoperative VAS scores were recorded as V_0. The measurements were repeated, as described above, on postoperative days 1, 3, 5, and 10 and were recorded as V_1, V_3, V_5, and V_{10}, respectively.

Table 1. COMMERCIAL NAMES, MANUFACTURERS, AND COMPOSITIONS OF THE MATERIALS USED IN THE PRESENT STUDY

Material	Manufacturer	Composition
Arnika Krem	MediTech, Istanbul, Turkey	Active ingredient: Herbal extract of *Arnica montana* Inactive ingredients: *Hypericum perforatum*, horse chestnut, and green tea extracts
Hirudoid Forte Krem	Santa Farma, Istanbul, Turkey	Active ingredient: 445 mg/100 mg (40000U) Mucopolysaccarite polysulfate (MPSP) Inactive ingredients: Isopropyl alcohol, 2-phenoxyethanol, imidurea, and rosemary oil

Abbreviations: MPSP, mucopolysaccharide polysulfate.

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Technique Used for Analyzing Edema

The level of edema was determined through a modified tape measuring method described by Gabka and Matsumara.[20,21] Specifically, three measurements were made between five reference points: (A) tragus; (B) lateral canthus of the eye; (C) commissure; (D) angulus; and (E) soft tissue pogonion. The three mean preoperative measurements (in mm; AC, tragus to commissure; AE, tragus to soft tissue pogonion; and BD, lateral canthus of the eye to angulus) were recorded as the E_0 values. These measurements were repeated on postoperative days 1, 3, 5, and 10 and were recorded by the same surgeon as E_1, E_3, E_5, and E_{10}, respectively.

The differences between the edema levels on postoperative days 1, 3, 5, and 10 and the preoperative measurements were recorded as ΔE_1, ΔE_3, ΔE_5, and ΔE_{10}, respectively.

Analysis of the Maximal Mouth Opening Values

The MMO value was described as the greatest distance (in mm) between the incisal edge of the upper central incisor and the incisal edge of the lower central incisor.[2] The patients' preoperative MMO values were recorded as M_0. This measurement was repeated on postoperative days 1, 3, 5, and 10, and the values were recorded by the same surgeon as M_1, M_3, M_5, and M_{10}, respectively.

To assess the effects of the topical agents on the degree of postoperative trismus, the differences between the MMO values on postoperative days 1, 3, 5, and 10, and the preoperative measurements were determined and recorded as ΔM_1, ΔM_3, ΔM_5, and ΔM_{10}, respectively.

The patients' demographic characteristics (age and sex), intraoperative values (duration of surgery), and postoperative variable values (pain, edema, and MMO) were recorded in the present study.

DATA ANALYSIS

The sample size was calculated according to the method set out in a previous article.[2] Specifically, to detect a difference of 1 cm on the VAS at $\alpha = 0.05$ with 90% statistical power, a total sample size of 57 was found adequate. The required data were collected synchronously during the study using Microsoft Excel 2019 MSO (Redmond, WA, USA). All the data analyses were performed using IBM SPSS Statistics for Windows, version 17 (IBM Corp., Armonk, NY, USA). A descriptive test was applied to all the variables. The patients' demographic and intraoperative information was assessed using Pearson's χ^2 or an analysis of variance, as shown in Table 2. Within-group and between-group comparisons of the outcome variables were conducted using one-way and repeated measures of analysis of variance. Post-hoc analyses were performed using Tukey's honestly significant difference test. The intra-rater reliabilities of the MMO and edema differences were evaluated using intraclass correlation coefficients.

Results

In total, 66 patients met all the inclusion criteria of the present study, but 6 patients were later excluded because they did not attend their follow-up visits. The data for the 60 remaining patients (n = 20 for each group) were ultimately analyzed (Fig 1). Overall, 33 (55%) female patients and 27 (45%) male patients, with a mean age of 26.98 ± 10.88 years (range: 16–68 years), were included. The mean operation time was 23.44 ± 3.10 min (Table 2). No statistically significant differences were found between the groups for either the patients' demographic data or the operation time (Table 2). The 60 patients complied with all the postoperative recommendations and took the prescribed antibiotics and NSAIDs for 5 days, as directed. The patients in the two experimental groups applied the cream prescribed to them every 8 h for 10 days.

The pain level was significantly lower on days 0, 1, 3, and 5 for the arnica group (0.6 ± 0.88,

Table 2. BIVARIATE ANALYSES OF THE COVARIATES VS TREATMENT GROUPS

Variable	Control (n = 20)	Arnica (n = 20)	MPSP (n = 20)	Total (n = 60)	*P* Value
Sex					.545*
Male	13	10	10	33	
Female	7	10	10	27	
Age (y)	29.3 ± 10.72	24.75 ± 11.36	26.9 ± 10.61	26.98 ± 10.88	.424†
Operative time (min)	23.8 ± 3.27	23.7 ± 3.57	22.83 ± 2.39	23.44 ± 3.10	.564†

Note: Data presented as means ±standard deviations or n.

Abbreviations: min, minutes; y, years.

* χ^2 test.

† Analysis of variance.

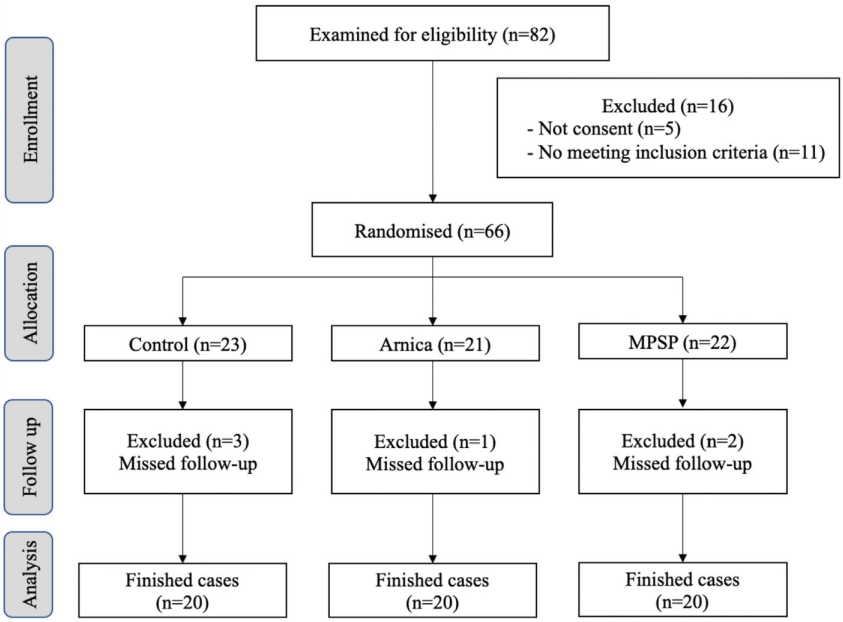

FIGURE 1. Consolidated Standards of Reporting TrialFlow Diagram according to the criteria adopted in this randomized controlled trial.

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3.75 ± 1.16, 4.75 ± 1.29, and 1.05 ± 1.10, respectively) and the MPSP group (0.35 ± 0.59, 3.25 ± 1.62, 5.0 ± 1.65, and 1.50 ± 1.32, respectively) than for the control group (1.30 ± 1.17, 5.75 ± 1.37, 7.05 ± 1.10, and 3.15 ± 1.53, respectively) ($P < .05$; Table 3). The highest pain levels were recorded on postoperative day 3 for each group (7.05 ± 1.10 for the control group, 4.75 ± 1.29 for the arnica group, and 5.0 ± 1.65 for the MPSP group).

Trismus was significantly lower on postoperative days 1, 3, and 5 in the arnica group (−8.05 ± 2.82, −12.15 ± 3.1, and −2.15 ± 1.81, respectively) than in the control group (−12 ± 3.82, −15.65 ± 4.81, and −4±2.81, respectively) ($P < .05$; Table 4). Trismus was significantly lower on postoperative day 1 in the MPSP group (−7.85 ± 2.94) than in the control group (−12 ± 3.82) ($P < .05$; Table 4).

The edema values on postoperative day 1 were 0.95 ± 2.21 for the MPSP group, 1.3 ± 0.57 for the arnica group, and 2.45 ± 0.99 for the control group. These differences were statistically significant for the two experimental groups ($P < .05$; Table 5). The edema values on postoperative day 3 were 1.75 ± 3.77 for the MPSP group, 1.95 ± 0.69 for the

Table 3. BIVARIATE ANALYSES OF TREATMENT GROUPS VS POSTOPERATIVE PAIN

Groups	V_0	V_1	V_3	V_5	V_{10}
Control	$1.30 \pm 1.17^{a,A}$	$5.75 \pm 1.37^{a,B}$	$7.05 \pm 1.10^{a,C}$	$3.15 \pm 1.53^{a,D}$	$0.30 \pm 0.66^{a,E}$
Arnica	$0.6 \pm 0.88^{b,A,D,E}$	$3.75 \pm 1,16^{b,B}$	$4.75 \pm 1.29^{b,C}$	$1.05 \pm 1.10^{b,D}$	$0.00 \pm 0.00^{a,E}$
MPSP	$0.35 \pm 0.59^{b,A}$	$3.25 \pm 1.62^{b,B}$	$5.0 \pm 1.65^{b,C}$	$1.50 \pm 1.32^{b,D}$	$0.10 \pm 0.45^{a,A}$

Note: Lower superscript letters (a, b): different letters in the same column indicate a significant difference in mean VAS scores. Upper superscript letters (A, B, C, D, E): different letters in the same row indicate a significant difference in mean VAS scores. For example. 1) The V_3 values of treatment groups were presented in the same column. The V_3 value of the control group (labeled as superscript a) was significantly different than that of Arnica and MPSP groups (labeled as superscript b). 2) V_0, V_1, V_3, V_5, and V_{10} values of the MPSP group were presented in the same row. V_0 and V_{10} values of the MPSP group (labeled as superscript A) were not significantly different than each other, but they were significantly lower than V_1 value of the MPSP group (labeled as superscript B).

$P < .05$ significant.

Abbreviations: MPSP, mucopolysaccharide polysulfate; V_0, preoperative VAS score; V_1, VAS score of the first day; V_3, VAS score of the third day; V_5, VAS score of fifth day; V_{10}, VAS score of tenth day.

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Table 4. THE MEANS (MM) ± SDS AND COMPARISON OF MMO OUTCOME VARIABLE BETWEEN AND WITHIN GROUP DIFFERENCES

MMO	ΔM_1	ΔM_3	ΔM_5	ΔM_{10}
Control	$-12 \pm 3.82^{a,A}$	$-15.65 \pm 4.81^{a,B}$	$-4 \pm 2.81^{a,C}$	$1.1 \pm 2.15^{a,D}$
Arnica	$-8.05 \pm 2.82^{b,A}$	$-12.15 \pm 3.1^{b,B}$	$-2.15 \pm 1.81^{b,C}$	$0.8 \pm 1.36^{a,D}$
MPSP	$-7.85 \pm 2.94^{b,A}$	$-12.8 \pm 3.9^{a,b,B}$	$-2.4 \pm 2.41^{a,b,C}$	$0.6 \pm 1.5^{a,D}$

Note: Lower superscript letters (a, b): different letters in the same column indicate a significant difference in mean MMO scores. Upper superscript letters (A, B, C, D): different letters in the same row indicate a significant difference in mean MMO values. $\Delta M_1 = M_1\text{-}M_0$; $\Delta M_3 = M_3\text{-}M_0$; $\Delta M_5 = M_5\text{-}M_0$; $\Delta M_{10} = M_{10}\text{-}M_0$ (M_0, preoperative MMO value; M_1, MMO value of the first day; M_3, MMO value of the third day; M_5, MMO value of the fifth day; M_{10}, MMO value of the tenth day).

$P < .05$ significant.

Abbreviations: MPSP, mucopolysaccharide polysulfate; MMO, maximum mouth opening; mm, millimeter.

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arnica group, and 3.6 ± 0.82 for the control group. The two experimental groups had lower edema values than the control group on postoperative day 3, but only the edema values of the MPSP group were statistically significantly different from those of the control group ($P < .05$; Table 5).

There were no significant differences in pain, trismus (MMO), and edema between the two active treatments, arnica and MPSP (Tables 3-5).

The first (i) null hypothesis (ie, the use of topical agents would not influence the pain values on postoperative days 1, 3, 5, and 10 following impacted mandibular third molar surgery) was rejected for the first 5 days after the surgery. The second (ii) null hypothesis (ie, the use of topical agents would not influence the MMO values on postoperative days 1, 3, 5, and 10 following impacted mandibular third molar surgery) was rejected for arnica group during the first 5 days after the surgery. The third (iii) null hypothesis (ie, the use of topical agents would not influence the edema values on postoperative days 1, 3, 5, and 10 following impacted mandibular third molar surgery) was rejected for group MPSP during the first 3 days after the surgery.

The intraclass correlation coefficient results ranged from 0.76 to 0.90 (average = 0.84) for MMO and from 0.74 to 0.89 (average = 0.83) for edema. Both of these intraclass correlation coefficient values were >0.75; thus, the measured MMO and edema differences were considered to have good intrarater reliability according to the criterion set by Portney and Watkins (ie, values > 0.75 are indicative of good reliability).[22]

Discussion

The present study investigated the effects of topical application of arnica or MPSP cream on patients' pain, trismus, and edema after surgical extraction of an impacted mandibular third molar. Although various studies have examined the anti-edema and anti-inflammatory effects of arnica and MPSP administered in the form of an oral tablet, sublingual drop, or topical agent,[7,8,10,16,17] to the best of our knowledge, no comprehensive study has examined their local effects after surgical extraction of impacted mandibular third molars. A number of researchers have reported the risk factors associated with pain, trismus, and edema,

Table 5. THE MEANS (MM) ± SDS AND COMPARISON OF EDEMA OUTCOME VARIABLE BETWEEN AND WITHIN GROUP DIFFERENCES

Edema	ΔE_1	ΔE_3	ΔE_5	ΔE_{10}
Control	$2.45 \pm 0.99^{a,A}$	$3.6 \pm 0.82^{a,B}$	$1.3 \pm 1.3^{a,C}$	$-0.6 \pm 0.39^{a,D}$
Arnica	$1.3 \pm 0.57^{b,A}$	$1.95 \pm 0.69^{a,b,B}$	$0.7 \pm 0.57^{a,C}$	$-0.5 \pm 0.51^{a,D}$
MPSP	$0.95 \pm 2.21^{b,A}$	$1.75 \pm 3.77^{b,A}$	$1 \pm 0.86^{a,A}$	$-0.17 \pm 0.24^{a,B}$

Note: Lower superscript letters (a, b): different letters in the same column indicate a significant difference in mean edema values. Upper superscript letters (A, B, C, D): different letters in the same row indicate a significant difference in mean edema values. $\Delta E_1 = E_1\text{-}E_0$; $\Delta E_3 = E_3\text{-}E_0$; $\Delta E_5 = E_5\text{-}E_0$; $\Delta E_{10} = E_{10}\text{-}E_0$ (E_0, preoperative edema value; E_1, edema value of the first day; E_3, edema value of the third day; E_5, edema value of the fifth day; E_{10}, edema value of the tenth day).

$P < .05$ significant.

Abbreviations: MPSP, mucopolysaccharide polysulfate; mm, millimeter.

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including age, sex, and operation time, following surgery.[23,24]

Although the postoperative problems associated with impacted mandibular third molar surgery, including pain, trismus, and edema, are deemed minor and temporary morbidities, various procedures that serve to minimize inflammation can allow patients to resume their daily activities more easily following the surgery. Previous studies have reported that the use of corticosteroids can help control the pain, edema, and trismus associated with the removal of an impacted mandibular third molar.[25,26] The effectiveness of the use of topical corticosteroids for medication purposes has long been established in the field of dermatology;[27] however, these agents may have systemic adverse effects due to percutaneous absorption through the skin.[28] Thus, supplementary approaches, such as topical arnica and MPSP, have been proposed to reduce postoperative discomfort.[17,29-32] The topical application of arnica or MPSP offers many potential benefits with respect to relieving inflammatory conditions. Indeed, arnica and MPSP have a long history of use for this purpose, as clinicians prefer to prescribe the most evidence-based medications available. Additionally, both arnica and MPSP are largely nontoxic, although exceptions do exist.[17,33] The anti-inflammatory properties of both agents have been demonstrated in many studies.[16,29,34] Previous human studies in this regard have related perioperative findings concerning many surgeries, principally those involving dermatological lesions.[7,8,17,27,35]

The components of arnica can cause stress and increase steroid secretion. In addition, arnica inhibits cyclooxygenase-2 and phospholipase, regardless of age, sex, and operation time.[29] These responses obviate the need for exogenous corticosteroids to accompany arnica treatment due to the supplementary anti-inflammatory effects of arnica. Lökken et al[31] and Kaziro et al[32] suggested that arnica has no positive effects on pain or other inflammatory responses when used following mandibular third molar removal and administered via the oral route. However, Macedo et al[29] attributed these findings to insufficient time taken to observe the effect of arnica in the relevant studies. They reported that the effect of arnica on edema was better following sublingual application (3 days prior to the removal of an impacted mandibular third molar). However, Erkan et al[30] used a single sublingual dose of arnica before different oral surgeries and reported no positive effects on either pain or edema. The results of the present study show that the topical use of arnica postoperatively is effective in alleviating pain, edema, and trismus following the removal of an impacted mandibular third molar. Similarly, Mawardi et al[36] reported that systemic usage of arnica significantly decreased pain, trismus, and edema after impacted third molar surgery. Therefore, the administration route should be considered a determining factor for the effectiveness of arnica.

Topical MPSP can quickly penetrate the skin and reach the subcutaneous structures. MPSP inhibits the synthesis of prostaglandins by suppressing protease and hyaluronidase activity. It can also boost blood circulation by activating the fibrinolytic system.[7,16,27] In a previous clinical study, MPSP cream showed no anti-inflammatory effect when applied following bilateral mandibular osteotomies.[17] The authors attributed this to the differences in the inflammatory reaction in superficial thrombophlebitis following surgery. Rostami et al[15] reported that MPSP was effective in reducing both edema and ecchymosis following rhinoplasty, similar to the present findings that topical application of MPSP cream was effective in relieving postoperative edema. Simsek et al[7] concluded that topical application of both arnica and MPSP reduced edema after rhinoplasty, in agreement with the present findings that topical application of both arnica and MPSP reduced edema after mandibular third molar surgery.

The topical applications of arnica and MPSP have been investigated in some studies by comparing their efficacy to that of other topical agents in terms of reducing pain and inflammation. One study found that the topical application of arnica was as effective as ibuprofen gel and NSAIDs for reducing pain and improving hand function.[8] Additionally, the use of MPSP in combination with desonide ointment (a topical steroid) has been reported to have a better therapeutic effect than the use of desonide alone in terms of reducing the inflammatory reactions of the skin.[27] Local preparations, such as St. John's wort oil and extra virgin olive oil, have also been reported to be effective at reducing swelling, trismus, and pain following oral surgery.[37]

In the present study, all the data analyses were performed by the same evaluators. This represents a limitation of the present research. The results of the present study indicate that arnica and MPSP groups had significantly lower MMO and edema values than the control group. But a few mm of differences in MMO and edema from control group have questionable clinical significance. Statistically significant does not necessarily mean the difference will be clinically significant for the patients. Thus, the topical application of arnica or MPSP may be an effective supplementary therapy for relieving adverse postoperative symptoms and enhancing patient's quality of life during the early postoperative period. The administration methods and dosages of the topical agents, and the mandibular third molar inclusion modes were not considered or varied in the present study to ensure that the outcomes of

the variables remained simple; however, this represents a minor limitation for the present study. Either arnica or MPSP was used as an adjuvant to NSAID and antibiotic therapy in the experimental groups, and no group received combined arnica and MPSP. This may be another limitation of the present study. Moreover, the placebo effect was not considered, which represents a further limitation of the present research.

The findings of the study could also have been affected by individual patient attributes. Thus, future studies should adopt research designs involving different parameters. Both arnica and MPSP reduced postoperative sequelae in the early healing period; however, their long-term effects on bone maturation in the extraction cavity are unknown. A future long-term trial should explore this issue.

In conclusion, the separate topical use of arnica and MPSP was beneficial in relieving pain, trismus, and edema during the early healing period following the surgical removal of an impacted mandibular third molar. Both of the investigated topical agents were particularly effective in relieving pain. Thus, the use of arnica or MPSP could be recommended for accelerating patient recovery and improving patient comfort during the early postoperative healing period following surgery for an impacted mandibular third molar.

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