Comparison of the effects of submucosal hyaluronidase and dexamethasone on postoperative edema, pain, trismus, and infection following impacted third molar surgery

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Abstract

Background Limiting postoperative edema, pain, trismus, and infection is crucial for smooth healing. This prospective, controlled clinical trial investigated and compared the effectiveness of dexamethasone and hyaluronidase in relieving these complications.

Methods In groups Ia and IIa, 8 mg of dexamethasone and 150 IU of hyaluronidase were administered following the removal of impacted teeth, respectively. The contralateral sides (groups Ib and IIb) were determined as control groups. Edema, pain, trismus, and infection were clinically evaluated on the 1st, 2nd, 3rd, and 7th postoperative days.

Results 60 patients were enrolled in the study. Hyaluronidase provided significantly more edema relief than dexamethasone on the 1st, 2nd, 3rd, and 7th postoperative days (P = 0.031, 0.002, 0.000, and 0.009, respectively). No statistical difference was found between dexamethasone and hyaluronidase in VAS and rescue analgesic intake amount values for all time points. Hyaluronidase was more effective in reducing trismus than dexamethasone on the 2nd and 3rd postoperative days (P = 0.029, 0.024, respectively). Neither of the agents significantly increased the postoperative infection rate.

Conclusions Hyaluronidase can be selected when postoperative excessive edema and trismus are anticipated. Dexamethasone may be a cost–effective option if postoperative pain control is merely targeted.

Trial registration This trial was registered in the Clinical Trials Protocol Registration and Results System (ClinicalTrials.gov identifier number: NCT05466604) on 20/07/2022.

Keywords Enzyme therapy, Steroidal treatment, Surgical healing, Discomfort reduction, Restricted jaw movement, Post-surgery maintenance

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Introduction

Edema, pain, trismus, and infection are common complications following various maxillofacial surgical procedures. They can impair the healing of surgical sites in addition to increasing patient discomfort. Steroids [1], non–steroid anti–inflammatory drugs (NSAID) [2], ice compression [3], low–level laser therapy [4], drain placement [5], kinesio taping [6], platelet–rich plasma (PRP) [7], and platelet–rich fibrin (PRF) [7, 8] can be used to alleviate these issues. Furthermore, researchers seek new minimal invasive modifications of conventional surgical techniques to minimize the aforementioned complications of oral and maxillofacial surgical procedures [9].

Steroids control postoperative inflammation [1, 10] by inhibiting the enzyme phospholipase A2, which induces the synthesis of prostaglandins and leukotrienes [11]. Dexamethasone is a widely preferred steroid for craniofacial surgeries because of its higher anti–inflammatory potency and longer duration of action [12]. However, systemic use of steroids for more than 3 days has significant side effects, such as impaired wound healing and an increased risk of postoperative infection [13]. Topical administration of antibiotics with a novel matrix [14] or natural polymer [15] carriers also significantly reduces inflammation and infection in oral tissues. These techniques are preferred for prolonged antibacterial activity by the sustained release of antibiotics in a safer manner.

The extracellular matrix (ECM) is dominantly constituted from collagens. Disruption of the ECM provides the spreading of the fluids to a broader area in the interstitial space. Hyaluronan is a glycosaminoglycan providing compressive force strength of the ECM, and it is found at only 1% of the collagen concentration. Hyaluronan has a short turnover period with a half–life of 15–20 h, while collagen has a half–life of almost 15 years [16, 17]. All the features above make hyaluronan a more suitable component than collagen for targeting to degrade with the aim of increasing the dispersion of the fluids inside the ECM, even though hyaluronan is found in a lesser concentration. Hyaluronan also has a 10-fold higher fluid–retention capacity than collagen [16, 18]. Hyaluronidase is an endogenous glycosidase that enhances the permeability of the ECM by degrading hyaluronan [17, 19]. Hyaluronidase has been utilized to improve the dispersion of locally injected anesthetic agents [17], insulin, monoclonal antibodies [18], proteins, anti–cancer drugs [20], and chemical agents [21] since 1948 [19] as an adjuvant. The enzyme also increases the healing capacity of the damaged tissues, which are injured because of filler applications, contrast medium, or chemotherapeutic agent extravasations, and lessens the necrosis possibility of the tissues [22, 23]. The efficiency of the enzyme on the rejoining of the fluids from the interstitial space to the systemic circulation makes the researchers of the present study suspect the potential suitability of hyaluronidase in reducing the edema fluid, which also develops in the intercellular area. The increased secretion of hyaluronidase in malign tissues was also demonstrated [24], and this finding is a suitable evidence for the high spreading–increaser capacity of hyaluronidase in tissues. However, there is inadequate proof in the literature about the trismus and pain-relieving effects of hyaluronidase as well as edema, particularly for oral and maxillofacial surgeries.

Several animal studies have demonstrated the potent anti–edema effects of hyaluronidase [25, 26]. The enzyme also induces significant edema and pain relief following guided bone regeneration surgery in humans [27]. These promising outcomes of hyaluronidase provide a basis for evaluating its potential effects on relieving trismus, edema, pain, and infection following one of the most frequent oral surgical procedures, wisdom tooth surgery [28]. To determine whether hyaluronidase is more effective than dexamethasone, a commonly used anti-inflammatory agent, in reducing postoperative edema, pain, trismus, and infection, the present study compared the effectiveness of hyaluronidase to that of dexamethasone.

Materials and methods

Registration and study protocol

The present prospective split–mouth clinical trial was approved by the Scientific Studies Ethics Committee of Yakın Doğu University (approval number: 2019/74–921) and conducted in accordance with the Declaration of Helsinki for Medical Research Involving Human Subjects. A CONSORT flowchart is shown in Fig. 1 to adhere to the 2010 guidelines, outlining the participant flow of the trial. The study is registered in the Clinical Trials Protocol Registration and Results System (ClinicalTrials.gov identifier number: NCT05466604) on 20/07/2022.

Sample size calculation was performed using G Power version 3.1.9.7 software (Heinrich Heine University, Düsseldorf, Germany), at a significance level of 0.05, and an effect size of 0.43, with a statistical power of 95.03%.

Patient selection, group allocation, and surgical procedure

The inclusion criterion for the study was the presence of symmetrical, totally impacted mandibular wisdom teeth with class I, II, or III; level B or C; mesioangular, vertical, distoangular, or horizontal position characteristics according to the Pell–Gregory and Winter classifications. Exclusion criteria included acute infection in at least one of the teeth, systemic diseases, pregnancy, lactation, history of allergic reactions to the medications used in the study protocol, recent intake of antibiotics, analgesics, or anti–inflammatory drugs within one week before surgery, a time difference of 5 min or more between the extraction times of the right and left mandibular wisdom teeth, and refusal to comply with the study protocol. All
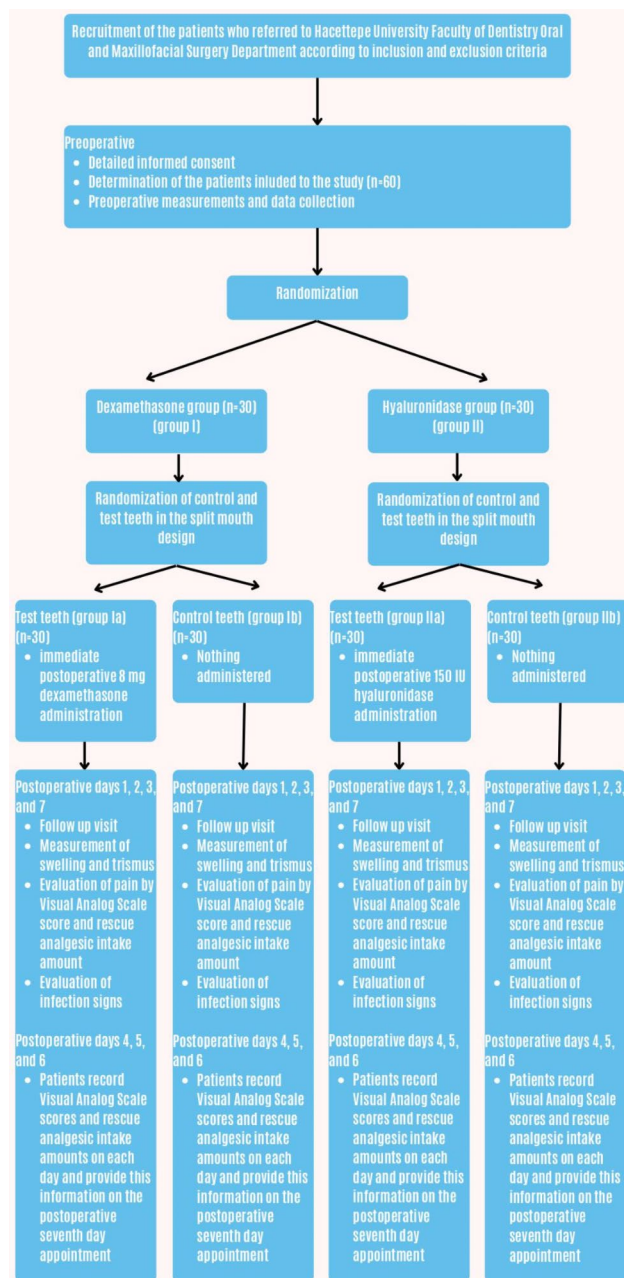
Fig. 1 Consort–2010 flow diagram of the study

patients provided informed consent after reading and signing a detailed informed consent.

Patients were randomly divided into two groups. In groups I and II, one tooth was assigned to group Ia (dexamethasone group) and group IIa (hyaluronidase group) by coin toss, while the contralateral tooth was assigned to group Ib (control group) and group IIb (control group), respectively. No treatment was administered in groups Ib and IIb to avoid potential placebo–induced edema [29, 30].

All extractions were performed by the same surgeon to mitigate potential differences arising from operator variability in Hacettepe University Dentistry Faculty Oral and Maxillofacial Surgery Department. The operations were conducted under local anesthesia using 160 mg of articaine hydrochloride+0,024 mcg epinephrine hydrochloride (Ultracain, Kırklareli, Turkey) in a 4 mL solution, administered via a modified indirect inferior alveolar [31] and infiltrative buccal nerve block techniques using 27–gauge needles. In this inferior alveolar block technique, the needle is inserted 6–8 mm above an imaginary midpoint between the upper and lower occlusal planes and 8–10 mm posterior to the anterior border of the ramus. After the initial bone contact, the needle direction was shifted towards the contralateral side and inserted at a depth of 21 to 24 mm. The position of the needle was then adjusted to a location closer to the mandibular foramen by repositioning the needle on the opposite side. A triangular flap was prepared using the number 15 scalpel tip and a periosteal elevator, extending from the 8 mm distal side of the impacted wisdom teeth to the mesiobuccal cusp level of the adjacent second molar, where the vertical incision was made. Bone removal and tooth sectioning were performed via rotary instruments using 18 mm diameter round and 14 mm diameter fissure burs (Meisinger, Neuss, Germany) under copious saline irrigation. The wound was closed using a 3.0 silk suture (Doğsan, Trabzon, Turkey). In groups Ia and IIa, 8 mg of dexamethasone (Dekort, Istanbul, Turkey) and 150 IU of hyaluronidase (Mesomedica, Dublin, Ireland) were locally administered to the adjacent buccal mucosa in 2 milliliters solutions from three different points immediately after the operation, respectively (Fig. 2). The first injection point was located 2 centimeters far from the impacted wisdom tooth on the buccal side. The second and the third points were located 2 centimeters posterior and anterior to the first one, respectively. In total, 8 mg dexamethasone and 150 IU hyaluronidase were divided into three equal doses, and 8/3 mg dexamethasone and 150/3 IU hyaluronidase were injected through a 27–gauge needle at each injection point in groups Ia and IIa, respectively. Amoxicillin (Largopen, Tekirdağ, Turkey), paracetamol (Parol, İstanbul, Turkey), and chlorhexidine mouthwash (Andorex, İstanbul, Turkey) were prescribed to the patients. Clindamycin (Klindan, Kocaeli, Turkey) was preferred for patients allergic to amoxicillin. Patients were instructed to take two analgesic tablets whenever they felt pain because the analgesic effect of paracetamol begins at doses over 1000 milligrams [32]. Each patient was scheduled for examinations 1 day, 2 days, 3 days, and 7 days after the surgery. There was a 3–week interval between the experimental and control side surgical extractions to prevent interactions between groups [33]. The order of surgery on the experimental and control
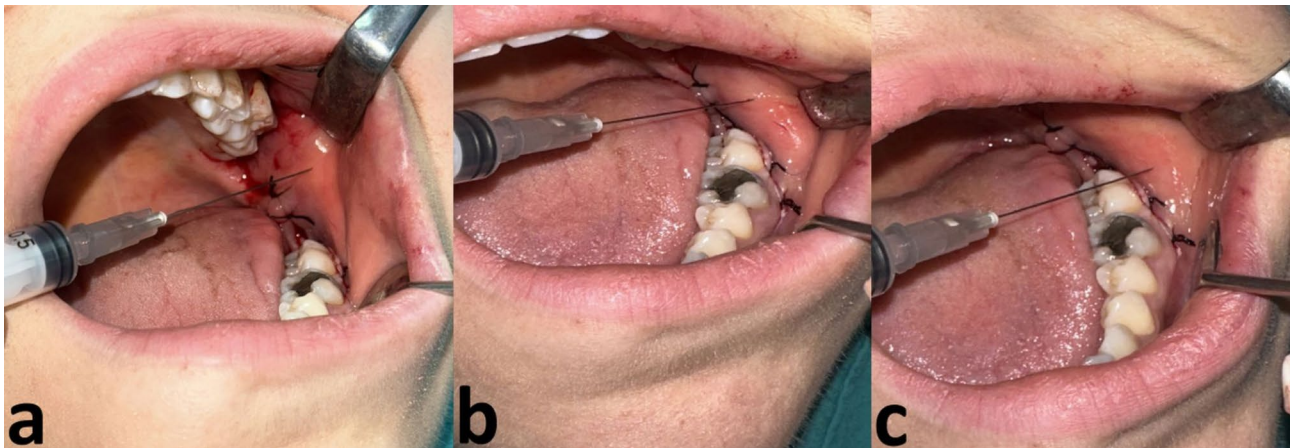
Fig. 2 Injection points of dexamethasone in a patient of group Ia (**a**) The posterior injection point. (**b**) The middle injection point. (**c**) The anterior injection point

sides was randomized using the coin toss method for each patient to prevent potential bias.

The solutions for the experimental side had the same color and transparency and were prepared by non–clinician personnel with numerical codes 1 or 2. The content of each numerical code was manifested to the practitioner and patients after statistical analyses by the non–clinician personnel. The non–clinician personnel were not involved in the statistical analyses. Although this procedure provides blinding to the practitioner between the test groups, it does not ensure blinding between the experimental and control groups. Patients were not informed about the medicine they received on their experimental side for blinding. However, no blinding could be provided between the control and experimental sides because the patients could see an additional injection on the experimental side.

Development of serious complication, death, and insufficient data collection were determined to be early termination criteria of the study.

Evaluation of outcome variables

Linear measurement is a widely used method for assessing facial edema [34, 35]. The technique described by Gabka and Matsumura [36] was preferred in the present study. Tragus–cheilion, tragus–soft tissue menton, and lateral cantus–soft tissue gonion distances were measured using a roller tape in millimeters before the operation and 1 day, 2 days, 3 days, and 7 days after the procedure. The points used in the measurements were preoperatively identified using a non–erasable pen. The sum of the distances was determined as the facial surface length value of each patient [37]. The edema value of each patient was calculated by subtracting the preoperative facial surface length value from the postoperative value at the aforementioned time points.

Pain was evaluated using a visual analog scale (VAS) (ranging between 0 and 10) and the rescue analgesic counting technique. The patients were also instructed to use analgesics when experiencing unbearable pain, to record the number of painkillers used daily, to record the VAS score daily, and to provide this information during appointments.

Trismus was evaluated by measuring the interincisal distance between the mesioincisal points of the maxillary and mandibular right first incisors before the operation and 1 day, 2 days, 3 days, and 7 days after the operation, using a sterile ruler in millimeters. The postoperative distance was subtracted from the preoperative one to determine the trismus value for each patient on the specified evaluation days.

To determine the effects of dexamethasone and hyaluronidase on edema, pain, and trismus relief separately, the edema, VAS, rescue analgesic amount, and trismus values of groups Ia and IIa were statistically compared to those of groups Ib and IIb, respectively.

In the split–mouth study design, the amount of edema relief on the experimental side according to the control side was also calculated by subtracting the edema value of the test side from that of the control side of each patient in the literature [38]. To compare the effects of dexamethasone and hyaluronidase on edema, pain, and trismus relief, the edema, VAS, rescue analgesic amount, and trismus values of groups Ia and IIa were subtracted from those of groups Ib and IIb for each patient, respectively. The absolute values of the results were recorded as the difference values of group I or group II (the edema difference value of group I=edema value of group Ib - edema value of group Ia) for each variable. The difference value refers to the amount of lessening in each variable after the administration of the agent, compared to the control group. Edema, VAS, rescue analgesic amount, and trismus amount difference values of group I were

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Table 1 Average edema and edema difference values of the groups at the evaluation time points

		1 day later the surgery	2 days later the surgery	3 days later the surgery	7 days later the surgery
Edema values	Group Ia	0.61±0.80	0.53±0.60	0.28±0.44	0.04±0.08
	Group Ib	1.02±0.69	1.26±0.43	0,58±0.27	0.08±0.16
Edema difference values	Group I	0.42±1.20	0.70±0.86	0.30±0.59	0.05±0.18
Edema values	Group IIa	0.47±0.47	0.49±0.32	0.23±0.20	0.01±0.07
	Group IIb	1.44±0.59	1.82±0.61	1.26±0.64	0.25±0.32
Edema difference values	Group II	0.97±0.67	1.33±0.62	1.03±0.67	0.24±0.34

The values are given as mean±standard deviation in terms of millimeters

statistically compared to those of group II for each evaluation time point. The edema values of groups Ia and IIa were also compared for each evaluation time point to reveal the swelling amounts regardless of the control sites when dexamethasone and hyaluronidase were administered, respectively.

Evaluation of postoperative infection was based on the presence of throbbing pain, erythema, edema, pus drainage at the operation site, salty taste, malodor in the mouth, acute submandibular lymphadenopathy, systemic fever, and loss of function. Surgical sites exhibiting more than four of the abovementioned findings were categorized as infected during the respective evaluation time.

Statistical analysis

All descriptive statistics were presented as mean±standard deviation. Differences in the quantitative values between groups Ia and Ib, and IIa and IIb were evaluated using Paired Samples T–Test. Differences between group I and group II were assessed using Independent Samples T–Test. A 2×2 contingency table was constructed for postoperative infection incidences, and differences in this qualitative variable between groups Ia and Ib, and IIa and

IIb were evaluated using the chi–square test. All analyses were conducted using SPSS version 23 (IBM Co., New York, USA) software. P values less than 0.05 were considered significant in all analyses.

Results

Study sample

A total of 60 patients (40 females and 20 males between 16 and 28 years, mean age±SD: 21.13±3.12 years) with 120 mandibular wisdom teeth were enrolled in the present study. Groups I (20 females and 10 males, mean age±SD: 20.33±3.07 years) and II (20 females and 10 males, mean age±SD: 21.93±3.02 years) had 30 patients each. No significant side effects were observed in any patient during the study. Groups Ia, Ib, IIa, and IIb had 30 teeth each. The trial was completed following the operations, and measurements of all participants were performed.

Edema values

The edema values of group Ia (dexamethasone group) were significantly lower than those of group Ib (control group) on the 2nd and 3rd days after the operation (P=0.000 and 0.009, respectively) (Table 1). The edema values of group IIa (hyaluronidase group) were significantly lower than those of group IIb (control group) on the 1st, 2nd, 3rd, and 7th days after the operation (P=0.000, 0.000, 0.000, and 0.001, respectively) (Table 1). The edema difference values of group II were significantly higher than those of group I on the 1st, 2nd, 3rd, and 7th days after the operation (P=0.031, 0.002, 0.000, and 0.009, respectively) (Table 1). No statistically significant difference was found between the edema values of groups Ia and IIa at any of the evaluation time points.

Pain amounts

VAS values of group Ia (dexamethasone group) were significantly lower than those of group Ib (control group) only on the 2nd day after the operation (P=0.000) (Table 2). VAS values of group IIa (hyaluronidase group) were significantly lower than those of group IIb (control group) only on the 1st day after the operation (P=0.042)

Table 2 Average VAS and VAS difference values of the groups at the evaluation time points

		1 day later the surgery	2 days later the surgery	3 days later the surgery	4 days later the surgery	5 days later the surgery	6 days later the surgery	7 days later the surgery
VAS values	Group Ia	3.00±2.26	1.73±1.66	1.27±1.60	0.93±1.20	0.77±1.38	0.47±1.07	0.37±1.00
	Group Ib	3.90±2.84	3.23±2.33	2.07±1.96	1.17±1.68	0.90±1.65	0.73±1.31	0.47±1.11
VAS difference values	Group I	0.90±2.73	1.50±1.76	0.80±2.31	0.23±1.52	0.13±1.57	0.27±1.23	0.10±0.99
VAS values	Group IIa	3.17±2.35	2.27±2.27	1.63±1.94	0.67±1.47	0.47±1.17	0.40±1.07	0.23±0.77
	Group IIb	4.33±2.40	2.93±2.30	1.97±2.11	1.27±1.70	1.03±1.35	0.73±1.05	0.30±0.65
VAS difference values	Group II	1.17±3.01	0.67±3.01	0.33±2.20	0.60±2.14	0.57±1.61	0.33±1.42	0.07±0.98

The values are given as mean±standard deviation

Table 3 Average rescue analgesic intake amount and rescue analgesic intake amount difference values

		1 day later the surgery	2 days later the surgery	3 days later the surgery	4 days later the surgery	5 days later the surgery	6 days later the surgery	7 days later the surgery
RAIA values	Group Ia	2.83 ± 2.35	1.70 ± 2.29	1.20 ± 2.34	0.43 ± 0.97	0.37 ± 0.85	0.27 ± 0.83	0.17 ± 0.59
	Group Ib	3.20 ± 1.88	2.47 ± 2.06	2.10 ± 2.26	0.87 ± 1.25	0.50 ± 1.17	0.33 ± 0.99	0.27 ± 1.11
RAIAD values	Group I	0.37 ± 2.14	0.77 ± 2.45	0.90 ± 2.89	0.43 ± 1.04	0.13 ± 0.97	0.07 ± 0.64	0.10 ± 0.66
RAIA values	Group IIa	2.97 ± 1.56	2.13 ± 1.48	1.23 ± 1.55	0.50 ± 0.94	0.20 ± 0.55	0.33 ± 0.84	0.30 ± 0.84
	Group IIb	3.23 ± 2.06	2.53 ± 2.11	1.47 ± 1.70	0.80 ± 1.32	0.50 ± 0.86	0.43 ± 0.82	0.07 ± 0.25
RAIAD values	Group II	0.27 ± 1.76	0.40 ± 1.99	0.23 ± 1.77	0.30 ± 1.32	0.30 ± 0.95	0.10 ± 1.12	0.23 ± 0.90

The values are given as mean ± standard deviation. RAIA: rescue analgesic intake amount, RAIAD: rescue analgesic intake amount difference

Table 4 Average trismus amount and trismus amount difference values

		1 day later the surgery	2 days later the surgery	3 days later the surgery	7 days later the surgery
Trismus amount values	Group Ia	16.20 ± 9.18	13.63 ± 9.22	10.37 ± 7.98	3.10 ± 5.40
	Group Ib	18.70 ± 8.66	17.33 ± 10.33	14.40 ± 10.06	7.37 ± 7.95
Trismus amount difference values	Group I	2.50 ± 8.15	3.70 ± 7.99	4.03 ± 8.32	4.27 ± 7.88
Trismus amount values	Group IIa	12.60 ± 8.74	10.27 ± 8.22	8.43 ± 7.75	3.17 ± 4.50
	Group IIb	19.23 ± 8.05	18.60 ± 7.67	17.07 ± 7.59	8.30 ± 7.60
Trismus amount difference values	Group II	6.63 ± 9.22	8.33 ± 8.04	8.63 ± 7.02	5.13 ± 7.58

The values are given as mean ± standard deviation in terms of millimeters

(Table 2). Rescue analgesic intake amounts of group Ia (dexamethasone group) were significantly lower than those of group Ib (control group) only on the 4th day after the operation (*P*=0.030) (Table 3). No statistical difference was found between rescue analgesic intake amounts of group IIa (hyaluronidase group) and group IIb (control group) for all evaluation time points (Table 3). No statistical difference was found between the VAS difference values and rescue analgesic intake amount difference values of groups I and II for all evaluation time points (Tables 2 and 3).

Trismus amounts
Trismus amount values of group Ia (dexamethasone group) were significantly lower than those of group Ib (control group) on the 2nd, 3rd, and 7th days after the operation (*P*=0.017, 0.013, 0.006, respectively) (Table 4). Trismus amount values of group IIa (hyaluronidase group) were significantly lower than those of group IIb (control group) on the 1st, 2nd, 3rd, and 7th days after

the operation (*P*=0.000, 0.000, 0.000, 0.001, respectively) (Table 4). Trismus amount difference values of group II were significantly higher than those of group I on the 2nd and 3rd days after the surgery (*P*=0.029, 0.024, respectively) (Table 4).

Infection incidences
Postoperative infection incidences of groups Ia, Ib, IIa, and IIb were 0.00% (0 extraction site), 3.33% (1 extraction site), 6.67% (2 extraction sites), and 10.00% (3 extraction sites), respectively. The total postoperative infection incidence of all cases was 5%. No statistical difference was found between groups Ia and Ib, and IIa and IIb regarding postoperative infection incidences.

Discussion
In the present study, the local application of dexamethasone and hyaluronidase had a significantly positive impact on postoperative edema, pain, and trismus compared with the control groups. Although the edema amounts of dexamethasone and hyaluronidase were not significantly different at all evaluation time points, hyaluronidase provided higher edema relief than dexamethasone according to the control sites of the patients. Hyaluronidase also showed significant relief in trismus compared to dexamethasone, according to the control sites in the early period, although there was no difference in the amount of pain and infection rate between the hyaluronidase and dexamethasone groups.

There was a significant edema reduction in the dexamethasone group compared to the control group on the 2nd and 3rd days postoperatively. This result of the present study corroborates the literature [10, 39, 40]. However, the absence of a significant decrease in the edema value of the dexamethasone group compared to the control group on the 1st postoperative day proves that the anti−edema effect of dexamethasone does not become prominent during the first 24 h of application. This retarded activity of dexamethasone has not been clearly revealed in the literature before. Most studies that explore dexamethasone's anti−edema impact assess swelling beginning on the 2nd day after surgery [29, 35,

39]. Hence, they may overlook dexamethasone's inefficiency in alleviating postoperative edema on the 1st postoperative day. Dexamethasone's 1–day preemptive administration provides significantly higher edema relief than immediate postoperative administration on the 1st postoperative day [41]. Twelve hours of preemptive dexamethasone administration also ensured significantly less inflammatory mediator release on the 1st postoperative day [42]. These results indicate that dexamethasone's anti–edema effect substantially begins one day after the administration, and this handicap of the agent can be surpassed by preemptive administration.

The effectiveness of hyaluronidase in alleviating postoperative edema was proven by various animal studies [26, 43]. In the present study, compared to the control group, the existence of significant edema relief on the 1st postoperative day is an advantage of hyaluronidase over dexamethasone for immediate postoperative administrations. Although the edema values of dexamethasone and hyaluronidase were insignificant at all time points, the edema relief amounts of hyaluronidase administration (difference values in group II) were significantly higher than those of dexamethasone administration (difference values in group I) at all evaluation time points. Therefore, hyaluronidase can be a more effective and fast–acting anti–edema agent than dexamethasone for immediate postoperative submucosal administrations, and hyaluronidase can be chosen when preemptive administration is impossible.

Hyaluronan has a high fluid retention capacity in the ECM to provide mechanical strength, force absorption, intercellular signaling, and cell migration [44, 45]. Edema development can increase the amount of water that binds to hyaluronan. Degradation of hyaluronan by hyaluronidase could lessen the tissue's water binding capacity and allow a considerable amount of fluid to disperse quickly out of the region. This phenomenon could be one of the reasons for significant edema relief following the administration of hyaluronidase in addition to the spread–increasing effect of the enzyme on edema fluid.

Hyaluronidase enhances the rejoining of fluids from the interstitial space to the systemic circulation up to 20–fold and increases their dispersion, as mentioned above [16]. Thus, including the whole spread of edema in the measurement area is crucial to determine the edema amount in the hyaluronidase group accurately. The effect area of hyaluronidase surrounding the injection point is an average of 11.44 cm^2 [16, 17, 46]. In the present study, linear measurement points involve the whole effect area of injected hyaluronidase, and the linear measurement method ensures an accurate determination of the entire dispersed edema in the hyaluronidase group.

The effect of dexamethasone on postoperative pain is controversial. While several studies show significant results [10, 12, 40], others do not [1, 47]. In the present study, VAS values and rescue analgesic intake amount values of the dexamethasone group are significantly lower than those of the control group on the 2nd and 4th days after the operation, respectively. Significant pain relief 2 and 3 days after breast surgery was also proven when dexamethasone was administered postoperatively [48]. Therefore, dexamethasone demonstrated a delayed pain–relieving effect. Suggesting the use of dexamethasone via preemptive administration might increase its efficiency as a pain–reducing agent.

Effects of hyaluronidase on alleviating pain in patients with chronic pain and myofascial pain syndrome via disintegration of epidural adhesions and elimination of undesired attachments in the trigger points were demonstrated [21, 46]. Hyaluronidase also significantly increases the depth of local anesthesia as an adjuvant [17]. However, the performance of the enzyme on postoperative pain has not been broadly studied. The present study demonstrates that hyaluronidase significantly reduces pain only in the first 24 h after surgery, unlike Kwoen et al. [27]. They found no significant postoperative pain relief after hyaluronidase administration. They evaluated postoperative pain on the 2nd and 4th days after surgery and could miss detecting the pain–relieving effect of hyaluronidase on the 1st day after the operation. The rapid anti–inflammatory effect of hyaluronidase [49] could be the primary reason for the significant pain relief on the 1st day after surgery in the present study. No significant difference was found between dexamethasone and hyaluronidase regarding VAS and rescue analgesic intake amount values in all evaluation time points in the present study. For postoperative pain relief, none of the agents have a superior aspect over the other. Bupivacaine significantly reduces postoperative pain and opioid consumption, particularly in the early healing period [50]. Furthermore, the postoperative pain–relieving effect of bupivacaine can be extended for up to 72 h by liposomal bupivacaine infiltration [51]. Hence, if high–level postoperative pain is predicted, bupivacaine can be used as a local anesthetic agent. Although the effectiveness of bupivacaine and steroid combination on postoperative pain has been revealed by several studies [52, 53], the potential efficacy of bupivacaine and hyaluronidase combination on postoperative pain control has not been sufficiently demonstrated and should be studied in the future.

Pain is not an absolute perception, and can be modified by several conditions. Pain sensitivity increases significantly in patients with symptomatic temporomandibular disorders [54]. Poor sleep quality and low levels of life satisfaction also increase pain perception [55, 56]. The patients were not preoperatively evaluated for potential pain perception alterations owing to the aforementioned factors in the present study. Patients with symptomatic

temporomandibular disorders, poor sleep quality, and low levels of life satisfaction can be evaluated separately in future studies to reveal the effects of dexamethasone and hyaluronidase on postoperative pain changes in these patients more objectively.

Multimodal usage of different NSAIDs or opioid–NSAID–acetaminophen combinations is commonly used to control postoperative pain following surgical procedures [57, 58]. In addition to desensitizing patients to pain caused by dental injections [59], photobiomodulation therapy effectively reduces postoperative pain and edema following third molar surgery [60]. Transcutaneous Electrical Nerve Stimulation (TENS) [61], acupuncture [62], and Cognitive Behavioral Therapy (CBT) [63] are uncommon, but remarkable methods for pain control in patients undergoing various surgical procedures. Their efficacy as adjuvant therapies to control postoperative pain in patients who have undergone oral and maxillofacial surgeries should be broadly studied in the future.

Gomes et al. [64] revealed that hyaluronidase does not enhance pulpal anesthesia depth for the buccal infiltration technique in mandibular first molars. However, it increases the depth of anesthesia in adjacent soft tissues. It was remarked that hyaluronidase activity appears more robust in the maxilla compared to the mandible [27]. According to the studies above, the amount of trabecular bone seems to affect hyaluronidase activity, and the enzyme exhibits greater potency in soft tissues. Thus, the evaluation of hyaluronidase's efficiency in alleviating postoperative edema, which mainly occurs in soft tissues, appears to be a well–grounded hypothesis of the present study. The differences in hyaluronidase activities between the maxilla and mandible could serve as novel research areas for further studies.

The present study reveals that buccal submucosal administration of dexamethasone significantly reduces trismus on the 2nd, 3rd, and 7th days after surgery. Graziani et al. [35] also demonstrated that using dexamethasone as an endo–alveolar powder significantly reduces trismus 2 and 7 days after the operation. However, while some studies result in significant [30] trismus relief for buccal submucosal administrations of dexamethasone, others do not [35]. This controversy may occur because the injection traumas in the buccal region could trigger trismus development, and it could mask the effect of dexamethasone in trismus alleviation. Hence, if dexamethasone is chosen to reduce postoperative trismus, atraumatic administration methods like controlled dexamethasone releasing form for extraction sockets and dexamethasone soaked mucosal patch may be selected in patients with higher postoperative trismus development possibility. Avoiding injections inside the masseter muscle can also be another precaution for dexamethasone

and hyaluronidase to prevent trismus increasing effect of injection traumas.

Hyaluronidase significantly reduces trismus in the present study compared to the control group on the 1st, 2nd, 3rd, and 7th days after surgery. Lee et al. [65] also revealed that submucosal injection of hyaluronidase significantly reduces postoperative trismus 2 and 7 days after the operation. Hyaluronidase provided significantly higher trismus relief than dexamethasone in the present study on the 2nd and 3rd days after the operation. Dispersion of the edema fluid to a larger area may lessen injury to the muscles adjacent to the region. It may be the main reason for significantly less trismus development following hyaluronidase application. These effects of the enzyme encourage practitioners to use it as a trismus–reducing agent in immediate postoperative administrations.

Even though long–term steroid usage has various side effects [13, 66], the single–dose administration only increases blood glucose levels in the postoperative 24 h [66]. Single–dose dexamethasone administration does not significantly increase infection incidence in the present study, consistent with the literature [67]. However, an immediate increase in blood glucose may disrupt healing in the early postoperative period, and steroids should be cautiously administered in diabetic patients. Corticosteroids increase the tendency of medical related osteonecrosis of the jaws (MRONJ) development in patients treated with bisphosphonates, monoclonal antibodies, and tumor necrosis factor (TNF) inhibitors [68, 69]. Even though the harmful effects of steroids on healing were revealed, they can increase the healing quality when excessive inflammation disrupts this period [70]. These controversies of steroids in the healing process necessitate practitioners to choose postoperative steroid treatment very carefully in a specific group of patients. Therefore, the positive effects of steroids on tissue healing should be enlightened more comprehensively.

Several bacteria that cause septicemia and death are proven to gain virulence by their hyaluronidase secretion ability [71]. It corroborates the capacity of hyaluronidase to spread infection, which is the main drawback of hyaluronidase application in infected tissues. Even though administering hyaluronidase to infected areas following the placement of hyaluronic acid–based fillers leads to successful infection resolution without significant complications [72], practitioners should be aware of infection spreading risk and avoid the use of hyaluronidase in infected tissues. The present study is the first to prove that local submucosal hyaluronidase injection does not increase postoperative infection risk in non–infected tissues.

It was proved that pathologically developed several heavy–chain glycoprotein–hyaluronan complexes trigger

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inflammation [73]. Development of these pathological heavy–chain hyaluronan complexes can promote the loss of neurological functions in the central nervous system following an intraventricular hemorrhage. Degrading these pathological hyaluronan complexes by hyaluronidase promoted oligodendrocyte progenitor cell maturation, restored myelination, and recovered neurological function in infant rabbits [74]. This result could lead to future studies investigating whether periodic hyaluronidase administration could ensure myelination of the inferior alveolar nerve following traumatic injuries during oral and maxillofacial surgeries. A recent study on porcine menisci provides promising results about the effects of hyaluronidase on tissue healing [75]. The enzyme increases the migration of the cells responsible for healing after modifying the extracellular matrix microenvironment by removing the biophysical barriers. This proof enlightens the healing promoter capacity of hyaluronidase. It could be vital for improving the healing period of several oral and maxillofacial surgical procedures and should be broadly studied in future studies.

The future perspective of oral and maxillofacial surgical procedures is performing the operations via robotic surgery systems. These systems perform the surgeries with more limited incisions and have more predictable results than the conventional ones. Furthermore, the features of robotic surgery systems ensure less postoperative pain and edema [76–78]. Besides investigating the adjuvant medications for alleviating the postoperative unintended results of oral and maxillofacial surgical procedures, increasing the feasibility and universality of robotic surgery systems may ensure that practitioners effectively control postoperative edema, pain, trismus, and infection. So, further studies should also focus on improving robotic surgery systems to minimize postoperative edema, pain, trismus, and infection in oral and maxillofacial surgeries.

The main limitation of the present study was the lack of patient examinations on the 4th, 5th, and 6th postoperative days except for rescue analgesic intake and VAS records. Additionally, variables such as the amount of mobility and pain in the adjacent second molar, oral hygiene maintenance, and changes in the quality of life during the postoperative week could have been added to the present study. Although blinding was provided between the two test groups, no blinding was ensured between the test and control sites. The small number of participants and the small age range of the patients are other drawbacks of the present study. Further studies should be performed on different age groups of patients to achieve more comprehensive results.

Conclusion

Hyaluronidase may be a preferable option over dexamethasone for effectively controlling postoperative edema and trismus in the immediate postoperative administrations. If the main expectation of the practitioner is postoperative pain control, dexamethasone can be selected by preemptive administration to avoid the high cost of hyaluronidase. The alleviation of postoperative edema, pain, and trismus tends to commence more rapidly with the immediate postoperative administration of hyaluronidase compared to dexamethasone. Both agents can be preferred without the risk of increased postoperative infection in non–infected regions.

Abbreviations

ECM   Extracellular matrix
VAS   Visual analog scale
MRONJ   Medical related osteonecrosis of the jaws
TNF   Tumor necrosis factor

Data availability
No datasets were generated or analysed during the current study.

Declerations

Ethics approval and consent to participate
The present prospective split–mouth clinical trial was approved by the Scientific Studies Ethics Committee of Yakın Doğu University (approval number: 2019/74–921) and conducted in accordance with the Declaration of Helsinki for Medical Research Involving Human Subjects. The study is registered in the Clinical Trials Protocol Registration and Results System (ClinicalTrials.gov identifier number: NCT05466604) on 20/07/2022. All patients enrolled in the present study signed an informed consent.

Consent for publication
All patients gave their informed consent to the treatment and were informed that the recorded parameters would be used for statistical analyses related to the study. All patients and/or their legal guardian(s) have signed a consent for publication of identifying information/images in an online open access publication.

Competing interests
The authors declare no competing interests.

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