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Effect of submucosal injection of ketorolac versus dexamethasone on postoperative pain after third molar surgery: a randomized clinical trial

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Abstract

Background: One of the most common dentoalveolar surgeries is the removal of impacted third molars. Moderate to severe pain is predictable after these surgeries, usually leaving the patient in need of an effective analgesic for at least 24 h. Corticosteroids and NSAIDs are well-known medications used to reduce pain. This prospective, randomized clinical trial aimed to assess the effectiveness of two types of analgesics, ketorolac and dexamethasone, on pain experienced after unilateral impacted third molar surgery. The analgesics were injected sublingually after profound anesthesia was confirmed in 60 healthy adult patients. During this study, the patients were divided into three groups. The patients in group K received 1 mL of ketorolac (30 mg), while the patients in group D received 1 mL of dexamethasone (4 mg) sublingually. The patients in group C (the control group) received 1 mL of normal saline solution as a placebo.

Results: The mean pain scores reported by the patients in groups K and D were significantly lower than group C ($P = 0.002$ and $P < 0.001$, respectively). However, the difference between groups D and K was not significant ($P = 0.158$). The mean number of analgesics taken by patients in groups K and D 24 h after surgery was significantly lower than the control group ($P < 0.05$). At 48 and 72 h postoperatively, however, the difference was not significant between the study groups ($P > 0.05$). The mean time of the first analgesic taken by the patients in groups K and D was 200.94 and 214.74 min after surgery, respectively. Exhibiting a significant difference, it was 132.65 min for the patients in group C ($P = 0.003$).

Conclusions: Under this study's limitations, preoperative sublingual injection of ketorolac and dexamethasone were similarly effective in pain control after impacted third molar surgery.

Keywords: Third molar surgery, Ketorolac, Dexamethasone, Sublingual injection

Background

One of the most common dentoalveolar surgeries is the removal of impacted third molars (Grossi et al. 2007). Impacted third molar has often been associated with harmful conditions, including pericoronitis, cystic lesions, deep cavity, difficulty of oral hygiene, neoplasms,

and pathological root resorption that make surgical removal inevitable (Channar et al. 2013). The most common postoperative complaints after such surgeries are pain, trismus, and swelling, with considerable impact on the patient's quality of life (Grossi et al. 2007). Moderate to severe pain is predictable after these surgeries, usually leaving the patient in need of an effective analgesic for at least 24 h (Schou et al. 1998). NSAIDs, opioids, corticosteroids, and a combination of analgesics are commonly used pre- or post-operatively for pain relief. Preemptive

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analgesics have two major positive impacts; first, an analgesic which is prescribed before the procedure is more effective than prescribed afterward, and second, it would be advantageous to extend the pharmacological action of analgesic drugs (Ong et al. 2004).

Among the medications mentioned above, corticosteroids are well-known medications used to suppress inflammatory mediators and reduce pain, transudation of fluids, and edema (Gataa 2009).

Of various corticosteroids, dexamethasone has extensively been used to decrease inflammation after third molar surgery. The results of 11 clinical trials on the effect of submucosal injection of dexamethasone on impacted mandibular third molar surgery showed that it effectively reduces edema and trismus, making it one of the possible choices for dental surgeries (Chen et al. 2017); however, the effect of the submucosal injection of dexamethasone has been poorly investigated.

Another group of analgesic drugs is non-steroidal anti-inflammatory drugs (NSAIDs). Some of the drugs in this group are diclofenac sodium, ketorolac, ibuprofen, and paracetamol. Of these drugs, ketorolac is one of the most important analgesics used in clinical scenarios due to its pharmacokinetic and pharmacodynamic advantages. One of the injectable COX-1 and COX-2 NSAIDs is ketorolac (Macario and Lipman 2001).

Many studies, including five systematic reviews, 22 randomized controlled trials, and seven non-randomized studies, have shown that non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are effective in pain management of the patients undergoing surgical third molar extraction ((abstracts), A.f.S.T.M.E.-C.E.a.G.O.C.A.C.r.r.r.s.o 2018).

With this clinical background, this study aimed to clarify the possible role of two preoperative analgesics, either dexamethasone (4 mg) or ketorolac (30 mg) administered 10 min before surgery, in clinical recovery after third molar surgery.

Methods

This comparative, prospective, randomized, double-blind, controlled trial involving 60 patients was carried out in the Department of Oral and Maxillofacial Surgery from October 2018 to March 2019. The protocol of this study was approved by the Ethics Committee of University of Medical Sciences. And also, this study was approved in IRCT Trials at 2021-06-16 and its registration reference is IRCT20180906040960N1. Written informed consent was obtained from all the participants.

The sample size was calculated using the principal variable, the visual analog scale (VAS) for postoperative pain, and considering a difference of 15 mm as clinically significant and estimate mean standard deviation of 15–25 mm for VAS score. The α level type I error was

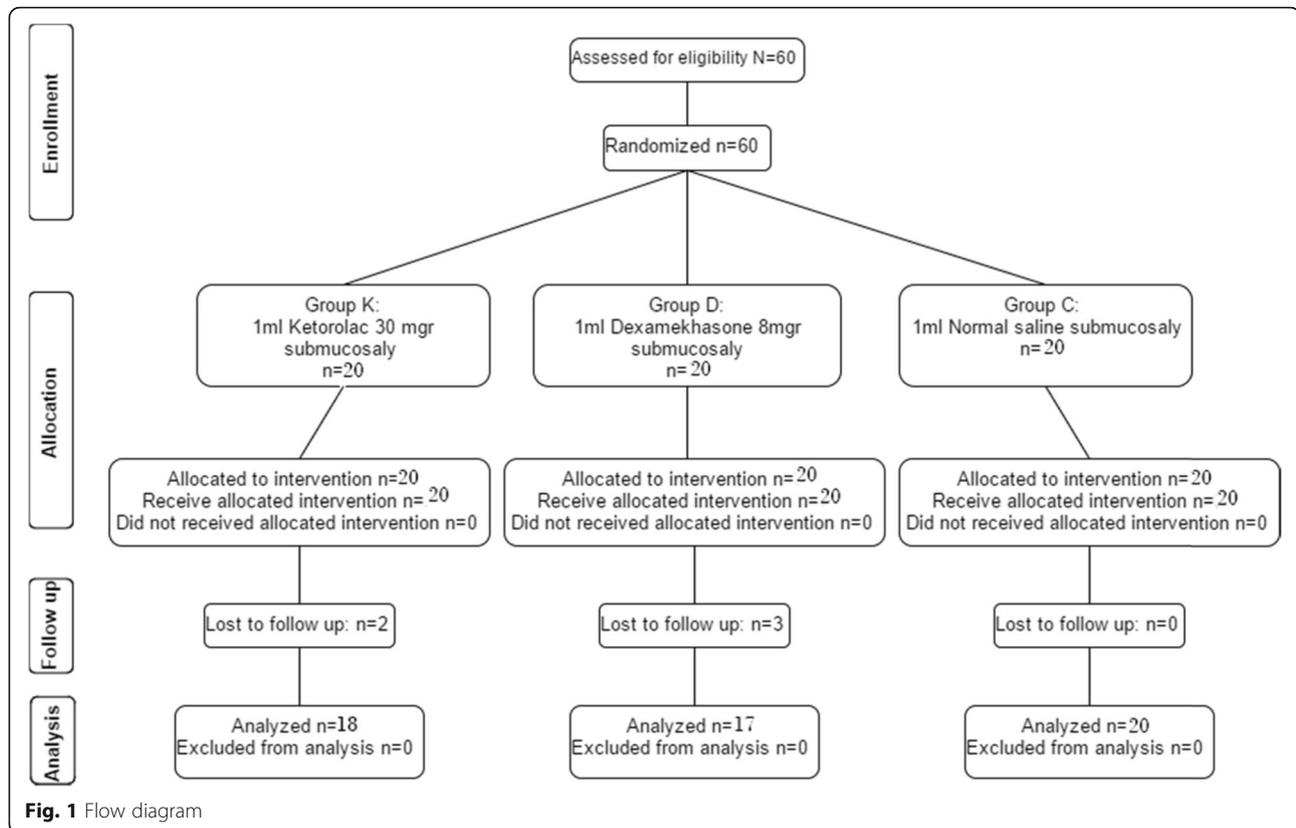
considered at 0.05 for a single-tailed test and β level type II error at 0.20. Moreover, a 10–15% drop-out rate was considered, and finally, 60 patients requiring elective surgical removal of impacted mandibular third molars under local anesthesia were included in the study.

The inclusion criteria were as follow: all the patients were > 16 years of age and ASA I or II (Keats, A.S.J.A.T.-J.o.t.A.S.o.A 1978) and had at least one impacted mandibular third molar detected by a panoramic radiograph. The impacted teeth categorized as class II relationship, position “B” angulation, were included in the study. The patients had no infection or pain in the week before surgery. Patients were excluded if they had a history of hypersensitivity to ketorolac and dexamethasone, or any contraindication for using these drugs, or if they had taken analgesics before the surgery, and if the surgical procedure exceeded 30 min. In addition, patients with gastrointestinal diseases, who could not take NSAIDs as a pain killer after surgery, were excluded. All the surgical procedures were performed by a single dentist (the first author).

The patients were randomly divided into three groups of 20 patients through random number generation. First, all the patients received local anesthesia with the standard inferior alveolar nerve block and long buccal nerve block techniques using 1.8 mL of 2% lidocaine hydrochloride with 1:80,000 epinephrine (Darupakhsh, Tehran). After the onset of local anesthesia was confirmed by lip numbness, the patients in group K received one single dose of 30 mg ketorolac tromethamine (30 mg/1 mL, Abu Raihan Pharmaceutical Co., Tehran) submucosally, while the patients in group D received one single dose of 4 mg dexamethasone sodium phosphate (4 mg/1 mL, Dexadic®, Caspian Tamin Pharmaceutical Co., Tehran) submucosally. The patients in group C (control group) received injectable normal saline solution (Iranian Parenteral & Pharmaceutical Co., Tehran) submucosally as a placebo. All the components were injected sublingually with insulin syringes far from the midline in tissues with high lost space (Fig. 1). Patients were informed about the drugs that might be selected for them; however, they were blinded to the specific type of medication they received.

The algorithm presented in Fig. 2 shows the progression of subjects through the different phases of the trial.

If profound lip numbness was not reported, the patient was excluded from the study. After profound anesthesia was confirmed, a standardized surgical approach was followed using a classic envelop flap with No. 15 scalpel blade. The incision was started at the distal line angle of the first molar, and then posteriorly, the incision was extended to the ramus to prevent lingual nerve damage. The flap was elevated and retracted using a Minnesota retractor; osteotomy and tooth sectioning were



performed. After the tooth was extracted, the flap was closed with (3-0) silk (Supasil, Karaj, Iran).

All the patients were asked to take the same prescriptions of acetaminophen 500 mg (Jalinus Co., Tehran) as-needed and use 0.2% chlorhexidine (Shahre daru® and

Iran Najo®, Tehran) twice a day as a mouthwash for 1 week. The patients were asked to return for the assessment of the surgical site and removal of sutures 7 days after surgery.

The patients were instructed to complete the forms provided for pain assessment. Each form contained twelve 100-mm VAS charts. In this chart, 0 means no pain, and 100 represents the most severe pain. The patients were asked to hourly mark the pain they experienced during the 12 h period after surgery. In addition, the exact time of the end of surgery was recorded, and the patients were asked to record the time they took the first prescribed analgesic. Moreover, they were asked to record the total number of pain killers used during the 72-h period postoperatively. All these data were received 7 weeks after surgery when the patients returned for suture removal. The data were analyzed by SPSS 23.0 (SPSS Inc., IL, USA).

The means and standard deviations were calculated. Independent *t* tests, Mann-Whitney test, and multiple comparisons including both Kruskal-Wallis and ANOVA with post hoc tests were used to determine significant differences. Differences in the anesthetic success of two groups were compared with chi-squared test and Fisher's exact test. The significance level was set at $P < 0.05$.



Results

The sample size consisted of 60 patients meeting inclusion criteria, randomly divided into three groups of 20. Two patients in group K and three patients in group D were excluded because they were not accessible for follow-up and did not return for postoperative assessment. Descriptive data, such as age, gender, the position of impacted teeth, and duration of surgery, are presented in Table 1.

There were no significant differences in these parameters between the three study groups.

Figure 3 presents pain severities reported by the patients in the three study groups from 1 h after surgery to 12 h after it (Fig. 3). There were significant differences in the mean pain scores of the patients between groups K and D and group C during the 12-h postoperative interval. Statistical analyses showed significant differences in the mean pain scores between groups K and C ($P = 0.002$) and groups D and C ($P < 0.001$). Besides, the mean pain score in group D was lower than that in group K; however, the difference was not significant ($P = 0.158$). Post hoc Tukey tests showed significant differences in pain severity scores between groups K and C from 3 h postoperatively to 7 h post-operatively ($P < 0.05$). However, such a significant difference between groups D and C was noted from 3 h postoperatively to 11 h postoperatively ($P < 0.05$).

When the patients had unbearable pain, they needed pain killers. Table 2 present the number of pain killers taken at 24, 48, and 72 h in the three study groups, with significant differences in the number of the analgesic tablets taken during the first 24 h after surgery between the three study groups ($P = 0.01$). However, the differences were not significant at the second and third 24-h postoperative periods.

The earliest time the patients took the first analgesic was 20 min in the control group, and the latest time was 402 min in group D. The analysis of the time the patients took the first analgesic showed no significant difference between groups D and K; however, the differences of these groups and the control group were significant (Table 3).

Discussion

The present study showed that the sublingual injection of ketorolac was as effective as the sublingual injection of dexamethasone in decreasing pain severity during the first 12-h period after impacted mandibular third molar surgery. Besides, ketorolac significantly decreased the patient's need for pain killers during the first 24 h after surgery compared to the control group. In addition, the time for taking the first pain killer after surgery by the patients receiving dexamethasone and ketorolac increased compared to the control group.

Consistent with the present study, comparison of intravenous injection of these two medications to relieve pain after impacted third molar surgeries with the group receiving normal saline solution showed that during the 10-h postoperative interval, the pain severity was not different between the two groups and was significantly less than that in the normal saline solution group (Claseman et al. 1998). In another study, 10 mg of oral ketorolac and 8 mg of oral dexamethasone were prescribed before impacted third molar surgeries. The results showed that these two medications were equally effective in decreasing pain severity and swelling postoperatively, consistent with the present study (Keats, A.S.J.A.T.J.o.t.A.S.o.A 1978).

Submucosal injection of 4 and 8 mg of dexamethasone in the buccal vestibule effectively decreased postoperative swelling due to impacted third molar surgery (Grossi et al. 2007) and increasing the time pain began after surgery (Claseman et al. 1998). Besides, Gozali et al. reported the efficacy of a sublingual injection of 8 mg of dexamethasone in decreasing pain after surgery (Gozali et al. 2017). Another study showed that the sublingual injection of dexamethasone was as useful as its intramuscular injection in decreasing pain and swelling after impacted mandibular third molar surgeries (Majid et al. 2011).

Several studies have evaluated the intramuscular (Shah et al. 2013) and intravenous (Gopalraju et al. 2014) injections and intranasal spray (Grant and Mehlisch 2010) and oral use of ketorolac to decrease pain severity after impacted third molar surgeries. Besides, one study evaluated the sublingual use of ketorolac after impacted third molar surgeries (Trindade 2012).

Table 1 Personal and surgical data

Variable	K	D	Control	Test/P value
Age: mean \pm SD	26.5 \pm 5	28.5 \pm 9	28 \pm 7	ANOVA/0.711
Position: Right molar (%) / left molar (%)	40/60	59/41	56.5/43.5	Chi-squared/0.418
Sex: Male (%) / Female (%)	36/64	23/77	43/57	Chi-squared/0.420
Duration of surgery (min) (mean \pm SD)	5 \pm 9.4	4 \pm 8.5	5 \pm 8.7	ANOVA/0.872
Weight (kg) (mean \pm SD)	64 \pm 12	68 \pm 17	71 \pm 2	ANOVA/0.239

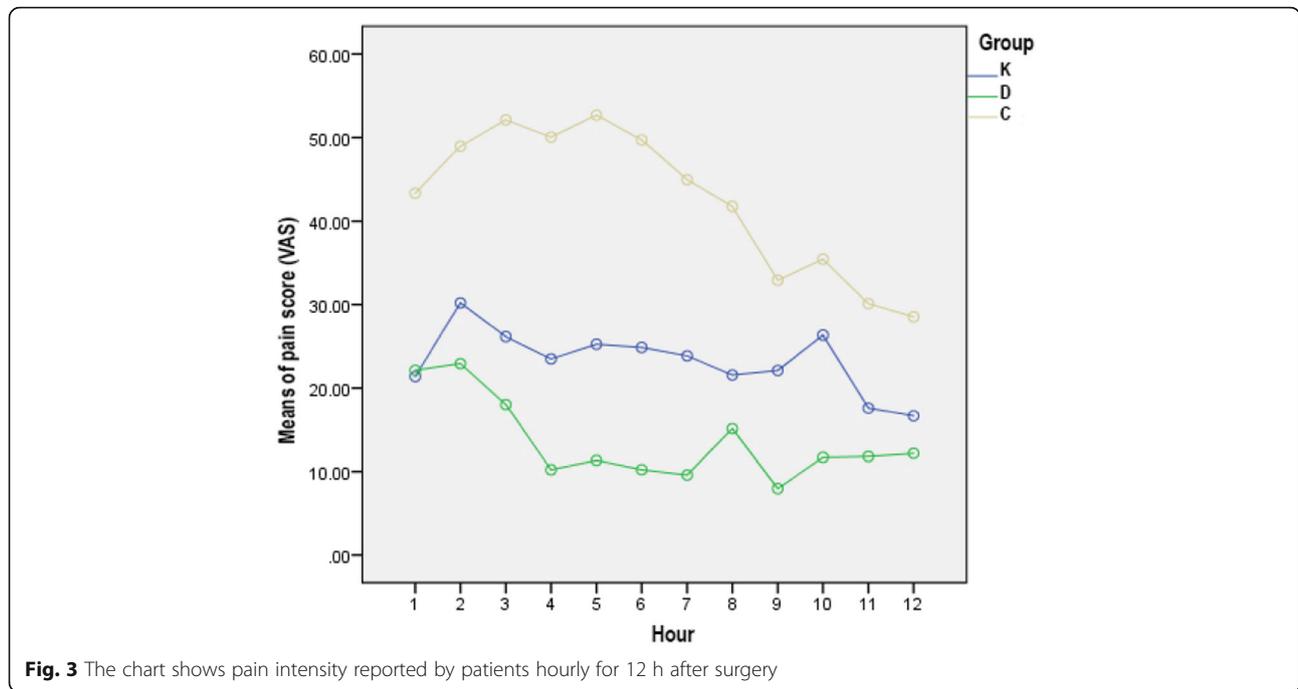


Fig. 3 The chart shows pain intensity reported by patients hourly for 12 h after surgery

There are certain advantages of administering analgesics sublingually compared with oral administration. In particular, the sublingual administration of a drug can relieve pain faster than oral administration because the sublingual administration route avoids the gastrointestinal tract and also the first passage of the drug in the liver where a portion of the drug would be metabolized. Also, some patients find it more comfortable to take medications sublingually than take medications orally (Trindade 2012).

To the best of our knowledge, no study has compared the effectiveness of sublingual dexamethasone with sublingual ketorolac for pain relief after third molar surgery.

According to the present study, it appears that dexamethasone was more effective than ketorolac in decreasing pain severity after impacted third molar surgeries, with a more prolonged effect. The patients reported less pain up to 11 h after surgery compared to those in the control group. However, this effect lasted for 7 h in the ketorolac group. These differences in the results might

be explained by evaluating the plasma half-life and the duration of the effect of these two medications (Table 4) (Kim et al. 2009).

Since the maximum pain after impacted mandibular third molar surgeries appears 6–8 h postoperatively (Seymour et al. 1985), ketorolac, too, can be used as a useful medication to manage pain after such surgeries.

However, the objective assessment of pain in terms of the number of analgesics taken during the first 24 h did not reveal any significant differences between groups D and K. This might be explained by personal and individual variability and the subjective nature of VAS evaluations. During the 24- and 48-h periods after surgery, there were no significant differences in the number of analgesics taken between the three study groups. Another study evaluated the effect of submucosal injection of dexamethasone on decreasing pain severity and swelling after impacted third molar surgeries. Consistent with the present study, the results showed that 48 h after surgery, there were no significant differences in the number

Table 2 Mean number of analgesic intake by patients 24, 48, and 72 h after surgery

Time after surgery	K	D	C	P value
	Mean ± SD	Mean ± SD	Mean ± SD	Kruskal-Wallis
24 h	2.6 ± 1.2 ^{ab}	3.13 ± 2.15 ^{bc}	3.82 ± 1.36 ^{ac}	0.01
48 h	1.53 ± 1.84 ^d	1.59 ± 2.12 ^d	2.12 ± 1.52 ^d	0.282
72 h	0.47 ± 0.83 ^f	0.71 ± 1.53 ^f	1.32 ± 1.58 ^f	0.20

^{abc}Mann-Whitney test

^aP = 0.005

b, c, d, f P > 0.05

Table 3 Mean interval (min) of first analgesic intake by patients after surgery

	K	D	Control	P value ANOVA
Mean ± SD	200.74 ± 9 ^{ab}	214.94 ± 5 ^{ac}	132.65 ± 2 ^{bc}	0.003
Min-max	80-300	52-402	20-300	

^{abc}Tukey test

^aP = 0.866

^bP = 0.02

^cP = 0.05

Table 4 Comparison of ketorolac and dexamethasone

Drug	Duration of action (h)	Plasma half-life (min)
Ketorolac	6-8	120-360
Dexamethasone	36-54	200

of analgesics taken between the dexamethasone and control groups (Nair et al. 2013).

The present study showed that ketorolac, as a non-steroidal analgesic, can exhibit performance similar to dexamethasone to manage postoperative pain. Studies comparing the effects of different forms of ketorolac with other medications have shown that ketorolac exhibited better effects of pain control after impacted third molar surgeries than a control group (Walton et al. 1993), tramadol (Gopalraju et al. 2014; Ong and Tan 2004), and sodium diclofenac (Mony et al. 2016).

Several studies are available on the commonly used routes and intervals of using NSAIDs and glucocorticoids; however, the sublingual use of these medications has not been adequately dealt with (Trindade 2012). Shetty et al. studied the effect of the submucosal injection of dexamethasone and reported no significant differences in patients' pain perception between the dexamethasone and control groups (Deo and Shetty 2011). In that study, dexamethasone was injected into the submucosal tissues exactly around the surgical area immediately before surgery, and it appears a large amount of the medication is removed due to elevating the flap in the adjacent tissue and irrigation during the surgical procedure. However, injection of this medication into the sublingual mucosa appears to solve this problem. The sublingual injection in the present study was undertaken after ensuring the success of the inferior alveolar nerve block procedure. However, three patients in the ketorolac group reported severe pain during injection, reported in previous similar studies, too (Trindade et al. 2012).

The sublingual administration of ketorolac will bring about a more rapid effect compared to its oral use for pain management (Trindade et al. 2012). Besides, the sublingual administration of dexamethasone immediately before the procedure increases its concentration at the surgical site and decreases its systemic absorption, which indicates the submucosal advantage of its submucosal administration (Chrousos and Margioris 2007).

One of the limitations of the present study was the effect of personal characteristics and differences on pain perception; different individuals in different groups might exhibit differences in pain perception and threshold. To resolve this problem, it is suggested that future studies use split-mouth designs and consider adequate wash-out periods.

Conclusions

Under the limitations of this study, it can be concluded that preoperative sublingual injection of ketorolac and dexamethasone are similarly effective in pain control after impacted third molar surgeries.

Abbreviations

NSAIDs: Non-steroid anti-inflammatory drugs; Group K: Ketorolac group; Group D: Dexamethasone group; Group C: Control group

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Not applicable.

Authors' contributions

DH performed all the surgeries. RF analyzed and interpreted the patient data regarding the pain intensity and the effect of different drugs. FM gathered all the information and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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None.

Availability of data and materials

The data sets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Vice-chancellor in Research Affairs-Medical University of Isfahan by IR.MUI.RESEARCH.REC.1398.142 approval ID. And also, this study was approved in WHO Registry Network in Iran (IRCT) at 2021-06-16 and its registration reference is IRCT20180906040960N1. Written informed consent was obtained from all the participants.

Consent for publication

Consent for publication was obtained from the participant whose photo appeared in this article.

Competing interests

The authors declare that they have no competing interests.

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