Randomised Controlled Trial

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Effects on ondansetron of postdural puncture headache after cesarean section under spinal anesthesia

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Background: Spinal anesthesia is commonly performed for cesarean section, however, postdural puncture headache (PDPH) is one of its most common adverse effects. Ondansetron is an antiemetic for cancer treatment and analgesia-induced nausea and vomiting. In this study, the authors aim to evaluate the effect of postoperative ondansetron on PDPH.

Methods: In this randomized controlled clinical trial study, 120 pregnant patients are ASA II, undergoing elective cesarean section, were randomized into two groups (placebo or study). The patients in the study group , immediately after the birth of a baby and 24 h after the operation, received ondansetron 4 mg IV while the placebo group received a placebo. The severity and incidence of headache, postoperative nausea and vomiting, dizziness, neck and lower back pain, and the use of analgesia was assessed in the two groups.

Results: The significant meaning of the time effect ($P < 0.001$) indicated that regardless of the group, for each unit increase in time, the chance of developing a headache increased by 23%, which was statistically significant. Also, the significant meaning of the group effect indicated that regardless of time, patients who did not take indomethacin had ~4.11 times higher chances of developing a headache compared to those who received the medication, which was statistically significant ($P = 0.004$).

Conclusion: The administration of ondansetron significantly reduces the occurrence of postspinal anesthesia headaches and neck pain. There was no significant difference in headache severity between the two study groups.

Keywords: headache, ondansetron, PDPH, postoperative, spinal anesthesia

Introduction

Spinal anesthesia has become a common choice for cesarean section (C-section) due to its low-to-no impact on child and mother[1,2]. Spinal anesthesia is known to be associated with a greater Apgar score, compared to general anesthesia[3,4]. Unstable hemodynamics such as hypotension and bradycardia are common complications of spinal anesthesia[5]. Pruritus and postoperative shivering is also common with the use of spinal anesthesia[6]. Postdural puncture headache (PDPH) is defined as a headache that is presented within 5 days following lumbar puncture and exacerbates in sitting and standing positions[7–9]. It is also accompanied by photo-sensitivity, and blurred vision that can be unresponsive to analgesics[10,11]. Hole in the meninges creates tension on pain-sensitive meningeal vasculature due to the loss of cerebrospinal fluid results in PDPH[12,13].

Conservative management of PDPH includes hydration and the use of analgesics like acetaminophen and NSAIDs[14]. However, side-effects related to these drugs are concerning[15]. Ondansetron is a selective 5-HT3 receptor antagonist (5-hydroxytropetamine 3) that has been reported for nausea and vomiting caused by chemotherapy, radiotherapy, and anesthesia. 5-HT3 antagonist, tropisetron, when administered intrathecally reduces hyperalgesia and allodynia[16]. Animal studies have also shown the effects of ondansetron in the management of neuropathic pain[17].

This study aims to evaluate the effects of postoperative ondansetron on PDPH among women undergoing C-sections under spinal anesthesia.

HIGHLIGHTS

- Spinal anesthesia is a commonly performed for cesarean section.
- Postdural puncture headache (PDPH) is one of its most common adverse effects.
- Ondansetron is an antiemetic for cancer treatment and analgesia-induced nausea and vomiting.
- The administration of ondansetron significantly decreased the incidence of PDPH.
- However, the severity of the headache did not differ significantly between the two groups.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Methods

This randomized controlled clinical trial was performed among women undergoing C-section at Asali Hospital, Khorramabad, Iran (during 2019–2020). Our inclusion criteria included women of their reproductive age undergoing C-section under spinal anesthesia, during the study period and those under ASA class I and II. Exclusion criteria of our study was women sensitive to spinal anesthesia, women with a history of headaches, opioid users, those taking selective serotonin reuptake inhibitors and cases of pre-eclampsia. Written consent was obtained from all the patients before they participated in the study.

The patients were randomly divided into two groups using computerized randomization. Patients, clinicians, and research data collectors were not aware of the grouping of the patients.

Owing to the scarcity of similar studies and based on the researchers' expectations to determine the effect of the intervention at the 95% confidence level, 80% test power, and the average effect size of 0.23, using 3.1.2 G-power software, the minimum sample size in each group was determined to be 47 samples and due to possible fall in each group, 60 samples were included in both the groups.

After taking the obtaining vessel by angio-catheter No. 20, at 20 cc per kg body weight, Ringer's serum was hydrated statically in the operating room before surgery. All the patients underwent spinal anesthesia with 0.5% Marcaine, 2.5–3 cc with a 25G needle between L4-L5 or L5-S1 in the sitting position. After the delivery of the newborn, patients in the study group received 4 mg (2 cc) of intravenous ondansetron by slow injection and patients in the placebo group received 2 cc of normal saline. On the second day, patients received 4 mg of intravenous ondansetron. Patients underwent blood pressure monitoring, pulse oximetry (arterial blood saturation percentage) and electrocardiography at pre-operative, intraoperative, and postoperative states, and every 5–10 min during surgery. The mean blood pressure was maintained between 80 and 120 mmHg and the heart rate was between 60 and 100. In case of systolic blood pressure less than 100 mmHg or a drop of more than 20% of the initial blood pressure, 10 mg ephedrine was administered.

If anesthesia was not sufficient and we had to use narcotics and other drugs to reduce pain, the patient was excluded from the study. Patients were excluded from the study if patients required re-dosing of ondansetron due to nausea and vomiting during surgery or recovery. For managing surgical site pain, patients received meperidine 1 mg per kg body weight up to 5 pain score and in case of pain more than 5, diclofenac suppository was administered.

Patients were examined in the ward and after discharge by telephone by a questioner who was unaware of the type of drug received by the patient. The main variable evaluated in this study was the incidence and severity of headache. The severity of patients' headache was evaluated on the 1st day after surgery at 12 and 24 h intervals. On the second day after surgery at 36 and 48 postoperative hours. The incidence and severity of headache, postural headache, neck pain and back pain, nausea, vomiting,

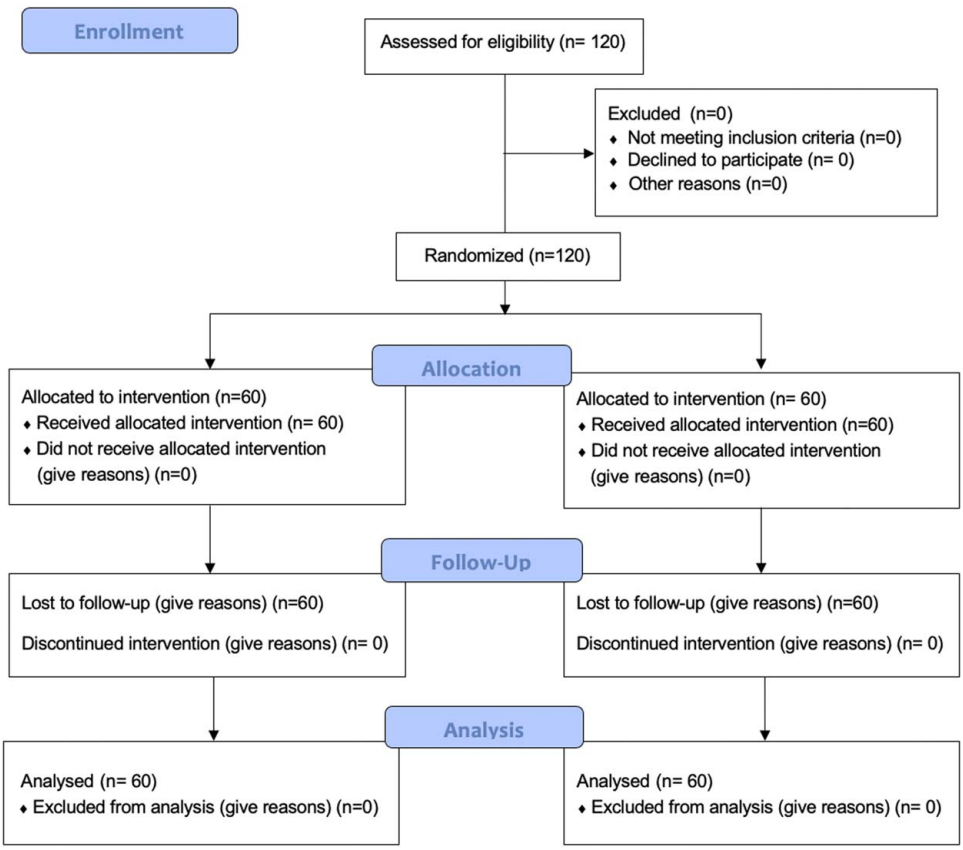

Figure 1. CONSORT flowchart.

Table 1

Modeling table of the effect of ondansetron on the incidence of headache at different times by modulating the effect of other variables using the GEE model with the logit link function

Variables		SD	Odd ratio (95% CI)	*P*
Control	1.41	0.48	4.11 (0.32–5.49)	0.00
Ondansetron	References			
Hypertension				
No	0.28	0.72	1.33 (0.33–5.49)	0.69
Yes	References			
Tachycardia				
No	−0.89	0.84	0.40 (0.07–2.15)	0.29
Yes	References			
Gravida	−0.00	0.25	0.99 (0.60–1.63)	0.97
Age	−0.06	0.03	0.74 (0.20–2.69)	0.08
25 < BMI	−0.30	0.65	0.74 (0.20–2.69)	0.64
18.5 < BMI < 25	−0.98	0.86	0.37 (0.69–2.02)	0.25
18.5 > BMI	References			
Patient evaluation times	0.21	0.04	1.23 (1.12–1.36)	0.00
Control group time	−0.11	0.06	0.89 (0.78–1.02)	0.10
Intervention group time	References			

dizziness and the need for analgesics and its type was recorded for all the patients.

The severity of headache was measured by vNRS (verbal numerical rating scale) method which is divided from 0 to 10. (0 = painless and 10 = worst pain that the patient is willing to kneel) also, patients' nausea was quantitatively and qualitatively measured using the same scale, 0–3 (mild), 4–6 (moderate), 7–10 (severe). Vomiting was scored as 0–1 times a day (mild), 2–3 times a day (moderate) and more than 4 times a day (severe).

Also, the location of the headache (occipital, frontal, temporal, parietal, and neck pain), the status of the headache (does lying down improve headache?), the presence of diplopia, lower back pain, and medication side effects (headache, fatigue, anxiety, urinary retention, itching, constipation, diarrhea, dizziness, and fever), the severity of pain at the surgical site based on vNRS, the need for further treatment, and its type were asked from the patient and recorded.

Data analysis

The data was computerized and analyzed statistically using SPSS v21. Central ratio and indices and appropriate dispersion were used to present the data. Independent *t*-test, χ^2, repeated measures analysis of variance and GEE model are used to analyze the data and *P*-value <0.05 was statistically significant.

This study was approved by the Research Ethics Board of Lorestan University of Medical Sciences (IR.LUMS.REC.1399.027).

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This manuscript adheres to the applicable CONSORT checklist and flowchart guidelines (Fig. 1)[18].

Results

Out of 120 study participants, 60 received ondansetron and 60 received a placebo, with both groups balanced in terms of age (over and under 30 years). The mean age in the study group was 29.98 ± 4.91 years, and in the placebo group, it was 30.7 ± 5.93 years. There was no significant difference in mean ages between the two groups ($P = 0.43$).

Regarding parity, the mean in the study and placebo groups was 2.05 ± 0.89 and 2.01 ± 1.01, respectively, with no significant difference observed ($P = 0.85$).

In the study group, 3.3% had a BMI less than 18.5 kg/m^2, while in the control group, this was observed in 1.7% of patients.

In the study group, one patient (1.7%) experienced hypotension, while six patients (10%) in the control group had hypertension. The difference between the groups was not statistically significant ($P = 0.11$). Regarding bradycardia, four patients (6.7%) in the study group and two patients (3.3%) in the control group exhibited this condition, with no significant difference observed ($P = 0.67$). The Table 1 illustrates the incidence of headaches in both groups. Notably, the maximum number of patients experiencing headaches occurred on the 3rd and 4th day after surgery in the ondansetron group, with 12 patients (20%), while in the control group, the highest incidence was observed on the 3rd-day postsurgery, with 20 patients (33.3%). Patients in the study group were headache-free at 12 and 24 h postsurgery, while those in the placebo group were headache-free at 12 h postsurgery. The peak incidence of headache occurred on the third and fourth days after surgery, with 20% in the study group and 33.3 and 31.7% on the third and 4th days, respectively, in the placebo group.

On the 3rd day, the mean headache severity was 2.35 ± 1.11 in the study group and 3.31 ± 2.25 in the placebo group, indicating a significant difference in severity between the two groups ($P < 0.001$). Over time, both the study and placebo groups experienced a significant decrease in the mean severity of headaches. However, there was no significant difference in the changes in headache intensity between the two groups at different times ($P = 0.25$, Table 2).

Regarding the location of headaches, in the study group, seven patients (5.8%) reported occipital area pain, five (4.2%) had pain in the forehead area, and three (2.5%) experienced pain in the parietal area. In the placebo group, six patients (13.3%)

Table 2

Comparison table of the average severity of headache between the two groups at different times

	Time										
Group	12 h	24 h	36 h	48 h	Third day	4th day	5th day	6th day	7th day	*P*-intergroup	Intergroup P (time interaction in group)
Ondansetron	0	0	0.11 ± 0.69	0.23 ± 1.31	1.11 ± 2.35	1.01 ± 2.19	0.88 ± 2.11	0.45 ± 1.50	0.31 ± 1.22	< 0.001	0.25
Control	0	0.45 ± 1.55	0.78 ± 2.05	1.00 ± 2.34	2.25 ± 3.31	1.96 ± 3.06	1.43 ± 2.70	0.70 ± 1.88	0.31 ± 1.15	< 0.001	

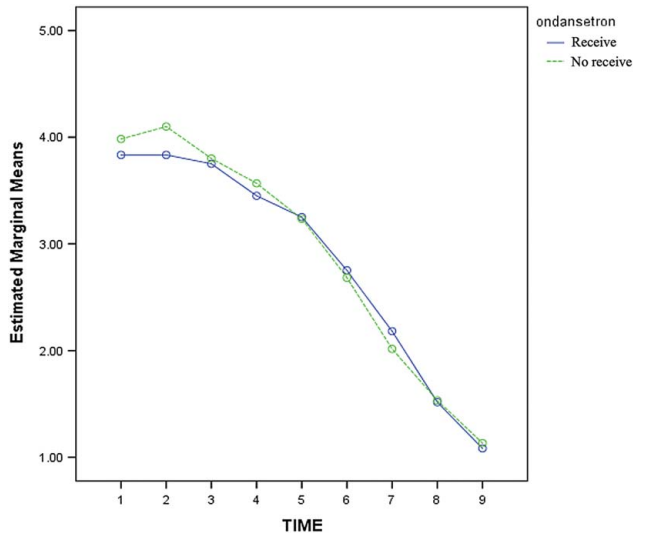

Figure 2. Comparison of the mean severity of headache between the two groups at different times.

experienced occipital area pain, three (2.5%) had pain in the forehead area, five (4.2%) in the parietal area, and one (0.8%) in the temporomandibular area (Fig. 2).

Neck pain peaked on day 3, affecting 14 patients (33.3%) in the study group and 24 patients (40%) in the control group. Analysis using the GEE model with a logit link function revealed that, after adjusting for other variables, there was no significant difference in the incidence of neck pain over time between the two groups ($P = 0.433$). However, a significant time effect ($P < 0.001$) was observed irrespective of the group, with a 17% increase in the chance of neck pain per unit time. Patients not administered ondansetron were nearly three times more likely to experience neck pain, which was statistically significant ($P = 0.028$) (Table 3).

Dizziness was most prevalent on the 4th, 5th, and 6th days postsurgery in the study group, affecting six patients (10%) each day. In the placebo group, the highest incidence occurred on the 3rd, 4th, and 5th days postsurgery, with eight patients (13.3%) each day. Postoperative pain intensity peaked at 24 h postsurgery in both the study group (3.83 ± 1.29) and the placebo group (4.36 ± 1.36). The lowest pain intensity was recorded on the 7th day postsurgery in both groups (study group: 1.74 ± 1.08; placebo group: 1.64 ± 1.13). Analysis revealed a significant difference in pain intensity changes within each group ($P < 0.001$). While both groups experienced a significant decrease in pain intensity over time, there was no significant difference in pain intensity changes between the two groups at different time points ($P = 0.4$, Table 4). The peak incidence of low back pain occurred on the 4th postoperative day, affecting 10 patients (16.7%) in the study group and on the 3rd postoperative day, affecting 14 patients (23.3%) in the placebo group. The overall frequency of low back pain was 11 patients (18.3%) in the study group and 20 patients (33.3%) in the placebo group (Fig. 3).

Meperidine usage was highest at 12 and 24 h postsurgery, with two patients (3.3%) in the study group and at 12 h postsurgery, with five patients (8.3%) in the placebo group.

In the study group, one patient (1.7%) required additional analgesia at 36 and 48 hours postsurgery and on the 3rd postoperative day, respectively. Similarly, in the placebo group, one patient (1.7%) required additional analgesia at 12 h, 36 h, and on the 3rd day postsurgery.

The need for diclofenac was highest at the 12th postoperative hour in both groups, with 49 patients (81.7%) in the study group and 47 patients (78%) in the placebo group.

Table 3

Modeling table of the effect of ondasterone on the incidence of neck pain at different times by modulating the effect of other variables using the GEE model with the logit link function

Variables		SD	Odd ratio (95% CI)	*P*
Control	1.107	0.504	3.026 (1.125–8.140)	0.28
Ondansetron	References			
Hypertension				
No	− 0.512	0.4713	0.600 (0.238–1.510)	0.278
Yes	References			
Tachycardia				
No	− 0.779	0.6834	0.459 (0.120–1.752)	0.29
Yes	References			
Gravida	− 0.114	0.2063	0.892 (0.595–1.337)	0.580
Age	− 0.042	0.285	0.959 (0.906–1.014)	0.138
25 < BMI	− 0.068	0.5515	0.934 (0.317–2.754)	0.902
18.5 < BMI < 25	− 0.886	0.7286	0.412 (0.99–1.719)	0.224
18.5 > BMI	References			
Patient evaluation times	0.159	0.0525	1.172 (1.058–1.299)	0.002
Control group time	− 0.055	0.700	0.947 (0.825–1.086)	0.433
Intervention group time	References			

Discussion

The present study was conducted to investigate the effect of ondansetron on the occurrence and severity of postspinal anesthesia headache in women undergoing C-section. The study demonstrated that administering ondansetron at a dose of 4 mg immediately after spinal anesthesia during C-section and then readministering it at a dose of 4 mg the day after surgery significantly reduces the occurrence of postspinal anesthesia headache in patients. Specifically, without considering the group, for each unit increase in time, the chance of developing headache increased by 23%, which was statistically significant. Additionally, the significant group effect indicates that, regardless of time, patients who did not receive ondansetron were almost 4.11 times more likely to develop headaches compared to those who received the drug, which was statistically significant.

Furthermore, the findings of this study indicate that there was a significant difference in the changes in headache intensity over time in the ondansetron-receiving group, with a significant decrease observed in the average headache intensity over time[19,20]. Similarly, a similar result was obtained in the control group, where a significant decrease in the average headache intensity over time was observed. However, the results of the time interaction effect in the group showed that there was no significant difference between the changes in headache intensity between the two groups at different time points[21].

A study conducted by Dehghanpisheh and colleagues in 2019 showed that while 0.15 mg of ondansetron does not affect the occurrence of PDPH, it does reduce headache severity[22]. Additionally, it helps maintain patients' blood pressure in the operating room, reduces the incidence of hypotension, and the

Table 4

Comparison table of mean pain intensity at the operation site between the two groups at different times

	Time										
Group	12 h	24 h	36 h	48 h	Third day	4th day	5th day	6th day	7th day	p-intergroup	Intergroup P (time interaction in group)
Ondansetron	3.83 ± 1.27	3.83 ± 1.29	3.75 ± 1.21	3.45 ± 1.26	3.25 ± 1.27	2.75 ± 1.68	2.18 ± 1.81	1.51 ± 1.82	1.08 ± 1.74	< 0.001	0.4
Control	3.98 ± 1.48	4.1 ± 1.36	3.80 ± 1.39	3.56 ± 1.38	3.23 ± 1.36	2.86 ± 1.81	2.01 ± 1.78	1.53 ± 1.76	1.13 ± 1.64	< 0.001	

need for vasopressor medications like ephedrine. This study also indicates that aminophylline does not affect the occurrence or severity of PDPH. Prevention of hypotension may also be effective in reducing the occurrence of PDPH. Furthermore, the data suggest that significant hypotension during surgery is twice as likely to occur as PDPH over time. While hypotension was not observed in the two study groups in the present study.

Furthermore, in the present study, the administration of ondansetron at the specified doses significantly reduces the incidence of neck pain. Patients who did not receive ondansetron were almost three times more likely to develop neck pain compared to those who received the drug, which was statistically significant.

A comparison of the average intensity of surgical site pain in the present study shows that in the group receiving ondansetron, the highest mean intensity of surgical site pain at 24 h postoperation was 1.29 ± 3.83, and the lowest mean intensity of surgical site pain in the ondansetron group was on the 7th-day postoperation, which was 1.74 ± 1.08. In the control group, the highest mean intensity of surgical site pain at 24 h postoperation was 1.36 ± 4.1, and the lowest mean intensity of surgical site pain on the 7th-day post-operation was 1.64 ± 1.13.

Based on repeated measures analysis, the results of intragroup analysis showed that in the ondansetron-receiving group, there was a significant difference in the changes in surgical site pain intensity over time, with a significant decrease observed in the average pain intensity over time. Similarly, a similar result was obtained in the control group, where a significant decrease in the average pain intensity over time was observed. However, the results of the time interaction effect in the group showed that between the changes in pain intensity in the two groups at times when ondansetron was received and no adverse effects of ondansetron were observed in the placebo group.

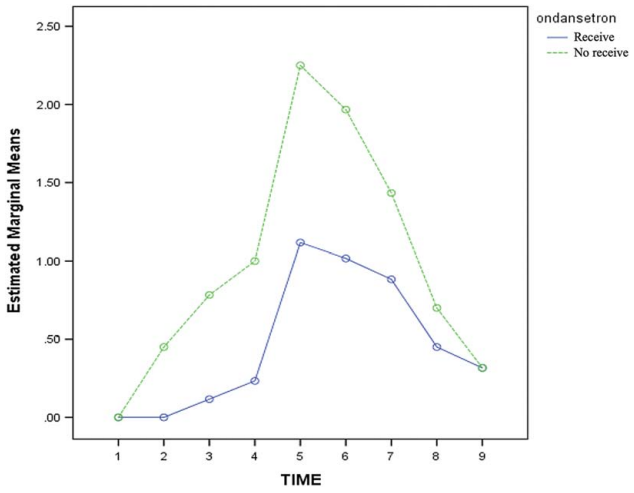

Figure 3. Comparison of the average pain intensity at the operation site between the two groups at different times.

In a study conducted by Pazoki and colleagues in 2018, the effects of 4 mg and 8 mg doses of ondansetron in preventing postspinal anesthesia headaches and PONV were investigated. They showed that ondansetron improves postpartum headache after C-section over 24 h, 48 h, and 4 days, with the effect of 8 mg of ondansetron being greater than 4 mg. Overall, postspinal anesthesia headaches were higher in the group receiving the medication at any given time compared to other groups[23].

The frequency distribution of it in the 8 mg ondansetron group, the 4 mg ondansetron group, and the placebo group was 92.34%, 94.35%, and 87.71%, respectively. Additionally, a significant difference was observed in the incidence of nausea and PONV between the placebo group and other groups. However, in the present study, the incidence of nausea and vomiting in patients was very low, and there was no significant difference between the two study groups.

In a study conducted by Fattahi and colleagues in 2015, they stated that ondansetron can reduce the incidence of postspinal anesthesia headache and PONV while also preventing hypotension[24]. Other studies have also shown that ondansetron can significantly reduce postpuncture headaches in patients undergoing C/S[25,26].

Conclusion

This study found that administering ondansetron significantly reduced the occurrence of postspinal anesthesia headaches and alleviated neck pain following spinal anesthesia. However, there was no significant difference in headache severity between the two groups.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Consent to participate: Written consent was obtained from all the participants for the participation in the study.
Consent for publication: Not applicable.

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No funding was secured for this study.

Author contribution

Dr S.V.: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Dr F.B.: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript; S.B.: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Conflicts of interest disclosure

The authors deny any conflict of interest in any terms or by any means during the study.

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Guarantor

Dr Sepideh Vahabi.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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