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Response to question: Is intranasal oxytocin useful in preventing post-dural puncture headache in caesarean section? A randomised clinical trial

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Post-dural puncture headache (PDPH) as an annoying complication after spinal anaesthesia and is of great importance in patients undergoing caesarean section.
Objectives. This study aimed to evaluate the effect of nasal oxytocin on the incidence and severity of PDPH after caesarean section.
Material and methods. This double-blinded randomised clinical trial was carried out on 170 patients undergoing elective caesarean section in Kamali Hospital, Karaj, Iran, from May 2021 to September 2021. Participants were randomly assigned to receive three puffs of intranasal oxytocin (30 IU) (intervention group) or intranasal normal saline (0.3 ml of 0.09% saline solution) (control group) as a placebo right after delivery. The occurrence of PDPH was the primary outcome, and participants were also asked about the use of analgesics and associated symptoms.
Results. The results showed that the rate of PDPH was not significantly different between the two groups at 12 (p = 0.108) and 72 (p = 0.245) hours after surgery, but it significantly reduced the incidence of PDPH at 24 (p = 0.022) and 48 hours (p = 0.042). Oxytocin did not reduce the analgesic requirement compared to the control group (p > 0.05). Oxytocin did not significantly mitigate PDPH associated symptoms, including tinnitus, vertigo, nausea and double vision (p > 0.05).
Conclusions. Administration of intranasal oxytocin in combination with routine analgesic for post-dural puncture headache after caesarean section is beneficial and reduces the incidence of headache after 24 and 48 hours of surgery. Use of nasal oxytocin has no effect on the need for sedation and reduction of associated symptoms (dizziness, diplopia, nausea, tinnitus).
Key words: oxytocin, spinal anaesthesia, post-dural puncture headache, caesarean section.

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Background

Spinal anaesthesia for women undergoing caesarean section is preferable to general anaesthesia [1]. Post-dural puncture headache (PDPH) is a common complication of spinal anaesthesia caused by leakage of cerebrospinal fluid (CSF) through the dural hole created by the needle. Although it is not a life-threatening complication, it is troublesome for the patient [2]. When the rate of CSF leakage exceeds the rate of CSF production, headaches may develop due to reflex cerebral vasodilation [3, 4]. Spinal anaesthesia is done using a much lower dose of the drug and with a minimal risk of poisoning the mother or transferring the drug to the foetus [5]. There are some risk factors associated with PDPH, including female gender, pregnancy and younger age [6]. Use of larger gauge needles, midline insertion, cutting bevel spinal needles and multiple attempts are associated with higher rates of PDPH [2, 3, 6–8]. Migraines are also a risk factor for PDPH due to the similar pathophysiology pathway [9]. There is evidence that the use of intravenous oxytocin alleviates migraine headaches by central vasoconstriction [10]. Nasal oxytocin reaches the central nervous system (CNS) throughout olfactory and trigeminal nerves. Additionally, it is known that oxytocin has a potential therapeutic effect for pain [11–13]. Accordingly, we have designed a study to evaluate the effect of nasal oxytocin on the incidence and severity of PDPH after caesarean section, as well as the analgesic requirement after surgery.

Material and methods

Design and settings

This study was a double-blinded randomised clinical trial carried out on 170 patients undergoing elective caesarean section in Kamali Hospital, Karaj, Iran, from May 2021 to September 2021. The indication for caesarean section was according to the American College of Obstetricians and Gynecologists (ACOG) guidelines [14]. Exclusion criteria were having heart failure, liver disease, renal failure, body mass index (BMI) higher than 35 kg/m^2, history of allergic reaction to oxytocin, neuromuscular disease, diabetes mellitus, hypertension, prior PDPH, history of recurrent headache, e.g. migraine, psychiatric disorders, opioid use or need for a second attempt at spinal anaesthesia.

Intervention

Both groups received spinal anaesthesia with 2–3 ml of 0.5% Bupivacaine. All spinal anaesthesia procedures were done by an anaesthesiologist using the same technique at the L3–L4 interspace in the sitting position. A 25-gauge spinal needle (Dr. J k-3 point) was used for all patients in the midline approach. The needle bevel was aligned with dura fibres during insertion. In case of the need for a second attempt, the patients were excluded from the study. After delivery, each patient received three puffs of intranasal oxytocin spray (30 IU) (intervention group) or intranasal normal saline (0.3 ml of 0.09% saline solution) (control group) as a placebo.

Randomisation and concealment

Participants were randomly assigned to group A or B using random allocation software (RAS) for block randomisation with block sizes of two, four and six to be allocated in the intranasal oxytocin or placebo groups. The study products were labelled as A and B by an independent partner not taking part in the study. The active study product contained 100 IU of oxytocin in each millilitre (each puff contained 10 IUs of oxytocin produced by Alborz Darou Company) (Figure 1).

Outcomes

Our primary outcome was the occurrence of PDPH. Patients were asked about having any headache, analgesia request (need to prescribe analgesic drug requested by the patients to relieve PDPH-associated pain) or associated symptoms (i.e. tinnitus, vertigo, nausea, double vision) 12, 24, 48 and 72 hours after delivery. We used the visual analogue scale (VAS) for pain to evaluate pain intensity in patients who reported headache. PDPH is alleviated by resting in a horizontal position, so all participants were assessed in the upright position [6].

Ethical issue

The research was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Alborz University of Medical Sciences approved this study and accepted all study protocols (IR.ABZUMS.REC.1400.047). Accordingly, written informed consent was taken from all participants before any intervention. The trial protocol was registered in the Iranian registry of clinical trial (#IRCT20201215049725N1; https://en.irct.ir/trial/53008).

Statistical analysis

The data was analysed using SPSS version 20. The descriptive data was presented in mean, standard deviation, frequency and percentages. Quantitative variables were compared between the groups using the independent *t*-Test. Chi-square was used for categorical variables. A *p*-value less than 0.05 were considered statistically significant.

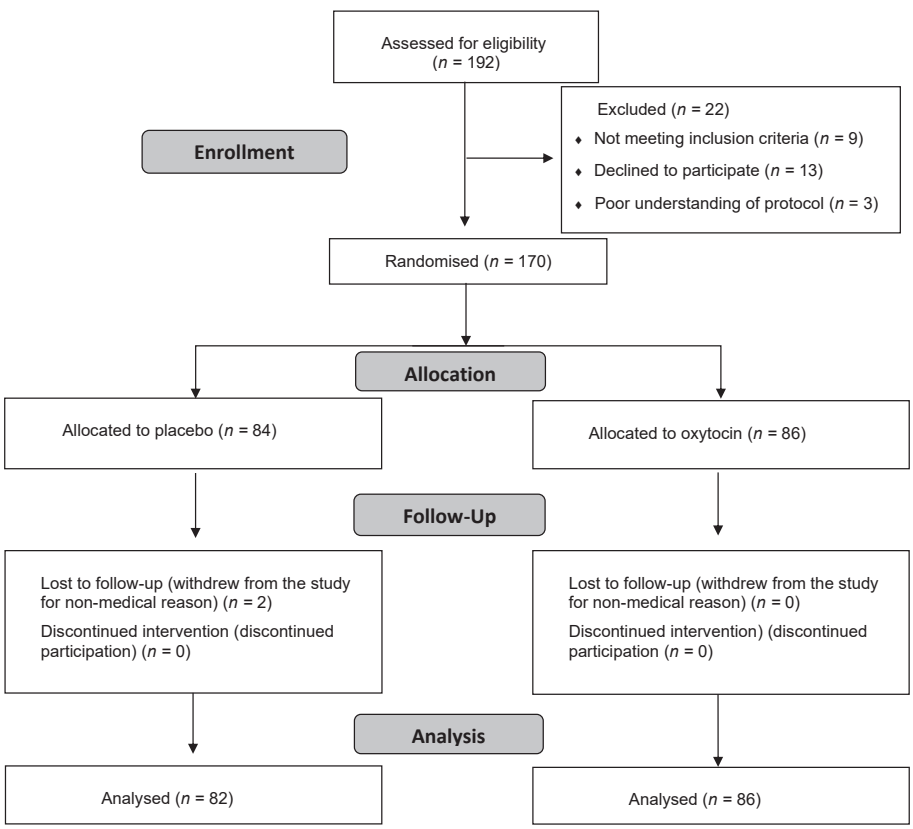

Figure 1. CONSORT flowchart

Table 1. Baseline comparison in both studied groups			
Variable	Control (*n* = 82)	Oxytocin (*n* = 86)	*p*
Age, year	30.2 ± 6.15	31.1 ± 5.52	0.356
BMI, kg/m^2	29.54 ± 5.56	30.46 ± 4.41	0.285
Gestational age, week	39.1 ± 2.31	37.8 ± 1.93	0.865
Height, cm	159.72 ± 6.4	160.92 ± 5.06	0.219
Weight, kg	76.26 ± 13.77	78.81 ± 12.67	0.235

Table 2. Comparison of the incidence of PDPH in both groups			
Variable	Control (*n* = 82)	Oxytocin (*n* = 86)	*p*
12 hours after caesarean	17 (20.73)	10 (12.19)	0.108
24 hours after caesarean	22 (26.82)	11 (12.79)	0.022
48 hours after caesarean	18 (21.95)	9 (10.46)	0.042
72 hours after caesarean	17 (20.73)	12 (13.95)	0.245

Table 3. Comparison of the frequency of patients' requests to prescribe an analgesic drug to relieve PDPH-associated pain in both groups			
Variable	Control (*n* = 82)	Oxytocin (*n* = 86)	*p*
12 hours after caesarean	3 (3.65)	1 (1.16)	0.288
24 hours after caesarean	1 (1.21)	0 (0)	–
48 hours after caesarean	4 (4.87)	4 (4.65)	0.786
72 hours after caesarean	5 (6.09)	0 (0)	–

Table 4. Comparison of the rate of PDPH-associated symptoms in both groups			
Variable	Control (*n* = 82)	Oxytocin (*n* = 86)	*p*
12 hours after caesarean	3 (3.65)	4 (4.65)	0.747
24 hours after caesarean	4 (4.87)	4 (4.65)	0.944
48 hours after caesarean	5 (6.09)	1 (1.16)	0.084
72 hours after caesarean	4 (4.87)	1 (1.16)	0.156

Results

We enrolled 170 pregnant women, of which 84 were assigned to the control group, and 86 to the oxytocin group. 2 patients in the control arm left the study for personal reasons.

In baseline comparison, both groups were homogeneous regarding age (p = 0.356), BMI (p = 0.285), gestational age (p = 0.865), weight (p = 0.235) and height (p = 0.219) (Table 1).

The rate of PDPH was not significantly different between the two groups at 12 (p = 0.108) and 72 (p = 0.245) hours after surgery, but it reduced the incidence of PDPH at 24 (p = 0.022) and 48 hours (p = 0.042) (Table 2).

The results of VASP at 12, 24, 48 and 72 hours after surgery are illustrated in Table 3. Oxytocin did not reduce the analgesic drug request to relieve PDPH-associated pain compared to the control group (Table 3). Oxytocin did not significantly mitigate PDPH associated symptoms, including tinnitus, vertigo, nausea and double vision (Table 4).

Discussion

Oxytocin, as a well-known neurohypophysial hormone synthesised in the hypothalamus, is secreted from the posterior pituitary into the systemic circulation and plays a fundamental role in reproduction. Oxytocin binding sites are located in various regions of the CNS, which play an important role in nociception. In a study done by Matsuura et al., pain modulation and anti-inflammation by oxytocin were revealed [15]. In a systematic review by Rash et al., biologically and psychologically plausible mechanisms linking oxytocin and pain were shown through animal models [16].

According to the results of studies on animals and human, on samples taken from the spinal cord, it has been shown that most studies supported the hypothesis that oxytocin decreases sensitivity to noxious stimuli [17]. Reeta et al. also showed that oxytocin is accompanied by an analgesic response in formalin tests, and delta, kappa-opioid receptors and voltage-gated calcium channels are involved in the antinociception induced by oxytocin [18]. Additionally, Witt et al., in 1992, reported on the effect of oxytocin in increasing the tolerance to pain [19].

In our research, administration of intranasal oxytocin reduced the incidence rate of PDPH. There were no significant differences in the analgesic request and associated symptoms. Both central and peripheral administration of oxytocin increases pain tolerance in animal models. Human studies, however limited, have revealed encouraging results [16]. Intraperitoneal administration of oxytocin increased pain tolerance. This effect was neutralised by intraperitoneal administration of an oxytocin antagonist [20]. In contrast to humans, intracerebroventricular and intracerebral administration of oxytocin could be utilised in animal models. Oxytocin neuropeptide does not readily cross the blood-brain barrier. Therefore, in most human studies, oxytocin is administered intranasal to achieve direct access to CSF. Intranasal administered oxytocin reaches CSF through the nasal cavity membrane or the olfactory or trigeminal nerve [21].

Evidence suggests that acute pain stimulates oxytocin exerting neurons in the paraventricular nucleus of the hypothalamus, which reduces pain sensation through peripheral and central mechanisms. It may also modulate nociception at the spinal cord level. In human studies, the analgesic effect of oxytocin is not as consistent as in animal studies, so further studies are needed in this regard [21]. The lateral part of the central amygdala is composed of oxytocin excreting cells, which respond to pain [21]. Oxytocin downregulates the hypothalamus-pituitary-adrenal axis through acting on the amygdala; subsequently, it reduces stress hormone cortisol production, attenuating its effect on no-

ciceptive signalling [17]. In animal models, oxytocin modulates the activity of limbic and cortical brain regions, affecting the cognitive and emotional processing of pain stimuli [21].

Animal studies have shown that naloxone, an opioid antagonist, reduces the analgesic property of endogenous and exogenous oxytocin [17, 22]. Oxytocin affects the endogenous opioid system [23]. The distribution of opioid receptors is similar to oxytocin in the CNS [17]. Russo et al. reported that central administration of oxytocin can reduces hyperalgesia induced by intraplantar injection of carrageenan, and this effect may be achieved via opioid and cannabinoid systems. The cannabinoid receptor I antagonist reduces the anti-hyperalgesic effect of oxytocin. Thus, the endocannabinoid plays a role in its analgesic effect [22].

Patients with acute and chronic lower back pain, tension-type headache, migraine and chronic constipation reported a reduction in pain perception after intrathecal or intranasal oxytocin. Intravenous oxytocin increased pain tolerance in patients with irritable bowel syndrome. Conversely, oxytocin had no effect on women with fibromyalgia [17]. It should be noted that Phillips et al., in their two case reports, presented one adult and one paediatric patients in which acute migraine headache was rapidly relieved by intravenous oxytocin. Both had classic vascular symptoms. Pain relief was rapid and temporally related to oxytocin administration. Pathophysiology of vascular headache and oxytocin mechanisms were discussed in this study so their similar actions can justify the effect of oxytocin on headache [10]. Recently, Krause et al. indicated that oxytocin prevents migraine attacks [24].

According to our findings, Table 3 shows that 12 hours after spinal anaesthesia, 3 patients from the control group and 1 patient from the intervention group needed Novafen pain reliever (combined pain reliever: acetaminophen + caffeine + ibuprofen) or oral acetaminophen to control headache. At 24 hours after spinal anaesthesia, 1 patient from the control group and no one from the intervention group needed the aforementioned pain reliever to control headache. At 48 hours after spinal anaesthesia, 4 patients from the control group and 4 patients from the intervention group needed painkillers to control headache. At 72 hours after the spinal anaesthesia, 5 patients from the control group and no one from the intervention group required the aforementioned painkillers to control headache. As shown in Table 4, the symptoms associated with headache include vertigo, nausea and vomiting, double vision, tinnitus and dizziness. 12 hours after spinal anaesthesia, 3 patients in the control group had dizziness and nausea, and 4 patients in the intervention group had vomiting, nausea and dizziness. At 24 hours after spinal anaesthesia, 4 patients in the control group had symptoms such as dizziness, vomiting and heaviness of the head, and 4 patients from the intervention group also expressed nausea and dizziness. At 48 hours after spinal anaesthesia, 5 patients in the control group had dizziness and vertigo, and only 1 patient in the intervention group had dizziness. At 72 hours after spinal anaesthesia, 4 patients in the control group had tinnitus and nausea, and 1 patient in the intervention group had dizziness.

In our study, the incidence of PDPH was equal at 48 hours as it routinely improves after two days; thus, it is logical that both groups are the same. We believe that we must use oxytocin alone cautiously, because in severe pain, it is better to use it in combination with a routine analgesic agent, and further clinical trials with a large sample size are required with different combination arms. Considering that we are in the period of the COVID-19 pandemic, and this disease is of great importance due to the many complications and the involvement of many organs [25–29], it should be noted that oxytocin as an antiviral can be effective in the treatment of coronavirus [31, 32]. We know that oxytocin is a safe, available and cheap drug, so it is better to include it in a clinical trial as an adjuvant drug alongside the standard treatment of COVID-19 in order to determine its effects more accurately.

Conclusions

The intranasal administration of oxytocin in combination with a routine analgesic for post-dural puncture headache after caesarean section is beneficial and reduces the intensity of headache after 24 and 48 hours of caesarean section. It also reduces the incidence of headache after 24 and 48 hours of surgery. Use of nasal oxytocin has no effect on the need for sedation and reduction of associated symptoms (dizziness, diplopia, nausea, tinnitus). It is recommended to do more research on the effect of oxytocin in a combination of routine analgesics to consider more ethical issues.

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