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ORIGINAL ARTICLE

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Effect of preoperative pregabalin on post-caesarean delivery analgesia: a dose-response study

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ABSTRACT
Introduction: We hypothesised that preoperative administration of a single-dose of pregabalin would be associated with lower morphine consumption after uncomplicated caesarean delivery.
Methods: After Institutional Ethics Committee approval, 135 parturients scheduled for elective caesarean delivery under spinal anaesthesia were randomly allocated to receive either placebo, or oral pregabalin 150 mg or 300 mg, one hour before induction of anaesthesia. Maternal cumulative morphine requirement at 24 h, pain scores, sedation scores, nausea and vomiting, pruritus, pregabalin-related adverse effects, Apgar scores, Neurologic and Adaptive Capacity scores and umbilical cord acid-base status were recorded.
Results: Compared with placebo or pregabalin 150 mg, the use of a preoperative dose of pregabalin 300 mg resulted in significantly lower cumulative morphine consumption at 24 h (mean dose: placebo 12.9 mg [95% CI 11.6 to 14.2]; pregabalin 150 mg 11.9 mg; [95% CI 10.7 to 13.1]; pregabalin 300 mg 6 mg [95% CI 5.4 to 7.3]; $P<0.001$). Pregabalin 300 mg resulted in lower pain scores at 4 h and 6 h after delivery ($P<0.001$), and fewer instances of nausea, vomiting and pruritus ($P<0.009$). Dizziness and abnormal vision were observed most frequently in the pregabalin 300 mg group ($P<0.05$ and $P<0.009$, respectively). The three groups were similar in terms of maternal sedation, Apgar scores, Neurologic and Adaptive Capacity scores and umbilical cord acid-base status. Three babies in the pregabalin 300 mg group (6.7%) experienced short-term poor latching-on for breastfeeding.
Conclusion: In our study, preoperative administration of pregabalin 300 mg reduced postoperative morphine consumption and early postoperative pain in parturients undergoing elective caesarean delivery, although maternal side effects were more common.

Keywords: Caesarean delivery; Spinal anaesthesia; Pregabalin; Opioid consumption; Postoperative analgesia

Introduction

Effective analgesia after caesarean delivery is essential for early mobilisation so that the mother can care for her baby. Several choices are available for post-caesarean analgesia including spinal or systemic opioids, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetic wound infiltration and transversus abdominis plane blockade. Choice is determined by drug availability, individual preferences, resource limitations and financial considerations.[1] Maternal opioid use may be associated with nausea, vomiting, pruritus, sedation, and occasionally neonatal respiratory depression.[2]

Pregabalin, a drug structurally related to the inhibitory neurotransmitter γ-aminobutyric acid (GABA), exerts its action by presynaptic binding to the α-2-δ subunit of voltage-dependent calcium channels which are widely distributed in the spinal cord and brain. Pregabalin reduces calcium-dependent release of excitatory pro-nociceptive neurotransmitters, thus inhibiting hyperalgesia and central sensitization.[3] Of note, a meta-analysis in non-obstetric subjects demonstrated that pregabalin has the potential to reduce cumulative morphine consumption and opioid-related adverse effects during the first 24 h after surgery. Compared with low-dose pregabalin, doses >300 mg reduced opioid consumption by a further 53%.[4]

A recent study showed that women who received a perioperative course of oral gabapentin had a clinically insignificant improvement in analgesia and a higher incidence of sedation after caesarean delivery under spinal anaesthesia.[5] However, compared with gabapentin, the preoperative use of a single dose of pregabalin has been shown to be more effective in extending the duration of analgesia after gynaecological surgery.[6,7] Pregabalin has

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a similar pharmacological profile and efficacy to gabapentin, although at much lower doses. Thus, it is likely that pregabalin may be associated with fewer dose-related adverse events.

To our knowledge, the efficacy and safety of a single preoperative dose of pregabalin has not been previously studied for the treatment of pain after caesarean delivery. We hypothesised that the preoperative administration of a single-dose of pregabalin 150 mg or 300 mg would be associated with lower cumulative morphine consumption after uncomplicated caesarean delivery under spinal anaesthesia.

Methods

Following Institutional Review Board approval and informed written consent, parturients aged 18–38 years, with American Society of Anesthesiologists physical status classification of I to II, with uncomplicated, singleton pregnancies of at least 36 weeks of gestation who were scheduled for elective caesarean delivery via a Pfannenstiel incision under spinal anaesthesia from November 2012 to June 2015, were included in this controlled, randomised, prospective, double-blind study. As part of the informed consent process information was provided to all participants that there was little or no information regarding the safety of pregabalin during pregnancy, particularly its effect on the neonate. The study was registered with www.clinicaltrials.gov (NCT01719705) and was performed at the Mansoura University Hospital, Egypt, a tertiary referral obstetric hospital with approximately 7000 deliveries per annum, of whom approximately 50% undergo caesarean delivery.[8]

Women with a history of chronic pain, significant cardiovascular, pulmonary, hepatic, renal, endocrinal, or neuropsychiatric illness, prolonged P-R interval, diabetes mellitus, anaemia, bleeding or coagulation disorder or thrombocytopenia (platelet count $<100 \times 10^9$/L), pre-pregnancy body mass index $\geqslant 35 kg/m^2$ or known allergy to pregabalin were excluded from the study. Patients receiving pregabalin, anticonvulsants, antidepressants, antipsychotics, alcohol or drugs of abuse, NSAIDs, opioids or benzodiazepines within the last week or those with communication barriers, pregnancy-induced hypertension, or evidence of intrauterine growth restriction or fetal compromise were also excluded.

An independent investigator who was not involved in the study instructed patients preoperatively on how to use a visual analogue scale (VAS) for measurement of pain intensity using a horizontal line, 100 mm in length, anchored by word descriptors at each end (0 = no pain, 100 mm = worst imaginable pain).

Random Allocation Software, version 1.0.0 (Isfahan University of Medical Sciences, Isfahan, Iran) was used to generate random numbers (45 patients in each group). Random allocation cards were made and put into sequentially numbered sealed opaque envelopes. One hour before induction of anaesthesia subjects received a capsule containing sugar placebo (placebo group), pregabalin 150 mg (Lyrica; Pfizer Inc., Egypt, Cairo) or pregabalin 300 mg. Both placebo and pregabalin capsules were coated with opaque gelatin capsules which were provided by a local pharmacist not otherwise involved in the study, and were indistinguishable from one another.

Anaesthetic management was standardised. All parturients received oral ranitidine 150 mg with 0.3 mol/L sodium citrate 30 mL 15 min before induction. An 18-gauge peripheral intravenous cannula was inserted in a large forearm vein. Maternal monitoring included pulse oximetry, electrocardiography, heart rate (HR) and non-invasive blood pressure (BP). Lactated Ringer's solution 7 mL/kg was commenced at the time of spinal injection and completed within 5 min, followed by a constant infusion at a rate of 2 mL/kg/h. Spinal anaesthesia was performed in the sitting position via a 27- or 25-gauge Whitacre spinal needle at L3–4 or L2–3 using 0.5% hyperbaric bupivacaine 12.5 mg and fentanyl 20 μg. All patients received the same dose regardless of height or weight. Patients were repositioned in the supine position with left uterine displacement and surgery commenced after a T6 sensory level to pinprick was achieved. Supplemental oxygen was delivered using a facemask (5 L/min) if peripheral oxygen saturation dropped below 95% and in response to the demand of the parturient. If patients experienced intraoperative discomfort, rescue doses of intravenous fentanyl 0.5 μg/kg could be administered.

After the umbilical cord was clamped, a 10 IU infusion of oxytocin in 500 mL of lactated Ringer's solution was started. If systolic BP dropped to <20% of baseline, lactated Ringer's solution 250 mL was administered; if this was not sufficient, repeated doses of intravenous ephedrine 5 mg were administered.

The same paediatrician, who was blinded to study group allocation, recorded Apgar scores at 1 and 5 min, umbilical cord blood gas analysis, and Neurologic and Adaptive Capacity Score (NACS) at 15 min, 2 h, and 24 h after delivery. Neurologic and Adaptive Capacity Score has a maximum of 40 with a score >35 denoting vigor.[9] The percentage of infants scoring <35 was assessed.

The postoperative analgesic regimen was standardised in all parturients with intramuscular diclofenac 75 mg at 12-h intervals started immediately at the end of surgery and intravenous morphine patient-controlled analgesia (PCA), which was started before discharge from the post-anaesthesia care unit (PACU). The PCA pump was programmed to deliver a bolus of morphine 1 mg with an 8-min lockout time with no basal rate and a maximum dose of 170 mg per 24 h.

Patients who had a postoperative nausea and vomiting score >0 (0 = no nausea; 1 = nausea no vomiting;