Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

The Effects of Different Doses of Gabapentin on Relieving Pain Due to Cesarean Section: A Randomized Clinical Trial

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Article Info

10.30699/jogcr.8.6.559

Received: 2022/07/20;
Accepted: 2022/09/11;
Published Online: 11 Nov 2023;

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ABSTRACT

Background & Objective: Some types of major surgeries are associated with postoperative pain, sometimes during the days after surgery. These pains mainly lead to the use of various analgesics and, ultimately, patient dissatisfaction. In the present study, we evaluated the effect of gabapentin at doses of 600 and 1200 mg on relieving pain due to cesarean section.

Materials & Methods: In this randomized clinical trial, patients were randomly divided into three equal-size groups (25 patients in each group) through balanced block randomization. The first group was given 600 mg of gabapentin, the second group was given 1200 mg of gabapentin one hour before surgery, and the control group received a placebo. The pain intensity, nausea, vomiting, and drowsiness, as well as the need for postoperative analgesics, were assessed initially and at 2, 6, and 12 hours after surgery. The occurrence of nausea and drowsiness between groups was compared using the chi-square and Fisher's exact tests.

Results: The mean (SD) age of patients in the gabapentin 1200 mg, gabapentin 600 mg, and placebo groups was 26.32±6.15, 27.43±6.38, and 26.59±5.88, respectively (P=0.34). Pain intensity and the rate of analgesic consumption at different time points during the first 12 hours of surgery were significantly lower in the receiving gabapentin groups than in the placebo group (P<0.05). Comparing the prevalence rates of nausea and vomiting and also drowsiness, as the drug-related side effects don't show a significant difference across the three groups at the different investigated time points (*P*>0.05).

Conclusion: Gabapentin with a minimum therapeutic dose can successfully reduce postoperative pain intensity and also needs analgesic use after a cesarean section.

Keywords: Gabapentin, Cesarean Section, Pain, Analgesic

Introduction

Today, cesarean sections are one of the most common gynecological surgeries, the number of which is also increasing in our society, so that in public hospitals, this rate reaches 40 to 50% **(1)**. Pain after cesarean section is a major concern for many women because in this period, in addition to enduring the pain caused by cesarean section, the mother must be able to take care of the baby, so she needs special care **(2)**. Reducing pain after cesarean section is important because of the increased risk of thromboembolic disease, which may be exacerbated by postoperative pain immobility **(3)**. The consequences of these complications lead to numerous economic and medical problems, such as the need for readmission, increasing the length of hospital stay, increasing the cost of treatment, and finally, patients' dissatisfaction with hospital care **(4)**. Therefore, pain is considered the fifth vital sign due to the importance and necessity of pain control in preventing mortality and complications after surgery **(5)**.

Traditional methods for managing acute postoperative pain mainly include oral or injectable analgesics **(6)**. Drugs are widely used to relieve acute pain **(7, 8)**. Pain is a multifactorial phenomenon that is not completely cured by monotherapy. In addition, opioid use is associated with dose-dependent side effects such as respiratory depression, nausea and vomiting, urinary retention, itching and skin irritation, and postoperative drowsiness **(9)**. Therefore, it seems reasonable to use compounds that can exacerbate the analgesic effects of drugs and thus produce better analgesic effects by consuming fewer opioids **(10)**.

Numerous studies have shown that drugs such as gabapentin and pregabalin can not only reduce the severity of acute postoperative pain and reduce the

dose of opioids, but may also play a role in preventing chronic postoperative pain **(11)**. A systematic review showed that taking gabapentin before surgery significantly reduced postoperative pain compared to the control group, and could also reduce the dose of opioids and their side effects **(12)**. The most well-known mechanism for the analgesic effect of gabapentinoids is binding to the pre-synaptic voltage-dependent subunit of α2δ and modulating the release of excitatory neurotransmitters (especially glutamate) from activated nociceptors, which reduces neuronal excitability and inhibits central sensitization, hyperalgesia, and allodynia **(13, 14)**. Other mechanisms that have been proposed for these drugs include activating noradrenergic pain inhibitory pathways in the spinal cord and brain, increasing the activity of voltage-dependent potassium channels, and the effect of N-methyl D-aspartate receptors **(15)**. But to what extent these mechanisms are involved in the analgesic effects of these drugs is not yet fully understood.

Due to the effectiveness of gabapentin in reducing pain and the fact that little research has been done on different doses of gabapentin, this study aimed to determine the efficacy and safety of gabapentin in reducing pain and compare the effect of two different doses of gabapentin in preventing pain after cesarean section.

Methods

Study population

This study was performed as a randomized clinical trial to compare the effect of two different doses of gabapentin on reducing postoperative pain in pregnant women referred to Mousavi Hospital in Zanjan in 2019. We used non-probability convenience sampling for choosing patients, and in continuation, they were randomly assigned to one of three groups: Group A: gabapentin 600 mg; Group B: gabapentin 1200 mg; and Group C: placebo. Balance-block randomization was used to allocate participation in one of the three above-mentioned groups.

Eligibility criteria

The inclusion criteria were willingness to participate in the study, insensitivity to gabapentin, and age between 20 and 45 years. The exclusion criteria were: prolongation of cesarean section for more than 2 hours; increase in incision length for any reason; history of chronic pain or mental illness; occurrence of any unusual complication during surgery; conversion of spinal anesthesia to general anesthesia for any reason; contraindications to spinal anesthesia such as patient dissatisfaction and coagulation disorder; infection at the needle site; and receiving painkillers during surgery.

Measurement tool

We used a researcher-made checklist for gathering the information. After enrolling patients, demographic information, including age, history of underlying diseases such as diabetes, hypertension, and heart disease, history of smoking, and gestational-related diseases including gestational diabetes and gestational hypertension, and previous history of miscarriage, was asked the patients during interviewing and recording.

Study procedure

To conduct the research, after obtaining the necessary permits and after obtaining consent and explaining the research to patients, patients who were candidates for elective cesarean section with class I and II anesthesia (ASA) were anesthetized by spinal anesthesia with 2.5 cc of Bupivacaine at L4-L5 level. The initial selection of patients was due to the conditions of the study units. Patients were randomly divided into 3 groups: one group was given 600 mg of gabapentin, the second group was given 1200 mg of gabapentin one hour before surgery, and the third group, or the control group, received a placebo. Before the operation, the patient was explained about the visual analog scale (VAS), so that the number zero meant the patient's painlessness, and the number 10 was considered the worst pain. Patients' pain was measured and recorded by the researcher using the scale mentioned in recovery as well as at 2, 6, and 12 hours after in the ward. Possible side effects of the drug, including hypotension, bradycardia, seizures, loss of consciousness, itching and skin rash, respiratory depression, nausea, and vomiting, were also recorded over 24 hours during the study. At any time after a cesarean section when the patient expressed pain, the patient was asked to indicate the severity of the pain using a VAS scale **(16)**. In the cases where the VAS score was greater than or equal to 4, an additional dose of analgesia was given to the patient in the form of a 100 mg diclofenac suppository. The total dose of additional analgesia at the end of 24 hours was calculated and recorded in three groups based on mg. Finally, the total amount of analgesia received by patients within 24 hours was calculated and recorded.

Ethics

The ethics committee at Zanjan University of Medical Sciences has approved the study (Research Id: A_12_1005_3, Ethics code: IR.ZUMS.REC.1399.094). Moreover, all participants were asked to sign and submit a written consent form before participating in the study. Also, the protocol was registered in the Iranian Registry of Clinical Trials.

Statistical analysis

The study group was described using descriptive statistics, including mean and standard deviation (SD) for quantitative variables and frequency (percentage) for qualitative variables. We compared continuous variables using the ANOVA test. The Kruskal-Wallis

H test was used when the data did not appear to have a normal distribution or when the assumption of equal variance was violated among the study groups. A Chi-square test was used to compare classification variables between three different groups. A P value ≤ 0.05 was considered statistically significant. SPSS statistical software version 23.0 (IBM, Armonk, New York) was used for statistical analysis.

Results

Figure 1 shows the CONSORT flow chart. There were 96 patients at the enrollment phase, and a total of 75 patients met eligibility criteria and were allocated to one of the three treatment groups through balanced-block randomization. 25 patients were devoted to each group. No patients were dropped from follow-up, and finally, 75 patients were included in the final analysis.

As shown in Table 1, the patients in the three groups were homogenous in regard to age (P=0.34) and BMI (P=0.49).

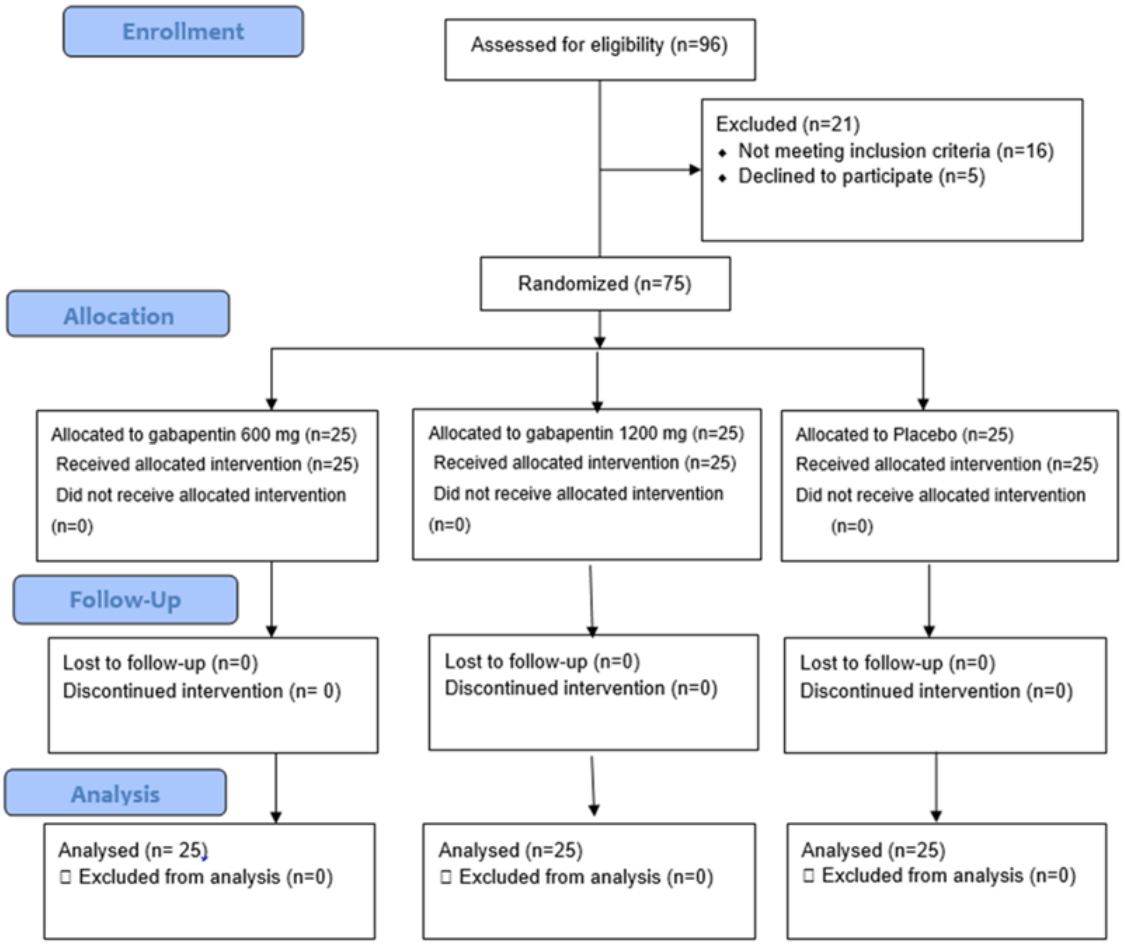

Figure 1. CONSORT flow chart

Table 1. Baseline characteristics of patients in the three investigated group

Variable		gabapentin 600 mg group	gabapentin 1200 mg group	Placebo group	P.Value
Age (Year)		26.32±6.15	27.43±6.38	26.59±5.88	0.34
BMI (Kg/m2)		24.02±3.11	23.26±3.08	23.75±2.68	0.49
Underline disease	DM	2 (8%)	1 (4%)	1 (4%)	-
	BP	3 (12%)	4 (16%)	2 (8%)	
	CVD	1 (4%)	0	0	

As shown in Table 2, pain intensity at the different time points during the first 12 hours of surgery (0, 2, 6 and 12) was significantly lower in the groups receiving 600mg and 1200mg of gabapentin as compared to the

placebo group (P<0.05). Results of the Tukey post-hoc test doesn't show any significant difference across the two groups receiving gabapentin with the different drug doses (P>0.05). Analysis of the trend of pain intensity change also showed a significant difference between the three groups (P=0.001). Comparing the prevalence rates of nausea and vomiting and also drowsiness as drug-related side effects (Table 3), showed no difference across the three groups at the different investigated time points (P>0.05). The mean dose of analgesic drugs used within 12 hours of surgery (Table 4) was significantly higher in the placebo group as compared to the two groups receiving drugs (P>0.05). Analysis of the trend of changing the concentration of analgesic consumption also showed a significant difference between the three groups (P = 0.001). In all evaluated times in all three groups, the neonatal Apgar score was 9 out of 10, indicating no difference between the three groups in terms of the neonatal Apgar score.

Table 2. The pain intensity within 12 hours of surgery in different groups

Group	Gabapentin 1200mg	Gabapentin 600mg	Placebo group	P value
Hours 0	3.72±1.40	3.36±1.82	5.40±2.38	0.001
Hours 2	3.32±1.43	3.44±2.08	5.68±2.05	0.001
Hours 6	3.20±1.55	3.76±2.48	5.00±1.80	0.007
Hours 12	2.92±1.28	3.04±1.42	4.40±2.04	0.005

Table 3. The occurrence of nausea and drowsiness within 12 hours of surgery in different groups

Group	Gabapentin 1200mg	Gabapentin 600mg	Placebo group	P value
Nausea/vomiting				
Hours 0	4 (16.0)	4 (16.0)	5 (20.0)	0.911
Hours 2	3 (12.0)	4 (16.0)	3 (12.0)	0.891
Hours 6	4 (16.0)	1 (4.0)	2 (8.0)	0.323
Hours 12	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Drowsiness				
Hours 0	0 (0.0)	1 (4.0)	0 (0.0)	0.363
Hours 2	1 (4.0)	0 (0.0)	0 (0.0)	0.363
Hours 6	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Hours 12	0 (0.0)	0 (0.0)	0 (0.0)	1.000

Table 4. The dose of analgesics used within 12 hours of surgery in different groups

Group	Gabapentin 1200mg	Gabapentin 600mg	Placebo group	P value
Mean dose, mg				
Hours 0	34.00±13.76	36.00±11.37	68.00±9.52	0.076
Hours 2	24.00±8.72	36.00±9.80	72.00±9.16	0.001
Hours 6	28.00±10.83	36.00±9.80	72.00±9.17	0.006
Hours 12	16.00±7.48	36.00±12.75	52.00±10.20	0.045
Rate of use				
Hours 0	6 (24.0)	8 (32.0)	17 (68.0)	0.003
Hours 2	6 (24.0)	9 (36.0)	18 (72.0)	0.002
Hours 6	6 (24.0)	9 (36.0)	18 (72.0)	0.002
Hours 12	4 (16.0)	7 (28.0)	13 (52.0)	0.021

Discussion

Types of major surgeries are associated with postoperative pain, sometimes during the days after surgery, which mainly leads to the use of various analgesics and ultimately patient dissatisfaction. A cesarean section, as one of the most common surgical interventions in the world, is no exception and in fact, within 48 hours after surgery, it is sometimes accompanied by severe local pain. The use of various analgesics and even opioid drugs reduces the pain caused by surgery, but the main problem in this regard is the occurrence of postoperative complications such as postoperative nausea and vomiting or adverse effects on the fetus, such as a decreased Apgar score, especially when opioid medications are used. Therefore, the use of safe drugs with minimal side effects to alleviate this pain in women undergoing cesarean sections is essential, and in this regard, the health of both mother and neonate should be considered **(17)**. In the present study, we evaluated the effect of gabapentin at doses of 600 and 1200 mg on relieving pain due to cesarean section. In addition to the effect of this drug on relieving surgical pain, adverse effects such as nausea and vomiting, drowsiness, and the need for supplemental analgesia were also examined and as an indicator of neonatal health, changes in the Apgar score were also examined. In the first place, it was found that gabapentin administration was significantly associated with a reduction in postoperative pain intensity. Along with this, the administration of gabapentin will reduce the need to prescribe analgesics after surgery. However, there was no difference between the gabapentin and control groups in terms of side effects such as nausea and vomiting, as well as postoperative drowsiness, so using both doses of gabapentin to relieve cesarean section pain is completely safe. But another important point about the results was the similarity of the analgesic effects of gabapentin at doses of 600 and 1200 mg. It seems that taking the same lower dose of 600 mg will in turn be enough to relieve the pain caused by cesarean section, and therefore the prescribed protocol of gabapentin with a minimum dose of 600 mg can reduce surgical pain appropriately.

A review of studies also emphasized the effectiveness of gabapentin at the same dose of 600 mg and sometimes at lower doses, and described it as completely safe. A systematic review and meta-analysis by Felder et al. found that women receiving gabapentin had significantly lower pain scores within 24 hours than the placebo group. There was also no difference between the two groups in terms of analgesic supplement use, opioid use, or maternal and neonatal complications **(18)**, which was completely consistent with our study. However, in their study, they mainly focused on the 600 mg dose of this drug. In the study by Anaraki et al., the severity of postoperative pain in the gabapentin group was even lower than that of fentanyl as a common drug for relieving surgical pain **(19)**. In the study of Khezri et al., the effect of gabapentin at a dose of 300 mg was also investigated, which indicated a significant reduction in pain following drug administration, and therefore showed that even a dose of 300 mg can be associated with acceptable analgesic effects **(20)**. In the study by Moore et al., administration of 600 mg was associated with a significant reduction in pain as well as maternal satisfaction, while there was no difference between the two groups in terms of opioid intake. There was no difference between the two groups in terms of Apgar score, intraoperative interventions, or umbilical artery pH **(21)**, which, of course, was not consistent with the present study in terms of reducing the need for analgesics. In the study of Monks et al., pain intensity during 24 hours in the group injected with gabapentin was significantly lower than in the placebo group. The level of patient satisfaction in the gabapentin group was much higher than in the placebo group **(22)**, which was again consistent with our study. Summing up the studies, it is suggested that the different doses of gabapentin can effectively reduce pain intensity after cesarean section, along with reducing the need for analgesics after surgery **(18, 23-25)**. It seems that the minimum dose of the drug (600mg) can be effective and achieve complete patient satisfaction.

Conclusion

The prescription of gabapentin at a dose of 600mg effectively reduces postoperative pain severity as well as the need for analgesic use in patients scheduled for cesarean section. Such a dose of the drug is also safe for the neonate.

Acknowledgments

None.

Authors' contributions

AK, VR and MG established the research idea and the study protocol, abstracted, and wrote the manuscript. MG and SAS contributed to the study design and analyzed the data. MG and AK contributed to the study's design and data collection. All authors approved the final version of the manuscript.

Funding

This study was funded by the Zanjan University of Medical Sciences, Iran.

Conflict of Interest

The authors have no conflicts of interest to declare.

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How to Cite This Article:

Kazemi, A., Rashtchi, V., Ghomi, M. The Effects of Different Doses of Gabapentin on Relieving Pain Due to Cesarean Section: A Randomized Clinical Trial. J Obstet Gynecol Cancer Res. 2023;8(6):559-65.

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