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Randomized controlled trial of two oral regimens of gabapentin versus placebo in patients for Cesarean section under spinal anesthesia regarding postoperative pain, sedation, nausea and vomiting

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ABSTRACT

Background and aim: Pain after Cesarean delivery parturients is the most common postoperative complaint, and gabapentin has been shown to reduce acute postoperative pain but with little experience in parturient.

Methods: After approval from the ethical committee in Kasr Al Aini University Hospital, forty-five consenting women aging 20–40 yrs old ASA physical status I or II, with uncomplicated pregnancies scheduled to undergo elective Cesarean section delivery under spinal anesthesia were randomly allocated into three equal groups who received 600 mg gabapentin G600, 900 mg gabapentin G900, and control group GC. The study medication was given orally one hour before the anticipated time of the surgical incision, and data measured include, the time of first rescue of analgesia, the total duration of analgesia, the incidence of post-operative nausea and vomiting (PONV), the level of sedation, and the Neonatal APGAR score at 1 and 5 min.

Results: The time for first rescue of analgesia was comparatively shorter in patients of group GC as compared to G600 and G900 groups (P value = 0.001). Total analgesic requirement of pethidine in first 24 h was significantly lower in groups G600 and G900 as compared to group GC (P value = 0.000) and we found that there was statistically significant increase in the sedation scores of the patients in the G900 group as compared to GC group and G600 group. By comparing the presence of nausea and vomiting in the two gabapentin groups with the control group as a reference value, and with each other in the post-operative periods, we found that there was statistically significant decrease in the nausea score in the G900 group as compared to groups G600 and GC with p value (0.06 and 0.4) respectively.

Conclusion: Gabapentin 900 mg was more effective than 600 mg in reducing post Cesarean section pain, opioid consumption, nausea, and vomiting.

1. Introduction

Postoperative pain, nausea and vomiting (PONV) continues to be one of the most common and unpleasant complications after surgery especially obstetric surgeries [1].

The traditional pain treatment with opioids alone is nowadays not adequate any more. To optimize pain treatment and postoperative outcome, new analgesics and new combination of already existing analgesics are searched for [2].

Gabapentin is a drug with chemical structure that mimics that of the neurotransmitter GABA (gamma amino butyric acid) and acts on the same brain receptors. However, the mode of action is not fully understood. Among other mechanisms like decrease in the synthesis of the neurotransmitter glutamate, gabapentin acts by binding to the α2δ subunit of voltage-dependent ca2+ channels. It has introduced as antiepileptic drug but proved to be effective in controlling neuropathic pain [3].

Recently, gabapentin has been used to reduce pre-operative anxiety, acute postoperative pain, postoperative opioid requirements and postoperative nausea, vomiting and delirium [4].

The efficacy and safety of preoperative oral Gabapentin on pain and opioids consumption were studied in patients undergoing a

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variety of surgical procedures [5] as total abdominal hysterectomy [6], vaginal hysterectomy [7], thoracotomy [8], and spine surgeries [9] but conclusions about optimal dose and duration of treatment cannot be made because of heterogeneity of the trials.

Because gabapentin seems to prevent acute nociceptive and inflammatory pain and might reduce postoperative pain, there were two previous studies previously tried gabapentin for post Cesarean section delivery pain as that have compared gabapentin (600 mg with either 300 mg or placebo), but the results were controversial [10]. The present randomized double-blind controlled study was designed to compare the efficacy of two different doses (600 mg and 900 mg) of oral gabapentin premedication on the postoperative duration of analgesia (whether gabapentin reduces the postoperative need for additional pain treatment), PONV, and postoperative side effects after elective Cesarean delivery under spinal anesthesia. We aimed at identifying the dose with the best effect and the least side effects.

2. Patients and methods

This study was conducted in Kasr Al Ainy Medical Hospital, faculty of medicine Cairo University, from April 2015 to March 2016. After approval of the hospital ethical committee and after obtaining a written informed consent, a total of 45 consecutive women aging 20–40 yrs old ASA physical status I or II, with uncomplicated pregnancies at term (>37 completed weeks) scheduled to undergo elective Cesarean section delivery under spinal anesthesia were included in this prospective, randomized double blinded clinical trial of two oral doses of gabapentin. However, patients with contraindication to neuro axial anesthesia, patients known to be epileptic or on antiepileptic medications, patient with kidney or liver function impairment, patients known alcoholic or IV drug users, pregnancies with any obstetric complications as hypertension, oligohydramnios, polyhydramnios, antepartum hemorrhage, a psychiatric disorder, or inability to communicate effectively were excluded from the study.

Study group allocation into three groups (15 patients each) was generated by a computer-generated random number table and was sealed in opaque envelopes that were opened by an anesthetist not involved in the intra- or postoperative care of the parturient.

- **G_C** (n = 15): control group received three placebo capsules which are empty capsules similar to those of gabapentin 300 mg.
- **G_{600}** (n = 15): gabapentin 600 mg group received two capsules of gabapentin 300 mg and third empty one similar to gabapentin.
- **G_{900}** (n = 15): gabapentin 900 mg group received three capsules of gabapentin 300 mg.

The study medication was given by mouth with a sip of water one hour before the anticipated time of the surgical incision.

The medication was administered by the anesthetist, who also performed the subsequent assessment.

The investigator was blinded to group assignment until all women had been recruited and assessments were completed.

No other premedication was given at this time.

Preoperative evaluation for all groups included a detailed history, physical examination and investigations (hemoglobin level, platelet count, random blood glucose, serum creatinine, liver function tests, prothrombin time (PT) and international normalized ratio (INR)). (All patients were instructed in the use of numerical rating scale by the investigator.)

Preparation of the drugs for spinal anesthesia: Lidocaine 2% (Xylocaine), Bupivacaine (heavy marcaine), and fentanyl, spinal needles, Sterilized towels and gauze, povidone iodine for sterilization, Syringes and adhesive tape, appropriate sizes of tracheal tubes, laryngoscopes with long and short blades, oxygen source and Disposable face mask were prepared for any possible intervention. Also Atropine 1 mg/ml, diluted with saline to a concentration of 0.1 mg/ml, and Ephedrine hydrochloride (Ephedrine) 30 mg/ml, diluted with saline to concentration of 3 mg/ml. And general anesthetics as standby for any complications.

- On arrival to the operating room all patients were continually monitored by automated noninvasive blood pressure monitoring (NIBP), pulse oximetry and 5 leads electrocardiography (ECG).
- Pre induction baseline reading for patient's hemodynamic state (mean blood pressure (MBP), heart rate (HR) and saturation (spo2)) was recorded for all groups.
- An 18 G intravenous cannula was inserted in an appropriate vein and a preload of 10 ml/kg Ringer's lactate was started, along with antibiotic prophylaxis.
- Then the parturient was supported to be in the sitting position for preparation for the administration of the spinal anesthesia. Complete aseptic precautions including sterilization with povidone iodine and draping were performed. The L4/L5 intervertebral space was located. Using a size 22 G hypodermic needle, the skin overlying the intervertebral space identified was anaesthetized with 3 mL of 2% lidocaine. Lumbar puncture was performed through a midline approach using a 25G spinal needle and 8 mg bupivacaine with 25 μg fentanyl was administered intrathecally; then, the patient was positioned supine with 15° left lateral tilt.
- When satisfactory spinal anesthesia (adequate sensory and motor blockade) achieved surgeon was allowed to start.
- At the end of surgery all patients were transferred to post anesthesia care unit (PACU) where they were observed for the following:
  (1) The time to first postoperative rescue analgesic request, the number of doses was recorded as well as total duration of analgesia (defined as time elapsed from the onset of spinal anesthesia to time of first call for analgesics), which was assessed by a numerical rating scale (NRS) a scoring system used by the patient, the patient put a mark on a horizontal line which reads "no pain at all" at one end at 0, and "worst pain imaginable" at the other end at 10 and recorded initially every 2 h for the first 10 h and then after every 4 h till 24 h. If NRS $\geqslant$ 4, intravenous meperidine (pethidine) 1 mg/kg intramuscular was given as rescue analgesia (repeated if needed during the first 24 h postoperatively), the number of doses and total analgesic requirement was recorded.
  (2) The incidence of postoperative nausea and vomiting (PONV) and nausea severity: for each patient was assessed by the simplified PONV impact scale which uses the nausea ordinal response to quantify nausea intensity, where (i) 0, (ii) 1, (iii) 2, (iv) 3 and the vomiting count to quantify vomiting intensity, scored as the number of vomits (0–2, or 3 if three or more vomits). When PONV impact scale $\geqslant$ 5→ Ondansteron (Zofran), 4 mg and Ranitidine (zantac), 50 mg was administered to the patient.
  (3) The level of sedation was assessed at 3 h intervals for the first 12 h and then every 6 h for the next 12 h postoperatively by using the modified Ramsay Sedation Score.

2.1. Ramsay sedation score

Score responsiveness

1 Patient is anxious and agitated or restless, or both.

2 Patient is cooperative, oriented and tranquil.
3 Patient responds to commands only.
4 Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.
5 Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6 Patient exhibits no response.

(4) Neonatal APGAR score at 1 and 5 min: was recorded, which is a quick test performed at 1 and 5 min after birth to determine the physical condition of the newborn.

2.1.1. Sample size (number of participants)

Power analysis was performed using one way ANOVA test for independent samples on VAS because it was the main outcome variable in the present study. A previous study was conducted for Gabapentin in CS3 showed that the standard deviation of VAS was about 15 in control group with a mean 41, and standard deviation of VAS was 15 in gabapentin group with mean 21. Taking power 0.8 and alpha error 0.025, a minimum sample size of 11 patients was calculated for each group. A total of patients in each group 15 were included to compensate for possible dropouts.

2.2. Statistical analysis

- Categorical data were presented as frequency (%) and analyzed using chi-square test.
- Continuous data were presented as Mean ± Standard deviation and analyzed using a paired *t*-test.
- Repeated measures were analyzed by ANOVA.
- P value less than 0.05 was considered significance.

3. Results

Forty-five patients were enrolled in, completed the study protocol and were included in the data analysis. Failed spinal anesthesia and conversion to general anesthesia were encountered in two cases from control group (G_C) which were replaced by another two cases to complete the sample size. Demographic characteristics in all three groups did not show any statistically significant difference (*P* value > 0.05) (Table 1).

All patients labs were normal regarding hemoglobin level, platelet count, random blood glucose, serum creatinine, liver function tests, prothrombin time (PT), prothrombin concentration (PC), and international normalization ratio (INR).

Comparing the outcome of the three groups:

All patients in the three groups remained hemodynamically stable with no statistically significant difference.

As regards postoperative NRS

(a) *Two hours postoperative:* There was statistically significant decrease in groups G_{600} and G_{900} as compared to group G_C (*P* value = 0.001), additionally, when comparing between G_{600} and G_{900} there was statistically significant decrease in groups G_{900} as compared to group G_{600} (*P* value = 0.001).

(b) *Four hours postoperative:* There was statistically significant decrease in groups G_{600} and G_{900} as compared to group G_C (P value = 0.001). Additionally, when comparing between G_{600} and G_{900} there was statistically significant decrease in groups G_{900} as compared to group G_{600} (P value = 0.001).

(c) *Six hours postoperative:* There was statistically significant decrease in group G_C when compared to groups G_{900} and G_{600} (P value = 0.0122). However, there was no statistically significant difference in group G_{900} as compared to group G_{600}.

(d) *Eight hours postoperative:* There was no statistically significant difference either when comparing G_C with G_{600} or G_{900} or when comparing between G_{600} and G_{900} (*P* value = 0.575).

(e) *Ten hours postoperative:* There was statistically significant decrease in groups G_{600} and G_{900} as compared to group G_C (*P* value = 0.022). Additionally, when comparing between G_{600} and G_{900} there was statistically significant decrease in groups G_{900} as compared to group G_{600} (*P* value = 0.022).

(f) *Fourteen hours postoperative:* There was statistically significant decrease in group G_{900} as compared to group G_C (*P* value = 0.025), additionally, when comparing between G_{600} and G_{900} there was statistically significant decrease in groups G_{900} as compared to group G_{600} (*P* value = 0.025). However, by comparing G_{600} group with G_C group there was no statistically significant difference.

(g) *Eighteen hours postoperative:* There was statistically significant decrease in group G_{900} as compared to group G_C. Additionally, when comparing between G_{600} and G_{900} there was statistically significant decrease in groups G_{900} as compared to group G_{600} (*P* value = 0.003). However, by comparing G_{600} group with G_C group there was no statistically significant difference.

(h) *Twenty-four hours postoperative:* There was no statistically significant difference when comparing each group of the three groups with each other (*P* value = 0.003). By comparison of the means of pain scores between the three groups we found that it was lowest in G_{900} group as compared to G_{600} which showed lower values than G_C i.e. $G_{900} < G_{600} < GC$ (Table 2 and Fig. 1).

By studying the total duration of analgesia we found that there was statistically significant difference in G_{900} group more than G_{600} and control group when both groups were compared to the control group ($p < 0.001$) and in addition, when G_{900} group and G_{600} group were compared together, there was statistically significant increase in the total duration of analgesia ($p < 0.001$) (Table 3 and Fig. 2).

As regards the frequency of pethidine doses administration in first 24 h, as an analgesic to cover the rest of the 24 h of the study, we found that the control group needed about 49 pethidine doses given to the fifteen patients as 11 patients needed three doses and 4 patients needed four doses of pethidine to cover the rest of 24 h of the study.

Table 1
The demographic profile of patients in the three groups.

Demographic profile	G_C (n = 15)	G_{600} (n = 15)	G_{900} (n = 15)	p-value
Age (years)	27.3 ± 5.5	28.2 ± 4.7	26.2 ± 4.2	0.530
Weight (kg)	84.8 ± 14.4	80.7 ± 16.9	83.0 ± 13.3	0.754
Height (cm)	160.3 ± 4.6	159.9 ± 3.7	160.4 ± 3.0	0.931
Gestational age (week)	38.1 ± 1.0	38.3 ± 1.1	38.4 ± 1.2	0.751

Numerical data were expressed as mean ± SD.
p value > 0.05 was considered insignificant.

Table 2
Numerical rating scale.

NRS	G_C (n = 15)	G_{600} (n = 15)	G_{900} (n = 15)	P_1 value P_2 value
NRS 1 h	2.9 ± 0.96	2.7 ± 1.03	1.4 ± 0.98[a]	0.001 (0.613)
NRS 2 h	5.1 ± 0.34	2.9 ± 0.52	1.7 ± 0.74[a,b]	0.001[a] (<0.001) [b]
NRS 3 h	2.2 ± 1.12	2.4 ± 1.21	2.1 ± 0.97	0.748 (0.457)
NRS 4 h	3 ± 0.5	2.7 ± 0.25	2.3 ± 0.42[a]	0.013[a] (0.113)
NRS 5 h	2.6 ± 1.2	2.9 ± 0.79	2.4 ± 0.32[b]	0.279 (0.031) [b]
NRS 6 h	2.9 ± 0.9	4.2 ± 0.81	2.8 ± 1.1[a,b]	0.001[a] (0.005) [b]
NRS 8 h	4.3 ± 0.74	2.3 ± 1.4[a,b]	4.0 ± 0	0.002[a] (0.000) [b]
NRS 12 h	2.3 ± 1.6	3.0 ± 0.80	2.1 ± 1.2[b]	0.128 (0.022) [b]
NRS 16 h	4.5 ± 1.2	2.7 ± 0.32	2.2 ± 1.4[a]	0.001[a] (0.188)
NRS 20 h	2.4 ± 1.51[a]	2.9 ± 0.89[b]	4.7 ± 0.37	0.000[a] (0.001) [b]
NRS 24 h	5.2 ± 0.82	3.0 ± 0.72	2.1 ± 0.75[a,b]	0.001[b] (0.002) [b]

Numerical data were expressed as mean ± SD.
P value < 0.05 was considered statistically significant.
(P_1 value = comparing both G_{600} and G_{900} with control group, P_2 value = between group G_{600} and group G_{900}).
[a] Denotes statistical significance compared to the control group (group C).
[b] Denotes statistical significance compared to the group G_{600}.

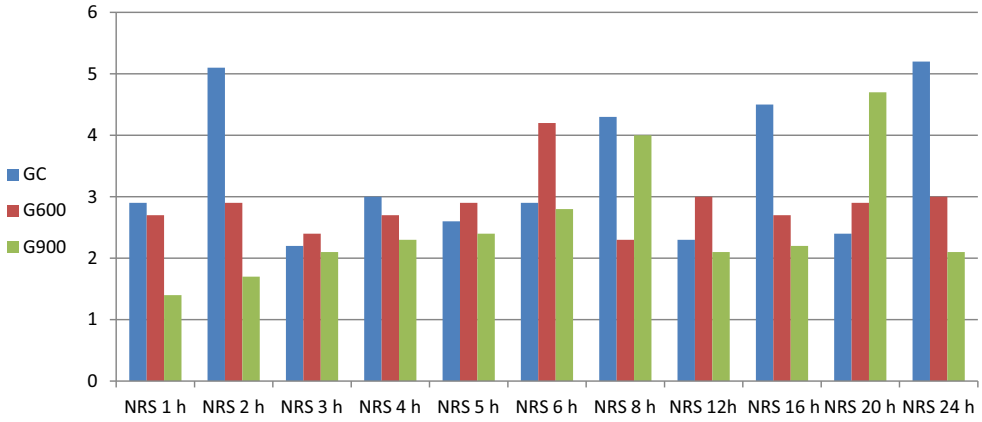

Figure 1. Numerical rating scale.

Table 3
Total duration of analgesia.

Total duration of analgesia (h)	G_C (n = 15)	G_{600} (n = 15)	G_{900} (n = 15)	P1 value	P2 value
Total duration of analgesia (h)	2.3 ± 0.25	6.9 ± 0.45	8.9 ± 0.8[b,a]	0.001 [a]	0.001[b]

Numerical data are given in mean ± SD.
P value < 0.05 was considered statistically significant (P_1 value = comparing both G_{600} and G_{900} with control group, P_2 value = between group G_{600} and group G_{900}).
[a] Denotes statistical significance compared to the control group (G_C).
[b] Denotes statistical significance compared to the group G600.

In group G_{600} they needed 33 pethidine doses distributed in the form of 12 patients asked for two consecutive doses while only 3 patients asked for three doses, to cover the study time.

However, group G_{900} needed only 24 doses of pethidine as 6 patients from 15 asked for an extra one dose while the other 9 patients asked for extra two doses (Table 4 and Fig. 3).

3.1. Regarding sedation score

By comparing the sedation scores of the two groups in 24 h with the control group as a reference value, we found that there was statistically significant increase in the sedation scores of the patients in the G_{900} group as compared to G_C group and G_{600} group

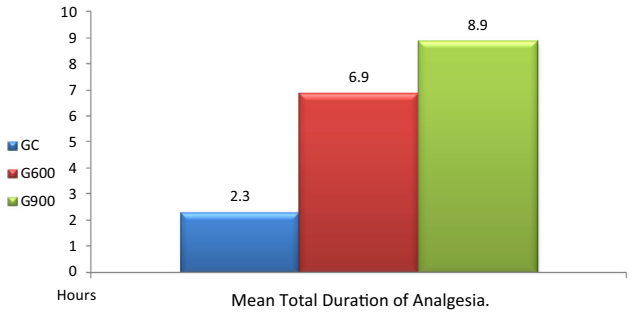

Figure 2. Mean total duration of analgesia.

Table 4
Postoperative analgesic requirements.

Postoperative analgesic requirements	G_C (n = 15)	G_{600} (n = 15)	G_{900} (n = 15)
One dose	–	–	6 (40%)
Two doses	–	12 (80%)	9 (60%)
Three doses	11 (73%)	3 (20%)	–
Four doses	4 (27%)	–	–
Total no. of pethidine doses	49	33	24

Numerical data were presented as no. (%).

especially at 6 h, 9 h, and 12 h with p value (0.008, 0.045, and 0.049) respectively, However there was no statistically significant difference was observed between control group and G_{600} group over the whole spectrum of the intraoperative and postoperative assessment duration having score of 1 or 2 (P > 0.05) (Table 5).

Regarding postoperative nausea and vomiting: By comparing the presence of nausea and vomiting in the two gabapentin groups (G_{600} and G_{900}) with the control group as a reference value, and with each other in the intraoperative and postoperative periods, we found that there was statistically significant decrease in the nausea score in the G_{900} group as compared to groups G_{600} and G_C with p value (0.06 and 0.4) respectively.

Additionally, the presence of vomiting was lower in the gabapentin groups G_{600} and G_{900}) as compared to the control group (G_C) which showed statistically significant decrease with p value (0.4 and 0.2) respectively (Table 6).

Regarding neonatal outcome all the babies delivered had Apgar scores ⩾ 7 and ⩾ 9 in the first and fifth minutes, respectively in the three study groups with no statistical difference (P > 0.05) (Table 7).

4. Discussion

Pain is the worst fear of women undergoing Cesarean delivery [11] and post Cesarean delivery pain hinders the mother's ability to care for and feed her newborn infant. Systemic and neuraxial opioid medications, nonsteroidal anti-inflammatory drugs, and acetaminophen, often in combination, are used to treat pain in this population; however, they do not completely relieve post Cesarean delivery pain, and have the potential for serious adverse reactions [12]. The perioperative use of gabapentin has been shown to decrease acute pain after various surgical procedures.

The concept of an antinociceptive treatment with analgesics to reduce postoperative pain which is called preemptive analgesia was founded on a series of successful experimental studies that demonstrated central nervous system plasticity and sensitization after nociception [13]. On the other hand, a recent quantitative analysis of evidence from RCTs was supportive for the use of preoperative gabapentin in PONV prophylaxis, especially in abdominal surgeries [14,15].

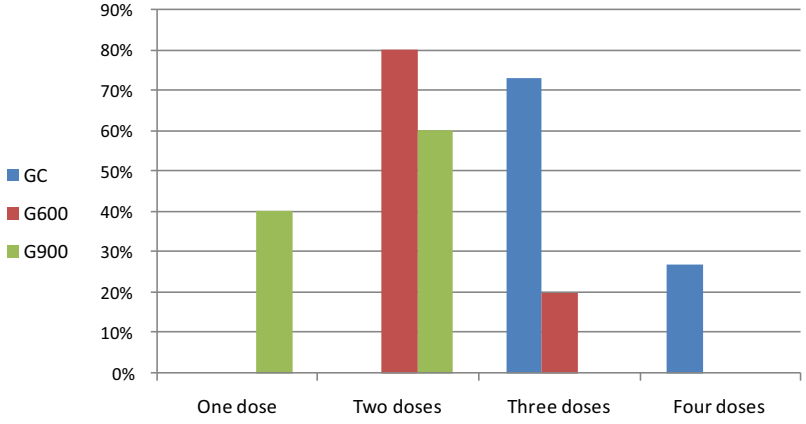

Figure 3. Postoperative analgesic requirements.

Table 5
Ramsey sedation scores.

RSS	G_C (n = 15)	G_{600} (n = 15)	G_{900} (n = 15)	*P* value
Sedation 1 h	1.4 ± 0.51	1.3 ± 0.49	1.6 ± 0.63	0.388
Sedation 3 h	1.3 ± 0.41	1.2 ± 0.47	1.5 ± 0.63	0.378
Sedation 6 h	1.2 ± 0.41	1.4 ± 0.51[a]	1.87 ± 0.74[a]	0.008
Sedation 9 h	1.2 ± 0.46	1.52 ± 0.49[a]	1.9 ± 0.80[a]	0.045
Sedation 12 h	1.33 ± 0.52	1.6 ± 0.51[a]	1.7 ± 0.594[a]	0.049
Sedation 18 h	1.67 ± 0.48	1.67 ± 0.62	1.47 ± 0.52	0.513
Sedation 24 h	1.7 ± 0.46	1.5 ± 0.54	1.6 ± 0.51	0.534

Numerical values are given in median and inter quartile range.
[a] Denotes statistical significance compared to the control group (group G_C).

Table 6
Comparing the presence of nausea and vomiting of the two groups with the control group as a reference value and to each other.

	Group C (n = 15)	Group G600 (n = 15)	Group G900 (n = 15)	P value
Nausea	0.4 ± 0.6	0.06 ± 0.2	0[a]	0.018
Vomiting	1.2 ± 1.2	0.4 ± 0.7[a,b]	0.2 ± 0.4[a,b]	0.008

Numerical data are presented as mean ± SD.
[a] Denotes statistical significance compared to the control group (group G_C).
[b] Denotes statistical significance compared to the group G_{600}.

Table 7
APGAR SCORE at 1 and 5 min.

	Group C (n = 15)	Group G600 (n = 15)	Group G900 (n = 15)	P value
APGAR (1 min)	9 ± 1	9 ± 1	9 ± 1.4	0.9
APGAR (5 min)	9.9 ± 0.2	9.8 ± 0.3	9.8 ± 0.5	0.8

Apgar score is given as median and range.

In this study that was double blinded randomized controlled clinical trial between two regimen doses of gabapentin 600 mg and 900 mg were given one hour before Cesarean section delivery under spinal anesthesia, in comparison with studies of other investigators who have compared gabapentin 600 mg with either 300 mg or placebo, we aimed at identifying the dose with the best effect and the least side effects.

By comparing the outcome of group GC (control group), Group G600 and group G900), we compared the effect of oral premedication with two different doses of gabapentin on postoperative maternal outcome such as, pain scores, total analgesic duration, total amount of opioid consumption, incidence of postoperative nausea and vomiting, sedation level, and neonatal outcome by Apgar score at 1, and 5 min.

Regarding the postoperative numerical rating scale we found that there was significant decrease in postoperative pain numerical scale at two hours, four hours, ten hours, fourteen hours, and eighteen hours postoperative in the both gabapentin groups (G600 and G900) as compared to control group (GC) with p = 0.001, 0.001, 0.122, 0.022, 0.025, 0.003 respectively. On consistency with our results, Moore et al. [16] who concluded that preoperative gabapentin 600 mg in the setting of multimodal analgesia reduces post Cesarean delivery pain and increases maternal satisfaction in comparison with placebo. Hurley et al. [17] concluded that the oral administration of gabapentin to patients was effective for acute postoperative pain, and Alparslan et al. [18] concluded that preoperative oral gabapentin decreased pain scores in the early postoperative period. Tiippana et al. [19] concluded that gabapentin effectively reduces postoperative pain. And also Sen et al. [20] found that gabapentin and ketamine are similar in improving early pain control; however, gabapentin also prevented chronic pain in the first 6 postoperative months. On contrast with our results, Short [10] who compared gabapentin 300 mg and 600 mg by a randomized double-blind, placebo-controlled dose-finding trial and could not determine whether a single preoperative dose of gabapentin (300 mg and 600 mg) improved post Cesarean analgesia compared to Placebo which may be explained by different sample size calculation. As regards time elapsed to start analgesia according to patients request and total supplemental pethidine requirements in the first 24 h, in our results the time for rescue analgesia was comparatively shorter in patients of group GC as compared to G600 and G900 groups who experienced prolonged pain free period and overall pain scores were lower with $P = 0.001$ while the difference in time to rescue analgesia between the two gabapentin groups was statistically insignificant (P value > 0.05). Also regarding total analgesic requirement of pethidine in first 24 h, it was significantly lower in groups G600 and G900 as compared to group GC ($P = 0.001$) while the difference in total analgesic requirement between groups G600 and G900 was statistically insignificant (P value > 0.05). On consistency with our results, Clivatti et al. [21] stated that gabapentin, used before as well as after surgery, decreased pain severity and the need of analgesic supplementation. Peng et al. [22] stated that gabapentin improves the analgesic efficacy of opioids both at rest and with movement.

Regarding postoperative nausea and vomiting, there was statistically significance decrease in the nausea score in the G900 group as compared to groups G600 and GC with p = 0.06 and 0.4 respectively. Additionally, the presence of vomiting was lower in the gabapentin groups (G600 and G900) as compared to the control group (GC) which showed statistically significant decrease with p value 0.4 and 0.2 respectively. On consistency with our results, Henderson et al. [23] demonstrated a higher incidence of nausea and vomiting in the placebo group as compared to the group who received pre-incisional analgesics. Yuan-Yi et al. [24] demonstrated that the incidence of nausea and vomiting varied (10–54%) in patients receiving patient controlled intravenous analgesia (PCIA) with morphine for postoperative pain management after general anesthesia with pre-incisional and post-incisional analgesics. Furthermore, three RCTs that studied the gabapentin alone [15] or its combination with dexamethasone [22] or rofecoxib [25] found a significant reduction of PONV in gabapentin group compared to placebo. However in contrast to our results, Dauri et al. [26] evaluated the effect of gabapentin and pregabalin on postoperative pain management and its effect on PONV and side effects such as dizziness and sedation and they concluded that it did not reduce PONV when compared with placebo but gabapentin and dexamethasone combination seems to have a synergic effect on reducing PONV in comparison with gabapentin or dexamethasone alone.

Our current study showed statistically significant increase in the sedation scores of the patients in the G900 group as compared to GC group and G600 group especially at 6 h, 9 h, and 12 h with p value of 0.008, 0.045, and 0.049 respectively. However there was no statistically significant difference was observed between control group and G600 group over the whole spectrum of the intraoperative and postoperative assessment duration. In consistency with our results, Henderson et al. [23] showed no difference in sedation scores among their groups. Also, Yuan-Yi et al. [24] stated that all patients could be easily aroused when visited, and there was no significant difference in sedation scores between the pre and postoperative analgesics groups. Irrespective of the dose these findings were in concordance with the results of study comparing 300 mg, and 600 mg Short [10], and the study comparing gabapentin

600 mg with placebo Moore et al. [16] as regards increase in maternal sedation (19% of women who received gabapentin experienced severe sedation), and contrasted with our results in the higher dose (900 mg) showed statistically significant difference while the lower dose of gabapentin (600 mg) had no statistically significant difference when compared with the control group and (2) mild level of sedation, only score of 1 or 2 at 6 h, 9 h, and 12 h. While in their results there was sever sedation level at 600 mg dose all over 48 h postoperatively, these differences between their results and ours may be due to the use of multimodal analgesics with gabapentin or the sedation scores used (high versus low) the ordinal nature of the sedation response, and the use of no validated score to assess sedation may led to unreliable sedation results of the study.

Furthermore, in contrast with ours Hatice et al. [25] concluded that the administration of gabapentin to patients may lead to side effects such as delayed increased sedation postoperatively. Also on contrast with Peng et al. [22] who stated that gabapentin is associated with an increased incidence of sedation and dizziness. Hatice et al. [25] found that the administration of gabapentin to patients undergoing craniotomy for supra tentorial tumor resection may lead to side effects such as delayed tracheal extubation and increased sedation postoperatively. We did not observe any potential effects of gabapentin on the neonates by Apgar scores at 1 and 5 min post-delivery in both groups of gabapentin which are consistent with the neonatal outcomes observed in the previous two studies. Although Gabapentin use in the pregnant population has been documented with no increased risk for fetal or neonatal outcomes, our study was not allowed to give firm conclusion about safety for maternal administration of gabapentin.

5. Limitation

The limitation of this study was low recruitment rate due to maternal refusal to take any drug that might harm the fetus and refusal of some obstetrician as they didn't recommend the gabapentin use for pregnant population.

6. Recommendation

Our results are encouraging about efficacy but larger sample sizes are recommended to determine optimal time for the drug administration and assess safety and the side effects of gabapentin in these population.

7. Conclusion

Higher dose of gabapentin 900 mg was more effective than 600 mg in reducing post Cesarean section pain, postoperative opioid consumption, nausea, and vomiting in the early postoperative period. However it was associated with increasing maternal sedation, but without any effect on neonatal outcome.

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