Original Research Article

Prospective comparative study of preoperative use of oral gabapentin with and without intravenous dexamethasone for postoperative pain, nausea and vomiting in patients undergoing cesarean section under spinal anaesthesia

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A R T I C L E  I N F O

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A B S T R A C T

Postoperative pain, nausea and vomiting remain the most common and unpleasant complications in women undergoing cesarean delivery, in turn hindering the mother’s ability to care for the newborn and herself. Traditional methods to alleviate pain such as systemic and neuraxial opioids, nonsteroidal anti-inflammatory drugs, often in combination, are used to treat pain in this population, but are found to be less effective and associated with adverse outcomes. Similarly various antiemetic agents alone or in combination have been tried to reduce the incidence of nausea and vomiting.

Gabapentin, is a structural analogue of neurotransmitter GABA (gamma amino butyric acid) and acts on the same receptors. It binds to α2δ subunit of the spinal voltage gated calcium channel and decreases the release of excitatory neurotransmitters.1 Initially introduced as an antiepileptic drug, it’s proven to be effective in treatment of acute and chronic pain extending into the perioperative period. The analgesic effects of steroids is through peripheral inhibition of phospholipase enzymes which decreases the products of the cyclooxygenase and lipoxygenase pathways in the inflammatory response.2

The efficacy and safety of preoperative oral Gabapentin and intravenous Dexamethasone, individually on postoperative pain, nausea and vomiting were studied in patients undergoing a variety of surgical procedures including cesarean section. But there are no studies to show its combined efficacy in cesarean section. Our aim is to compare preoperative use of oral gabapentin with and without intravenous dexamethasone in patients undergoing cesarean section under spinal anesthesia regarding postoperative pain, nausea and vomiting.

2. Materials and Methods

This study was conducted on inpatients at hospitals attached to Bangalore Medical College and Research Institute, Bangalore, between July 2018 to September 2018. After obtaining approval by the Hospital ethical committee and CTRI approval (CTRI/2019/04/018708), written informed consent and routine pre anesthetic evaluation, a total of 60 women aging 18–40 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 comparative study. However, patients with contraindication to neuraxial anesthesia, patients known to be epileptic or on antiepileptic medications, allergic to dexamethasone, opioids and local anesthetics, patients with kidney or liver function impairment, patients known to be alcoholic or IV drug abusers, pregnancies with any obstetric complications such as hypertension, oligohydramnios, polyhydramnios, antepartum hemorrhage, any psychiatric disorder or unable to give consent and emergency cesarean delivery were excluded from the study.

Patients were divided into 2 groups, using computerized program for randomization. Sealed envelope method is followed for allocation concealment which is opened by anesthetist not involved in the intra and postoperative care of the patient. 60 patients will be randomly allocated into two different groups of 30 each as described below.

Group A (n=30): Received Gabapentin 600mg- two capsules of gabapentin 300mg.

Group B (n=30): Received Gabapentin 600mg- two capsules of gabapentin 300mg + I.V Dexamethasone 4mg.

All patients were subjected to routine pre anesthetic evaluation, which included detailed history, general physical examination, systemic examination and routine investigations such as complete blood count, random blood sugar, liver function test, renal function test, electrocardiography (ECG), serum electrolytes, prothrombin test (PT) and international normalized ratio (INR). All patients were briefed about the use of Numerical Rating Scale (NRS).

All patients to be kept fasting overnight, patients will be given Tablet Alprazolam 0.5mg and Tablet Ranitidine 150mg on the previous night of surgery. The study medication was given by mouth with a sip of water, approximately one hour before the anticipated time of the surgical incision. I.V Dexamethasone was administered just before induction of anesthesia. The medication was administered by the anesthetist, who also performed the subsequent assessment. No other premedication was given at this time.

2.1. Anesthetic procedure

Preparation of the drugs for spinal anesthesia: Lidocaine 2% (Xylocaine), Bupivacaine (heavy), Fentanyl, spinal needles, Sterilized gauze, povidone iodine for sterilization, syringes. 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 6 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 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. Then the parturient was positioned in the left lateral position for the administration of the spinal anesthesia.

Complete aseptic precautions including sterilization with povidone iodine and draping were performed. The L3/L4 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 12.5 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) is achieved, surgeon was allowed to start.

At the end of surgery all patients were observed for the following:

A) 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) Figure 1, 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 ≥ 4, intravenous Inj Paracetamol 1gm is given as rescue analgesia (repeated if needed during the first 24 h postoperatively), the number of doses and total analgesic requirement was recorded.

B) Postoperative nausea and vomiting (PONV) severity was assessed by simplified PONV impact scale which uses the nausea ordinal response to quantify nausea intensity, scored as the number of vomits (0 – 2, or 3 if three or more vomits). When PONV impact scale ≥ 5, Ondansetron 4 mg was administered.

PONV Impact Scale Score-

![Fig. 1:](image-url)
Q1. Have you vomited or had dry-retching?

1. No
2. Once
3. Twice
4. Three or more times

Q2. Have you experienced a feeling of nausea ("an unsettled feeling in the stomach and slight urge to vomit")? If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally, or eating and drinking?

1. Not at all
2. Sometimes
3. Often or most of the time
4. All of the time.

To calculate the PONV Impact Scale score, add the numerical responses to questions 1 and 2. A PONV Impact Scale score of ≥ 5 defines clinically important PONV.

C) 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.

2.2. Sample size

Based on previous study of Hafez MHES et al, NRS score in Gabapentin 600mg group was 2.9±0.52 at 2 hours postoperatively and assuming equal variance and expecting minimum difference between 2 groups as 0.4, sample size is 26.4.

Therefore, n= 30 in each group with total of 60 patients.

2.3. Statistical analysis

Data will be exported into SPSS version 21.0. p < 0.001 will be considered statistically significant.

3. Results

60 patients completed the study and were included in the data analysis. Demographic characteristics in both the groups did not show any statistically significant difference (P value > 0.001). Routine investigations of all groups were within normal limits. All patients remained hemodynamically stable with no statistically significant difference.

3.1. Comparing the outcome of the two groups

With regards to postoperative NRS – By comparing the pain scores of the two groups at 2, 4, 6, 8, 10, 14, 18 and 22 hr postoperatively, it revealed that there was significant difference between group A and group B after 6hr postoperative period (p value < 0.001).

With respect to the mean duration of analgesia, in Group A it was 5.33±1.09 hrs whereas in Group B it was 8.27±1.14 hrs. The difference was statistically significant (p<0.001) between both the groups with group B providing superior analgesia in 24 hr postoperative period.

By comparing the number of Paracetamol doses administered in the first 24 hours, Group A required about 63 doses- 25 patients required 2 doses, while 4 patients required 3 doses and 1 patient required single dose.

Group B required about 38 doses- 22 patients required a single dose, while 8 patients required 2 doses.

Hence overall analgesic requirement was more in Group A compared to Group B

With respect to presence of postoperative nausea and vomiting, no statistically significant difference was found between Group A and Group B in terms of PONV impact scale score. (p- 0.309)

By studying the neonatal outcome, there was no statistically significant difference with regards to APGAR score at 1 min and 5 mins between both the groups. (p>0.001)

4. Discussion

Pain is the most dreaded outcome of women undergoing cesarean delivery, hindering the new mother’s ability to care for her newborn and herself. Nausea and vomiting is another complication associated with cesarean delivery. Traditional methods to alleviate pain such as systemic and neuraxial opioids, nonsteroidal anti-inflammatory drugs, often in combination, are used to treat pain in this population, but are found to be less effective and associated with adverse outcomes.

Gabapentin has been used for the treatment of chronic pain conditions, with its use been extended to treat acute pain conditions including peri-operative period.

The concept of preemptive analgesia, which means use of analgesics before surgery in order to prevent post-operative pain by preventing the central nociceptive sensitization, is gaining popularity in the recent times.

Postoperative pain is not purely nociceptive in nature and may consist of inflammatory, neurogenic and visceral components. Therefore, multimodal approach for treating postoperative pain by using a number of drugs acting via different mechanisms is used.

In this prospective comparative double blinded study, oral gabapentin 600mg was given 1 hour prior to cesarean section under spinal anesthesia in both the groups with one group receiving inj dexamethasone 4mg intravenously, just before incision. The effect of premedication on postoperative maternal outcomes such as pain, total duration of analgesia, requirement of opioids, postoperative nausea and vomiting and neonatal outcome based on APGAR score at 1 min and 5 mins was compared.

Based on numerical rating scale (NRS) we found that there was significant decrease in pain scores at 2, 4, 6,
Table 1:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>0 Point</th>
<th>1 Point</th>
<th>2 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Absent</td>
<td>Flexed arms and legs</td>
<td>Active</td>
</tr>
<tr>
<td>Pulse</td>
<td>Absent</td>
<td>Below 100bpm</td>
<td>Over 100 bpm</td>
</tr>
<tr>
<td>Grimace</td>
<td>Floppy</td>
<td>Minimal response to stimulation</td>
<td>Prompt response to stimulation</td>
</tr>
<tr>
<td>Appearance</td>
<td>Blue; Pale</td>
<td>Pink body, blue extremities</td>
<td>Pink</td>
</tr>
<tr>
<td>Respiration</td>
<td>Absent</td>
<td>Slow &amp; Irregular</td>
<td>Vigorous cry</td>
</tr>
</tbody>
</table>

Table 2:

<table>
<thead>
<tr>
<th></th>
<th>Group A (n= 30)</th>
<th>Group B (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.27 ± 4.34</td>
<td>24.63 ± 3.80</td>
</tr>
<tr>
<td>Weight</td>
<td>70.77 ± 12.25</td>
<td>74.57 ± 9.66</td>
</tr>
<tr>
<td>Gestational age</td>
<td>37.47 ± 1.73</td>
<td>37.87 ± 1.25</td>
</tr>
</tbody>
</table>

Table 3: Numerical Rating Scale

<table>
<thead>
<tr>
<th>NRS</th>
<th>Group A (n= 30)</th>
<th>Group B (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS 2 HR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NRS 4 HR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NRS 6 HR</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>NRS 8 HR</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NRS 10 HR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NRS 14 HR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NRS 18 HR</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NRS 22 HR</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4: Postoperative Analgesic requirement

<table>
<thead>
<tr>
<th>Postoperative analgesic requirements</th>
<th>Group A (n= 30)</th>
<th>Group B (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One dose</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Two doses</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Three doses</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Total no of doses</td>
<td>63</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 5: Presence of nausea and vomiting based on PONV impact scale score

<table>
<thead>
<tr>
<th>PONV impact scale score</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10± 0.30</td>
<td>0.03± 0.18</td>
<td>0.309</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: APGAR score at 1 min and 5 mins

<table>
<thead>
<tr>
<th>APGAR score</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>9.63± 0.49</td>
<td>9.80± 0.40</td>
<td>0.157</td>
</tr>
<tr>
<td>5 mins</td>
<td>9.93± 0.25</td>
<td>9.90± 0.30</td>
<td>0.647</td>
</tr>
</tbody>
</table>

10, 18 and 22 hours in gabapentin with dexamethasone group compared with gabapentin alone. This was similar to the findings of Agarwal N et al, who concluded that combination of oral gabapentin with I.V dexamethasone has better postoperative analgesia and less incidence of PONV than individual administration of each drug in gynaecological procedure. Moore et al concluded that gabapentin 600mg preoperatively decreases acute post cesarean delivery pain and improves maternal satisfaction. Cardoso M et al concluded that dexamethasone is associated with lower pain scores in the first postoperative day. In contrast to our study, Short et al concluded that a single perioperative dose of gabapentin does not improve post cesarean pain management. With regards to total duration of analgesia, rescue analgesic requirements in 24 hrs, there was statistically significant difference between the two groups with oral gabapentin with I.V dexamethasone group having prolonged duration of analgesia and reduced analgesic requirements compared to oral gabapentin group.
Gabapentin, is a structural analogue of neurotransmitter GABA (gamma amino butyric acid) and acts on the same receptors. It binds to α2δ subunit of the spinal voltage gated calcium channel and decreases the calcium influx, which decreases the release of glutamate and substance P (excitatory neurotransmitters) from primary nociceptive afferents, thereby modulating nociceptive transmission. Antiemetic effect is by mitigation of tachykinin neurotransmitter activity. Although the trans placental transfer of gabapentin does occur, no increased risks for adverse fetal or neonatal outcomes have been attributed to its use.

The analgesic effects of steroids are through peripheral inhibition of phospholipase enzymes which decreases the products of the cyclooxygenase and lipoxygenase pathways in the inflammatory response. Dexamethasone modulates neurotransmitter or glucocorticoid receptor density in the nucleus of the solitary tract, the raphenucleus and the area postrema thereby exerting its antiemetic effect. Dexamethasone crosses the placenta to the fetus and is excreted in the breast milk, without any adverse outcomes.

Based on Postoperative nausea and vomiting impact scale score, no statistically significant difference was found in the incidence of nausea and vomiting between the two groups. But in the previous randomized control trials, the incidence was lesser when compared to placebo groups. Achuthan et al concluded that, preoperative oral gabapentin was effective in preventing PONV in patients undergoing abdominal surgeries. Wang et al concluded that the prophylactic IV administration of dexamethasone immediately before the induction, rather than at the end of anesthesia, was more effective in preventing PONV.

Based on APGAR score at 1min and 5 mins, no statistically significant difference was found in neonatal outcome between the two groups. Results were consistent with the findings of Hafez MHES et al, who concluded that both oral gabapentin 900mg and 600mg were not associated any potential effects on the neonatal outcome.

5. Conclusion

Combination of Oral Gabapentin with I.V Dexamethasone is found to have superior analgesia compared to oral gabapentin alone in first 24 hrs postoperatively with reduced analgesic requirement and prolonged duration of analgesia. Both are effective in reducing nausea, vomiting in the early postoperative period without adverse neonatal outcome.

6. Source of funding

None.

7. Conflict of interest

None.