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Study of efficacy and safety of premedication with oral pregabalin on postoperative analgesia in parturient women undergoing elective caesarean delivery

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Abstract

Aim: Parturient women suffer unpleasant debilitating pain, post-operatively following caesarean section. Providing adequate postoperative analgesia facilitates early ambulation, shortens hospitalization, and improves function of the mother to give better care to her New-born. Hence in our study we evaluate the effect of pre-operative single oral dose pregabalin on post-caesarean pain, cumulative analgesic consumption and its safety profile.
Materials and Methods: 60 pregnant women posted for elective caesarean section were randomised into two groups, Pregabalin group (PREGABALIN, n=30) and Placebo group (PLACEBO, n=30). The study medication was given orally with a sip of water, approximately one hour prior to expected time of the surgical incision. Hemodynamic parameters, postoperative pain score by verbal numerical rating scale (NRS), time of first rescue analgesia, cumulative maternal analgesic requirement during first 24hrs, neonatal APGAR SCORE at 1 and 5 mins were evaluated. Adverse effects due to pregabalin if any due to use of pregabalin.
Results: Time to first rescue analgesic was prolonged in Pregabalin Group as compared to Placebo Group. Mean cumulative analgesic consumption was significantly lower ($p<0.0001$) in Pregabalin group as compared to Placebo group. Neonatal APGAR SCORE at 1 and 5 mins were similar in both groups.
Conclusion: Pre-emptively administered single oral 150mg dose of pregabalin provides excellent postcaesarean pain relief. It also resulted in decreased analgesic requirement and less postoperative nausea and vomiting (PONV) postoperatively in parturient women.

Keywords: Pregabalin, PONV, APGAR score, NRS

Introduction

Analgesia management in parturient women undergoing elective caesarean delivery is a vital concept of patient care in anesthesiology; as it serves the essential purpose of early ambulation, improves function of the mother to give care to her newborn.
The main aim of postoperative pain management is to minimize pain after caesarean delivery. Good pain relief will not only improve mobility but can also reduce the risk of incidence of events such as deep vein thrombosis, cerebrovascular accidents, myocardial ischaemia etc., which is increased during pregnancy [1].
The current concept of enhanced recovery programs incorporates multimodal analgesia

regimens comprising of combination of systemic and neuraxial opioid medications, NSAIDS, paracetamol, local anesthetic infiltration of wounds, transverse abdominis plane block and so on; used to manage pain in this population. However, they do not completely relieve post caesarean delivery pain, and have the potential for debilitating and serious adverse reactions [1].

Use of opioids is associated with adverse effects such as nausea, pruritus, excessive sedation, urinary retention, and occasionally respiratory depression [1].

Pregabalin is an anticonvulsant analgesic drug, a structural analogue of neurotransmitter gamma amino butyric acid (GABA). It exerts its action by presynaptic binding to α2δ subunit of the voltage gated calcium channels widely distributed in spinal cord and brain, thereby decreasing the calcium influx, which reduces the release of excitatory neurotransmitters such as glutamate, norepinephrine, calcitonin gene related peptide and Substance P from primary nociceptive afferents, thereby modulating nociceptive transmission, inhibiting hyperalgesia and central sensitization [8].

Previous studies have failed to prove significant postoperative analgesic effect of pregabalin, while Other previously reported studies convince pregabalin as an effective post-operative analgesic with opioid sparing effects.

With the above pretext, we intend to compare efficacy of single 150 mg oral dose of pregabalin and a placebo as pre-operative medication to assess post-operative pain relief in parturient women undergoing elective caesarean delivery under spinal anaesthesia while also studying adverse effects, if any due to pregabalin use.

Materials and Methods

The study was conducted on patients admitted in various hospitals attached to Bangalore Medical College and Research Institute. Our study is a Prospective randomized double-blind placebo-controlled study conducted on women aged 18-40 years, with uncomplicated pregnancy at term (>37 completed weeks), women belonging to American Society of Anaesthesiologists (ASA) I-II who are scheduled to undergo elective cesarean delivery under spinal anesthesia. The exclusion criteria included Patients with contraindication to neuraxial anesthesia, Patients known to be epileptics or on antiepileptic medications, Patients with deranged renal function tests or liver function tests, Pregnancies with obstetric complications like hypertension, oligohydramnios, polyhydramnios, antepartum hemorrhage, Patients with psychiatric disorder or unable to give consent, Patients scheduled to undergo emergency cesarean delivery, Patients who refused to give informed written consent.

Methodology

After obtaining approval by the Hospital ethics committee, written informed consent and routine pre anesthetic evaluation, patients were divided into two groups, using computerized program for randomization. The sealed envelope method was followed for allocation concealment which is opened by anesthetist not involved in the intra and postoperative care of the patient.

A proforma will be used to collect the data which includes patient's particulars, general physical examination, postoperative monitoring particulars, etc. In our study, 60 patients were randomly allocated into two groups of 30 each.

Pregabalin Group (n=30): Received oral pregabalin 150mg.

Placebo Group (n=30): Received an oral placebo.

All patients were kept fasting overnight, patients were given Tablet Alprazolam 0.5mg and Tablet Ranitidine 150mg on the previous night before surgery.

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

anesthetist, who also performed the subsequent assessment. No other premedication was administered.

Anesthetic procedure

On arrival to the operating room all patients were continually monitored by automated noninvasive blood pressure monitoring (NIBP), pulse oximetry and 5-lead electrocardiography (ECG). Pre induction baseline reading of patient's hemodynamic state was measured using mean blood pressure (MBP), heart rate (HR) and saturation (SpO2) in both groups. An 18-Gauge (G) intravenous cannula was inserted in a suitable vein and a preload of 10 ml/kg Ringer's lactate was administered. Then the parturient was supported to be in the left lateral position for preparation and for the administration of the spinal anesthesia.

Complete aseptic precautions including sterilization with povidone iodine and draping were undertaken. The skin overlying the L3/L4 intervertebral space was and 3 mL of 2% lidocaine was injected using a size 22-G hypodermic needle for anesthesia. Lumbar puncture was performed through a midline approach using a 25-G spinal needle and 8 mg bupivacaine was administered intrathecally. Then, the patient was positioned supine with 15º left lateral tilt. Surgeon was allowed to start once a satisfactory spinal anesthesia (adequate sensory and motor blockade) was achieved.

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

1) The time to first postoperative rescue analgesic request, the total number of doses, thetotal 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). Subsequently, this was recorded every 4 h for the first 12 h and then after every 6 h till 24 h. If NRS≥4, intravenous tramadol 50mg in 100ml Normal Saline (NS) was given as rescue analgesia (repeated if needed during the first 24 h postoperatively). In addition, The number of doses and total analgesic requirement were also recorded.
2) 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 (i) 0, (ii) 1, (iii) 2, (iv) 3 and the vomiting count to quantify vomiting intensity, scored as the number of vomiting episodes (0-2 or 3 if three or more vomiting episodes). When PONV impact scale≥5, Ondansetron 4 mg was administered.
3) Neonatal APGAR score at 1 and 5 min: was recorded (It is a quick test performed at 1 and 5 min after birth to determine the physical condition of the newborn).

STATISTICAL ANALYSIS

Statistical analysis of data or parameters will be done by descriptive statistics. Student T test will be used to find out significant difference between the groups. A Chi-square test will be used to compare categorical data between the groups. Data will be exported into SPSS version 21.0. $p<0.05$ will be considered statistically significant.

Results

It is a Comparative Prospective twogroup clinical study to evaluate the efficacy of single oral 150 mg dose of pregabalin and placebo as pre-operative medication to assess the post-operative pain relief in 60 elective caesarian delivery patients. There was no substantial difference among the groups regarding age, weight and hemodynamic parameters. Demographic and hemodynamic parameters were comparable in both groups. (Table 1, 2 &

3).

Table 1: Age in years-Frequency distribution in two groups of patients studied

Age in Years	Pregabalin Group	Placebo Group	Total
<20	1(3.3%)	3(10%)	4(6.7%)
20-30	24(80%)	22(73.3%)	46(76.7%)
31-40	5(16.7%)	5(16.7%)	10(16.7%)
Total	30(100%)	30(100%)	60(100%)
Mean ± SD	25.90±4.69	24.53±5.11	25.21±4.91

Samples are age matched with P=0.285, Student TTest.

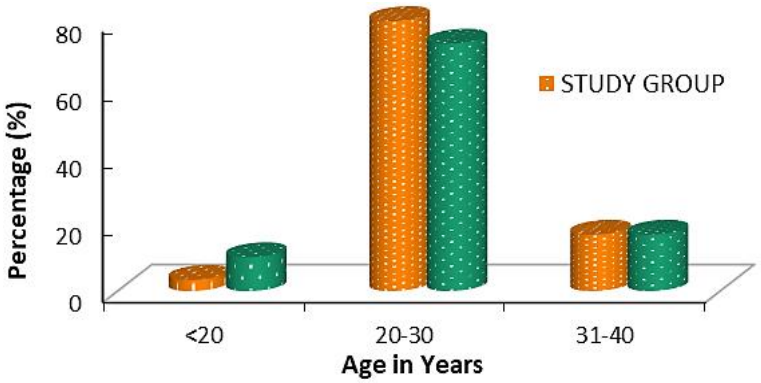

Fig 1: Age group

Table 2:HR (per min)-Comparison in two groups of patients at different points of time

HR(per min)	Pregabalin Group	Placebo Group	Total	P value
Preoperative	81.73±5.06	81.77±5.5	81.75±5.24	0.981
Intra Operative Parameters				
• Baseline	83.8±5.9	84.33±5.67	84.07±5.75	0.723
• 1 Min	85.3±5.97	81.87±9.49	83.58±8.05	0.099+
• 3 Min	80.77±6.87	77.5±8.02	79.13±7.58	0.095+
• 5 Min	75.43±7.54	72.2±6.58	73.82±7.21	0.082+
• 10 Min	71.6±5.63	71.47±5.12	71.53±5.33	0.924
• 20 Min	72.93±3.99	72.63±3.65	72.78±3.8	0.762
• 40 Min	72.4±3.48	72.8±3.54	72.6±3.48	0.660

Table 3:MAP(mm Hg)-Comparison in two groups of patients at different points of time

Map (mm Hg)	Pregabalin Group	Placebo Group	Total	P Value
Preoperative				
• <70	0(0%)	0(0%)	0(0%)	
• 70-100	30(100%)	30(100%)	60(100%)	1.000
• >100	0(0%)	0(0%)	0(0%)	
Intra Operative at 20 Mins				
• <70	0(0%)	0(0%)	0(0%)	
• 70-100	30(100%)	30(100%)	60(100%)	1.000
• >100	0(0%)	0(0%)	0(0%)	
Total	30(100%)	30(100%)	60(100%)	

Chi-Square Test/Fisher Exact Test

Comparison of pain scores between Pregabalin group and Placebo group showed significantly lower pain scores at 2hrs, 4hrs, 6hrs after caesarean section which was statistically significant (p<0.001). (Table 4)

Table 4: Post-Operative Parameters Numerical Rating Pain Score

Post-Operative Parameters Numerical Rating Pain Score	Pregabalin Group	Placebo Group	Total	P Value
2 HRS	0.13±0.35	2.33±1.18	1.23±1.41	<0.001**
4 HRS	1.97±1.03	4.9±1.21	3.43±1.85	<0.001**
6 HRS	3.67±0.8	4.77±1.22	4.22±1.17	<0.001**
8 HRS	4.17±1.15	4.77±1.1	4.47±1.16	0.044*
24 HRS	1.77±0.63	2.13±0.86	1.95±0.77	0.064*

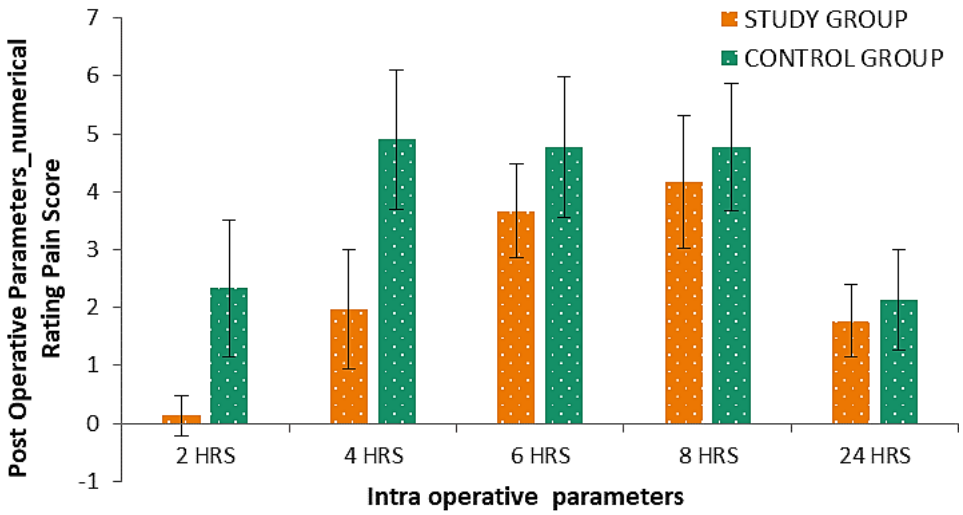

Fig 2: Pain score

Comparison of time needed for first rescue analgesia in Pregabalin group was (394+/- 62.41) mins when compared to Placebo group (203 +/- 62.33) mins which was significantly (p<0.001).

Total dose of analgesic (mg) consumption during the first 24hrs in Pregabalin group was (24.3+/- 8.96) when compared to placebo group (61+/- 18.46) which was statistically significant (p< 0.001). (Table 5)

Table 5: Post-Operative Parameters

Post-Operative Parameters	Pregabalin Group	Placebo Group	Total	P Value
Time of First Analgesic(min)	394.67±62.41	203.33±62.33	299±114.59	<0.001**
Total Dose of Analgesic (mg)	24.3±8.96	61±18.46	42.65±23.44	<0.001**

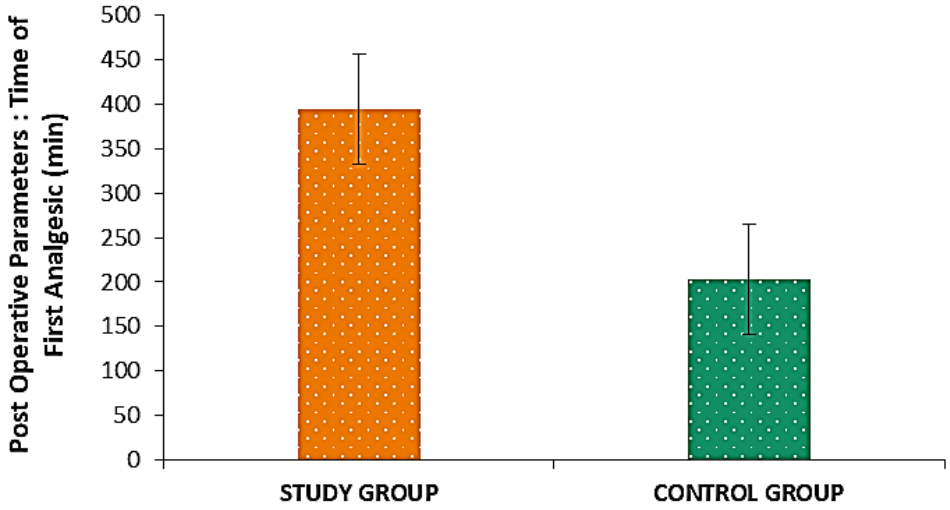

Fig 3: Time of first analgesic

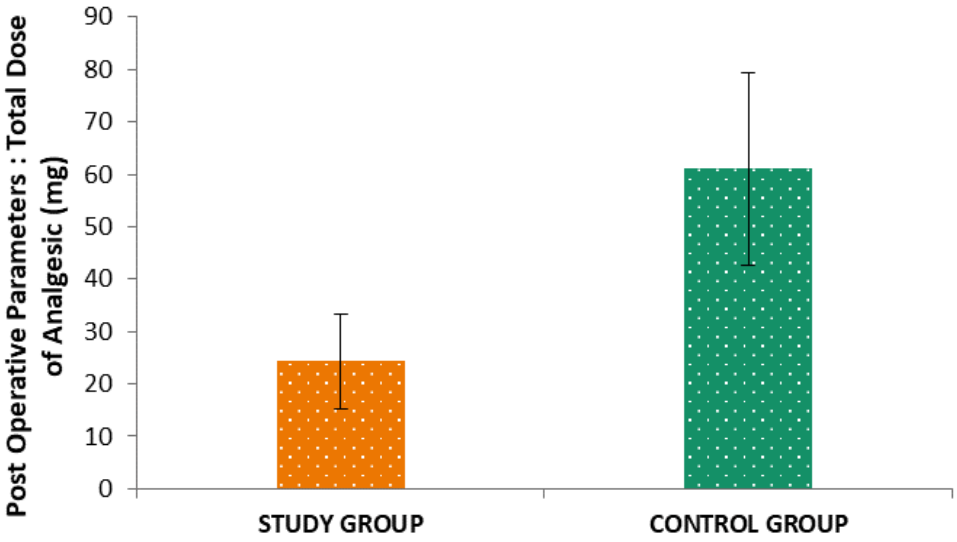

Fig 4: Total dose of analgesic

Adverse effects were comparable between Pregabalin and Placebo group. In our study results we observed that 6 patients had PONV in Pregabalin group when compared to Placebo group where 10 patients complained in Placebo group. But this was not statistically significant (p>0.001). (Table 6)

Table 6: Post-Operative Parameters_ Post-Operative Parameters

Post-Operative Parameters_ Adverse Effects	Pregabalin Group	Placebo Group	Total
No	21(70%)	24(80%)	45(75%)
Yes	9(30%)	6(20%)	15(25%)
• Drowsiness	3(10%)	1(3.3%)	4(6.7%)
• Nausea	2(6.7%)	2(6.7%)	4(6.7%)
• Vomiting	1(3.3%)	2(6.7%)	3(5%)
• Headache	1(3.3%)	1(3.3%)	2(3.3%)
• Dizziness	1(3.3%)	0(0%)	1(1.7%)
• Itching	1(3.3%)	0(0%)	1(1.7%)
Total	30(100%)	30(100%)	60(100%)

P=0.548, Not Significant, Chi-Square Test

Neonatal APGAR score at 1 and 5 mins were similar in Pregabalin group and Placebo group suggesting that single dose of Pregabalin as premedication did not cause any adverse effects to the newborn. (Table 7)

Table 7: Comparison of APGAR score in two groups of patients studied

APGAR Score	Pregabalin Group	Placebo Group	Total	P Value
1 min APGAR 1	6.4±0.62	6.37±0.72	6.38±0.67	0.848
5 mins APGAR 5	8.27±0.64	8.2±0.66	8.23±0.65	0.694

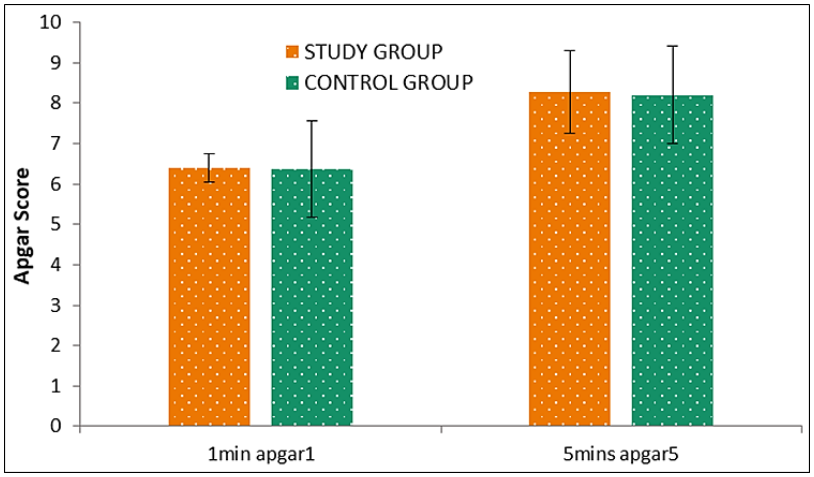

Fig 5: APGAR score

Discussion

Multimodal analgesic treatment combining systemic opioids and non-opioid analgesics and neuraxial blocks is recommended for post-operative pain after caesarean delivery. Gabapentinoids such as pregabalin were originally introduced as antiepileptics also have analgesic effects. As our study was conducted on pregnant women undergoing elective caesarean section under spinal anaesthesia, we saw that the pregabalin group showed prolongation of time to first rescue analgesia which was appreciably better than the placebo group.

EI-Kenany *et al*. In their study found that the use of single dose pregabalin 300 mg before caesarean delivery under spinal anesthesia resulted in lower morphine consumption and pain scores, and less frequent nausea, vomiting and pruritis when compared to placebo group and pregabalin 150 mg group. Pregabalin 300 mg was associated with increased maternal sedation, dizziness, and abnormal vision. Our results are in favour of this study. [1].

In another study byKohli M *et al*., pregabalin significantly reduced anxiety level, requirement of supplementary analgesics[2].

In a study conducted by Pandey *et al*., on 150 patients comparing efficacy of 2 doses of pregabalin 150mg and 300mg with a placebo for hysterectomy it was shown that pregabalin 150mg would be the optimal pre-emptive analgesic dose which is comparable with findings in our study [5].

Our study has demonstrated lower incidence of PONV during the first 24hrs in pregabalin group when compared to placebo group. Comparable results were found in a study conducted by EI Kenany *et al*., which also suggested fewer instances of post-operative nausea, vomiting and pruritis with the use of pregabalin 300mg compared to placebo or 150mg pregabalin [1].

In another study conducted by Michael G F *et al*., the authors concluded that there is a reduction in incidence of PONV and retching possibly either due to the decreased need for postoperative pain treatment or

because of an anti-emetic effect of gabapentin itself when compared to the placebo group which is comparable with results observed in our study[10].
Furthermore, in our study, we observed a decreased incidence of PONV in pregabalin (150 mg) compared to placebo group which were consistent with the results in a study conducted by Pandey C K *et al*., [5].
This study also demonstrated a decrease in the amount of tramadol consumption in pregabalin group, which is identical tothe study conducted by Pandey C K *et al*.
It is necessary that post caesarean delivery pain relief be safe and effective, that it does not interfere with the mother's ability to move around and care for her infant resulting in no adverse neonatal effects in breast-feeding women. Although more data is needed, our observations in the study suggest that breast-feeding in conjunction with pregabalin is safe. Comparable results were found in studies done by Gadsen M D *et al*., [3] and Ohman *et al*., [6].
Our study concluded that neonatal APGAR score was not altered in both pregabalin and placebo group at both 1-minute and 5-minute intervals.

Conclusion

Pre-emptively administered single oral 150 mg dose of pregabalin provides excellent post caesarean pain relief. Additionally, it reduces parenteral analgesic requirement and prolongs duration of analgesia in parturient women undergoing elective caesarean surgeries thereby contributing to better maternal satisfaction for rooming- in her newborn. Also, predelivery single exposure to pregabalin is safer in newborns.

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