Effect of Pre-Emptive Gabapentin for Post-Operative Analgesia in Vaginal Hysterectomy under Spinal Anaesthesia

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Abstract

Background and Aims: *Various drugs and methods have been tried to alleviate postoperative pain, perioperative anxiety, and apprehension. Opioids, Non-steroidal anti-inflammatory drugs, Cyclooxygenase inhibitors, and many local anesthetic techniques have been used, but every approach has their own side effects and limitations. Recent works have shown that gabapentin may have an opioid-sparing effect and anxiolytic property, without any respiratory depression, gastrointestinal, hematological, renal and hepatic adverse effects.*

We conducted this study to assess the efficacy of a single dose oral gabapentin as pre-emptive analgesia in comparison to placebo for postoperative pain control in adult subjects undergoing vaginal hysterectomy under spinal anesthesia.

Material & Methods: *This randomised double-blind study was conducted in 100 ASA grade I and II patients of age 40-60 years posted for abdominal hysterectomy. Patients were divided into two groups of 50 each. Group G received 600mg oral gabapentin 1 hour before vaginal hysterectomy and Group C received placebo. Total abdominal hysterectomy was carried out under spinal anesthesia. Pulse rate, SBP, DBP, and SpO$_2$ over a 24-hour period, Total tramadol consumption, sedation scores, incidence of nausea and vomiting and other adverse effects were noted. Data was analysed with SPSS version 23 using appropriate statistical tests.*

Results: *There were significantly lower pain scores and reduced analgesic requirements in gabapentin group over a 24-hour period. There was better hemodynamic stability in the gabapentin group. Incidence of nausea, vomiting, and adverse events was higher in patients of gabapentin group, although not significant statistically.*

Conclusion: *Gabapentin used a pre-emptive analgesic, reduces post-operative analgesic requirements.*

Keywords: *Gabapentin, Post-operative analgesia, Pre-emptive analgesia, Abdominal Hysterectomy.*

Introduction

Pain is associated with delayed recovery and mobilization in the immediate postoperative period. The most common psychological reactions to acute pain and pain of prolonged duration are anxiety, sleep disturbances and depression, which can increase the suffering of post-surgical patients. In fact, the apprehension of post-surgical pain sometimes overpowers the fear of surgery in patients and their relatives. It is the responsibility

of the anesthesiologists to provide adequate post-operative analgesia not only to suppress the adverse physiological responses to pain, but also to improve the quality of patient comfort following surgery. Various drugs and methods have been tried to alleviate postoperative pain, perioperative anxiety and apprehension, namely; opioids [1-4] non-steroidal anti- inflammatory drugs [5-7] cyclooxygenase inhibitors [8,9] and various local anaesthetic techniques [10,11] but every approach has its own side effects and limitations. [12-18]. Postoperative pain has multiple mechanisms. If analgesia is not provided at an appropriate time, pain sensitization occurs, and analgesia becomes ineffective or inadequate. Pre-emptive analgesia is defined as anti-nociceptive management which starts before actual nociception and prevents the establishment of altered central processing which amplifies postoperative pain [19-24]. Recently studies have shown that gabapentin may have an opioid sparing effect and anxiolytic property without causing respiratory depression or gastrointestinal, haematological, renal and hepatic adverse effects. Gabapentin, a structural analogue of gamma amino butyric acid, introduced in 1993, and used as an anticonvulsant drug, has been shown to have analgesic properties. It is effective in chronic pain conditions, including post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome (CRPS), inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, and headache. [25-33]. It also has a synergistic effect with morphine. [34]. Animal studies have shown that gabapentin reduces mechanical or thermal hyperalgesia [35], ameliorate pain in models of peripheral nerve injury [36], incisional injury [37] and inflammatory injury [38]. Various human studies and meta-analysis also have shown that gabapentin premedication can reduce postoperative opioid consumption in first 24 hours in various operations like abdominal hysterectomy, spinal surgery, vaginal hysterectomy, radical mastectomy and laparoscopic cholecystectomy [39-44].

We conducted this study to assess the efficacy of a single dose oral gabapentin as pre-emptive analgesia in comparison to placebo in postoperative pain control in adult subjects undergoing vaginal hysterectomy under spinal anaesthesia.

Material and Methods

This was a randomised double blinded study conducted after obtaining ethical approval of the Institutional Ethical Committee at VIMSAR Burla. 100 patients aged 40 to 60 years of ASA physical status I and II undergoing elective vaginal hysterectomy under spinal anaesthesia were included. Patient who had contradictions to spinal anaesthesia, patients with mental impairment, patients allergic to gabapentin, uncooperative patients, and those posted for emergency surgery were excluded from the study. Considering a power of 80% and alpha error of 0.05, 46 patients would be required in each group to detect 10% or more difference in tramadol consumption. So 50 patients were randomly allocated to each group.

All patients were kept nil per oral 8 hours before surgery but clear fluids were permitted till four hours prior to scheduled time of operation and only one hours before operation gabapentin tablets or placebo (sugar candy) with small sips of water were given. The patients were divided into two groups:

A) Group G -50 patients receiving 600mg oral Gabapentin

B) Group C -50 patients receiving placebo

No sedative premedication other than gabapentin was given to the patients. Upon arrival at operation room all the base line parameters like non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO$_2$), pulse rate, electrocardiography (ECG) were recorded. In all patients, subarachnoid block was performed in sitting position, through midline approach, with 25-gauge Quincke's type needle through L$_3$-L$_4$ intervertebral spaces by an anaesthesiologist who was not involved in data collection, maintaining

the standard protocol and strict aseptic measures & 3.0 ml of 0.5% hyperbaric bupivacaine. Motor block was assessed by modified Bromage scale and sensory block was assessed by cold touch with a spirit-soaked cotton ball. After achieving adequate sensory block up to T_{10} level, and motor block (Bromage scale 4) surgery was allowed.

Blood pressure including systolic and diastolic and mean arterial pressure was measured every 2 minutes for first 30 minutes after the block and then every 15 minutes. ECG and SpO_2 were monitored continuously throughout the perioperative period. After the surgery, the patients were shifted to the PACU where pulse rate, systolic blood pressure , diastolic blood pressure, respiratory rate, dizziness were recorded at 0 , 2 , 4 , 6 , 8 , 12 ,18 , 24 hour intervals. Postoperative pain was assessed by a 100mm VAS (0= no pain, 100= worst possible pain) scale at 0, 2, 4, 6, 8, 12, 18 and 24th hours. Inj. Tramadol (2mg/kg) intravenously was given as rescue analgesic whenever patients demanded and/or Pain score reached 40. Hypotension (defined as MAP 20% less than the baseline value for at least 60 seconds) were treated with Mephenteramine (5-10 mg in aliquots intravenously) and bradycardia (defined as HR< 50 beats per minutes for at least 60 seconds) was treated with inj. Atropine 0.02mg/kg body weight intravenously and incidence were recorded. Time to recovery of motor power were assessed by modified Bromage scale and time for gaining full motor power was noted. The time elapsed between the placements of subarachnoid block and patients' first request for analgesia and/or VAS pain score reached 40 was recorded. Total tramadol consumption over 24 hours was also recorded.

Incidence of postoperative side effects were also assessed, e.g. nausea, vomiting, sedation (assessed by numeric scale of 0-3 where 0= fully awake, 1= patient somnolent but responsive to command, 2= patients somnolent but responsive to tactile stimuli, 3= patients somnolent but responsive to painful stimuli only.), respiratory depression, dizziness, pruritus, urinary retention and hallucination were recorded.

The data was compiled systematically in Microsoft excel 2010 & analysed using IBM SPSS version 23. Parametric data were expressed in mean ± standard deviation (SD). Student's independent t-test was used for parametric data. For non-parametric data, chi-square test was used. P value of less than 0.05 was considered as statistically significant.

Results

Data was collected from 100 patients included in the study.
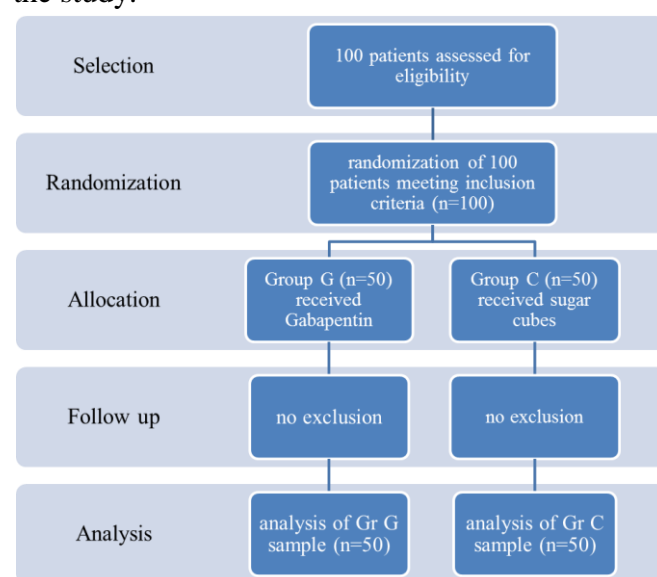

Table 1. Demographic data of patients

Variable	Gr C	Gr G	P value
Age(yrs.)	51.06±5.63	50.74±5.43	0.77
Weight (kg)	51.3±4.94	50.32±3.85	0.27
Duration of surgery(min)	55±6.05	55.68±4.68	0.53
Duration of motor block (min)	83.14±3.42	83.66±3.37	0.44
Duration of sensory block (min)	108.62±3.89	108.56±4.13	0.94
ASA Physical status I/II	28/22	27/23	0.84

No significant difference was observed between the two groups in terms of age, body weight, duration of surgery, duration of motor block, duration of sensory block and ASA physical status. (Table 1).

Table 2 Pulse rate

Time in hrs.	Gr C Mean ± SD	Gr G Mean ±SD	P Value
0	119.08±8.57	104.18±7.4	<0.001
2	114.96±9.49	99.36±6.53	<0.001
4	106.4±8.74	90.3±5.63	<0.001
6	102.18±7.38	88.66±6.70	<0.001
8	99.82±7.48	84.96±4.99	<0.001
12	95.54±7.46	82.24±6.35	<0.001
18	91.44±6.26	80.66±5.97	<0.001
24	89.94±6.38	77.92±5.95	<0.001

Table 2 shows the comparison of pulse rate between both groups. Pulse rate is significantly lower at all times in Group G as compared to Group C.
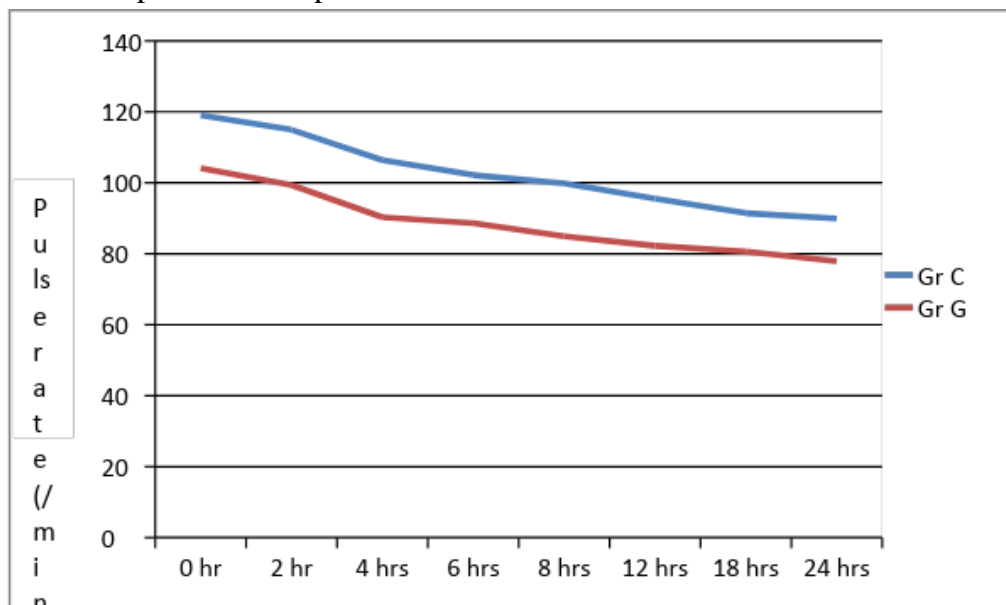
Figure 2: Pulse rate

Table 3 Systolic blood pressure

Time in hrs.	Gr C Mean±SD	Gr G Mean ±SD	P Value
0	113.76±10.25	113.68±10.17	0.96
2	135.4±7.00	127.36±5.7	<0.001
4	129.36±6.21	122.92±4.97	<0.001
6	128.26±6.27	122.84±4.03	<0.001
8	127.38±7.81	121.44±3.28	<0.001
12	127.02±4.72	121.24±4.86	<0.001
18	126.92±5.73	120.8±2.90	<0.001
24	125.44±4.55	120.56±3.69	<0.001

Table 3 shows the comparison of systolic blood pressure over 24 hours in between groups. The difference between the groups was non-significant at baseline. At all other times SBP was statistically lower in Group G than Group C.
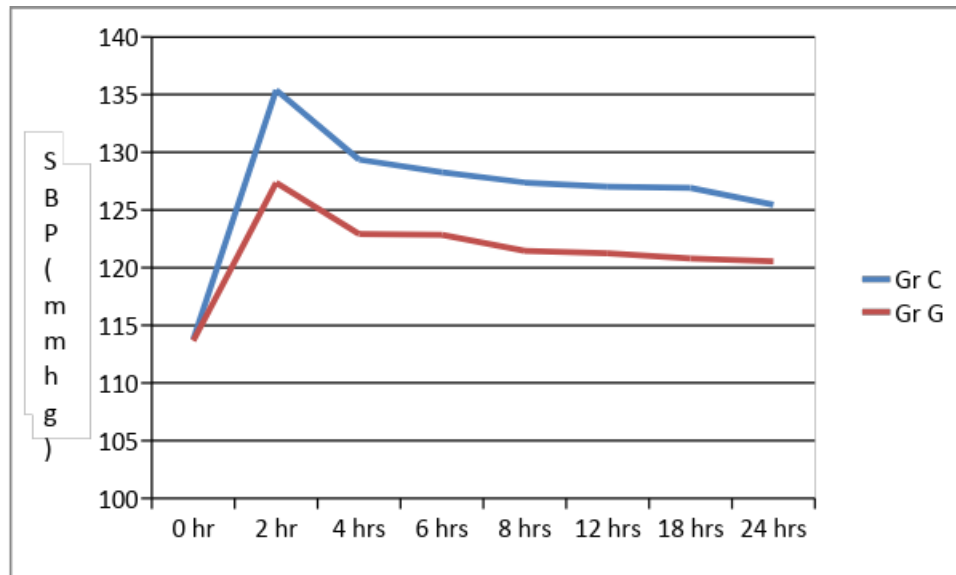
Figure 3**:** Systolic blood pressure

Table 4 Diastolic blood pressure

Time in hrs	Gr C Mean±SD	Gr G Mean ±SD	P Value
0	91.92±4.81	75.4±4.09	<0.001
2	90.44±4.00	85.44±4.04	<0.001
4	85.42±3.90	82.72±4.47	0.002
6	84.98±3.83	82.54±4.09	0.003
8	84.6±3.83	82±3.14	<0.001
12	84±3.60	81.46±4.05	0.001
18	83.12±3.61	80.7±4.17	0.002
24	82.58±3.20	80.12±3.85	<0.001

Table 4 compares that the diastolic blood pressure (DBP) of patients at various times in both groups. It was significantly lower at all times in Group G.
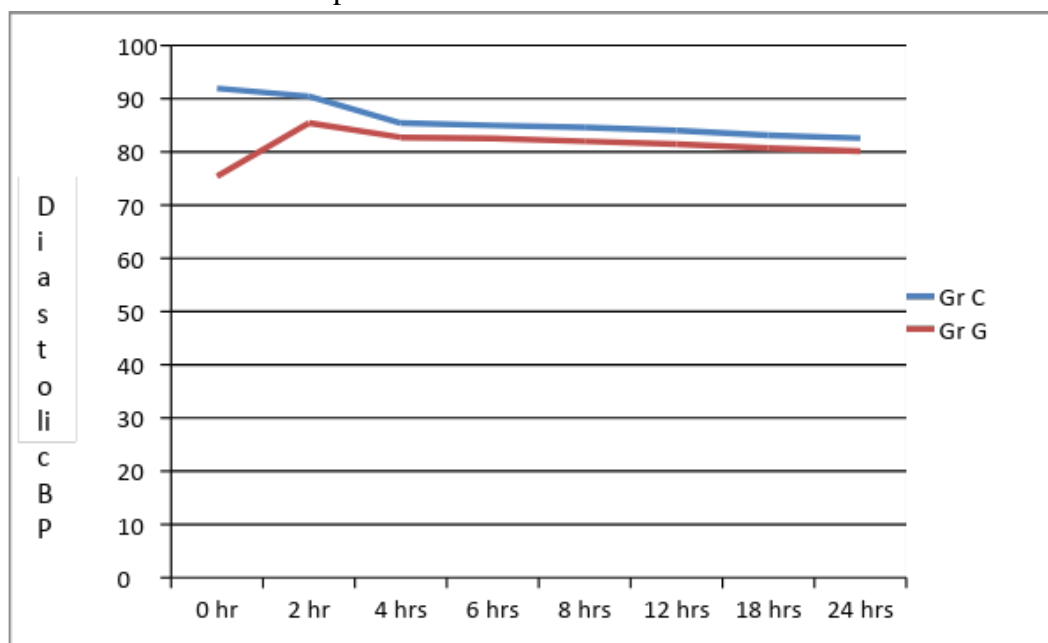

Figure 4: Diastolic blood pressure

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Table 5 SpO$_2$

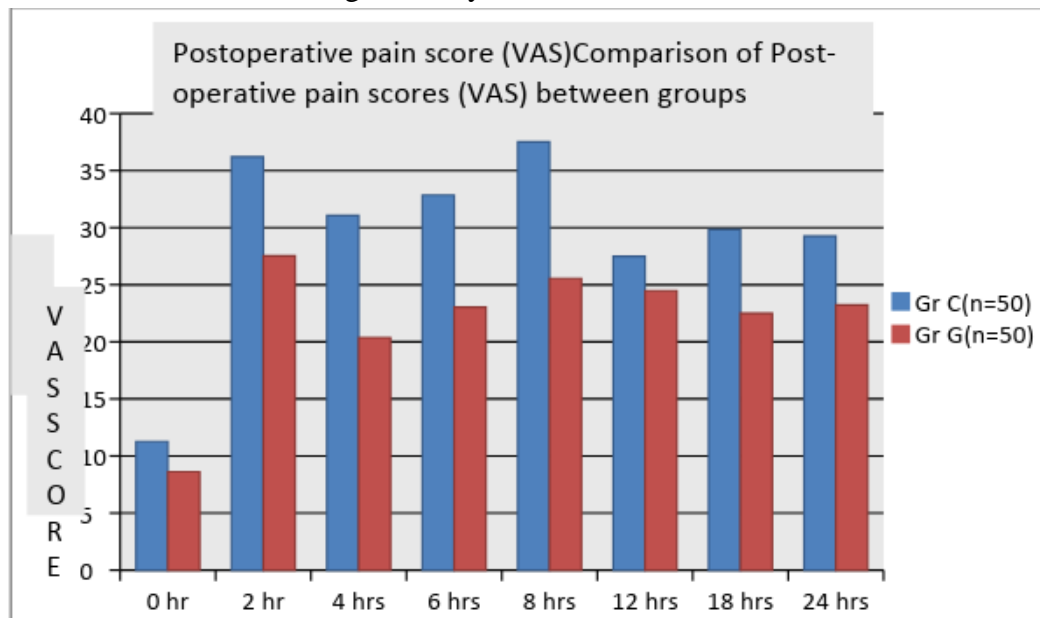| Time in hrs.	Gr C (Mean ± SD)	Gr G (Mean ±SD)	P Value
0	99.6±.57	99.42±.70	0.16
2	99.42±.64	99.3±.67	0.36
4	99.4±.53	99.46±.73	0.64
6	99.52±.54	99.54±.57	0.85
8	99.46±.54	99.54±.57	0.48
12	99.46±.54	99.54±.57	0.48
18	99.42±.60	99.54±.57	0.31
24	99.42±.60	99.54±.57	0.31

Table 5 shows that the comparison of SPO$_2$ in between two groups. It was non-significant at all times.

Table 6 Postoperative pain score (VAS)

Time in hrs.	Gr C Mean ± SD	Gr G Mean ±SD	P Value
0	11.26±2.13	8.62±2.70	<0.001
2	36.2±4.14	27.52±2.71	<0.001
4	31.06±3.19	20.36±3.04	<0.001
6	32.84±2.83	23.04±2.51	<0.001
8	37.5±4.78	25.54±4.87	<0.001
12	27.48±3.74	24.48±5.34	0.002
18	29.82±6.22	22.5±7.12	<0.001
24	29.26±4.48	23.22±5.74	<0.001

The mean VAS scores of all patients in each group at various times has been compared in Table 6. The mean VAS scores were significantly lower at all times in Group G as compared to Group C.


Figure 5 Comparison between VAS score.

Table 7 Postoperative Tramadol consumption

Groups	Gr C (Mean ± SD)	Gr G (Mean ± SD)	P value
Postoperative tramadol consumption	98.9±14.09	51.27±14.73	<0.001
Postoperative sedation score	1.74±0.52	2.78±0.67	<0.001

Postoperative consumption of tramadol and sedation scores have been compared in Table 7. The mean tramadol requirement was 51.27±14.73 mg in group G while it was 98.9±14.09 mg in group C, with a p value of <0.001 which was highly significant statistically. The mean sedation score in group G was 2.78±0.67 while that in group C was 1.74±0.52. Sedation scores were significantly higher in group G than group C.
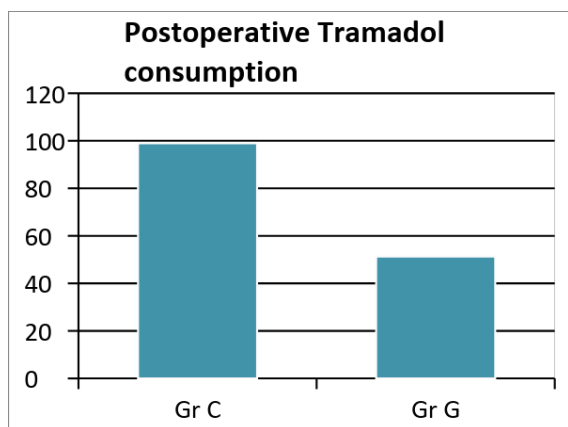
Figure 6. Tramadol consumption
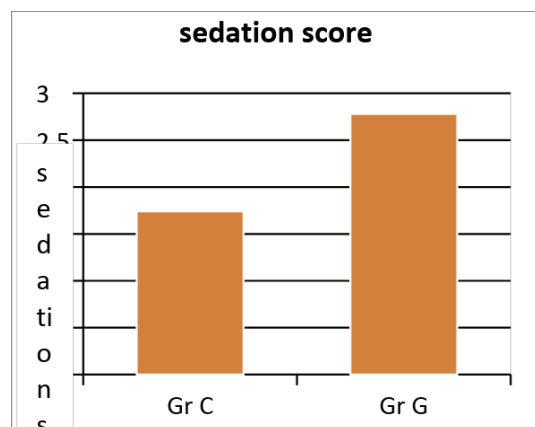
Figure 7. Sedation score

Table 8 Nausea and Vomiting

Groups	Nausea (%)	Vomiting (%)
Gr C	5 (10%)	2 (4%)
Gr G	13 (26%)	8 (16%)
P value	0.066	0.092

Table 8 shows the incidence of nausea and vomiting among the two groups. There were 5 (10%) incidents of nausea and 2 (4%) incidents of vomiting in group C while they were 13 (26%) and 8 (16%) in group G. There was no statistical significance in the incidence of nausea and vomiting among the two groups.

Table 9 Adverse events

Variable	Gr C	Gr G	P value
Dizziness	2(4%)	6(12%)	0.269
Dry mouth	0	0	-
Urinary retention	4(8%)	2(4%)	0.678
Hallucination	0	2(4%)	0.495

The incidence of adverse events has been shown in Table 9. None of the patients in group C had hallucinations but 2 patients in group G hallucinated (4 %). 2 in group C (4%) and 6 in group G (12%) felt dizzy. 4 (8%) patients in group C and 2 (4%) patients in group G had urinary retention. None of the patients in study groups had dry mouth in 24 hours of study period.

Discussion

A number of mechanisms may be involved in the actions of gabapentin [45]. Possible pharmacologic targets of gabapentin are selective activation of the hetero-dimeric $GABA_B$ receptors which consist of $GABA_{B1a}$ and $GABA_{B2}$ subunits[46,47]; enhancement of the *N*-methyl-D-aspartate (NMDA) current at GABAergic interneurons[48];

blocking alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated transmission in the spinal cord[49,50]; binding to the L Alpha amino acid transporter[51,52]; activating adenosine triphosphate sensitive K^+ (K_{ATP}) channels[53,54]; activating hyperpolarization-activated cation current (Ih) channels[55,56] and modulating Ca^{2+} current by selectively binding to [^{3}H]gabapentin (a radio-ligand), the alpha $_2$ delta subunit of voltage-dependent Ca^{2+} channels (VGCCs)[57,58,59]. Currently, VGCC is the most likely anti-nociceptive target of gabapentin. The proposed consequence of gabapentin binding to the alpha$_2$ delta subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyper-excitability. Gabapentin has been shown to inhibit the evoked release of glutamate [60], aspartate [61], substance P, and calcitonin gene-related peptide (CGRP) [62] from the spinal cord of rats. Interestingly, recent studies have demonstrated that the descending noradrenergic system, spinal □$_2$ adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to alpha$_2$delta interaction [63, 64].

Various studies have proven the efficacy of gabapentin preemptive analgesia as opioid sparing agent. In 2001, *Werner MU et al.* first showed the hopes of light in the field of post-operative analgesia that gabapentin has significant role in acute inflammatory pain in human beings [65]. *Gregg AK et al.* established role of gabapentin in post-operative analgesia as premedication in laparoscopic cholecystectomy [66].

Dirks J et al. concluded that in gabapentin group, 24 hour post-surgery morphine consumption was remarkably less than the placebo group [67]. *Fassoulaki A et al.* concluded that mexiletine 600mg/day, gabapentin 1200mg/day both reduced the postoperative analgesic requirements and particularly gabapentin reduced pain after movement in patients operated for carcinoma breast [68].*Dierking K et al.* found 32% reduction in morphine consumption in patients given with

1200mg of gabapentin in 1 hour preoperatively and then 600mg in 8, 12, 24 hours after the initial dose. [69].

Pandey CK et al. concluded that pre-emptive use of gabapentin (as compared to tramadol) significantly decreases postoperative pain and fentanyl consumption in laparoscopic cholecyst-ectomy [70] & in lumbar discoidectomy[71]. *Turan A et al.* concluded that preoperative oral gabapentin decreases pain scores in early postoperative period and postoperative morphine consumption in spinal surgery [72]. *Rorarius MGF et al.* concluded that gabapentin reduced the need for additional postoperative pain treatment (PCA boluses of 50microgram of fentanyl) by 40% during the first 20 postoperative hours compared to placebo controlled group [73].

Pandey CK, Navkar DV, Giri PJ et al compared different pre-emptive doses of gabapentin for postoperative pain relief after single-level lumbar discectomy and its effect on fentanyl consumption & concluded that increasing the dose of gabapentin from 600mg to 1200mg did not decreases the VAS score nor did the increasing dose of gabapentin significantly decreases fentanyl consumption. Thus, gabapentin 600mg is the optimal dose for postoperative pain relief following lumbar discectomy [74].

Turan A, Kaya G, Apfel CC et al demonstrated gabapentin as a good adjuvant for postoperative pain management in patients undergoing different lower limb procedures [75].

Al-Mujadi H et al. gabapentin 1200mg orally two hours prior to induction of anaesthesia to patients undergoing selective thyroidectomy significantly decreased pain scores and morphine consumption in the postoperative period [76].

Findings of the present study lend support to the observations by *Pandey et al* and also corroborates with the findings of other workers.

Gabapentin has been reported as an anxiolytic agent in previous studies [77- 80]. It was effective in treating anxiety associated with panic disorders. [78, 79, 81] De-Paris *et al*. [81] demonstrated that gabapentin attenuates anxiety associated with

simulated public speaking in volunteers. This disorder may be related to the preoperative anxiety state. The interest in using gabapentin preoperatively to decrease preoperative anxiety is due to its limited side effects in comparison to other standard mood-stabilizing agents. Moreover, gabapentin seems anxiolytic without exerting amnesic effects [82]. However, additional study is necessary to fully validate these promising aspects of gabapentin pharmacology.

Reducing preoperative anxiety with gabapentin may have contributed to the improved postoperative pain and to the reduced opioid use since there is a possible association between preoperative anxiety and postoperative pain[83,84]. But, whether preoperative anxiolysis without coping behaviour and preoperative information has an impact on the postoperative pain response and morphine requirements remains controversial [84].

The use of gabapentin might be limited by its previously reported side effects, e.g., dizziness, somnolence, confusion, and ataxia [85]. However, the incidences of such adverse effects were not significant in the present study.

Conclusion

We conclude that Gabapentin, when used as a pre-emptively, provides greater degree of analgesia with opioid sparing effect. It reduces postoperative pain and analgesic consumption & also provides anxiolysis.

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