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A comparison of effect of preemptive use of oral gabapentin and pregabalin for acute postoperative pain after Partial Thyroidectomy

Dr. Bimal Prasd Sahu
Department of Anesthesiology, SLN Medical College, Koraput, Odisha, India

Dr. Chandra Sekhar Behera
Department of Anesthesiology, SLN Medical College, Koraput, Odisha, India

Dr. Sunil Kumar Habada
Department of Anesthesiology, SLN Medical College, Koraput, Odisha, India

Dr. Debadas Biswal*
Department of Anesthesiology, SLN Medical College, Koraput, Odisha, India

***Abstract*---**Background and Aims: Preemptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and postoperative period. Pregabalinas considered in abolishing neuropathie component of acute nociceptive pain of surgery. Materials and methods: A study was done to know the effect of oral gabapentin and pregabalinath control group for post-operative analgesia. Materials and Methods: A total of 90 ASA grade I and II patients posted for elective Partial thyroidectomy were randomized into 3 groups (group A, B and C of 30 patients each). One hour before surgery the blinded drug selected for the study was given with a sip of water. Group C- received identical placebo tablet, Group B- received 800 mg of gabapentin tablet and Group A - received 150 mg of pregabalinablet . VAS score recorded for initial rescue analgesia, total duration of analgesia and total requirement of rescue analgesia were observed as primary outcome. Hemodynamics andside effects were recorded as secondary outcome in patients. Results: The analgesic requirement in both Pregabalinand Gabapentin groups are lower than the control group. Time for 1st dose of analgesic in pregabalingroup is 62.5+25.3 min, in Gabapentin group 64.2+26min and in control group is 27 8+14.8min, which was statistically significant then the Pregabalin and Gabapentin group. Conclusion: We found that preemptive use of gabapentin 800mg and pregabaling orally considerably reduces the postoperative rescue

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analgesic requirement and increases the duration of postoperative analgesia in patients undergoing partial thyroidectomy under General Anaesthesia.

***Keywords*---**preemtive analgesia, gabapentin, pregabalin, general anaesthesia, partial thyroidectomy.

Introduction

Postoperative analgesia is essential for achieving patient satisfaction and enhanced recovery. Inadequate pain control can lead to higher morbidity and mortality, prolonged hospital stay and the development of chronic postoperative pain. The aim of postoperative pain management is to decrease or eliminate pain and discomfort with a reduction of side effects. Various agents (opioid vs. nonopioid), routes (oral, intravenous, neuraxial, regional) and modes (patient controlled vs.as needed) for the treatment of postoperative pain exist. In general the treatment of postoperative analgesia is opioid based, gradually more support is present for a multimodal approach with the intent to reduce opioid side effects (such as nausea and ileus) and improve pain scores. Preemptive analgesia involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the aim of preventing sensitization of the nervous system to subsequent stimuli that could increase pain. Surgery is appropriate for use of preemptive analgesia because the timing of noxious stimuli is known.

If appropriate drug doses are administered to selected patients before surgery, intravenous opiates, local anaesthetic infiltration, nerve block, subarachnoid block and epidural block offer benefits that is observed as long as one year after surgery. The best preemptive analgesic regimens are those that has the ability of reducing sensitization of the nervous system during the entire perioperative period. Recent research of molecular mechanisms evolved multimodal analgesia and new pharmaceutical products for treating postoperative pain. Traditionally, the pathophysiology and treatment of acute pain and neuropathic pain have been considered as separate and distinct. Opioids, NSAIDs and local anesthetics were the tools of doctors dealing with acute pain; while tricyclic antidepressants and anticonvulsants were for the chronic pain. However, there's considerable overlap in their pathophysiology, Hyperalgesia and allodynia are cardinal signs and symptoms of neuropathic pain but they're also often present after trauma and surgery. The dorsal horn neuron sensitisation is the mechanism found in acute neuropathic pain. The persistence of this neuronal sensitization may be responsible for the occurrence of chronic pain after surgery.

Gabapentin is a structural analogue of Gamma Amino Butyric Acid (GABA), which was introduced in 1994 as an antiepileptic drug but gabapentin does not bind at GABA receptors. However, it has a high binding affinity for the α ,2δ subunit of the presynaptic voltagegated calcium channels which inhibits calcium influx and subsequent release of excitatory neurotransmitters in the pain pathways including glutamate, noradrenaline, dopamine, serotonin, and substance P. It is effective for neuropathic pain, postherpetic neuralgia, and reflex sympathetic dystrophy. It has an anti hyperalgesic property that selectively affects

the nociceptive process involving central sensitization. Moreover, gabapentin have anxiolytic effect. These properties suggest that gabapentin can be used preoperatively.

The use of gabapentin in the perioperative period has been evaluated in many studies, reporting promising reductions in postoperative analgesic consumption. Pregabalin, like gabapentin,a GABA analogue; it had been introduced and approved by FDA in 2005 for clinical use . It has analgesic, anxiolytic, anticonvulsant, and sleepmodulating activities. Pregabalin has similar pharmacological activity, but not identical with, that of gabapentin, it is pharmacologically better due to higher bioavailability (90% versus 33%-66%), rapid absorption and peak plasma level in1 hour versus 3-4 hours and along with increase in dose, there is linear increase in plasma concentration. Lower pregabalin doses have an identical analgesic effect.Both are well tolerated and related to mild to moderate side effects that are usually transient. In clinical trials, the most frequently reported adverse events are somnolence and dizziness. They have been used in the treatment of postoperative pain with good results, but the optimal doses for postoperative pain are still controversial gabapentin doses ranged from 300 mg to 1,200 mg, and pregabalin doses ranged from 50 mg to 300 mg(6,7,8,9,10). More studies on the optimal dosages of these two drugs are required.

Gabapentin, and pregabalin, have been compared to a placebo in many separate prospective randomized trials that evaluated their effectiveness in reducing postoperative pain. However, fewer studies compared pregabalin and gabapentin for post operative pain management[6,7,8,9,10]. The null hypothesis was the supposition that total analgesic requirements dose not differ between pregabalin and gabapentin when gabapentin dose is five times higher. We planned our study to examine their analgesic and anxiolytic efficacy, as well as safety against control group in patients undergoing partial Thyroidectomy

Methods

After approval of the local ethics committee, this prospective, randomized, double blinded study consists of 90 patients of American Society of Anesthesiologists (ASA) physical status I and II, aged between 20 and 60 years, scheduled for Partial Thyroidectomy surgery, were enrolled to participate in this study after obtaining informed patient consent. Using a computer-generated randomization schedule, they were randomly assigned into three equal groups: Pregabalin, Gabapentin and Control of 30 patients each. Exclusion criteria included age older than 60 years or younger than 20years, ASA III and above, obesity (>35 BMI), allergic and/or contraindicated to the study drugs, regular medication with analgesics, history of chronic pain, analgesic use within 24 hours of surgery, alcohol or drug abuse, diabetes mellitus, psychiatric disorders, epilepsy, cardiovascular, renal, or hepatic diseases. One hour before surgery, patients were educated to use the 100-mm visual analog scale (VAS): a pain VAS (0 = no pain to 100 = worst imaginable pain) and an anxiety VAS (0 = no anxiety to 100 = worst imaginable anxiety) , and received our single dose study drug by a physician, who was not a member of the anesthesia or surgical team. The patients, anesthesiologists and surgeons were blinded to the drug administered.

Patients in Pregabalin Group (n = 30) received pregabalin 150 mg, patients in Gabapentin Group (n = 30) received gabapentin 800 mg, and patients in Control Group (n = 30) received placebo. No sedative premedication was given. Respiratory Rate (RR), oxygen saturation (SpO2), anxiety VAS score and Numeric Sedation Scores (NSS; 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimuli) [2] , were recorded before the operation. Heart rate (HR) and mean arterial blood pressure (MBP), were recorded before the operation, after induction of anesthesia at 5, 10, 15, 30 minutes and every 30 minutes till the end of surgery. In all patients, anesthesia was induced with propofol 1% (2 mg/kg), Nalbuphine (0.2mg/kg), and atracurium (0.5 mg/kg). Maintenance of anesthesia was achieved with 66% N2O IN O2 With isoflurane in vaporisor (1- 1.5 vol % with dial setting)and atracurium in the one fifth of loading dose(0.1 mg/kg). Paracetamol infusion was given if there is increase in HR or MBP by 20% . At the end of surgery reversal was done with inj Neostigmine and Glycopyrolate and recovery time were recorded.

After awakening, the patients were transferred to the post anesthesia care unit (PACU), postoperative analgesia was provided by titrating nalbuphine until the pain VAS was ≤30 mm. Titration was stopped if the sedation score was > 2 or the respiratory rate <10 breaths per min. Total nalbuphine consumption and the time till first request for analgesic medication were recorded. Pain scores were recorded at 1h, 2h, 4h, 6h, 12h and 24h after surgery. We also evaluated potential side effects, including drowsiness, headache, dizziness, visual disturbances (blurred or double), nausea and/or vomiting, urinary retention, pruritus, and respiratory depression (defined as a respiratory rate <10 breaths/min). Sample size were calculated Using G*Power 3.1.9.2 program depending on our primary outcome (total analgesic requirements), we were planning a study of a continuous response variable in order to detect 20% difference in analgesic requirements, and a power of 80% (1-β), at 5% significance level (α). The minimum sample size was to study 25 patients in each group (and increase 10% [3 patients] for dropout) to be able to reject the null hypothesis. Data was analyzed using SPSS version 17 statistical software. Data were presented as mean ± SD or number and percentage. ANOVA followed by posthoc test (using Tukey adjustment) were used for comparison of parametric data. Kruskal Wallis test was used to compare non-parametric data while Mannwhitney used to compare between two groups. Chi-square test x2 was used for comparison between frequencies. $P < 0.05$ was considered significant.

Observation and Result

No significant statistical difference was found among the study groups in respect of age, sex, weight, duration of surgery, and baseline laboratory investigations such as pulse rate, mean arterial pressure, and respiratory rate as shown in [Table 1]. Preoperative HR,MBP and Anxity VAS are significantly high in control group but no significant difference in SpO2 or NSS. All groups reported no sedation except one Pregabalin and two Gabapentin patients (NSS-2).(Table -2). Intraoperative HR and MBP are significantly higher in control group after 5 and 10 min. Where as the difference is not significant after that. (table 3&4). Duration of surgery and recovery time were comparable among groups.(Table -5).

[Table 6] shows pregabalin and gabapentin group had prolonged timing of first rescue analgesic compared to placebo group (62.5± 25.3, 64.2±26 , 27.8± 14.8) min and pregabalin and gabapentin groups consumed significantly less opioids in comparison to placebo group (61.5 ±17.5, 65.1 ± 18, 121.6 ±34.4) mg. The gabapentinoids, pregabalin group and Gabapentin group had lower VAS score [Table 6], prolonged timing of first rescue analgesic and less opioids consumption than the control group [Table 7]. Pregabalin and gabapentin provided better analgesia than the placebo. As shown in [Table 8], the side effects seen in this study were sedation, nausea, vomiting, respiratory depression,headache were comparable (P > 0.05).

Results

Table 1
Patients' characteristics

	Pregabalin (n=30)	Gabapentin (n=30)	Control (n=30)	P-value
Age (years)	41.8±11.2	42.3±8.7	40.7±8.6	> 0.05
Sex male\female	12/18	14/16	18/12	> 0.05
Weight (kg)	55.1±5.6	56.9±6.2	57.8±7.1	> 0.05
ASA I\II	20/10	18/12	17/13	> 0.05

Table 2
Preoperative assessment

	Pregabalin(n=30)	Gabapentin(n=30)	Control(n=30)	P-value
HR	76.5±11.1	78.5±10.3	93±11.7*	< 0.005
MBP	86.9±9	88.9±9.3	97.1±8.2*	< 0.005
RR	13.8±2.3	13.6±2.1	13.7±2	>0.05
SPo2	98.5±1.1	98.2±1.3	98.4±1.1	>0.05
NSS	1;1(1-2)	1;1(1-2)	1;1(1)	>0.05
Anxiety VAS	24.5±11	30±10	49±13.4*	< 0.005

*significantly high vs. other groups**(NSS)Data is presented as :mode;median(range)

Table 3
Intraoperative HR

	Group P (n=30)	Group G (n=30)	Group C (n=30)	P-value
5	77±10.1	79±10.8	96.5±8*	< 0.005
10	75.8±9	77.6±9.4	94±7.5*	< 0.005
15	74.7±8.7	76.3±9	80.8±7.9	> 0.05

30	73±8	73.6±8.2	77.9±6.7	> 0.05
60	77±10.6	80±10.3	82.3±9.6	> 0.05

*significantly high vs other groups

Table 4
Intraoperative MBP

	Group P (n=30)	Group G (n=30)	Group C (n=30)	P-value
5	88.2±10.2	92.1±9.4	102.4±9.8*	< 0.05
10	85.3±11	90±11.1	99.1±12.1*	< 0.05
15	90±11	92±11.1	93.5±11.6	>0.05
30	89.3±13.2	90.7±13.9	88±12.5	> 0.05
60	88.9±12.8	90±13.4	91±11.7	> 0.05

*significantly high vs other groups

Table 5
Operative data

	Group P (n=30)	Group G (n=30)	Group C (n=30)	P-value
Duration of surgery (min	91.3±13.1	92.5±14.7	89.4±14.2	> 0.05
Recovery time (min)	15.4±4.3	14.7±5	14.2±4	> 0.05

Table 6
Postoperative pain VAS and analgesic requirement

Pain VAS	Pregabalin (n=30)	Gabapentin (n=30)	Control (n=30)	P-value
1hr	18.1±10.2	21.6±9.2	47±13*	<0.005
2hr	17.5±9.4	20.7±8.9	40±11.8*	<0.005
4hr	15.8±9	18.9±8.4	32±10.8*	<0.005
6hr	14±7.9	15.5±7.6	25±8.3*	<0.005
12hr	12.8±7.5	13.1±7	15.2±6.5	>0.05
24hr	8.9±5.4	9.1±5.5	10.3±4.7	>0.05

*significantly high vs other groups

Table 7
Analgesic Requirment

1st analgesic request(min)	62.5±25.3	64.2±26	27.8±14.8*	<0.005
Total requirement(mg)	41±9.8	43.7±9.2	70.1±10.7*	<0.005

*significantly high vs other groups

Table 8
Postoperative secondary complications

	Group P (n=30)	Group G (n=30)	Group C (n=30)	P-value
NOUSEA	4(13.3%)	6(20%)	10 (33.3%)	> 0.05
VOMITING	5(16.6%)	6 (20%)	9(30%)	> 0.05
DIZZINESS	5(16.6%)	6 (20%)	2(6.6%)	> 0.05
DROWSINESS	2(6.6%)	4 (13.3%)	0(0%)	> 0.05
HEADACHE	1(3.3%)	3 (10%)	1(3.3%)	> 0.05
VISUAL DISTURBANCE	1(3.3%)	0 (0%)	0(0%)	> 0.05
URINE RETENTION	0 (0%)	0 (0%)	1(3.3%)	> 0.05
PRURITUS	0(0%)	1 (3.3%)	0(0%)	> 0.05
RESPIRATORY DEPRESSION	0 (0%)	0 (0%)	0(0%)	

Data expressed as number(%).

Discussion

Postoperative pain is defined as a condition of tissue injury along with muscle spasm after surgery. At present, peripheral and central sensitization is shown in the mechanism of postoperative pain generation. Postoperative analgesia is a component of postoperative management of pain and is required for gaining patients satisfaction and smooth recovery. Adequate pain management leads to early mobilization and decrease in cardiac and respiratory complications reducing the stress response leading to good wound healing and recovery. Inadequate pain control leads to higher morbidity and mortality, prolonged hospital stay and the development of chronic postoperative pain. Pain management is therefore best achieved by an approach which acknowledges the complex interactions between biological , psychological and socio-cultural factors. Effective pain management requires thorough patient preparation and education to manage expectations and a robustly structured inpatient service for postoperative pain management and continues staff education.

Abandoning the old opioid-centric model, physicians are focusing more on nonsteroidal anti-inflammatories like acetaminophen, gabapentinoids, NMDA antagonists, alpha-2-agonists, and sodium and calcium channel blocking agents. Such multimodal therapy has at least two desirable effects. First, a multimodal approach may decrease the use of opioids and associated side effects (e.g. delirium ,respiratory depression ,tolerance, and diversion).Second , a multimodal approach may be a more effective pain control strategy, potentially decreasing the complications associated with suboptimal pain control , such as pneumonia, deep venous thrombosis, and postoperative cognitive dysfunction.

Gabapentinoids (Gabapentin and pregabalin) are anticonvulsant agents commonly used as preoperative analgesics. Both agents bind to voltage-gated calcium channels and promote antinociceptive actions by inhabiting the release of excitatory neurotransmitters. These medications were initially used for treatment of chronic neuropathic pain, but they may also work to prevent and reduce acute pain and opioid consumption. Meta analyses indicate that a single dose of gabapentin or pregabalin administered preoperatively is associated with decrease in postoperative pain and opioid consumption at 24 hours but an increase in postoperative sedation, dizziness, and visual disturbances. In Jokela,etal study patients reported Dizziness and Blurred vision but even those who were on 600 mg Pregabalin per day did not report any severe symptoms. Recent evidence also suggests that they may reduce chronic postsurgical pain (CPSP), although more clinical trials are needed. As such, in elderly patients, these agents should be used with caution or the dose should be decreased. Gabapentanoids are renally excreted; thus, the dose should be decreased in patients with renal dysfunction.

In our study we compared the anxiolytic and analgesic effects provided by single dose pregabalin 150 mg given 1 hours preoperatively versus gabapentin 800 mg, against control group, in patients undergoing partial thyroidectomy. Present study showed that the effect of 150mg pregabalin is compared to gabapentin 800 mg as both cause fall mean arterial pressure and pulse rate near equally compared to placebo group, time to first request of analgesics was also compared in both groups, pregabalin group (214 min) compared to Gabapentin (217min).VAS scores difference seen with pregabalin and Gabapentin were insignificant. Similar results have been observed by Ghai A Study[11]. Oral pregabalin and Gbapentin are useful adjuvants for the management of post operative pain by providing analgesia through a different mechanism than opioids making addition to multimodal therapy if not as sole analgesic and with higher patient satisfaction.

Conclusion

Our study concluded that the anxiolytic, analgesic efficacy of 150 mg pregabalin given 1 hour preoperatively was equivalent to that provided by Gabapentin 800 mg for post operative pain. Post operative pain relief duration was prolonged in both groups than the placebo group. Preemptive analgesia with pregabalin 150 mg appears to be equal in safety, analgesic requirement and patient satisfaction to gabapentin 800mg as a part of multimodal preoperative and post operative management in partial thyroidectomy.

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