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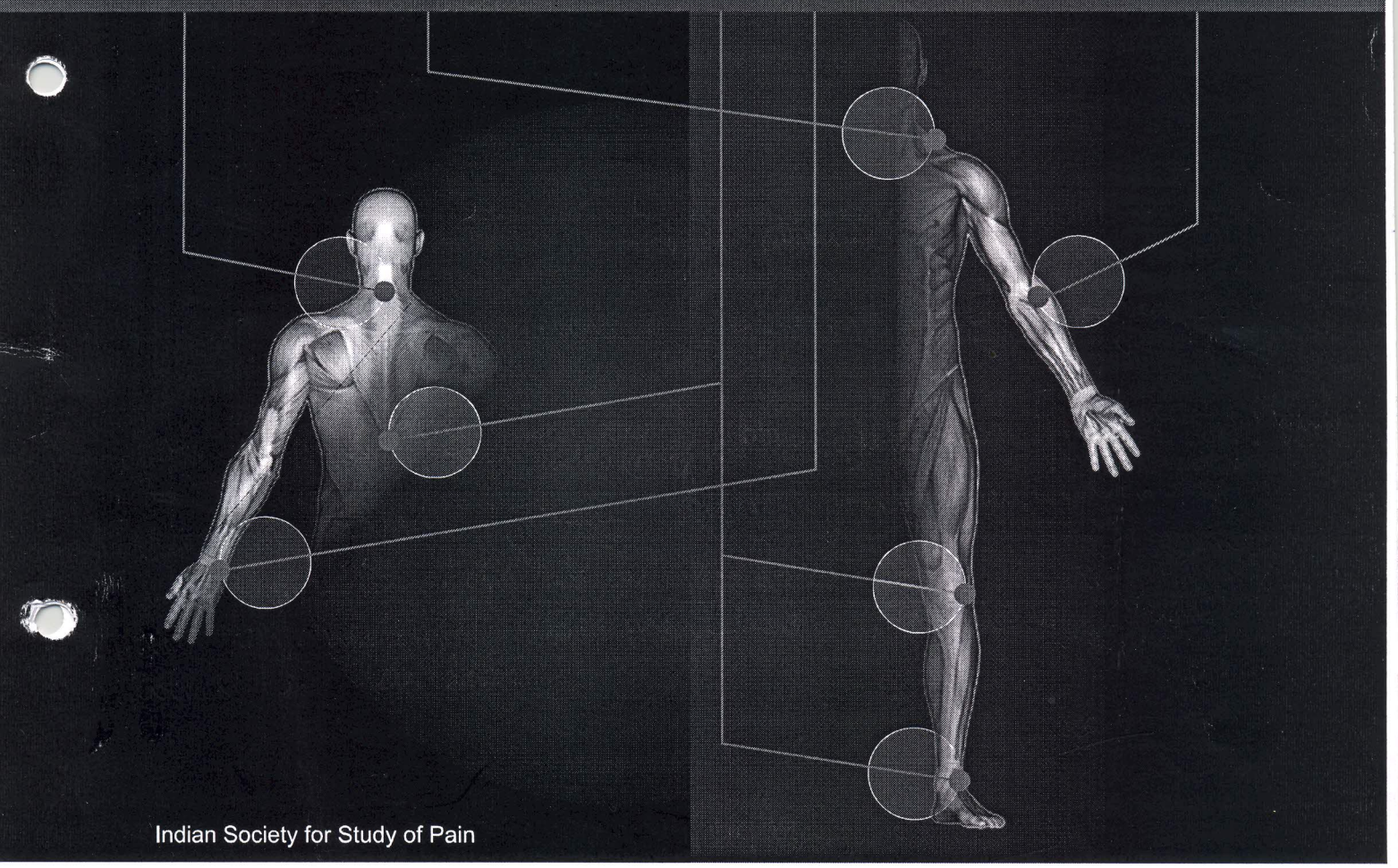

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Prospective, randomised, double blinded controlled trial of gabapentin and pregabalin as pre emptive analgesia in patients undergoing lower abdominal and limb surgery under spinal anaesthesia

Induja Rajendran, Asha Basavareddy[1], Bikash Ranjan Meher[2], Srikanth Srinivasan[3]

Third Year MBBS Student, [2]Departments of Pharmacology and [3]Community Medicine, Sri Venkateshwaraa Medical College and Hospital, Pondicherry, [1]Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India

ABSTRACT

Introduction: Postoperative pain management of high quality is important and in majority of post surgical cases pain is not treated adequately. We have evaluated the efficacy and safety of pregabalin and gabapentine as preemptive analgesic for post operative pain management in patients undergoing lower abdominal and lower limb surgery under spinal anesthesia. **Materials and Methods:** In a randomized double blind study, 90 patients were divided into three groups. Group G received tab gabapentin 900 mg, Group P received tab pregabalin 300 mg and Group C received placebo tablet orally 1 hour prior to surgery. All patients underwent surgery under spinal anesthesia using 0.5% Bupivacaine. Assessment of postoperative pain was made with visual Analogue Scale (VAS) score at 1, 2, 4, 6, 8, 12, 18, and 24 hours post operatively. Injection tramadol 100 mg was given as rescue analgesic intramuscularly when VAS score was > 7 in all the groups. Time to first rescue analgesics and number of rescue analgesics received were noted in all groups. The occurrences of side effects were noted in all groups. **Results:** The tramadol as rescue analgesia consumption was less in pregabalin and gabapentin groups compared to control and was statistically significant ($P < 0.001$). Initial VAS scores were lower in pregabalin (3.2 ± 0.4) and gabapentin (3.63 ± 0.32) groups compared to control (6.60 ± 0.77) and was statistically significant ($P < 0.001$). Time to first rescue analgesia was significantly longer for pregabalin (24.6 hours) followed by gabapentin (20.76 hours) and control (4.93 hours) groups. **Conclusion:** Pregabalin 300 mg single dose given 1 hour prior to surgery is superior to 900 mg gabapentin and placebo in attenuating post operative in patients undergoing lower abdominal and lower limb surgery. Both drugs are better than placebo.

Key words: Analgesia, gabapentin, pain, preemptive, pregabalin

Introduction

Postoperative pain management of high quality is utmost important but still remains a challenge.[1] Among all the surgical procedures, it is thought that pain is inadequately treated in almost 50% cases.[2] Central neural hyperexcitability is one of the factor that aggravate post operative pain, recent studies have suggested that some drugs can prevent or attenuate the central neural hyperexicitability.[3,4] gabapentine and pregabalin were originally developed to treat spastic conditions and as adjuvant for the management of resistant epilepsy.[5] Gabapentin is a lipophilic structural analogue of gamma-aminobutyric acid (GABA) and is N-methyl-D-aspartate receptor (NMDA) antagonist which binds to voltage dependent L-type of calcium channels.[6] Pregabalin is an anticonvulsant drug used for neuropathic pain which causes influx of calcium and release GABA.[7] Pregabalin is more lipid soluble and has better pharmacokinetic

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Address for correspondence:
Dr. B. Asha,
Associate Professor, Department of Pharmacology,
Sri Devaraj Urs Medical College, Tamak,
Kolar - 563 101, Karnataka, India.
E-mail: dr.ashareddy@gmail.com

profile with fewer drug interactions in comparison to its developmental predecessor gabapentin.[8]

Gabapentin has been found to be useful in postoperative pain after breast surgery[9], spinal surgery,[10] and laproscopic cholecystectomy.[11] Similarly pregabalin is claimed to be useful in preventing acute nociceptive pain of surgery, to reduce opioid consumption post operatively.[12,13] Pregabalin may be useful in amelioration of postoperative anxiety as its effectiveness in treating generalized anxiety disorder has been proved in several clinical trials.[14-16] None of these studies compare pregabalin 300 mg and gabapentin 900 mg in surgeries under spinal anesthesia. The present study was therefore designed to evaluate and compare the role of preoperative single dose of pregabalin with gabapentin for attenuating postoperative pain, rescue analgesic requirement and safety profile in patients undergoing surgeries under spinal anesthesia.

Materials and Methods

This study was registered with clinical trial registry of India with trial registry number CTRI/2014/03/004509. After getting written informed consent from each participant 90 subjects (males and females) in the age-group of 18-70years with ASA grade I and II undergoing surgeries under spinal anesthesia using 0.5% bupivacaine were included in the study. Patients aged more than 70 years having contraindications to the use of pregabalin, gabapentin or current use of gabapentinoids, taking analgesics for chronic pain, sedation, epileptics, impaired renal functions, and body weight > 20% of the ideal body weight were excluded.

Study design and outcome

This was prospective, randomized, double blind, placebo controlled, comparative clinical study. Patients meeting inclusion criteria during preanesthetic evaluation were randomly assigned into three groups of 30 each with the help of a computer-generated table of random numbers, to receive either pregabalin 300 mg, gabapentin 900 mg or matching placebo. The study medications looked identical and were packed and sealed in opaque covers labeled with investigators name, project title and randomization number. Each patient received appropriate randomized number and allocated to their group according to the number. No anesthetist or assessor was aware of the group assignment until the entire 90 patients were included and the assessment was completed. These 90 patients were matching placebo. The study drug was administered orally 1 hour prior to surgery. No other sedative preanesthetic medication was administered. Patients were familiarized with the use of a 10 cm linear Visual Analogue Scale (VAS) for pain, which ranges from 0 (no pain) to 10 (worst imaginable pain). In the operation theatre, pulse oximeter, heart rate, noninvasive blood pressure and electrocardiogram (ECG) were monitored. Anesthesia was standardized in all patients, 10 ml/kg ringer lactate was preloaded in all patients before giving spinal anesthesia for various surgical procedures. Spinal anesthesia was instituted wit 15 mg of 0.5% bupivacaine. Intravenous (IV) fluids were continued intraoperativey. After surgery all patients were transferred to surgical intensive care unit (SICU). In SICU pain was assessed immediately by VAS and thereafter assessed at every 2 hours for 24 hrs assessment was done by a trained nurse and medical student. If VAS score was more than 7, patient received injection tramadol 100 mg intramuscularly and was noted. Time for first dose of rescue analgesia and total dose of rescue of rescue analgesia in 72 hours was recorded and considered as primary outcome.

Any complications like dizziness, somnolence, post operative nausea, vomiting (PONV), confusion, urinary retention of adverse events were recorded in 72 hours of postoperative period. The severity of PONV was graded on a four-point ordinal scale (0 = no nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea with vomiting). The Ramsay sedation scale (awake levels were 1 = anxious, agitated; 2 = oriented, co operative, tranquil; 3 = responds to command; asleep levels were dependent on patients response to a light glabellar tap or loud auditory stimulus; 4 = brisk response; 5 = sluggish response; and 6 = no response) was used to assess sedation score in all groups. The data were unblinded at the end of the study.

Statistical analysis

Data were analyzed using SPSS version 16. Sample size was calculated keeping power of 80% and α value to 0.05 for comparing two means (gabapentin and pregabalin) with anticipated standard deviation being 3.1 and difference between the means as 2.5. The calculated sample size for each group came up to 24. We have taken 30 patients in each group keeping dropouts into consideration. One way analysis of variance (ANOVA) was used for comparing total analgesic consumption over 72 hours and time interval to first analgesic. Post hock Bonferroni test was used for intergroup comparison. Non parametric Krushal Wallis test was used for comparing sedation scores over 24 hours. The chi-square test was used to find association between side effects and study drug. Descriptive variables expressed as mean ± SD.

Results

This study was conducted at Sri Venkateshwaraa Medical College Hospital and Research Center, Pondicherry, India. The numbers of patients screened were 96, out of whom 90 were enrolled in the study and all patients completed the study. The groups were comparable with respect to age, weight, sex, ASA grade I/II, and duration of surgery [Table 1]. Patient distribution according to the type of surgery is comparable in all groups [Table 2]. The time to first analgesic and total consumption of tramadol as rescue analgesic are shown in Table 3. The difference in time to first rescue analgesia was significant in group P ($P < 0.001$) and group G ($P < 0.001$) compared to group C. Two patients in group P did not require rescue analgesic. The total consumption of tramadol in 72 hours was 386.5 ± 20.12 for control, 90.65 ± 9.25 with pregabalin and 200.77 ± 16.77 with gabapentin. The VAS scores postoperatively at regular intervals of all the groups are depicted in Table 4. There is significant difference ($P < 0.001$) between all groups from first hour to 8 hour. The VAS scores of gabapentin ($P = 0.206$) at 12 hour was not significantly reduced compared to control. The total VAS scores of pregabalin and gabapentin were significantly ($P < 0.001$) less compared to control. The total VAS score of pregabalin was significantly less ($P = 0.023$) compared to gabapentin. The sedation scores at different time interval are shown in Table 5. The incidence and severity of PONV, incidence of headache, dizziness, and urinary retention are presented in Table 6. Respiratory depression was not observed in any patient.

Discussion

In the present study we have observed that preoperative single dose of pregabalin (300 mg) resulted in significant reduction in postoperative analgesic requirement compared to gabapentin (900 mg) and placebo in infraumbilical surgeries under spinal anesthesia. The VAS scores were significantly reduced in the initial hours of recovery. The antinociceptive and antihyperalgesic properties of gabapentin and pregablin have been demonstrated in experimental animal models of neuropathic and inflammatory pain.[1] The central nervous system (CNS) is well-protected from harmfull effect of noxious stimuli and hyperalgesia by administering preincisional analgesia. Several studies have reported the effectiveness of gabapentin and pregabalin in neuropathic pain, acute postoperative pain by reducing postoperative analgesic requirement with better patient satisfaction[17] in surgeries like vaginal hysterectomy[18], thyroid surgery[19] and also in epidural analgesia.[20]

The mechanism of action of pregabalin and gabapentin are same as they both are GABA analogues. Pregabalin is required in lesser dose and is associated with few dose related adverse effects compared to gabapentin as it has better pharmacokinetic profile.[8] Most of the previous studies have reported 1200 mg of gabapentin.[12,17,18,20,21] One study by Ghai A ., have used gabapentin 900 mg for pain management after abdominal hysterectomy.[22] As there was paucity of studies using gabapentin 900 mg and no study had been reported in lower abdominal and lower limb surgeries under spinal anesthesia, we designed this controlled clinical study to compare gabapentin 900 mg with pregabalin 300 mg. In this study we have also calculated the total analgesic consumption for 72 hours, which is significantly less ($P < 0.001$) with pregabalin compared to gabapentin and control.

Many studies reported ineffectiveness of pregabalin in the dose of 50 mg[12], 100 mg in gynecological surgeries[23] and 150 mg in day care laproscopic surgeries.[24] In contrast to the above studies Agarwal A ., showed 150 mg pregabalin was effective in attenuating postoperative pain after laproscopic cholecystectomy[25] and laproscopic hysterectomy.[26] There was decrease in pain scores in our study with pregabalin and gabapentin which is consistent with previous studies.[17-19] There was significant difference

Table 1: Patient Demographic and intraoperative variables (Values expressed as mean ± SD, numbers)

Variables	Group C ($n = 30$)	Group P ($n = 30$)	Group G ($n = 30$)	*P* value
Age (years)	42.2±10.03	43.4±12.8	42.3±12.7	CαP=0.821 CαG=0.954
Weight (kgs)	66.5±9.70	64.3±9.45	67.45±9.9	CαP=0.767 CαG=0.865
Gender M/F	18 (60%)/12 (40%)	17 (56.6%)/13 (43.4%)	21 (70%)/9 (30%)	CαP=0.977 CαG=0.874
ASA grade I/II	25/5	26/4	24/6	CαP=0.926 CαG=0.926
Duration of surgery (mins)	45.6±21.62	48.17±27.60	46.7±22.66	CαP=0.639 CαG=0.822

All groups were comparable *P* value > 0.05, age, weight and duration of surgery by unpaired t-test, Gender and ASA grade by Fisher exact test

Table 2: Patient distribution according to type of surgery (*n*)

Type of surgery	Group C	Group P	Group G	*P* value
Hydrocele	6	6	3	CαP=1.00
				CαG=0.06
Inguinal hernia	6	6	8	CαP=1.00
				CαG=0.67
Fissure in Ano	4	4	4	CαP=1.00
				CαG=1.00
Skin graft	0	0	2	
Appendicectomy	6	7	7	CαP=0.987
				CαG =0.987
Varicose vein	4	4	2	CαP=1.00
				CαG=0.06
Haemarroidectomy	2	1	2	CαP=0.639
				CαG =1.00
Anal poly	2	2	2	CαP=1.00
				CαG=1.00

All the groups are comparable with respect to type of surgery $P > 0.05$

Table 3: Comparison of Post operative analgesia (values in mean ± SD and number)

Variables	Group C	Group P	Group G	*P* value
Time to first rescue analgesic (hrs)	4.93±2.77	24.06±5.76*	20.76±4.35*	PαG=0.06
Mean number of doses of rescue analegesics in 72hrs (*n*)	3.86	0.9*	2*	PαG<0.001
Total dose of rescue analgesic in 72 hours (mg)	386.5	90.5*	200.77*	PαG<0.001

CαP and CαG, *$P < 0.001$ highly significant

Table 4: Post operative VAS scores (values in mean ± SD)

VAS score (hours)	Group C	Group P	Group G	*P* value
VAS-1 hour	6.60±0.77	3.2±0.4*	3.6±0.32*	
VAS-2 hours	6.53±0.81	3.2±0.4*	3.87±0.34*	
VAS-4hours	6.60±0.84	3.2±0.4*	4.03±0.41*	
VAS-6hours	6.50±0.73	3.5±0.5*	427±0.52*	
VAS-8 hours	6.23±0.81	3.63±0.6*	4.7±0.53*	
VAS-12 hours	5.63±0.76	4.03±0.6	5.83±0.37#	*P*=0.206
VAS-18 hours	5.83±0.91	5.7±0.63#	6.40±0.62	*P*=0.468
VAS-24 hours	6.03±0.80	6.77±093	6.1±0.66#	*P*=0.75

*$P < 0.001$ PαG, PαC, GαC, #$P > 0.05$

Table 5: Sedation scores at various time intervals

Time (hours)	Group C	Group P	Group G
1 hour	1.35±0.50*	2.36±0.25	1.88±0.27
2 hours	1.42±0.57*	2.10±0.1	1.97±0.19
6 hours	0.57±0.37*	1.92±0.30	1.89±0.25
12 hours	0.17±0.27*	1.27±0.22	1.35±0.47

C α P, G ($P < 0.001$)

in score for initial 12 hours which is much longer than the plasma t1/2 of Pregabalin (6-8 hours). Time to first analgesic was significantly longer with pregabalin due to its quicker and consistent action compared to gabapentin. The incidence of side-effects were comparable in all the groups except for sedation which is an expected, harmless side effect.

Table 6: Comparison of side effects (*n*)

Variables	Group C	Group P	Group G
PONV			
No	16	18	16
Mild	4	2	4
Moderate	7	8	9
Severe	3	2	1
Headache	1	–	–
Dizziness	3	4	3
Urinary retention	–	1	–

No significant difference between the groups by chi square test ($P > 0.05$), PONV: Postoperative nausea and vomiting

Limitations of our study are only single dose of gabapentin and pregabalin are used which does not infer the long term benefits to the patient. Study with different doses needs to be conducted for both gabapentin and pregabalin to arrive at an appropriate analgesic dose. More studies are to be conducted to compare the pre and post operative analgesic effects of gabapentin and pregabalin.

In conclusion, preemptive pregabalin 300 mg reduced the analgesic requirement compared to gabapentin 900 mg and placebo in lower abdominal and lower limb surgeries. The side effect profile was comparable in all the groups. We suggest use of pregabalin 300 mg in treating post operative pain after lower abdominal and lower limb surgeries under spinal anesthesia.

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