COMPARATIVE STUDY OF PREEMPTIVE ORAL GABAPENTIN WITH PREGABALIN FOR POSTOPERATIVE ANALGESIA IN PATIENTS UNDERGOING ABDOMINAL HYSTERECTOMY UNDER SUBARACHNOID BLOCK

Anesthesiology

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ABSTRACT

Introduction: Pain management is important for early mobilization and well-being of the surgical patient. So we compared pregabalin and gabapentin as preemptive analgesic for post operative pain management in patients undergoing abdominal hysterectomy under subarachnoid block.

Material And Methods: In this randomized controlled double blinded study, 60 elective patients posted for abdominal hysterectomy were randomly divided into two groups of 30 patients each. Group G900 received 900 mg Gabapentin and group P300 received 300 mg Pregabalin, administered orally 1 hour prior to administration of spinal anesthesia. VAS scores, first rescue analgesic time, total analgesic requirement, and any adverse effects in first 24 hours postoperatively were compared.

Results: Mean total analgesic dose and mean no. of doses in first 24 hour post-operatively were significantly lower while time to first rescue analgesic was significantly more in pregabalin compared to gabapentin.

Conclusion: Preemptive pregabalin is more effective for postoperative pain relief compared to gabapentin.

KEYWORDS

Pregabalin, gabapentin, preemptive analgesia, subarachnoid block

INTRODUCTION

Pain is a predictable part of any kind of surgical intervention yet its appropriate management has always been a challenging task since not achieving the same can result in clinical and psychological changes which increases morbidity and mortality as well as costs leading to decreased quality of life. Prevention and treatment of postoperative pain thus plays an important role in the early mobilization and well-being of the surgical patient.

The concept of multimodal analgesia developed by Kehlet and Dahl¹ took into account a combination of drugs which act by different mechanisms, so as to reduce the dosage and side effects of opioids. However, each of them had its own set of adverse effects. Interventional techniques such as epidural analgesia require additional expertise and carry the potential risk of further complications such as epidural hematoma, intravascular injection, hypotension, and local anaesthetic toxicity.

The introduction of preemptive analgesia by Crile and further developed by Wall and Woolf revolutionized postoperative pain relief². The aim of pre-emptive analgesia was to prevent the abnormal pain sensitivity postoperatively, by introducing an analgesic regimen before the onset of noxious stimuli, in order to prevent the nervous system sensitization to subsequent stimuli that could amplify pain. This also added to improved quality of recovery and prevention of development of chronic pain³. And surgery is the most desirable setting for the implementation of such preincisional analgesia as the timing of noxious stimuli is already known.

Recent evidence suggests that using a combination of preemptive techniques involving centrally acting analgesic drugs like gabapentinoids (gabapentin and pregabalin) would be beneficial in improving postoperative analgesia and decreasing opioid consumption. The mechanism of action of both, Gabapentin and Pregabalin, being similar, acts by interacting with voltage-gated calcium channels and decreasing calcium-dependent release of pronociceptive neurotransmitters, hence decreasing neuronal hyperexcitability⁴. Along with a better pharmacokinetic profile, Pregabalin is claimed to be more effective comparatively in preventing neuropathic components of acute nociceptive pain of surgery, perioperative anxiety and also has opioid sparing effect⁵.

We hereby carried out this study in order to evaluate the post-operative analgesia in terms of quality and duration, the time of first rescue analgesia and the subsequent number of analgesic doses along with the adverse effects of pre-emptive oral Pregabalin (300mg) and oral Gabapentin (900mg) in patients undergoing abdominal hysterectomy under spinal anaesthesia^{5,6}.

MATERIALS AND METHODS

After taking written informed consent of the patients, 60 patients of

ASA grade I/II (age 35-60 years) posted for elective abdominal hysterectomy under spinal anaesthesia were selected for the study.

Exclusion Criteria:

- Patient refusal,
- allergic to the study drugs,
- ASA grade III/IV
- any contraindication to neuraxial anesthesia,
- kidney or liver dysfunction or any co-existing diseases,
- h/o chronic pain or daily intake of analgesics,
- h/o intake of non steroidal antiinflammatory drugs within 24 h before surgery.

After undergoing pre anaesthetic evaluation, routine blood and radiological investigation, Patients were explained about Visual Analogue Scale score (VAS) in preoperative visit and again in the operating room.

Patients were randomly divided into two groups of 30 each as below:

Group G900: received single dose of oral gabapentin 900 mg (1 capsule-300 mg)

Group P300: received single dose of oral pregabalin 300 mg (1 capsule-150 mg).

The above drugs were given 1 hour prior to administration of spinal anaesthesia in the preoperative ward in patients scheduled for abdominal hysterectomy.

No other sedative preanesthetic medication was administered.

In the operating room patients were preloaded with Ringer lactate 15ml/kg IV. Monitors were applied and baseline vitals like Heart Rate (HR), ECG, O₂ saturation (SpO₂) and noninvasive Blood pressure (BP) were recorded and monitored throughout the surgery. Subarachnoid block was given in sitting position under strict aseptic precautions, using 0.5% hyperbaric bupivacaine 3.5 ml, after confirming the free flow and clear aspiration of CSF (cerebrospinal fluid). The level of spinal anaesthesia was checked and surgery was started after achieving T6 level.

Hypotension, defined as systolic blood pressure below the 20% of baseline value or value below 90 mmHg, was treated with Inj. Mephentermine (3 mg bolus) I.V. Bradycardia, defined as heart rate below the 20% of baseline value or rate below 50/min, was treated with Inj. Atropine 0.6 mg I.V.

Post-operatively the patients were kept under observation for 24 hours.

Pain intensity was measured using Visual analogue scale till 24 hours postoperative. VAS (0-10 point scale): 0 – no pain; 1-3-mild pain; 4-7-moderate pain; 8-10-severe pain. Patients were given Inj. diclofenac 75 mg I.V. when the VAS score was 4 or greater, at the interval of assessment or whenever patient complained of such VAS. Time since spinal anaesthesia to first rescue analgesic (T1), Total analgesic requirement in first 24 hours, Any complications like dizziness, somnolence, nausea, vomiting, confusion, vertigo, ataxia, visual disturbances and urinary retention were recorded in the first 24 hours.

Statistical Analysis

Data analysis was performed, on a sample size of 60, by using Statistical package SPSS by microsoft excel 2010. Numerical variables were presented as mean & standard deviation (SD) while categorical variables were presented in percentage. As regard to numerical variables, unpaired student-t test was done. p-value <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

Table 1 : Demographic Profile

	G900(Mean ± SD)	P300(Mean ± SD)
AGE(years)	51.8 ± 6.5	51.1 ± 6.36
BODY WEIGHT(kg)	55.16 ± 5.57	58.6 ± 8.414
ASA PHYSICAL STATUS(I/II)	(20/10)	(21/9)
HEIGHT(cm)	154.4 ± 3.02	153 ± 3.11
BMI(kg/m ²)	24.21 ± 2.21	23.24 ± 2.26
DURATION OF SURGERY(minutes)	112.36 ± 8.38	113 ± 8.49

Amongst both the groups, there were no analytical variance in patient's demographic data, duration of surgery or ASA physical status as shown in Table 1.

The intraoperative hemodynamic parameters i.e. mean blood pressure, heart rate and SpO₂ were similar in both the groups.

Table 2:

	G900(Mean±SD)	P300(Mean±SD)	p Value
Time to rescue analgesia (T1)(hours)	7.63 ± 1.76	15.76 ± 3.5	<0.0001
Total analgesia in 24 hours (mg)	109.62 ± 34.34	84.13 ± 22.2	=0.0012

VAS Scores:

Group G900 showed an increase in the VAS scores till 6 hours postoperatively after which a decline was observed which reflected the administration of first dose of rescue analgesic. Similarly, in group P300, an increase in VAS scores till 12 hours postoperatively followed by decrease in the VAS scores suggested the administration of first dose of rescue analgesics. The total VAS scores in group P300 were significantly less as compared to the group G900 (p < 0.0001).

The Mean time for the first rescue analgesic dose (i.e. time duration from administration of spinal anaesthesia to the first dose of analgesic required postoperatively) was 7.63 ± 1.76 hours in group G900 and was 15.76 ± 3.5 hours in group P300 and it was highly significant (p value < 0.0001).

The Mean Dose Of Analgesic Required In The First 24 Hours was lower in group P300 (84.13 ± 22.2 mg) as compared to that in group G900 (109.62 ± 34.34 mg), which was reflected by the lower number of analgesic doses required in group P300 (1.2 ± 0.62) as compared to group G900 (1.83 ± 0.72), the difference being statistically significant (p value < 0.001).

Total number of analgesic doses in 24 hours: in group G900, 15 patients required a single dose, 10 patients required two and 5 patients required three analgesic doses whereas in group P300, 24 patients required a single dose, 4 patients required two analgesic doses. However, in our study, there were 2 patients in group P300 who were completely pain free and didn't need any analgesic in first 24 hours postoperatively.

Table 3 Sedation Scores At Various Time Intervals

Time(hours)	G900	P300
1 hour	1.86±0.36	2.07±0.30
2 hours	1.97±0.17	2.00

6 hours	1.90±0.26	1.90±0.30
12 hours	1.36±0.48	1.27±0.50

Sedation Scores:

Ramsay Sedation scores were comparable at all time intervals in both the groups except for in the first postoperative hour which was expected but a harmless side effect.

Adverse Events:

13.3% patients in group G900 and 6.67% patients in group P300 had nausea and vomiting. 20% patients in group G900 and 16.6% in group P300 had dizziness. Somnolence was observed in 23.3% in group G900 patients and 26.6% in group P300 patients. Other adverse effects like vertigo, ataxia, urinary retention were not observed in either of the groups.

DISCUSSION:

Clinical pain can be subdivided into inflammatory and neuropathic pain. Inflammatory pain refers to pain associated with peripheral tissue damage, produced during surgery. It is characterised by changes in sensitivity, notably a decrease in the pain threshold so that stimuli which generally doesn't cause pain, begins to do so (allodynia). There is also an exaggerated response to noxious stimuli (hyperalgesia) along with hypersensitivity caused to non injured tissue (secondary hyperalgesia)⁸.

Two mechanism operate to produce these changes exclusively found in inflammatory pain. The first is peripheral sensitization, where there is an increase in sensitivity of the transduction mechanism of high threshold nociceptor primary sensory neurons at their peripheral terminals because of exposure to a cocktail of inflammatory mediators and other chemicals liberated by, or in reaction to, tissue damage^{8,9}. This contributes to the changes in thermal sensitivity in the immediate vicinity of tissue injury^{8,10,11}. The second mechanism is central sensitization where there is change in excitability of neurons in the spinal cord, triggered by and outlasting the nociceptive afferent inputs¹².

Having antiallodynic and antihyperalgesic properties in addition to antianxiety properties with only a minimal effect on normal nociception, gabapentinoids makes an attractive choice of drug for decreasing acute postoperative pain¹³.

In an animal model of postoperative pain, it was found that pretreatment with a single dose of gabapentin blocked the development of hyperalgesia and tactile allodynia for up to 2 Days¹⁴.

Also, a multiple dosing regimen exaggerated the central nervous system side-effects of gabapentinoids (i.e., sedation and dizziness) which could be troublesome to patients especially in the postoperative ambulatory period.

These drugs are only available for oral administration and the absorption of gabapentin is slow and limited by active transport in the gastrointestinal tract^{14,15}. So the time lag from its administration till the peak effect was reached (i.e. 2-3 hours) was compensated by the surgery carried out under subarachnoid block.

Khan and colleagues¹⁶ observed that in the first 12 hours, morphine consumption and pain scores were lower, the time to the first rescue analgesia was longer, in groups receiving either 900 mg or 1200 mg gabapentin, compared with placebo or 600 mg gabapentin. Also plasma concentrations of gabapentin do not increase proportionally with increasing dose (non-linear absorption) and that the bioavailability of gabapentin drops to almost half as the dosage increases from 900 mg to 3600 mg¹⁷. On the other hand, The bioavailability of pregabalin is high and exceeds 90% irrespective of the dosage. Being 6 times more potent than gabapentin in binding affinity, its absorption is more rapid and without a ceiling of amount absorbed^{18,19,20}. The efficacy of 300 mg pregabalin has been well proven in previous trials and it has proven efficacious at doses 2-4 fold lower than that of gabapentin. All the above factors was the basis of our study where in a single equipotent dose of gabapentin 900 mg was chosen in comparison to single 300 mg pregabalin.

In our study, there was a decrease in pain scores for a considerable time, as depicted by the VAS score with pregabalin and gabapentin which is consistent with the studies by Tippana et al²¹, Rorarius MG et al²² and Al-Mujadi H et al¹⁵. A significant difference was observed for the initial

12 hours which is much longer than the plasma t_{1/2} of Pregabalin (6-8 hours). Time to first analgesic was significantly longer with pregabalin (15.76±3.5 hours) due to its quicker and consistent action as compared to gabapentin (7.63±1.76 hours), results being similar to studies done by Saraswat et al²³ and Pal et al²⁴.

The 24 hours analgesia requirement was significantly low in group Pregabalin compared to gabapentin, comparable to the studies conducted by Trivedi et al⁴, Khetarpal et al²⁵.

The mean number of analgesic doses were significantly lower in pregabalin group as compared to gabapentin group similar to the study done by Thakur et al³ and Ghai et al⁵ as against the study done by Saraswat et al²³ who did not find any significant difference between number of analgesic doses in both the groups.

The incidence of adverse effects though present in both of the groups were not incapacitating. Similar observation was seen in studies conducted by Basavareddy et al⁶ and Prasad et al²⁶. The only limitations of our study is that due to lack of facility in our setup, we could not measure the levels of the study drugs, and only single doses of pregabalin and gabapentin were used which may have resulted in decreased effect over time and does not reflect on the long-term benefits to the patients.

CONCLUSION

With respect to the above observations, we conclude in our study that preemptive gabapentin and pregabalin can significantly reduce the need of postoperative rescue analgesia, and increase the duration of post spinal analgesia without altering the intraoperative hemodynamics, pregabalin being a better choice in terms of safety, quality and duration of analgesia and patient satisfaction.

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