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Original Research Article

To evaluate efficacy of pregabalin as premedication for post-operative analgesia in open appendicectomy

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ABSTRACT

Background: Pregabalin is gamma amino butyric acid (GABA) structural analogue, effectively used in management of different neuropathic pain, incisional and inflammatory injuries. Current study aimed to evaluate the efficacy of pregabalin 75 mg with a placebo as premedication for post-operative analgesia in patients posted for open Appendicectomy under regional anesthesia.
Methods: A randomized controlled trial was conducted on 90 patients undergoing open Appendicectomy under regional anesthesia. The patients were divided in two groups of 45 each: group C (placebo); group P (75 mg pregabalin), drug was administered orally 60 minutes before surgery. The Ramsay sedation scale (RSS) was used for assessment of sedation and the visual analog scale (VAS) was used to determine pain at rest and cough, along with assessment of time required for rescue analgesics on the first post-operative day.
Results: The RSS scores were significantly higher in groups P as compared to the controls ($p<0.001$). Postoperative VAS scores for pain both at rest and on cough were significantly reduced in group P ($p<0.001$). Rescue analgesic consumption decreased significantly in group P ($p<0.001$). The time at which first dose of rescue analgesia administered was 4.50±3.04 hours in group C, 10.90±5.37 hours in group P ($p<0.001$).
Conclusions: Pregabalin as premedication prolong the postoperative analgesia in addition to decreased consumption of analgesics.

Keywords: Open appendicectomy, Post-operative analgesia, Pregabalin

INTRODUCTION

Pain has been a significant concern for all individuals and many efforts have been done to understand and manage it. Postoperative pain is an acute pain which starts with surgical incision decreases as tissue heals. Despite advances in the knowledge, skill, and technology in the treatment of pain, patients continue to experience postoperative pain.

Postoperative analgesia helps the patients to recover fast with shorter hospital stay. A effective postoperative analgesia is provided by multimodal approach which includes administration of various combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and local anesthetics in perioperative period. But this approach has its own concerns, such as use of opioids may be associated with adverse side effects such as nausea, vomiting, excessive sedation, respiratory depression, pruritus, and urinary retention.[1,2] NSAIDs can lead to gastritis and upper gastro intestinal ulceration.[3] In addition invasive techniques such as epidural analgesia carry the potential risk of further complications such as hypotension and local anesthetic toxicity.[1]

Pregabalin is a structural analogue of gamma amino butyric acid (GABA). It acts by binding to the

presynaptic alpha-2-delta subunit of voltage gated calcium channels in both spinal cord and brain, where they are widely distributed. There by, it modulates the release of many excitatory neurotransmitters, such as glutamate, norepinephrine, substance-P, and calcitonin gene related peptide. It causes inhibitory modulation of overexcited neurons and restores them to a normal state. Pregabalin centrally decrease the hyperexcitability of the dorsal horn neurons due to tissue damage.[4,5]

Several studies have reported pregabalin as an effective post-operative analgesic with opioids sparing effects.[6-8] In contrast to this, there are some studies which have been contrary reporting that pregabalin has no significant post-operative analgesic effects.[9] Therefore our study aimed to compare the efficacy of pregabalin with a placebo administration for post-operative analgesia in patients undergoing appendicectomy under spinal anesthesia along with its adverse effects.

METHODS

After institutional ethical committee approval, a prospective randomized control study was conducted on 90 patients, posted for open appendicectomy under spinal anesthesia from Jan 2019 to Dec 2019 at Al-Ameen Medical College, Vijayapur, Karnataka, India. After informed written consent from all the patients, they were explained the visual analogue scoring (VAS) system. Patients aged 20-45 years with ASA class 1 and 2; BMI 18-30 kg/cm^2 were enrolled in the study.

Patients who refuse to participate in the study, had history of drug/alcohol abuse; history of headache, dizziness, or significant post-operative nausea or vomiting after any previous surgery; on anti-anxiety drugs; history of chronic pain and daily intake of analgesic drugs; history of epilepsy; contraindication to spinal anesthesia; and failed spinal anesthesia, were excluded from the study.

The study subjects were allocated into 2 groups of 45 patients each using a computer-generated random number table, group P (75 mg pregabalin): a pregabalin75 mg capsule was administered to the patient orally 60 minutes before shifting to the operation theatre. Group C (control): a placebo capsule was administered to the patient orally 60 minutes before shifting to the operation theatre.

The pre-operative baseline blood pressure and heart rate (before premedication, at 30 minutes after premedication, and at 60minutes after premedication) were recorded. The Ramsay sedation score (1 to 6) was assessed 1 hour after administering the drug. A score of 3 or more was taken as implying that adequate sedation had been obtained.

All of the patients were administered spinal anesthesia in lateral position, between the 3rd and 4th lumbar intervertebral space with a 26-gauge Quinke needle (0.5% hyperbaric bupivacaine at 0.35 mg/kg intrathecally). For post-operative analgesia, intravenous paracetamol of 1 gm 8th hourly was given to all patients. Rescue analgesics were administered if VAS>4. The first rescue analgesic was intravenous tramadol of 50 mg, and intravenous diclofenac of 75 mg was given if VAS>4 persisted for 30 minutes after the first rescue analgesic.

The following parameters were assessed: 1) VAS was assessed for pain at rest and on cough at 30 minutes, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours post-operatively. The number of doses of rescue analgesics required and the time to first or second rescue analgesic was noted on post-operative day one; 2) post-operative sleep quality was assessed on a grade of 1 to 5, where grade 1 meant "could not sleep at all," grade 2 meant "difficulty in falling asleep," grade 3 meant "woke up two or more times during the night;" grade 4 meant "woke up once during the night," and grade 5 meant "did not wake up even once during the night. A grade of 4 or 5 was considered as adequate post-operative sleep; 3) other adverse effects such as dizziness, nausea, and vomiting were also noted.

Descriptive and inferential statistical analysis was carried out. The results of the continuous measurements are presented as mean±SD (minimum - maximum), and the results of the categorical measurements are presented as numbers (%). The significance level was assessed at 5%.

Chi-square and Fisher's exact tests were used to determine the significance of the study parameters on a categorical scale between two groups. Statistical software, SAS 9.2 and R environment version 2.11.1 were used for the analysis of the data. A p value of <0.05 was taken as significant.

RESULTS

In terms of the demographic profile, the two groups were comparable with respect to age and BMI (Table 1).

Table 1: Comparison of age and BMI distribution.

Demographic data	Group C	Group P
Age, years	45.74±9.83	46.71±9.56
BMI	24.51±3.85	25.92±3.90

Values are expressed as mean±SD.

After comparing the preoperative Ramsay sedation score (RSS) between the groups one hour after receiving premedication, it was found that a majority of patients (43 or 95.55%) had an RSS score of 1 or 2. In group P, 11 patients (24.4%) and in group C, (2.2%) had an RSS score of ≥3. With respect to the inter-group comparison for patients with RSS ≥3, in group P versus group C, the p value was 0.002, and thus group P had significantly more patients with RSS scores of ≥3.

With respect to the VAS scores, as shown in Table 2, the pain scores were lower for group P compared to group C

at all times. When comparing group P with group C, it was seen that the pain scores were significantly low (p<0.05) for group P at all times except at 6 hours, 12 hours and 24 hours.

Table 2: Comparison of VAS scores at rest in the two groups.

VAS at rest	Group C	Group P	P value
30 minutes	2.48±0.95	1.50±0.74	<0.001
1 hour	2.99±0.72	1.71±0.66	<0.001
2hours	3.32±0.85	2.39±0.75	<0.001
6 hours	2.79±1.12	2.59±0.68	>0.05
12 hours	2.89±0.96	3.24±1.01	>0.05
24 hours	3.40±0.77	3.30±0.79	>0.05

Table 3: Comparison of VAS scores on cough in the two groups.

VAS on coughing	Group C	Group P	P value
30 minutes	3.14±0.98	2.42±0.74	<0.001
1 hour	3.63±0.91	2.60±0.62	<0.001
2 hours	4.44±1.06	3.22±0.83	<0.001
6 hours	3.81±1.25	3.56±0.75	>0.05
12 hours	3.86±1.043	4.34±1.21	<0.05
24 hours	4.43±0.92	4.34±0.92	>0.05

Table 3 shows the VAS results for pain on coughing. Pain scores were lower in group P compared to group C for most observations. Upon inter-group comparison between group P and group C, group 1 had significantly lower pain scores (p<0.001) at all times except at 6 hours, 12 hours, and 24 hours post-op. Ultimately, these values revealed that pregabalin 75 mg reduced post-operative pain at rest as well as on coughing.

Table 4: Rescue analgesics.

Rescue analgesics	Group C	Group P	Total
0 dose	4 (8.9)	20 (44.4)	24 (26.6)
1 dose	18 (40)	16 (35.6)	34 (37.7)
2 doses	23 (51.1)	9 (20)	32 (35.5)
Total	45 (100)	45 (100)	90 (100)

Values are expressed as No. (%).
Group C-group P: p<0.001

Table 4 shows the values for the rescue analgesics. An inter-group comparison between group P and group C showed that there were significantly lower (p<0.001) requirements for rescue analgesics as compared to those required for group C.

Table 5 shows the average times for the first rescue analgesic, which was 4.50 hours for group C, 10.90 hours for group P. Inter-group comparison revealed a significant difference in time for the first rescue analgesic consumption with a P value of <0.001 for each comparison.

Table 5: Time to rescue analgesic: a comparison of the two groups.

Time; rescue analgesic	Result		P value
	Group C	Group P	
First dose, hours	4.50±3.04	10.90±5.37	<0.001
Second dose, hours	17.79±4.16	19.66±4.04	<0.05

Concerning post-operative sleep, in the placebo group, a majority of patients had grade 3 (41.98%) or grade 4 (35.82%) sleep character; 8 (17.77%) of the patients had grade 2, and there was 1 (2.22%) patient each in the grade 1 and grade 5 groups. In group P, a majority of the patients had grade 4 sleep character 25 (55.55%); 9 (20%) patients had grade 5 sleep, 8 (17.77%) patients had grade 3, and 3 (6.66%) patients had grade 2 sleep character. With respect to inter-group comparison, significant differences were seen between the groups (p<0.05) which revealed that patients in group P had better sleep than those in group C. With respect to other adverse effects, the incidence of nausea was 80% (36 patients), 86.66% (39 patients) in groups C and P, respectively. The incidence of vomiting was 33.33% (15 patients), 26.66% (12 patients), in each of the respective groups. Nausea and vomiting were comparable between the groups with p>0.05. The incidence of dizziness was significantly higher (p<0.001) in group P (30 patients or 66.66%) and whereas in group, only one patient (2.22%) had dizziness.

DISCUSSION

Post-operative pain is due various inflammatory mediators and neurotransmitters which release from peripheral nociceptors activation due to surgical tissue injury.[10] The intensity of post-operative pain is an important determinant of chronic pain. Therefore, a successful management of pain in perioperative period will reduce the long-term morbidity with better quality of life.[11] Multimodal analgesia such as use of opioids, NSAIDs, gabapentinoids and many regional analgesic techniques to provide a superior pain relief in post operative period.[12,13]

Pregabalin is effectively used in management of pain due to neuropathy, inflammatory and incisional injuries. It has been shown that pregabalin produces slow-wave sleep in healthy persons, which is one of important factor in wound healing.[5,14,15] Thus our study aimed to find out the effect of pregabalin (75 mg) on postoperative pain when used as pre-operative medication.

This study compared the effects of pregabalin (75 mg) with a placebo as pre-operative medication on post-operative pain relief in patients undergoing open Appendicectomy. In our study, VAS scores were significantly lower (p<0.001) in the pregabalin group

with respect to placebo at 30 minutes, 1 hour, and 2 hours post-operatively. The pain scores were comparable at 6 hours, 12 hours, and 24 hours post-operatively both at rest and on coughing. These findings can be explained by elimination half-life of pregabalin after single dose which is 4.6 to 6.8 hours. Jokela and colleagues and Agarwal et al.[9,16] reported lower VAS score both at rest and upon movement with single preoperative dose of pregabalin, their findings are consistent with our study. Similarly, lower pain intensity was reported by Alimian et al studied pregabalin as premedication to reduce postoperative pain in patients undergoing laparoscopic gastric bypass, also concluded that intensity of pain is much less in pregabalin group.[17] However, Paech et al in their study have not reported any reduction in VAS score with pregabalin group.[18]

The results of this study have revealed that the time for first rescue analgesic was significantly increased ($p<0.001$) in the pregabalin group. Post-operative rescue analgesic requirements were also significantly lower in the pregabalin group (group p<group C). Similar findings have been reported by many studies.[7-9,16,17,19] These reports suggest that pregabalin as premedication provides significant analgesia in immediate postoperative period. In addition, sedation which has been described as a significant pharmacological effect of pregabalin.[4] In this study we found that pregabalin patients were adequately sedated (RSS>3) one hour after administration with better sleep profiles in postoperative period. Dizziness has been described as the most frequent adverse effect after a single dose administration. Our study also reported dizziness in pregabalin group much higher than the control group, other studies also observed similar results.[7,16,17] Agarwal et al in addition reported significant nausea and vomiting in the pregabalin group, but not a single patient had such adverse effect in our study.[16] Therefore, it can be said that the benefits clearly outweigh the potentially adverse effects.

A study carried out by Kohli and colleagues on the "optimization of subarachnoid block by oral pregabalin for hysterectomy" with 3 groups, group 1 was the control group, group 2 was administered 150 mg pregabalin, and group 3 was administered 300 mg pregabalin, all of which was given orally one hour before surgery.[7] It was observed that the time required for the first rescue analgesia with pregabalin 150 mg as premedication was 178.38±4.80 minutes post-surgery, and with the placebo group, it was 131.38±5.15 minutes post-surgery.

Hu et al in their network meta-analysis, analysed a total 79 randomized controlled trials with 6,201 patients receiving single dose of pregabalin or gabapentin as premedication, to validate the analgesic effect and incidence of adverse events of various doses.[20] Their results suggested that the analgesic and adverse effects of pregabalin or gabapentin may be dose related. Study concluded that a dose-response relationship was detected in opioid consumption and postoperative pain for a single-dose preoperative administration of PGB and GBP. In our study single minimal dose of pregabalin is effective in prolonging the analgesia with significant reduction in rescue analgesic dose.

One of the limitations of this study is that the total duration of surgery was not variable in the final results. Longer surgery would have involved more tissue handling and subsequently more post-operative pain. To keep the surgical time comparable, only those cases which could be completed within the duration of spinal anesthesia with bupivacaine were included. Cases where the surgical time exceeded the duration of spinal anesthesia and required an intravenous supplementation of opioids or local surgical site infiltration or those converted to general anesthesia were excluded from the study.

CONCLUSION

The present study clearly reveals the analgesic and sedative efficacy of pregabalin administered as premedication in patients undergoing open Appendicectomy under spinal anesthesia. Thus, pregabalin 75 mg may be the optimal pre-emptive dose for open appendicectomy under spinal anesthesia.

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