

A Randomized, Placebo Controlled Study of Peri-Operative Pregabalin for Early and Late Post-Operative Pain in Patients Undergoing Open Urological Surgery

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Abstract

Introduction: Pregabalin has been used in the peri-operative period for a variety of surgeries and in variable doses. Some studies favor while others refute its role as a pre-emptive and protective analgesic. We hypothesized that Pregabalin would reduce the severity of acute post-operative pain as well as chronic post-surgical pain. **Subjects and Methods:** A randomized double-blind placebo-controlled study including a total of 120 patients was designed to find the efficacy and safety of Pregabalin in reducing acute as well as chronic post-surgical pain after open urological surgery. **Results:** The time to rescue analgesic (NRS > 4) was 356.2+101.3 minutes in study group and 267.2+67.79 minutes in control group (p < 0.01). The total dose of rescue analgesic required (mg of Tramadol) in study group (320 + 50.5 mg) was less than the control group (462 + 35.4 mg). **Conclusion:** Oral Pregabalin was effective in reducing the severity of acute post-operative and chronic post-surgical pain and reducing the dose of rescue analgesic required. However, the incidence of side effects, though minor, was higher in the study group.

Keywords: Pregabalin, Protective Analgesia, Post-Operative Analgesia.

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Introduction

Management of acute post-operative pain is an entity which changes the whole peri-operative experience of a patient. If inadequately treated it can cause an otherwise excellent surgery to be a nightmarish experience for the patient and the attending doctor. Inadequate pain management adds to significant morbidity including adverse cardiovascular, respiratory and neuro-psychological effects often leading to ICU admission which could very well be prevented. This leads to additional psychological and financial burden on patients and their attendants. That is the reason why pain has been recognized as the fifth vital sign. Untreated acute post-operative pain may develop into chronic persistent neuropathic pain.

‘Preemptive analgesia’ aims at preventing the sensitization of the nervous system, which can be prevented by initiating analgesia prior to the pain stimulus and continuing the same

in the intra- and post-operative periods. ‘Protective analgesia’ is a technique wherein the drugs used are adjuvant drugs like Gabapentin and Pregabalin, typically used in chronic and neuropathic pain syndromes.^[1,2]

Pregabalin is a synthetic analogue of GABA, acting as the $\alpha_2\delta$ -subunit calcium channel ligand. Clinically, it acts as an analgesic, anti-convulsant, anxiolytic and sleep-modulator. It reduces the hyper-excitability of dorsal horn neurons following surgical trauma.^[3,4]

Majority of Urological surgeries are performed endoscopically/minimally invasively. Still, there remain some indications for which open surgery is necessitated; leaving a relatively large scar in the flank region. This leads to acute to chronic pain of varying severity, adding to significant morbidity. As many patients in the proposed study group would have nephrectomy and deranged renal function, NSAIDs were ruled out as analgesics.

We designed this prospective, randomized, double-blind, placebo-controlled study to evaluate the efficacy of peri-operative Pregabalin in reducing acute and chronic post-operative pain after open urological surgeries under general anesthesia.

Subjects and Methods

After approval by the Institutional Ethics Committee, 120 ASA I/II adult (18-60 years) patients of either sex were enrolled in this prospective, randomized, double-blind, placebo-controlled study. Since the study design involved long follow-up, attrition was kept in mind while formulating. They were to undergo elective open urological surgery under general anesthesia. All patients were examined in the PAC clinic/Bedside as per the Department's protocol. For all patients enrolled in the study, written informed consent was obtained.

Exclusion criteria for the study included patients having neurological or coagulation disorder, abnormal liver or renal function tests, uncontrolled hypertension, uncontrolled diabetes mellitus, Body mass index (BMI) > 30.

Patients were then assigned to either of the two groups with computer-generated randomization. They were to receive either study drug (Pregabalin 150 mg) or matching placebo at bed time a day prior to surgery, on the day of surgery and for the next 14 days.

Anesthesia and surgical techniques were followed according to the routine standard of care. Intra-operative and early post-operative vitals were recorded. Intra-operative analgesia included Paracetamol 1g infusion and Fentanyl 2 mcg/kg. Post-operative analgesia was provided in the form of slow intravenous infusion of Paracetamol 1g thrice a day for 2 days followed by oral Paracetamol 650 mg thrice day for 3 days and then on an as needed basis. Rescue analgesic in the form of slow intravenous infusion of Tramadol 100 mg was added for breakthrough pain.

Patients were followed in the post-operative period and assessed for pain, need for rescue analgesic and side effects were noted. Pain assessment was done using a Numeric Rating Scale (0 = no pain and 10 = worst pain). After discharge patients were followed in the surgeon's OPD at post-operative day 10, 30, 60 and 90 and assessed for pain using NRS and side effects were noted.

Sample size of at least 50 was taken as the minimum so as to ensure that the results are statistically significant. Student's t-test and Fisher's exact test were employed to find the significance of the results obtained. p-value < 0.05 was considered statistically significant.

Aims and Objectives

Aims of this study were to evaluate among the two study groups

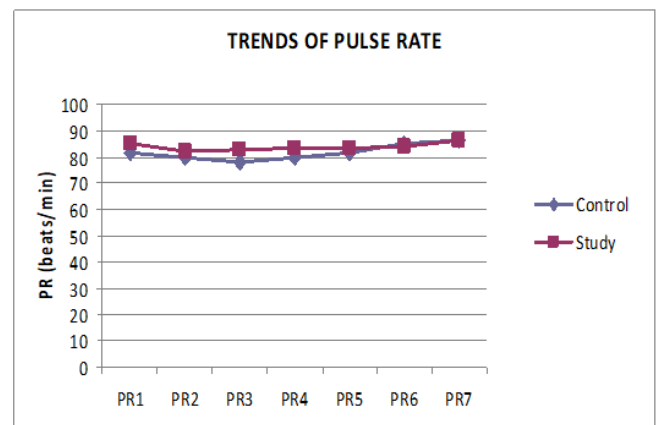
1. Severity of pain in early post-operative period (until discharge)
2. Time to first rescue analgesic and total dose of rescue analgesic needed
3. Effect on hemodynamics
4. Side effects, if any, attributable to the drug
5. Chronic post-surgical pain

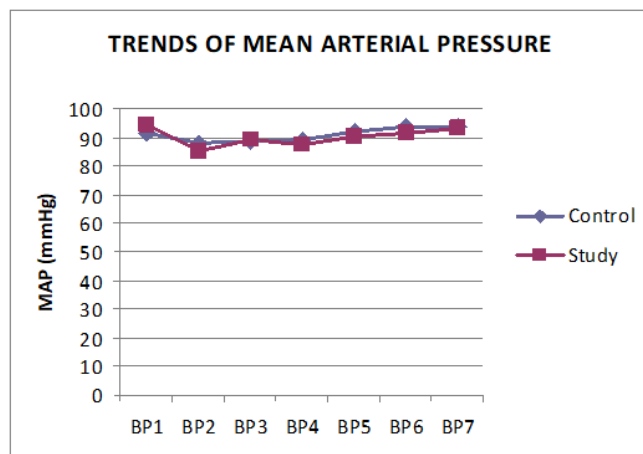
Results

A total 120 patients were enrolled, of which 105 completed the follow-up and were analyzed for the study (53 in Pregabalin group and 52 in Control group).

There was no statistically significant difference amongst the two groups with respect to age, sex or duration of surgery.

Parameter	-Study group	Control group	P
Age (years)	38.12 + 10.02	37.68 + 10.93	0.7381
Sex	M-31/F-22	M-33/F-19	0.718
Duration (minutes)	89.4 + 23.1	92.4 + 31.34	0.3273





The hemodynamic parameters (intra and post-operatively) and the fluid and vasopressor requirement were comparable in the two groups.

There was no significant difference in the acute post-operative pain scores (until discharge) amongst the two groups.

The time to rescue analgesic (NRS > 4) was 356.2±101.3 minutes in study group and 267.2±67.79 minutes in control group ($p < 0.01$). The difference was highly significant.

The total dose of rescue analgesic required (mg of Tramadol) in study group (320 + 50.5 mg) was less than the control group (462 + 35.4 mg) and statistically significant.

On evaluation of chronic post-operative pain, patients in the study group had significantly lower scores at day 90.

Of the noted complications; nausea (9 patients in study group, 3 patients in control group), vomiting (2 in each group), confusion (10 in study, 1 in control), dizziness (12 in study, 2 in control), somnolence (11 in study, 2 in control). None of the complications in either group were serious and did not require any other intervention apart from re-assurance.

Discussion

Pregabalin has an established role in treatment of chronic pain syndromes like post-herpetic neuralgia, diabetic neuropathy and fibromyalgia syndrome. In addition, it has also been used for the treatment of generalized anxiety disorder and partial onset epilepsy in adults.

Sensitization of the dorsal horn neurons has been demonstrated in acute pain models and Pregabalin has shown to reduce their hyperexcitability. This has led to the use of Pregabalin for post-operative analgesia. However, there are studies that both support and refute its usefulness in acute post-operative setting. Also, there is no standard protocol for the use of

this drug in this setting and doses used also have large variations.^[5,6]

Agarwal et al evaluated the efficacy of single pre-operative dose of Pregabalin 150 mg for attenuating post-operative pain and fentanyl consumption after laparoscopic cholecystectomy and found it to be effective.^[7]

Saraswat and Arora compared the efficacy of single dose 1200 mg Gabapentin versus 300 mg Pregabalin and found that Pregabalin was superior in terms of duration of post-operative analgesia and reduction in total analgesics required.^[8]

Paech et al concluded in their study that 100 mg single pre-operative dose of Pregabalin does not reduce acute pain or improve recovery after minor surgery involving only the uterus.^[9]

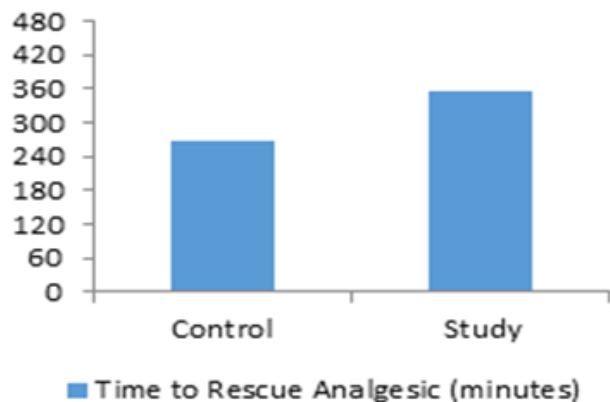
Buvanendran et al used peri-operative pregabalin in patients undergoing total knee arthroplasty and found it to be effective in reducing chronic post-surgical pain.^[10]

Cheung et al used a crossover design to examine the efficacy of preoperative versus immediately postoperative administration of 75 mg of oral pregabalin. Patients were followed for 72 h after surgery, and the area under the curve for numerical rating scale in the first 24 h was significantly lower at rest for patients receiving postoperative pregabalin. However, the overall impression conveyed by their data was that any difference that exists between preoperative dosing and postoperative dosing appears to be quite small.^[11]

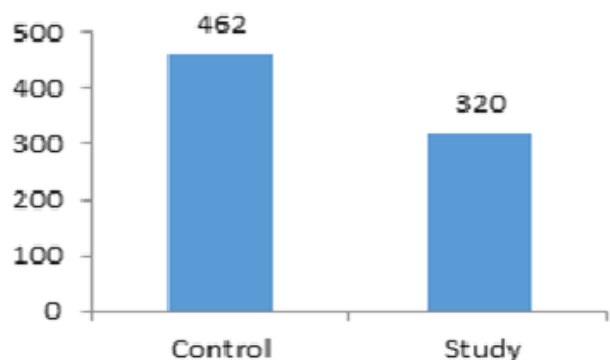
In our previous study, we found peri-operative pregabalin effective in reducing the dose of rescue analgesic required and prolongation of post-operative analgesia in patients undergoing lower limb orthopedic surgery under spinal anesthesia.^[12]

In our study, we observed that peri-operative Pregabalin resulted in prolongation of post-operative analgesia and reduction of total dose of rescue analgesic (Tramadol) required in early post-operative period. However, the larger goal would not be simply to increase the duration of analgesia or to reduce the analgesics required but to prevent the development of chronic pain syndromes in post-operative patients. For this purpose, long term treatment and follow-up was needed. This was effectively reduced in the study group patients. Side effect profile, although minor, was worse in the study group patients.

Time to Rescue Analgesic (minutes)



Total Analgesic Required (mg of Tramadol)



Thus, we conclude that peri-operative Pregabalin has been effective in increasing the duration of post-operative analgesia and decreasing the total dose of analgesics required in early post-operative period. Also, chronic post-operative pain was much less in Pregabalin treated patients but definitely with significantly more side effects, although minor.

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