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A prospective, randomized clinical study for evaluation of pregabalin for post-operative analgesia in infraumbilical surgeries

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ABSTRACT

Background: Preemptive analgesia is about the administration of an analgesic agent before the initiation of noxious stimulus, aiming of preventing sensitization of the neural system to successive stimulus that could intensify pain perception. Pregabalin is derivative of gabapentinoid which exhibits analgesic properties. **Aims and Objectives:** This clinical study designed to evaluate the effectiveness of pregabalin for post-operative analgesia in infraumbilical surgeries. **Materials and Methods:** This prospective clinical study was conducted in a medical college hospital of central India after obtaining approval from institutional ethics committee and informed written consent from the selected patients over the period of 1 year. A total of 60 patients between the ages of 20 and 40 years of ASA Grade I/II were randomly assigned into two groups (n = 30, each) using an online randomization tool. Patients in Group P received oral Pregabalin 150 mg and Group D received oral Diazepam 10 mg, 1 h before induction of anesthesia. Both the groups uniformly received Tablet Paracetamol 1 gm, 2 h after completion of surgery. Patients experiencing pain with visual analogue scale (VAS) score ≥3, were injected Inj. Tramadol 100 mg, as rescue analgesia. Outcome variables such as need for rescue analgesia, sedation, VAS score, and other adverse events were noted at time intervals of 2, 4, 6, 12, and 24 h. **Results:** The mean VAS scores in patients of Group P were significantly lower than Group D ($P < 0.0001$), over 24 h of post-operative period. In Group P, rescue analgesic Inj. Tramadol was given after 12.33 ± 3.47 h as compared to 3.47 ± 8.19 h in Group D ($P < 0.0001$) with total need of 133.56 ± 49.27 mg and 210.73 ± 63.35 mg over 24 h in patients of Groups P and D, respectively ($P < 0.0001$). **Conclusion:** Pregabalin 150 mg in pre-operative period provides superior post-operative analgesia and considerably reduces need of rescue analgesia postoperatively.

Key words: Diazepam; Preemptive analgesia; Pregabalin; VAS score

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INTRODUCTION

Pain is an obnoxious sensation that initiates from continuing and imminent tissue injury. Acute pain accompanies nearly all surgical procedures. Satisfactory pain relief is mandatory for a rapid return to regular physiological activity and prevents the development and progression of chronic pain. Traditional way to provide post-operative analgesia involves nonsteroidal anti-inflammatory drugs (NSAIDS), opioids, and nerve blocks. Complications associated with high doses of opioids are vomiting, sedation, respiratory depression, risk of pulmonary aspiration, pruritus, immune dysfunction, constipation, and urinary retention.[1] NSAIDS may cause gastrointestinal bleeding, thromboembolic complications, and renal toxicity. Nerve block techniques involve extra intervention and risk of hemodynamic instability and drug toxicity. In view of such limitations, an ideal drug should have anxiolytic property but without above mentioned side effects, may be a better choice for post-operative pain relief.

Preemptive analgesia, involves the administration of an analgesic regime before the commencement of noxious

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stimulus, so that sensitization of the neural pathway can be prevented which could augment pain perception.

Pregabalin is a gamma-amino-butyric-acid analog with better pharmacokinetic profile than its predecessor Gabapentin.[2] Pregabalin has a recognized role in the treatment of peripheral neuropathy seen in diabetes mellitus and post-herpetic neuralgia.[3,4]

Hence, the present study was considered for the evaluation of pregabalin given preoperatively for post-operative analgesia in infraumbilical surgeries, need of additional rescue analgesic agent and the potential adverse effects.

Aims and objectives

This clinical study designed to evaluate the effectiveness of pregabalin for post-operative analgesia in infraumbilical surgeries.

MATERIALS AND METHODS

This prospective comparative single center clinical study was pre-approved by the Institutional Ethics Committee (IEC) for the final permission (vide letter no. 219-225/Bio/Ethical/MC/03/11). After obtaining the permission of IEC, the study was conducted in a medical college hospital of central India. Well informed written consent was obtained from the selected patients over the period of 1 year.

Inclusion criteria

Patients between the ages of 20–40 years of both sexes with ASA-I/II, scheduled for infraumbilical surgeries under subarachnoid block were included in the study.

As calculated from a previous study[5,6] to get a clinically relatable variation in the interval of post-operative analgesia, 30 patients were required in each of the groups with a power of study 80% at 95% confidence interval (alpha=0.05). Total number of patients=60; they were randomly assigned into two groups (n=30, each) using an online randomization tool. Patients in Group P received oral Pregabalin 150 mg and Group D received oral Diazepam 10 mg, one hour before induction of anesthesia.

Exclusion criteria

Patients with psychiatric illness, renal or hepatic impairment, pregnant or lactating women, patients having a known allergy to study drugs and any contraindication to subarachnoid block were excluded.

All the selected patients were carried out with preanesthetic checkup comprising complete clinical history, general physical examination, airway assessment, systemic examination along with routine laboratory investigations, ECG and CXR and details about visual analog scale (VAS)[5,6] (0–10 cm) was explained 1 day before surgery. Patients were furthermore counseled regarding procedures of subarachnoid block and post-operative pain relief and all queries and doubts were answered to get their confidence and support. After placing the study drugs in lookalike capsules, they were additionally sealed in a plastic pouch labeled with randomization digit. The medicines were administered to the patients by an anesthesiologist totally unaware of the study 1 h before the induction of anesthesia. The observer anesthesiologist was also uninformed of which drug was given to which patient to avoid observer bias.

After taking the patient in the operation theater, intravenous cannulation was done and ringer lactate infusion was started. Standard basal parameters had been recorded. Subarachnoid block was administered under all aseptic precautions with 25 G Quincke's spinal needle at L3–L4 intervertebral space and inj. Bupivacaine heavy 0.5% injected after validating free flow of cerebrospinal fluid. After attainment of adequate level of anesthesia, surgery was performed. Both the groups uniformly received tablet Paracetamol 1 gm, 2 h after completion of surgery. Assessment of pain was done at 2, 4, 6, 12, and 24 h using VAS[5,6] score ranging between 0 cm and 10 cm; 0=no pain; and 10=worst possible pain.

Vital parameters were recorded at regular time intervals in the post-operative period.

Patients experiencing pain with VAS score ≥3 were injected Inj. Tramadol 100 mg, as rescue analgesia. Overall consumption of inj. Tramadol over 24 h was noted and modified Ramsay sedation scale was used to grade sedation in patients.

Modified Ramsey sedation scale[7]

1. Patient is anxious and agitated or restless or both.
2. Patient is co-operative, oriented and tranquil.
3. Patient is drowsy and responds to commands only.
4. Patient exhibits brisk response to light glabellar tap or loud noise.
5. Patient exhibits a sluggish response to light glabellar tap or loud noise.
6. Patient exhibits no response and unarousable.

The parameters studied for comparing adverse effects: Dizziness, diplopia, post-operative nausea and vomiting, (graded as 0=no nausea/vomiting; 1=mild nausea; 2=moderate nausea; and 3=severe nausea with vomiting),[6] confusion (assessed by asking time, place, and person); urinary retention in a non-catheterized patient; respiratory

depression in terms of respiratory rate <8 bpm and SPO_2 <90% without oxygen supplementation]. Any complications which occurred were recorded in the first 24-h post-operative period.

Statistical analysis

The sample size was calculated according to the previous reference studies where pregabalin was used for preemptive analgesia. At least 30 patients in each arm were required as calculated by Open Epi Version 3 online software, a 10% difference could be determined between the group at 80% power and 5% significance (α=0.05, β=0.80). The Microsoft Excel 2013 and Statistical Package for the Social Sciences version 21.0, Chicago, USA was used to analyze data. Qualitative variables between studied groups were compared using the Chi-square test. Student "t" test was used to test for statistical significance in the differences of the two means. P<0.05 was considered as statistically significant.

RESULTS

A total of 60 patients who underwent different infraumbilical surgeries under spinal anesthesia were included in the study and were randomly allocated into two groups of 30 each. The ASA physical status was similar in both the groups. The demographic profile of both the groups was comparable with respect to age, weight and height, and duration of surgery (Table 1).

The Median VAS score in Group P was below the Median VAS score at 2, 4, 6, and 24 h. In Group D all 30 cases had VAS above Median at 2 h, 17 cases > Median 4 h and 6 h, 11 cases > Median at 24 h. On comparison statistically, VAS score was significantly lower in Group P at 4, 6, 12, and 24 h (P<0.0001) (Table 2).

In Group P, rescue analgesic Inj. Tramadol was given after 12.33±3.47 h as compared to 3.47±8.19 h in Group D (P<0.0001) with total need of 133.56±49.27 mg and 210.73±63.35 mg over 24 h in Group P and Group D, respectively (P<0.0001) (Table 3).

Median of sedation score in the studied groups, at 2 h, 10 cases in Group P and 3 in Group D were > median MRSS scores. At 4 h, 7 cases in Group P and no case in Group D showed > median MRSS scores. While at 6, 12, and 24 h, in both the groups, cases were higher than the median MRSS score. Hence, the level of sedation at 2 and 4 h in Group P was significantly higher (P<0.05) as compared to Group D. Level of sedation at 6, 12, and 24 h was comparable between the two groups (P>0.05) statistically not significant (Table 4).

Post-operative nausea, vomiting, headache, and dizziness were not statistically significant between groups. Four patients had complained of nausea and dizziness in Group P (Table 5).

Table 1: Distribution of demographic profile and duration of surgery

Parameters	Group P (Mean±SD)	Group D (Mean±SD)	P-value
Age (in years)	30.68±6.89	30.4±6.23	0.869
Weight (in kgs)	60.28±8.64	60.18±9.56	0.966
Height (in meters)	1.674±0.042	1.668±0.048	0.608
Duration of surgery (in minutes)	106.34±12.98	107.88±10.96	0.621

DISCUSSION

Management of pain and its complications in the post-operative period still is a major challenge. Preemptive analgesia prevents the development of the alteration in the sensory processing which can augment post-operative pain. Analgesia before giving incision has been the most effective way to control post-operative pain. Pregabalin and gabapentin both have established role as antihyperalgesic and antiallodynic for the treatment of neuropathic pain and can also be valuable in acute post-operative pain.[4,8-10]

Pregabalin and gabapentin suppress secondary hyperalgesia by inhibiting hyperexcitability of the dorsal horn neurons induced by tissue injury, but have not shown significant effects on primary hyperalgesia.

Table 2: Median VAS score at different time intervals

Median VAS Scores	Group P	Group D
VAS2		
>Median	0	30
≤Median	30	0
VAS4		
>Median	0	17
≥Median	30	13
VAS6		
>Median	0	17
≤Median	30	13
VAS24		
≤Median	0	0
≥Median	30	30

Table 3: Total rescue analgesia (inj. Tramadol in mgs) requirement

Groups	Time of first rescue analgesia in hours	Rescue analgesia in 24 hours (inj. Tramadol in mg)
Group P	12.34±3.48	133.57±49.28
Group D	3.48±8.18	210.74±63.36

Table 4: Median test showing sedation score

Modified Ramsey sedation scale	Group P	Group D
MRSS2		
>Median	10	1
≤Median	20	29
MRSS4		
>Median	07	0
≥Median	23	30
MRSS6		
>Median	0	0
≤Median	30	30
MRSS12		
>Median	0	0
≥Median	30	30
MRSS24		
≤Median	0	0
≥Median	30	30

Table 5: Incidences of side effects

Side effects	Group P	Group D
Nausea	4 (13.33%)	0
Vomiting	0	0
Headache	1 (3.34%)	2 (6.67%)
Dizziness	4 (13.33%)	2 (6.67%)
Respiratory depression	0	0
Total	30	30

Pregabalin and gabapentin bind to the α(2)-δ subunit of voltage-gated calcium channel and exert their analgesic action. Pregabalin has 6 times more strong affinity to this subunit as compared to gabapentin and so having lesser side effects than gabapentin.[11]

Pregabalin demonstrates highly predictable and linear pharmacokinetics, a profile that makes it easy to use in clinical practice. It is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentration occurring ~1 h after single or multiple doses, and steady state being achieved within 24–48 h after repeated administration.[2] It can be started at an effective dose of 150 mg day[1,2] the dose of pregabalin used in the present study. The oral bioavailability of pregabalin is high at ≥90% and is independent of dose.[2] Furthermore, the administration of pregabalin with food has no clinically relevant effect on the amount of pregabalin absorbed,[2] thus providing for a dosing regimen that is uncomplicated by meals.

Pregabalin has shown to be effective against inflammatory injury, incisional injury and neuropathic pain. Pregabalin given preoperatively decreases opioids requirement and adverse effects related to it in the 1st 24 h of post-operative period.[4,12]

In some of the studies conducted with pregabalin as preemptive analgesic, like randomized controlled trials in patients undergoing dental surgery[13] spinal fusion surgery,[14] gynecological uterine surgeries by Paech et al.,[15] in 2007, day-case gynecological laparoscopic surgery by 2008 Jokela et al.,[16] and laparoscopic cholecystectomy by Agarwal et al.,[17] Pregabalin 100–150 mg as a single dose was used.

A randomized, double-blind, placebo-controlled, and parallel-group trial was performed by Hill et al.,[13] to compare pregabalin 50 and 300 mg with placebo and ibuprofen 400 mg using a dental pain model. There were statistically significant differences in pain relief, pain intensity difference, and pain relief intensity difference between the 300 mg pregabalin group and placebo. In addition, the 300 mg pregabalin group had a significantly longer duration of analgesia than the ibuprofen group and had the highest score on the patient global impression of study medication.

Reuben et al.,[14] observed that in patients undergoing lumbar laminectomy, pregabalin 150 mg before and after surgery was as effective as celecoxib in reducing postoperative pain and patient-controlled morphine consumption and the combination of both drugs was the most effective.

Paech et al.,[15] in 2007, conducted the study in 90 women having minor gynecological surgery involving the uterus. Patients received either oral pregabalin 100 mg or placebo approximately 1 h before surgery. There was no significant difference between the groups regarding pain experienced in the recovery room or thereafter or for recovery room fentanyl requirement (42% group pregabalin vs. 27% group placebo, P=0.12) or the quality of recovery at 24 h postoperatively.

Agarwal et al.,[17] in 2008, evaluated the efficacy of 150 mg pregabalin given 1 h before surgery for post-operative analgesia and fentanyl consumption after laparoscopic cholecystectomy compared to the placebo. Results revealed that patient-controlled fentanyl requirement in post-operative period and post-operative pain were greatly reduced in the pregabalin as compared to placebo (P<0.05).

150 mg single dose of pregabalin was used in present study and that too in infraumblical surgery in which, pregabalin showed a very significant reduction in the total analgesic consumption as compared to control group. Our results are well in accordance to Schulmeyer et al.[18]

Sahu et al., in 2010[19], evaluated the efficacy of pregabalin for post-operative analgesia and need of rescue analgesic in below umbilical surgeries under regional anesthesia. In this study, placebo capsule and

pregabalin 150 mg, given twice, 12 h and 1 h before surgery, according to study groups. Then assessment for pain score by VAS scale, hemodynamic parameters and need of rescue analgesics (injection tramadol IV) was done every 2 hourly for 24 h.

In the present study, only one preemptive dose of 150 mg pregabalin was used instead of two doses at 12 h intervals and inj. Tramadol was used as rescue analgesic. Pregabalin group had shown significantly lower mean VAS score and greatly decreased need for rescue analgesic consumption postoperatively as compared to the control group ($P<0.05$), which were nearly similar to our results.

Gajraj[20] reviewed the pharmacology of pregabalin and found that somnolence (29.2%) and dizziness (22.2%) were the most common side effects, contrary to our study where incidence of nausea, dizziness, and headache was 13.33%, 13.33%, and 3.34%, respectively.

Limitations of the study

The present study has limitation of small sample size. Further studies are required to compare the different doses and frequency of administration of pregabalin as preemptive analgesic on a larger population.

CONCLUSION

Pregabalin 150 mg in pre-operative period provides superior postoperative analgesia and considerably reduces need of rescue analgesia postoperatively.

Pregabalin may effectively be used as a part of the multimodal analgesia regimen to provide adequate post-operative analgesia and to prevent development of chronic pain syndrome.

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MB - Concept and design of the study; **KU -** Statistical analysis and interpretation, reviewed the literature; **SB -** Concept and design of the study, prepared first draft of manuscript; **ST -** Concept, coordination, interpreted the results, preparation of manuscript and revision of the manuscript.

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