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ORIGINAL ARTICLE

EFFECT OF PREOPERATIVE PREGABALIN ON POSTOPERATIVE ANALGESIC REQUIREMENT AFTER SKIN GRAFTING

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ABSTRACT: BACKGROUND: Pain relief after surgical procedures continues to be a major medical challenge. The alleviation of pain is given a high priority by the medical profession and health authorities. Preemptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input which amplifies postoperative pain. The present study evaluated the efficacy of two different doses (75mg & 150mg) of pregabalin on post-operative analgesia. **METHOD:** This randomized, double blind study was conducted in 90 patients of ASA grade I & II, aged (20-60 yrs.) undergoing lower limb plastic surgery (SSG) under spinal anesthesia. All patients were randomly allocated into 3 groups of 30 each. Group I received oral pregabalin 150mg, group II oral pregabalin 75mg and group III oral diazepam 5mg. All groups in addition received 1gm paracetamol orally. All drugs were given with a sip of water one hour before spinal anesthesia. After 4 hours of surgery, 1gm paracetamol was given and then repeated every 8 hrs. Rescue analgesia was provided with tramadol 100mg I/V when VAS>3. Patients VAS score was recorded at rest and during motion at 2, 4, 6, and 24 hours after operation. Request for additional analgesia, nausea, number of vomits, sedation and dizziness were noted. **RESULT:** After observation in all 3 groups it was found that VAS score was significantly lower in group I than group II and III. Level of Sedation at 2 & 4 hrs. was significantly higher in group I as compared to II and III but at 6 and 24 hrs. difference was not significant. Total amount of rescue analgesia required was significantly less in group I as compared to group II and III. It was less in group II as compared to group III. **CONCLUSION:** Preemptive use of pregabalin 150mg in patients undergoing SSG under spinal anesthesia resulted in significant analgesia, decreased need for rescue analgesia, favorable sedation and anxiolysis without cardiovascular, respiratory adverse effects.

KEYWORDS: Postoperative Analgesia, Preemptive analgesia, central sensitization, pregabalin diazepam.

INTRODUCTION: High quality pain control after surgery still remains a therapeutic challenge.[1, 2] Anesthesiologist succeed to a greater extent by rendering patient absolutely pain free during surgery but despite advances, many patient continue to experience considerable discomfort in postoperative period.

The ultimate goal should be that patient awakens after surgery with excellent pain control and this should be maintained throughout the period of convalescence. This concept has led to the emergence of preemptive analgesia. Pre- emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injury occurring during surgery and early post operation period.[3- 5] This concept was formulated by crile.[6]

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Neuropathic pain is a complex chronic pain state with wide range of presentation i.e. shooting; burning, stinging, numbness usually accompanied by tissue injury and is often seen during extraction of graft for SSG.

Pregabalin is structurally and functionally related to inhibitory neurotransmitter GABA and has anti allodynic and antihyperalgesic properties[7, 8] if used preemptively in indicated clinical situations. It is chemically described as (S) -2 (Amino methyl) – 5 methylhexanoic acid. It acts by decreasing the synthesis of neurotransmiter glutamate to act on the central neurvous system and has analgesic, anticonvulsant and anxiolytic activity. It is effective in preventing neuropathic [9] component of acute nociceptive pain of surgery. It is rapidly absorbed when administered on an empty stomach, with peak plasma concentration occurring within one hour and pregabalin undergoes negligible metabolism. Approximately 98% of the radioactivity recorded in urine was unchanged pregabalin.

The purpose of this study is to evaluate and compare the efficacy of two different doses i.e. 75mg and 150mg of preoperative pregabalin on intensity and duration of postoperative analgesia. Also to assess the requirement of postoperative rescue analgesia and side effect profile i.e. incidence of visual disturbance, sedation dizziness and headache.

METHOD: After obtained approval from the institutional ethics committee, this study was conducted in the Department of Anesthesiology, N.S.C.B. Medical College, Jabalpur (M.P.). This randomized, double blind study consisted of 90 patients of age 20-60 years belonging to ASA class I and II, scheduled for lower limb plastic surgery (SSG) under spinal anesthesia.

The exclusion criteria were patient refusal for consent, coagulopathy and bleeding diathesis, anticoagulant therapy, spinal deformity, treatment with antacid or antidepressants, history of epilepsy or diabetes mellitus, allergy to any drug in the study, history of impaired renal function and history of addiction.

All 90 study patients were randomly allocated into 3 groups of 30 each. The study drugs were packed in identical capsule and were coded and sealed in an opaque plastic container. The randomization and administration of study drug was performed by a senior resident who did not participate in this study from this stage onwards. Decoding was done at the completion of the study.

Group I received pregabalin 150mg, group II received pregabalin 75mg and group III received diazepam 5mg. All patients received the capsule containing the study drug and 1 gm oral paracetamol with a sip of water 1 hr. before spinal anesthesia.

Before operation all patients were introduced to the concept of visual analogue scale (VAS).

After securing IV line, preloading was done with 10ml/kg of ringer lactate 15mts before the spinal. Noninvasive monitors like ECG, NIBP and pulse oximeter were attached. Spinal anesthesia was given in sitting position with 25G Quincke's needle; at L3-4 inter space using 3ml of 5% heavy bupivacaine.

After 4 hrs. of surgery 1gm oral paracetamol was given and then repeated every 8 hrs. Assessment of pain was done using VAS.

Post operatively vital parameters like PR, BP, respiratory rate and pain (by VAS score) were recorded at 2hrs /4hrs/ 6 hrs. and 24hrs. Rescue analgesia was provided with tramadol 100mg I/V when VAS >3. Total dose of tramadol consumption in Ist 24hrs was noted and level of sedation was defined in accordance with the Modified Ramsey Sedation scale.

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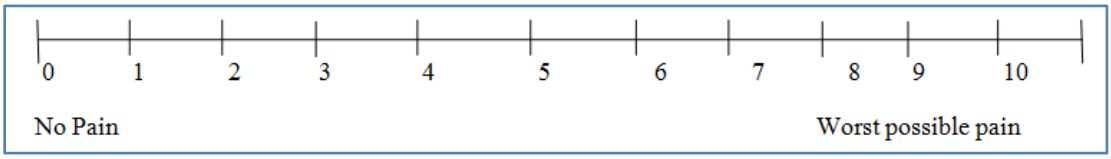
Visual analogue scale in a 10cm scale in which one end ("0") indicates no pain and other end ("10") indicate worst possible pain.



Scanning of sedation was done using Modified Ramsey sedation scale.[10]

Score	Response
1.	Anxious, agitated, rest less
2.	Cooperative, Oriented, Tranquil
3.	Drowsy, but responds to commands only
4.	Brisk response to light glabbellar tap or loud noise
5.	Sluggish response to light glabellar tap or loud noise
6.	No response, unarousable

RESULTS: In this study of 90 patients, 3 groups were made having 30 patients in each group. All the 3 groups were comparable with respect to demographic and operational factors. There was no substantial difference among the groups with regard to age, sex (Table 1).

Demographic Profile	Group I (P 150)	Group II (P 75)	Group III (D z5)
Age (Years)	34.97 ± 10.247	34.10 ± 8.185	33.77 ± 10.960
Sex ration (M:F)	21:9	18:12	17:13

Table 1: Demographic Detail

The mean heart rate, mean SBP and mean RR in all the 3 studied groups were comparable and were statistically insignificant. (Table 2, 3, 4)

Group	HR 2 (Mean ±SD)	HR4 (Mean ±SD)	HR 6 (Mean ± SD)	HR24 (Mean ± SD)
Pregabalin 150mg	80.00 ± 5.63	79.83 ± 5.32	79.53 ± 4.80	79.93 ± 4.47
Pregabalin 75mg	79.23 ± 6.46	81.10 ± 5.99	81.33 ± 5.97	82.07 ± 6.20
Diazepam 5 mg	81.93 ± 11.24	83.80 ± 5.04	83.80 ± 5.04	84. 93 ± 5.08
Total	80.39 ± 8.15	81.54 ± 5.66	81.56 ± 5.52	82.31 ± 5.63

Table 2: Comparison of Mean HR

Group	SBP 2 (Mean ± SD)	SBP 4 (Mean ±SD)	SBP 6 (Mean ± SD)	SBP 24 (Mean ± SD)
Pregabalin 150mg	117.73 ± 4.748	117.73 ± 4.29	117.93 ± 3.80	118.27 ± 4.19
Pregabalin 75mg	117.47 ± 4.55	119. 33 ± 3.03	120.13 ± 2.46	121.13 ± 2.14
Diazepam 5 mg	117.33 ± 3.03	118.73 ± 3.80	119.00 ± 3.62	119.87 ± 3.27
Total	117.51 ± 4.13	118.60 ± 3.76	119.02 ± 3.43	119.76 ± 3.48

Table 3: Mean Systolic Blood Pressure (mm of Hg)

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Group	SBP 2 (Mean ± SD)	SBP 4 (Mean ±SD)	SBP 6 (Mean ± SD)	SBP 24 (Mean ± SD)
Pregabalin 150mg	16.60 ± 0.93	16.67 ± 0.95	16.67 ± 0.95	16.67 ± 0.95
Pregabalin 75mg	18.00 ± 6.0	18.67 ± 0.95	18.40 ± 0.81	18.00 ± 00
Diazepam 5 mg	17.87 ± 1.38	18.00 ± 1.17	18.53 ± 1.27	18.80 ± 0.99
Total	17.49 ± 1.14	17.78 ± 1.32	17.87 ± 1.33	17.82 ± 1.18

Table 4: Mean Respiratory Rate

VAS score at time interval of 2, 4, 6 and 24 hrs. showed that mean pain score of group I (P 150) was considerable lower than those of group II (P75) and group III (Dz5). Group II (P75) shows considerably better VAS result than those of group III (Table 5).

	Group		
	Pregabalin 150mg	**Pregabalin 75mg**	**Diazepam 5 mg**
VAS 2 > Medium	0	0	30
< = Medium	30	30	0
VAS 4 > Medium	0	19	17
< = Medium	30	11	13
VAS 6 > Medium	0	16	17
< = Medium	30	14	13
VAS 24 > Medium	0	2	0
< = Medium	30	28	30

Table 5: VAS Score Over 24 Hrs.

Level of sedation was observed with MRSS (Modified Ramsey Sedation Score), which shows sedation level was significantly higher at 2 and 4 hrs. in group I (P150) as compared to group II (P75) and group III (Dz5). Level of sedation at 6 and 24 hrs. was comparable in all 3 groups statistically not significant (Table 6).

	Group		
	Pregabalin 150mg	**Pregabalin 75mg**	**Diazepam 5 mg**
MRSS 2 > Medium	10	0	1
< = Medium	20	30	29
MRSS 4 > Medium	7	0	0
< = Medium	23	30	30
MRSS 6 > Medium	0	0	0
< = Medium	30	30	30
MRSS 24 > Medium	0	0	0
< = Medium	30	30	30

Table 6: MRSS Score Over 24 Hrs.

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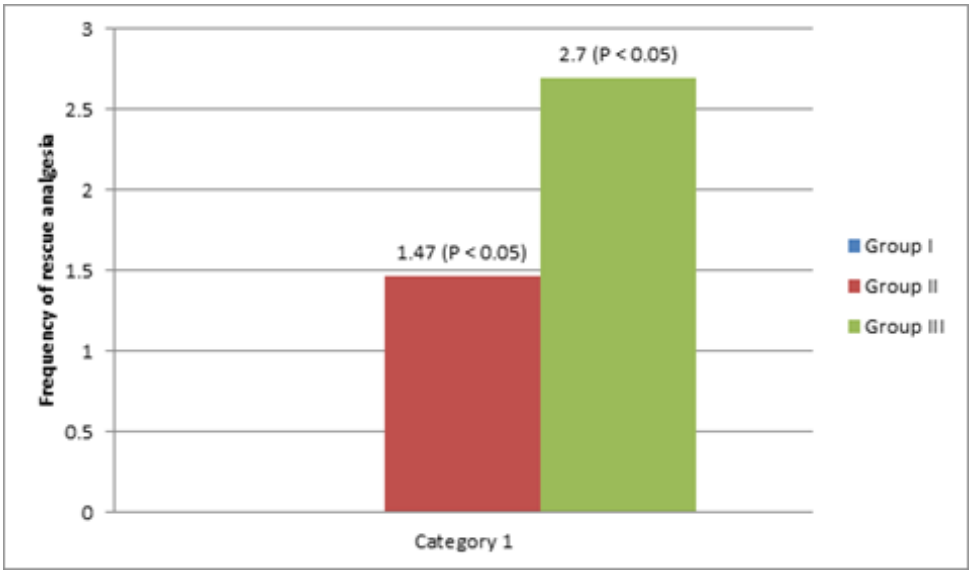
Total amount of rescue analgesic required was significantly less in group I (P150) as compared to group II (P 75) and III (Dz5) in that order I<II<III. (Table 7)



7. Shows Frequency of rescue analgesia over 24 hrs

Overall incidence of side effects in all 3 groups was comparable. Dizziness was found in two cases of pregabalin 150mg group (Table 8).

Side Effect	Group			Total
	Pregabalin 150mg	Pregabalin 75mg	Diazepam 5 mg	
Nil	24 (80%)	26 (86.7%)	25 (83.3%)	75 (83.3%)
Nausea	4 (13.3%)	4 (13.3%)	5 (16.7%)	13 (14.4%)
Dizziness	2 (16.7%)	0 (0%)	0 (0%)	2 (2.2%)
Total	30	30	30	90

Table 8: Side Effects

DISCUSSION: Preincisional analgesia has been shown to be more effective in control of postoperative pain by protecting the central nervous system from deleterious effects of noxious stimuli and resulting allodynia and hyperalgesia. The preemptive multimodal analgesia not only improves the quality of analgesia but also leads to reduction in opioid related side effects.

The purpose of present study was to evaluate the effect of preemptively administered pregabalin on postoperative requirement and to assess the efficacy of 2 different doses of preoperative pregabalin (75mg, 150mg) for post-operative analgesia to come up with an optimal dose for this setting.

Neuropathic pain is complex chronic pain state and in often seen during extracting graft for SSG. It responds poorly to standard pain treatment and may get worsen with standard therapy. Pregabalin is structurally and functionally related to GABA and has antiallodynic and

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antihyperalgesic properties which are (allodynia and hyperalgesia) the cardinal sign and symptoms of neuropathic pain after skin grafting.

In our study we observed the preoperative pregabalin 150mg was effective in reducing post-operative pain and requirement of rescue analgesia. The HR and mean systolic BP difference in all 3 groups was not statistically significant. There was a significant reduction in rescue analgesia requirement in group I compared to II and III. The level of sedation at 2 and 4 hrs. in group I is significantly higher as compared to group II and III. Level of sedation at 6 and 24 hrs. is comparable in all 3 groups and statistically not significant. This is in concordance with the findings of O. Mathiesen et al.[11]

The common adverse effects of pregabalin are dose dependent drowsiness and dizziness. In our study dizziness was reported in 2 cases of group I and no patient complained of visual disturbance, headache.

Pain VAS score was analyzed with the Kruskal Wallis test. The results showed the lower VAS score in group I subjects compared to group II and III. The result of our study as in agreement with the study conducted by R. Jokela et al.[12] in which VAS score of pain at rest and in motion were lower during early recovery after medication with pregabalin 150mg than with diazepam 5mg all combined with ibuprofen 800mg.

It is possible that higher dose of pregabalin could have more analgesia potency but also more side effects. In different studies[13-16] single or multiple doses of pregabalin ranging from 75 to 300mg was used. Out of four positive studies on the analgesic effects of pregabalin two showed only opioid sparing effects at the expense of an increase in pregabalin related side effects such as dizziness, blurred vision or sedation. Pregabalin dose 300 mg was implicated for the increased side effects in both studies. Pregabalin 75 mg was chosen in two preoperative trials. In one trial a single preoperative dose did not result in any analgesic benefit. In another trial, pregabalin was administered in twice daily dosing for seven consecutive days resulting in superior analgesia and lower analgesic consumption throughout the seven day of study. The discrepancy between results can be due to the procedure specific analgesic response, difference in the study and quality of design. In another study by R Jokela et al a notable opioid sparing effect with pregabalin 600 mg a day without any concomitant NSAID was seen. But the incidence of dizziness and blurred vision was higher after the high dose of pregabalin than the 10 mg dose of diazepam.In the first published clinical trial on pregabalin, in which 50 and 30 mg doses of pregabalin was compared with ibuprofen 400mg in a dental pain model, the 300mg dose of pregabalin induced considerably more side effects than did ibuprofen. The most common of these side effects were dizziness, somnolence and vomiting. In another study in which a 150 mg dose of pregabalin was compared in combination with celecoxib with both of the analgesics alone after spinal fusion surgery. The incidence of side effects after the combination of pregabalin 150 mg and celecoxib 400mg was lower than after placebo.

Peach et al[17] reported that a single preoperative dose of 100mg pregabalin was ineffective in reducing acute post-operative pain or improving recovery after minor surgery involving only the uterus. This could be possible because Peach and colleague administered a smaller dose (100mg) against the recommended dose of 150mg or because of the difference in nature of surgery.

In a study conducted by R. Jokela et al they found that 300mg of pregabalin was more effective than pregabalin 150mg. The incidence of dizziness, headache and blurred vision were

higher in the 300mg pregabalin group and patient satisfaction showed almost equal between 150mg and 300mg group.

It is important to determine the lowest optimal dose of pregabalin for analgesic use without adverse outcomes of drowsiness and dizziness. In the background of observations made by the aforementioned studies we decided to compare 75mg and 150mg as the two most plausible doses of pregabalin to achieve a meaningful prolongation of postoperative pain relief. Out of two doses of pregabalin we found that pregabalin 150mg would be the correct dose for pre emptive analgesia in this case with reduced requirement of rescue analgesia along with very minimal side effects.

The selection of diazepam 5mg as an active placebo in this study is based on the fact that since pregabalin in addition to it analgesic properties causes noteworthy sedation, a drug having similar pharmacodynamic properties such as sedation and anxiolysis was needed to prevent observational bias. The anxiolytic & sedation properties of pregabalin can be better appreciated in surgeries under regional anesthesia.

Judging from the results of all these pregabalin trials it is possible that the concomitant administration of NSAIDS and pregabalin is beneficial as regards the side effect profile of pregabalin. In fact this finding is in accordance with the original idea of a multimodal analgesic approach.[18] This is the reason why we kept acetaminophen as background analgesic in our study.

CONCLUSION: Pregabalin 150mg would be the optimal preemptive dose for patients undergoing SSG under spinal anesthesia. Pregabalin being an oral drug would be easy for the patient to take and also its prolongation of neuraxial block helps in immediate postoperative analgesia and further reduction of rescue analgesia. There was favorable sedation and anxiolysis and no cardiovascular or respiratory adverse effects seen.

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