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Analgesic Effects of Different Doses of Pregabalin in Chronic Low Back Pain: an Observational Study

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ABSTRACT

Background: Chronic Low Back Pain (CLBP) is very common and is associated with significant patient burden, and health resource expenditure. A large proportion of CLBP patients are treated with routine analgesic medications with unsatisfactory results leading to frequent exploration of second line options including pregabalin. Therefore this study was conducted to assess the efficacy of pregabalin in decreasing CLBF and compare its different doses using visual analogue scale (VAS).

Materials & Methods: A 24 weeks, prospective, non-interventional, observational study was performed on patients of either sex, aged 18 years to 60 years, belonging to ASA I, II and III categories. Patients were divided into 3 groups A, B and C according to different doses of pregabalin i.e. 75mg once per day, 75mg twice per day and 50mg twice per day respectively. Effectiveness was measured from the patient's perspective using reduction of Visual Analogue Scale (VAS) score. All the patients who enrolled in different study groups also received the following concomitant medications; Tablet Paracetamol 500 mg twice daily, Tablet Amitriptyline 10 mg once daily at bed time, Tablet Methylcobalamin 1500 mcg once daily, Capsule

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(Pantoprazole 40mg + Domperidone 30 mg) once daily. Choice of therapy was determined solely by the clinical judgment of the treating physician.

Results: The study reflected greater reduction in VAS score of less than 5 ($p < 0.05$) in Group B followed by Group C and A at 8th week and a score of less than 3 ($p < 0.05$) at 24th week of follow up.

Conclusion: When used in conjunction with standard therapy, pregabalin can relieve chronic low back pain. Pregabalin dosages of 75 mg twice daily followed by 50 mg twice daily, and 75 mg once daily are the most effective. These findings support pregabalin's therapeutic effectiveness and validate its applicability in the management of patients with this difficult ailment.

KEY WORDS: Chronic Low Back Pain, Pregabalin, Visual Analogue Scale (VAS)

RUNNING TITLE: Pregabalin doses and its analgesic effects

INTRODUCTION:

Pain is defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1]Physical discomforts with pain affecting the lower half of the back with varying intensity from dull ache to incapacitating intermediate low back pain.[2] Pain is considered chronic when it persists for more than 3 months and exceeds the body's natural healing process. Chronic low back pain (CLBP) is one of the most common major health problems in India, and is ranked among the top ten health problem worldwide.[3] People of all ages can be affected by CLBP. It is associated with significant patient burden and heath resource expenditure. Common causes of CLBP are lumber herniated disc, degenerative disc disease, internal disc disruption, facet joint, dysfunction, sacroiliac joint dysfunction, spinal stenosis, spondylolisthesis, osteoarthritis.[4] There are multiple modalities of treatments for CLBP like conservative; non steroidal anti inflammatory drugs, Opioids, selective serotonin reuptake inhibitors, selective nor epinephrine reuptake inhibitors, gabapentinoids, physiotherapy, lifestyle modifications), intervention (Caudal Epidural Steroid Injection, Trans foraminal Steroid Injection) or surgery.[5] A large proportion of CLBP patients are treated with routine analgesic medications with unsatisfactory results leading to frequent exploration of second line options including pregabalin. In particular, the use of pregabalin is made on the rationale of modulating the enhanced neurotransmission at the level of pre synaptic receptors of the afferent neurons.[6] Pregabalin primarily act on the α-2 delta-2 sub unit of the voltage-dependent calcium channels and reduce neuropathic pain transmission. Pregabalin blocks the

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VGCC (voltage gated calcium channels) and hence decrease glutamate and sensory neuro peptides (substance P and CGRP) release at synapse by decreasing Ca2+ influx. EAATS (excitatory amino acid transporters) activity is increased by pregabalin which caused more decrease in synaptic availability of glutamate. Decreased glutamate levels further inhibited the activation of NMDA and decreased the neuronal firing.[7] Additionally pregabalin also activates different potassium channels including KATP channels which also contribute to inhibition of neuronal excitation. Pregabalin through all these pathways ultimately provides significant pain relief in various neuropathic pain states. Use of pregabalin for CLBP requires slow titration to therapeutic doses and establishing maintenance on a long-term basis.[7] With prolonged treatment, the potential gain over possible adverse effects and risks is not clear. Therefore this study was undertaken to assess the effectiveness of pregabalin in CLBP in decreasing pain and compare different doses by using visual analogue scale (VAS).

METHODOLOGY:

After obtaining approval from the institutional ethics committee and written informed consent from the patients a 24weeks, prospective, non-interventional, observational study was performed at Pain Clinic, R. G. Kar Medical College & Hospital. The study population includes patients aged 18 years to 60 years of either sex with American Society for Anaesthesiologist (ASA) physical status I, II and III who visited pain clinic for chronic low back pain. All the screened patients underwent proper history taking physical examination, relevant investigations as indicated.

Patient who did not attended any fallow up visit, uncontrolled diabetes, patient with spinal canal stenosis diameter < 10 mm, fracture or displaced vertebrae, caries spine, traumatic low back pain, spondylolysthesis, Red flag sign, Non-cooperative patients are excluded from our study .All the recruited patients from different study groups were made aware of somnolence, fatigue, nausea that may occur for first 2-4 weeks of initiation of therapy to minimize drop outs. Patients were divided into 3 groups A, B and C according to different dose of pregabalin i.e. 75mg once per day, 75mg twice per day and 50mg twice per day respectively. All the patients who enrolled in different study groups also received the following concomitant medications; Tablet Paracetamol 500 mg twice daily, Tablet Amitriptyline 10 mg once daily at bed time, Tablet Methylcobalamin 1500 mcg once daily, Capsule (Pantoprazole 40mg + Domperidone 30 mg) once daily. Choice of therapy was determined solely by the clinical judgment of the treating physician. Effectiveness was measured from the patients perspective using reduction of visual Analog Scale (VAS) Score at 0, 2, 4,8,12 and 24^{th} weeks interval. Visual Annual Scale (VAS) score was used to asses intensity of pain .VAS Score < 3 was taken to be satisfactory .

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RESULTS:

A total n=247 patients completed the study among them n= 81 were in Group A, n=80 were in Group B and n= 86 were in Group C. The baseline demographic and clinical characteristics are similar between treatment groups (P value>0.05). Statistical data collected and analyzed using SPSS vv20.

Quantitative data were defined as mean ± standard deviation (SD).For comparing variables with Normal distribution, ANOVA test was used. P < 0.05 was considered to be significant.

Table 1: Baseline demographic and clinical characteristic of the different treatment groups

Variable	Group A (n=81)	Group B (n=80)	Group C (n=86)	P value
Age	45 ± 3.65	44.86 ± 4.60	44.60 ± 3.361	**0.810**
Height	155.01 ± 6.28	154.05 ± 5.36	155.7 ± 5.90	**0.182**
Weight	64.85 ± 5.65	63.43 ± 4.33	65.58 ± 4.48	**0.160**
BMI	26.95 ± 1.45	26.76 ± 1.34	27.04 ± 1.42	**0.401**
VAS	**7.99 ± 0.60**	**7.95 ± 0.48**	**7.92 ± 0.41**	**0.673**

Baseline clinical characteristics among all the participated groups were comparable. Maximum and minimum VAS score found among the Groups A, B and C were around 9 and 7 respectively. Mean VAS score at the starting of the study in Group A was 7.99 ± 0.60, group B was 7.95+ 0.48, and Group C was 7.92 ± 0.41 (p value 0.673).

There was a gradual decreasing trend of VAS score in all groups during follow up. Clinically significant mean VAS score (p<0.05) achieved from their baseline mean VAS score at the 4th week of the study and after the 8th week of the study mean VAS score were less than 5 among all three study group. The VAS pain score improvements were also observed at the primary endpoint of 24 weeks also with the mean score well below 3 in all the groups with significant decrease in Group B (p<0.05) as compared to Group A & B.[**Fig 1**], **[Fig 2].**

Figure 1: Mean VAS score of the different study groups at 0, 2, 4, 8, 12, 24th weeks interval

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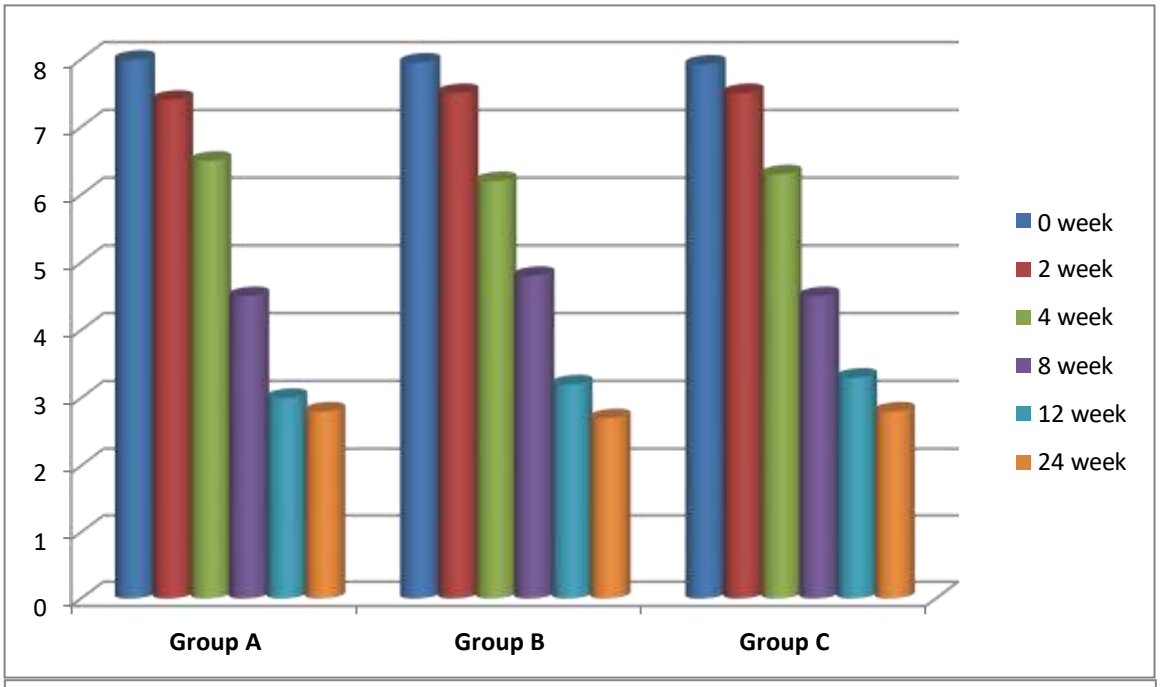

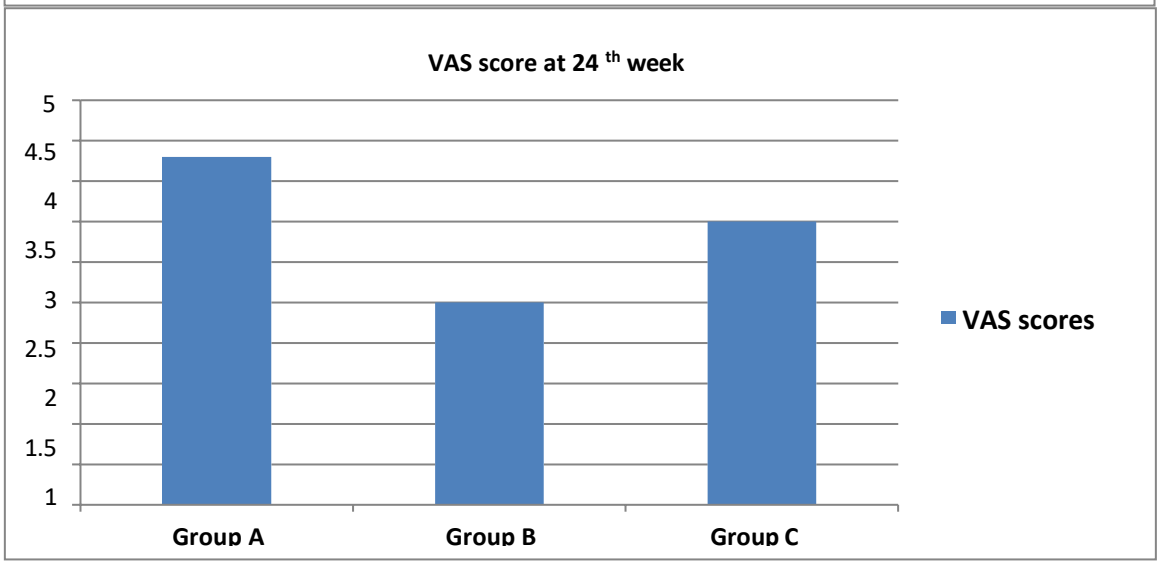

DISCUSSION:

The results of this prospective, non-interventional, observational study of CLBP patients treated with pregabalin showed significant improvements in pain. These improvements were not only observed at the primary endpoint of 24 weeks, but also showed significance after 4 weeks of treatment. After the 8 weeks of the study mean VAS score were less than 5 among all 3 groups. Though Group B only achieved satisfactory goal, other groups also improved significantly from their baseline mean VAS score. Dosing in this study was made flexible, reflecting real-world clinical practice and the dose range was 75-150 mg/day. Pregabalin was found to be safe and well tolerated.

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As the doses administered were much less than the maximum recommended dose/day i.e. (600mg/day) [1] and with prior counseling of the patients none of the patient experienced common side effect of pregabalin and there were n=0 drop outs. Observations from previous studies of pregabalin in CLBP conditions also showed significant effects on pain. In 2015, Toshihiko Taguchil, Ataru Igarashi, Stephen Watt et al. [8]observed significantly improved in pain compare to usual care in treatment of chronic low back pain using pregabalin. In 2015, Sakai et al [9] also observed no significant difference in effectiveness between opioids and pregabalin in chronic low back pain. In 2016, Godfrey Pariyo et al [10] showed oral pregabalin has good effect on treatment of patient with chronic low back pain. In 2016, Kelvin Robertson and David Plummer et al. [11] favored pregabalin over gabapentin for treatment of chronic low back pain. While in 2017, Harsha Shanthanna, lan Gilron, Manikandan Rajarathinam et al. [12] demonstrated the use of gabapentinoids in CLBP is limited and are not helpful for non specific chronic low back pain.

LIMITATIONS:

As the study was a single centric study so there was limited scope of ethno-racial evaluation. The number of patients recruited was too small to evaluate demographic data related correlation in results. The duration of the observational study was only 6 months which assessed only the short term effects. However the present study showed Pregabalin is useful in chronic low back pain and significantly reduces pain in all groups.

CONCLUSION:

Pregabalin reduces chronic low back pain in combination with usual care. 75 mg twice daily dose of Pregabalin is more effective followed by 50 mg twice daily and 75mg once daily dose. These results provide evidence of the clinical benefit of pregabalin and confirm its usefulness for treating patients with this challenging condition.

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