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THE NOVEL NEUROPROTECTIVE AGENT PREGABALIN – A DRUG OF CHOICE IN THE MANAGEMENT OF POSTOPERATIVE PAIN

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ABSTRACT

Background: Pregabalin is a structural analogue of gamma-amino butyric acid (GABA), which act as inhibitory neurotransmitters of brain having a strong affinity to the α2 subunit of pre-synaptic voltage – gated calcium channel receptor to decrease post synaptic excitatory neurotransmitter release. This binding of pregabalin leads to its anxiolytic, anticonvulsant and antinociceptive effects. The efficacy of pregabalin in acute postsurgical pain has been demonstrated in numerous studies; however, the analgesic efficacy and adverse effects of using pregabalin in various surgical procedures remain uncertain.

Data Sources: The literature for the study was collected from January 2010 to November 2018, using PubMed, Google scholar, NCBI and Clinical Trials.gov with no limitation on publication year or language. Studies considered for inclusion were randomized controlled trials with treatment of perioperative pregabalin.

Therefore the present study was focused in the assessment of postsurgical analgesic efficacy after pregabalin administration under different spine surgical categories using appraised research studies.

Conclusion: Upon reviewing various literatures, we uphold the preferential use of pregabalin over gabapentin based on its superior pharmacokinetics and pharmacodynamics.

Keywords: Pregabalin, Neuropathic pain, Postoperative pain, Spine surgeries, Gabapentin

INTRODUCTION

PREGABALIN – THE ANALGESIC AGENT

The development of postoperative pain is an unpleasant and dominant complaint of surgery that seriously affects the quality of patients' life. Clinically, the acute postoperative pain sometimes transforms into chronic pain **[1]**. In recent years, numerous articles have been stating that preoperative use of pregabalin could effectively alleviate postoperative pain.

Pregabalin was first introduced in 2004 as an anti-epileptic drug and potent successor to gabapentin. At present, the Food and Drug Administration (FDA) and Health Canada approve the use of pregabalin for seizures and chronic pain (postherpetic neuralgia, fibromyalgia, and diabetic peripheral neuropathy) **[2]**. In the European Union, pregabalin was also approved for the use in generalized anxiety disorders **[3]**.

Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA). However, it does not act like GABA and it does not bind to the GABA receptors, but act as a potent ligand for alpha 2-delta subunits of the voltage – gated calcium channels in the nervous system. It's potent binding at this site results in a reduction in the depolarization – induced Ca^{2+} influx at the presynaptic nerve endings and therefore, reduces the release of excitatory neurotransmitters including glutamate, noradrenalin, dopamine and serotonin **[4, 5]**. Usage of pregabalin range from treatment of neuropathic pain to being an adjust in the multimodal management of postsurgical pain **[6]**. Thus, this study assesses the efficacy of pregabalin as analgesic after spine surgeries and to provide a useful reference in perioperative care.

The key findings of various studies concluding regarding the efficacy of pregabalin as analgesic were tabulated in **Table 1**.

Efficacy of gabapentinoids as neuroprotective agents:

Gabapentinoids (pregabalin, vigabatrin, gabapentin etc.,) belong to the GABA analog group of anticonvulsants and it is a well-tolerated drug in most patients, with a mild side – effect profile. The main antiepileptic mechanism of action is binding to the voltage – gated Ca^{2+} channel α2 - δ1 auxiliary subunit with selective inhibition of the channel **[7, 8]**. Considering the neuroprotective drugs like Topiramate (TPM), which block ionotropic glutamate receptors **[13]**, could interfere with neuronal plasticity, which is also regulated through

glutamate neurotransmission **[9]**. Bogdan *et al.,* in their study – Gabapentin is neuroprotective through glutamate receptor-independent mechanisms in staurosporine – induced apoptosis of cultured rat cerebellar neurons, reported that gabapentin is neuroprotective through glutamate - receptor independent mechanisms without alteration of cultures rat cerebellar markers in their model **[10]**. Burak *et al.,* in their study – Neuroprotective effects of Pregabalin against spinal cord ischemia – reperfusion injury in rats, stated that pregabalin as pretreatment has neuroprotective effect by decreasing caspase dependant apoptosis, and inflammatory and oxidative stress markers **[11]**. The same is also stated in Archana Jorige *et al;* study – Neuroprotective and antioxidant role of pregabalin in streptozotocin induced neurotoxicity that the anti-neuropathic effect of pregabalin was not only mediated through its action on voltage gated Ca^{2+} but also through its antioxidant action by the restoration of endogenous antioxidant enzyme levels **[12, 13]**.

Thus the neuroprotective potential of anticonvulsants with similar properties could be an important issue for developing combined treatment strategies in stroke or neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease. However, The Food and Drug Administration (FDA) has approved gabapentinoids for the treatment of postherpetic neuralgia (gabapentin, pregabalin), fibromyalgia (pregabalin) and neuropathic pain associated with diabetes or spinal cord injuries (pregabalin). Few clinical trials had assessed the use of gabapentinoids in common pain syndromes for which they are prescribed off-label and many of those trials were uncontrolled or inadequately controlled and of short duration **[14]**.

Efficacy of Pregabalin for post operative pain than other analgesics

The damage of the nervous system can cause neuropathic pain. It is different from pain messages that are carried along healthy nerves from damaged tissue (for example, from a fall or a cut, or from an arthritic knee). Neuropathic pain is often treated by different medicines (drugs) from those used for pain from damaged tissue, which we often think of painkillers **[17]**. Apart from all these, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen, acetaminophen, and naproxen are also very commonly prescribed. The most important thing while taking these types of medications is to be careful about the side effects of these medications, especially the alteration of the kidney

function in diabetic people. All the above medications have proved to be useful for treating the mild to moderate pain but not the severe pain **[15]**. To treat severe pain, the drugs which are prescribed are narcotic pain relievers like oxycodone, codeine, fentanyl, etc. Most of the narcotic pain relievers cause respiratory depression, urinary retention, and, blurring of vision.

Recent guidelines from the Centers for Disease Control and Prevention (CDC) recommend gabapentinoids (gabapentin or pregabalin) as first-line agents for neuropathic pain. However, that gabapentinoids are being prescribed excessively – partly in response to the opioid epidemic. The Food and Drug Administration (FDA) has approved gabapentinoids for the treatment of postherpetic neuralgia (gabapentin, pregabalin), fibromyalgia (pregabalin) and neuropathic pain associated with diabetes or spinal cord injuries (pregabalin). Pregabalin which is now considered to be first-line medication in the treatment of post-SCI (Spinal cord injury) neuropathic pain, mimic the neurotransmitter GABA and show indirect interaction with the GABA receptor. Interaction with voltage gated N-type calcium ion channels at the α2δ subunit and also indirect interaction with the NMDA receptor could increase the activity of inhibitory neurons, causing a decrease in the transmission of nociceptive signals **[28]**. Pregabalin is not associated with these kinds of adverse drug reactions of other drugs. Moreover, it is free from protein binding and has very less metabolism. This proves to be fruitful for the diabetic people who mostly are on the other drugs alongside **[16]**.

Bauer *et al* demonstrated the importance of increased trafficking of the Ca_V α_2-δ-1 subunit from the dorsal root ganglia to the dorsal horn in the development of neuropathic pain. Furthermore, the elevated α_2-δ-1 protein in the dorsal horn, but not in the DRGs was significantly reduced by chronic treatment with pregabalin for 8 days following spinal nerve ligation, indicating that pregabalin interferes with transport of α_2-δ-1 to its terminal zones [**28**]. This concludes that pregabalin provides analgesic action by binding to the α_2-δ subunit of VDCC and inhibits its functional expression (membrane and anterograde trafficking) along with inhibition of Ca^{2+} mediated excitatory neurotransmitter glutamate release at neuronal synapse **(Figure 1) [7]**.

There is evidence showing that oral pregabalin at doses of 300 mg or 600 mg daily has a positive effect on pain in patients with moderate or severe neuropathic

pain after shingles, or due to diabetes. . Ahn *et al*. **[29]** conducted a before-and-after trial of SCI patients with pain, in which they found that pregabalin was effective in decreasing neuropathic pain refractory to conventional analgesics. Low-quality evidence suggests that oral pregabalin is effective after trauma due to stroke or spinal cord injury. Pregabalin appears not to be effective in neuropathic pain associated with HIV as very limited evidence is available for cancer pain, and some other forms of neuropathic pain **[7]**.

Table 1: Evaluation of various studies showing the efficacy of pregabalin as analgesic

		Intervention	*Outcomes*	*Results*
Reference and year	***Procedure***	***Experimental &comparision groups(n), pregabalin dose and administration***	***Primary outcome follow up time and pain scoring system***	***2h pain score 6h pair score 8h pain score 24hr pain score 24hr total morphine consumption***
Burke *et al*. 2010 [18]	**Elective lumbar discectomy for chronic lumbar sacral radiculopathy**	**Pregabalin 300 mg (18), Placebo (20), Orally 1.5 h prior to surgery (300 mg) and 12 and 24 h post-operatively (150mg).**	**Cumulative analgesic requirement 0-24 h post-operation; 3 months; (VAS scores).**	**No data on pain scores. Morphine consumption, pregabalin, 1.55 (2.10), control, 3.30 (3.80).**
Spreng *et al*. 2011 [19]	**Elective lumbar single-level microdiscectomy**	**Pregabalin 150 mg (22), Placebo (24), 60 mins prior to surgery.**	**VAS up to 120 mins post-surgery; 24 h; (VAS scores).**	**2 h pain score, pregabalin 2.72 (2.0), control 3.78 (2.5). 24 h pain score, pregabalin 2.36 (1.5), control 2.62 (1.4) Morphine consumption, pregabalin, 25.0, control, 36.0.**
Hegarty *et al*. 2011 [1]	**Elective lumbar discectomy**	**Pregabalin 300 mg (14), Placebo (18), Orally 60 mins prior to surgery.**	**Reduction in morphine consumption; 24 h; (VAS scores).**	**No data on pain scores. Morphine consumption, pregabalin, 5.00, control, 9.00.**
Kim *et al*. 2011 [20]	**Elective posterior lumbar spinal fusion**	**Pregabalin 75 mg (28), Pregabalin 150 mg (28), Placebo (28), Orally 1 h prior to surgery and 12 h post-surgery.**	**Cumulative fentanyl PCA; 48 h; (VAS scores).**	**2 h pain score, pregabalin 3.0 (2.0), control 4.0 (2.0). 24 h pain score, pregabalin 3.0 (2.0), control 3.0 (2.0).**
Ozgencil *et al*. 2011 [21]	**Elective decompressive lumbar laminectomy and discectomy**	**Pregabalin 150 mg (30), Placebo (30), Gabapentin 600 mg (30), 2 h prior to surgery, and 10 and 22 h post-surgery.**	**VAS from 0-24 h post-surgery; 24 h; (VAS scores).**	**2 h pain score, pregabalin 4.5 (1.3), control 5.7 (1.1). 24 h pain score, pregabalin 1.1 (1.2), control 1.5 (0.8). Morphine consumption, pregabalin, 0.36 (0.13), control, 0.51 (0.14).**
Choi *et al*. 2012 [22]	**Elective lumbar laminectomy with or without fusion, for chronic lumbo-sacral radiculopathy due to herniated lumbar disc or degenerative spinal stenosis**	**Pregabalin 150 mg (36), Placebo (36), Placebo with dexamethasone (36), Orally 60 mins prior to surgery.**	**Post-operative pain 6 – 24 h post-surgery; 1 month; (VAS scores).**	**2 h pain score, pregabalin 3.30 (2.4), control 3.70 (2.5). 24 h pain score, pregabalin 2.20 (2.1), control 3.00 (2.1). No data on morphine consumption.**
Gainesello *et al*. 2012 [23]	**Elective decompressive lumbar laminectomy with spinal fusion for degenerative spinal stenosis**	**Pregabalin 300 mg (30), Placebo (30), Pregabalin 150 mg twice daily for 48 hrs post-surgery. Orally 60 mins prior to surgery.**	**Reduction in morphine consumption; 1 year; (VAS scores).**	**2 h pain score, pregabalin 1.80 (0.4), control 3.10 (0.7). 24 h pain score, pregabalin 0.60 (0.8), control 0.20 (0.5). Morphine consumption, pregabalin, 3.00 (2.00), control, 9.50 (2.50).**
Kumar *et al*. 2013 [24]	**Elective decompressive lumbar laminectomy**	**Pregabalin 150 mg (25), Placebo (25), Tramadol 100 mg (25), Orally 1 h prior to surgery.**	**Pain score up to 6 h post-surgery; 6 h; (VAS scores).**	**2 h pain score, pregabalin 2.9 (1.2), control 5.5 (1.3). No data on 24 h pain scores. Morphine consumption, pregabalin, 1.9 (1.6), control, 2.0 (2.0).**

Khurana *et al*. 2014 [25]	Lumbar discectomy for intervertebral disc prolapsed without ligament hypertrophy	Pregabalin 75 mg (30), Gabapentin 300 mg (30), Placebo (30), 60 mins prior to surgery and every 8 h post surgery for 7 days.	Pain score up to 72 h post-surgery; 3 months; (VAS scores).	2 h pain score, pregabalin 3.0, control 9.0. 24 h pain score, pregabalin 0.3, control 1.0.
Rahul *et al*. 2018 [26]	Elective lumbar laminectomy and discectomy	Pregabalin 150mg (20), Pregabalin 300mg (20), placebo (20)	Pain score up to 8h post surgery; (VAS scores)	8 h pain score, pregabalin 150mg 17.5, pregabalin 300mg 14, control 43.5
Sidharth *et al*. 2018 [27]	Elective lumbar discectomy and spinal tumor surgeries	Gabapentin 300mg (25), Pregabalin 150mg (25), placebo (25)	Pain score up to 24hr post surgery (VAS scores)	No data on pain scores.

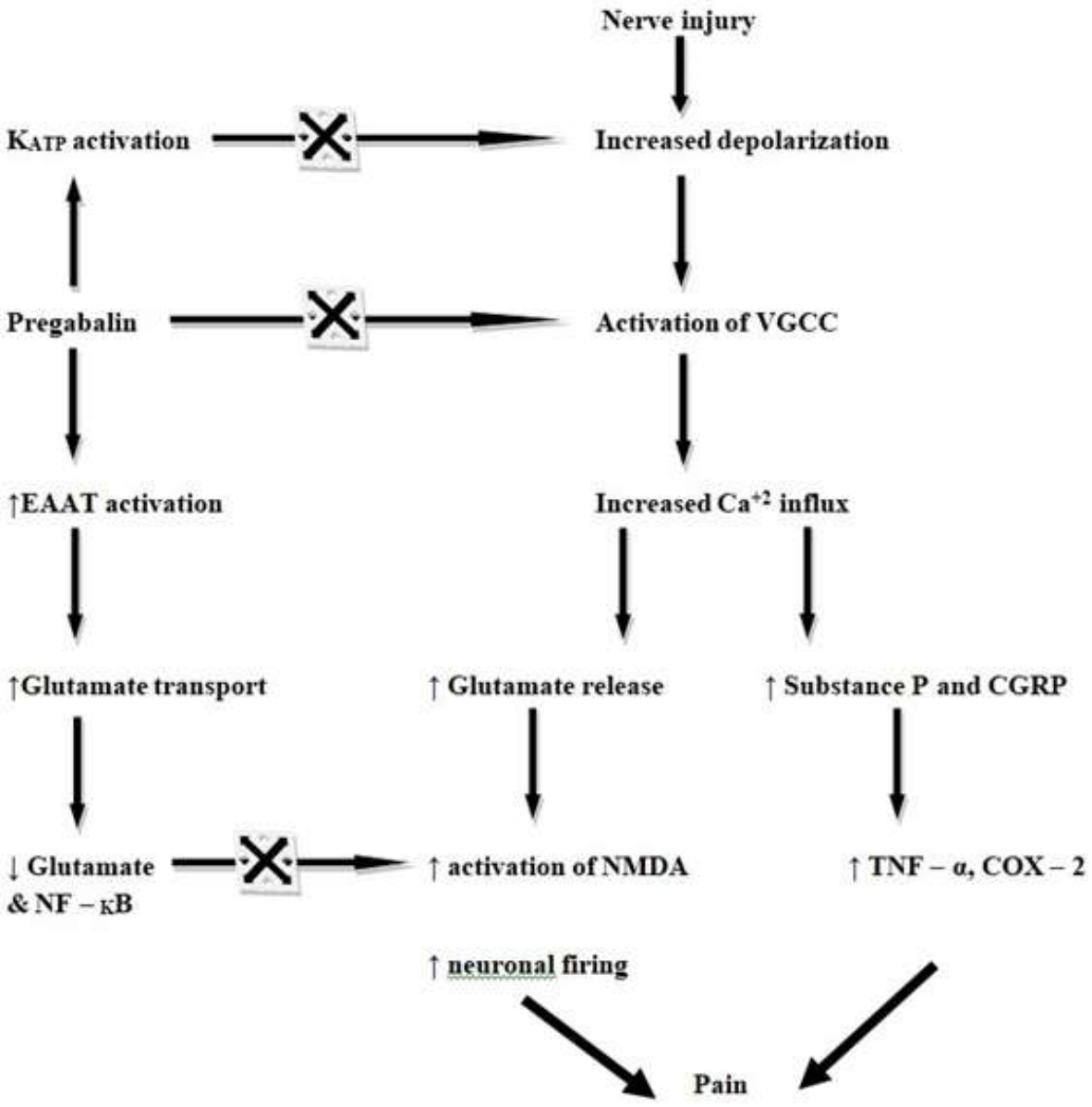

Figure 1: The Mechanism of action of pain alleviation by Pregabalin

DISCUSSION:

Pre-emptive analgesia given before incision focuses on managing post operative pain including decreasing the consumption of analgesics as well as give out to neuroprotective characteristics. The present review shows that perioperative administration of pregabalin was associated with a statistically significant reduction in pain scores at rest, during movement, and opioid consumption after surgery compared with placebo.

Many studies have done investigating the analgesic effect of perioperative pregabalin or gabapentin administration so far in various surgical procedures. It has long recognised that different surgical procedures require procedure – specific pain management. It is evident that the degree of pain experienced by patients after different surgical procedures is not universal. In this study we focus on the different spine surgical procedures together, results showing that pregabalin is useful in reducing post surgical pain as well as reducing morphine consumption. Recently conducted Meta – analysis on 55 randomised controlled trails concluded that when all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 hrs compared with placebo. Thus from the studies of Spreng, khurana, Kim, Kumar shows that there is a reduction in pain scores rest 2 hours post surgery (p = 0.001) and the morphine – equivalent consumption (P = 0.005). With regards to the study conducted by Choi, Ozgencil, Gianesello, a large decrease in pain at 2 hours and total morphine consumption was seen, although there was less reduction in pain at 24 hours post surgery.

The administration of pregabalin was associated with a significantly higher incidence of sedation relative to placebo. Of note, pregabalin – treated patients achieved hospital discharge criteria earlier than controls. In this study these effects are seen in the studies with a high dose (≥ 150mg - ≥ 300mg) of pregabalin that increases the rate of dizziness and sedation.

LIMITATIONS:

We only included endpoints regarding opioid consumption and pain scores with the follow up at 24 hours. The relatively small sample size of the certain included studies may had affected the accuracy of the effect size estimation.

CONCLUSION:

From the above data we conclude that preoperative pregabalin is propitious for postoperative analgesia and condemn the

administration of opioids, but its therapeutic efficacy range from pregabalin dose to surgery types. Preclinical as well as clinical studies illuminate pregabalin as a very effective agent for treating neuropathic pain with a very good safety profile. The inhibition of voltage gated Ca^{2+} channel is the most likely target for pregabalin action, which contributes to the reduction of excitatory neurotransmitters release and inhibition of synaptic transmission. The modulation of K^{+} channel conductance, excitatory amino acid transporter and inflammation are other possible mechanisms responsible for its analgesic actions. Therefore, we uphold the preferential use of pregabalin over gabapentin based on its superior pharmacokinetics and pharmacodynamics.

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