

**Preoperative Pregabalin Prolongs Duration  
of Spinal Anesthesia and reduces Early  
Postoperative Pain A double- Blinded  
Randomized Clinical Consort Study**

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## **List of abbreviations**

|      |                                   |
|------|-----------------------------------|
| AED  | : Antiepileptic drug              |
| AE   | : Adverse effect                  |
| AUC  | : Plasma concentration–time curve |
| CLCR | : Creatinine clearance            |
| GBP  | : Gabapentin                      |
| PGB  | : Pregabalin                      |
| NeP  | : Neuropathic pain                |
| NPRS | : The Numeric pain rating scale   |
| VB   | : Vertebral body                  |

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# Introduction

Various adjuvants have been used to prolong spinal anesthesia, with the additional advantages of delaying the onset of postoperative pain and reducing postoperative analgesic requirements.

Pregabalin is an *R*-aminobutyric acid analog that binds to the  $\alpha 2$ - $\delta$  subunit of presynaptic voltage-gated calcium channels.

It reduces the depolarization-induced calcium influx at nerve terminals, with a consequent reduction in the release of several excitatory neurotransmitters, including glutamate, noradrenaline, substance P, and gastrin-releasing peptide (*Ben-Menachem, 2004*).

The administration of oral pregabalin preoperatively has been reported to reduce acute postoperative pain<sup>(</sup>and to prolong the duration of anesthesia produced by single-injection peripheral nerve blockade (*Cegin, et al., 2016*).

However, no clinical study to date has yet fully investigated whether or not pregabalin premedication affects sensory and motor blocks using spinal anesthesia and its effect upon early postoperative pain management.

Preemptive analgesia is analgesic administration that precedes the painful stimulus, thus improving postoperative pain control. It is an antinociceptive treatment that prevents the establishment of altered processing of afferent input, which amplifies postoperative pain<sup>(</sup>

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This technique is utilized in acute postsurgical pain management to improve the efficacy of analgesics and thereby reduce the requirement for opioids (*Bromley etc, 2006*).

In this prospective, randomized, double-blind, and placebo-controlled study, It is hypothesized that single dose 150mg pregabalin premedication would prolong the sensory blockade of spinal anesthesia used bupivacaine.

A secondary objective of this study was to determine if premedication with pregabalin also reduces the need for medication to relieve postoperative pain.

## **Aim of the Work**

The aim of this work is to evaluate the efficacy of a single dose of pregabalin in duration of spinal blockade and its potential opioid-sparing effect during the first 24 hours postoperatively

## Pregabalin Background

Pregabalin (PGB) is a newer generation gabapentinoid which followed the use of gabapentin (GBP). Originally synthesized over four decades ago (*Satzinger et al., 1976*), GBP was initially developed for use as an adjuvant antiepileptic drug (AED). However, after its release nearly two decades ago, off-label prescriptions for conditions other than epilepsy make up about 90% of GBP's use (*Tansey, 2004*). This was secondary to limited efficacy in epilepsy as an adjuvant AED, but also because of a series of case reports describing the benefits of GBP in the treatment of neuropathic pain (NeP). After publication of randomized controlled trials in NeP conditions, GBP became a widely used pharmacotherapy for NeP, despite being off label (*Rice and Maton, 2001*)

PGB is a newer gabapentinoid, with great structural similarity to GBP. Just as with GBP, the use of PGB in epilepsy is limited. Instead, nearly all of PGB's use is for treatment of NeP, for which PGB was more directly targeted than with GBP. In addition, PGB is used frequently in the treatment of anxiety. Although the mechanism of action has not been completely revealed, one known mechanism of action likely contributes to PGB's efficacy, even though other potential mechanisms may also occur (*Eroglu et al., 2009*).

PGB was approved for NeP management in 2004 within the USA and Europe, and PGB has received further

indications for various NeP conditions. Of the many treatments available for NeP management, gabapentinoids including GBP and PGB are considered as first-line treatment for most clinical guidelines. Currently, PGB is indicated for the management of NeP associated with diabetic peripheral neuropathy (DPN) (*Arezzo et al., 2008*).

In North America. In the USA as well as in Europe, PGB is also indicated as adjunctive therapy for adult patients with partial onset seizures. PGB is the only medication in Europe approved for the treatment of central NeP. In Europe, it is also indicated for the treatment of peripheral NeP and generalized anxiety disorder, but not for fibromyalgia treatment.

Defined as pain arising from a lesion or disease affecting the somatosensory pathways

within the peripheral or central nervous system, NeP is a common disorder, impacting on between 4% and 16% of the population. Fortunately, PGB is one of several pharmacotherapies used in NeP management which can modulate pain relief and also assist with management of comorbidities (*Bouhassira et al., 2008*).

### **Mechanism of action, metabolism and pharmacokinetics:**

The mechanism of action for PGB is not completely understood. As the S-enantiomer of 3-(amino methyl)-5-methylhexanoic acid, PGB binds with high affinity to the  $\alpha_2\delta 1$  site (a subunit of voltage-gated calcium channels (VGCCs) in the central nervous system (*Field et al., 2006*).

These high-affinity GBP- and PGB-binding sites are present throughout the dorsal spinal cord and brain. This is a presynaptic channel which modulates release of excitatory neurotransmitters vital for both nociception and epileptogenesis (*Taylor et al., 2007*).

It is known that gabapentinoids prevent trafficking of the  $\alpha_2\delta 1$  subunit from the dorsal root ganglia neurons to the dorsal spinal cord within animal models of NeP. This  $\alpha_2\delta 1$  subunit binding is thought to be responsible for both antinociceptive and probably its antiseizure effects as well (*Vartanian et al., 2006*).

, A reduction in the excessive release of multiple excitatory neurotransmitters occurs; these neurotransmitters include noradrenaline, serotonin, dopamine, glutamate and substance P.

Finally, PGB may elicit the internalization of VGCC at a cellular level.

PGB's effect is dependent upon the existence of hyperexcitation of the presynaptic neuron with minimal effects shown to occur during normal neuronal activity (*Fink et al., 2002*).

PGB is structurally related to the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA), just as with GBP (*Brawek et al., 2009*). In addition to its impact on the  $\alpha_2\delta 1$  subunit, there are suggestions that PGB may also modulate GABA concentrations and the glutamate synthesizing enzyme, branched-chain amino acid transaminase (cytosolic form). GBP may also modulate

glutamate synthesis indirectly and increase nonsynaptic GABA responses at the GABA-A or GABA-B receptors (*Parker et al., 2004*). In addition, PGB may enhance activity of the neuronal glutamate transporter type 3, increasing glutamatergic responses. The AED mechanism for gabapentinoids is uncertain, but in animal models, gabapentinoids prevented seizures in rodent models for both maximal electroshock and pentylenetetrazole seizure models (*Vartanian et al., 2006*). Finally, another potential mechanism may be gabapentinoid-mediated synaptogenesis (*Eroglu et al., 2009*) with potential blockade of new synaptic formation. When studied in animal analgesic models, gabapentinoids modulate both hyperalgesia (exaggerated response to a painful stimulus) and allodynia (pain-related behavior in response to a normally innocuous stimulus).

Although differences do not appear to be present between PGB and GBP for mechanisms of action, PGB's affinity and potency for the  $\alpha_2\delta 1$  subunit, speculated to be higher than that of GBP,

After oral administration, PGB is subject to rapid absorption. Oral bioavailability is over 90% and independent of the dose received. This is compared with 30–60% bioavailability for GBP. Following either single (25–300 mg) or multiple dose (75–600 mg/day) administrations, there is a linear association for maximum plasma concentrations ( $C_{\max}$ ) and area under the plasma concentration–time curve (AUC) values. There is a difference between PGB and GBP for gastrointestinal absorption, although both gabapentinoids are absorbed across the gastrointestinal tract using a system-L

transporter system, GBP absorption is solely mediated by this system L transporter, leading to limitation through this saturable, active and dose-dependent transporter, producing nonlinear pharmacokinetics. PGB, however, has nonsaturable absorption, providing linear pharmacokinetics. Both gabapentinoids are also absorbed across the intestinal apical membrane via Na<sup>+</sup>-independent amino acid transporters (*Piyapolrungrroj et al., 2001*). However, gabapentinoid transport across the intestinal basolateral membrane is likely mediated by the system L transporter. These factors may also contribute to saturable absorption of GBP across the gastrointestinal tract, as high affinity and lower capacity of GBP saturable transport and its dose-dependent decrease in oral absorption (*Bockbrader et al., 2010*). As such, the rate of PGB absorption is threefold higher than that of GBP. These factors explain how PGB achieves a faster peak blood concentration (1 h post dose) compared with GBP (3 h) (*Bockbrader et al., 2010*).