Ondansetron versus Pregabalin in Control Emetic Attacks during Surgery with Spinal Anesthesia: Review Article

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ABSTRACT

Background: All anesthesiologists find it difficult to control intraoperative nausea and vomiting during spinal anesthesia (SA) procedures, mostly due to its multifactorial nature. During operations, SA is a frequently employed method that provides anesthesia without the hazards of general anesthetic (GA). SA can have certain hazards. Hypotension from a nearly total sympathetic block is the most frequent adverse outcome. Antiemetic medications are used to prevent or treat nausea and vomiting, which makes them not only an unpleasant and disturbing experience during the post-operative phase but also potentially a significant contributing element to the post-operative convalescence.

Objective: This study aimed to compare between Ondansetron and Pregabalin for control of emetic attacks during surgery with SA.

Methods: A thorough search for material on Ondansetron versus Pregabalin in control of emetic attacks during surgery with SA was done in PubMed, Google Scholar, and Science Direct. Only the most recent or thorough investigation, which ran from December 2000 to May 2024, was taken into account. The writers evaluated relevant literature references as well. Because there are insufficient resources for translation, documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts, and unpublished manuscripts.

Conclusions: The most prevalent empirical application of ondansetron is to alleviate nausea and vomiting. Most often, this medication is used to stop nausea and vomiting after surgery. This 5-hydroxytryptamine receptor 3 antagonist, which inhibits serotonin's action, is a strong anti-emetic. In a variety of groups, pregabalin has been used to treat anxiety disorders, chronic pain, and epileptic patient pain.

Keywords: Ondansetron, Pregabalin, Emetic attacks, SA.

INTRODUCTION

SA is a commonly used regional anesthetic procedure that entails injecting local anesthetics into the subarachnoid space, usually between the intervertebral spaces L3-L4 or L4-L5. Deep anesthesia is produced underneath the block's level as a result of the reversible blocking of sensory, motor, and autonomic nerve fibers. When it comes to lower abdominal, pelvic, and lower extremity procedures, SA is very helpful since it provides quick onset, efficient intraoperative analgesia, and less discomfort after surgery. It is linked to decreased rates of thromboembolic events, respiratory problems, and post-operative nausea and vomiting (PONV), avoids airway manipulation, and lowers systemic drug exposure [(1)]. A specific antagonist of the 5-hydroxytryptamine 3 receptor, ondansetron has demonstrated encouraging results in the management and control of nausea and vomiting brought on by opioid analgesics and intra- and post-operative anesthesia. In contrast, ondansetron with dexamethasone has been shown to significantly lower the incidence of nausea and vomiting compared to ondansetron alone [(2)].

Pregabalin is one of the medications utilized; it is an anticonvulsant that works by preventing calcium from entering the body. People with epilepsy, chronic pain, and anxiety problems have all been treated with pregabalin to lessen their suffering. Few studies have looked at how pregabalin affects nausea and vomiting, despite research on various groups [(3)]. Therefore, this review aimed to compare between ondansetron and pregabalin for control of emetic attacks during surgery with SA.

SPINAL ANESTHESIA

The brain and spinal cord make up the central nervous system (CNS). The administration of local anesthetic (LA) in or near the central nervous system is known as neuraxial anesthesia. LA is positioned directly in the intrathecal space (subarachnoid space) during SA, a neuraxial anesthetic procedure. SA is utilized for lower abdominal, pelvic, and lower extremity surgeries and is carried out in the lumbar spine. Proper placement and knowledge of neuraxial anatomy are necessary for SA administration. Getting the right amount of anesthetic into the intrathecal (subarachnoid) region is the aim [(4)].

- **Indication criteria:** Surgery involving the lower abdomen, pelvis, perineum, and lower extremities frequently uses SA; it is advantageous for operations performed below the umbilicus**.** Orthopedic procedures, such as joint replacement and arthroplasty, for the pelvis, hip, femur, knee, tibia, and ankle [(4)].
- Vascular surgery for the legs.
- Endovascular treatment of aortic aneurysms.
- Intestinal or epigastric hernias.
- Hemorrhoidectomy; and nephrectomy and cystectomy combined with GA.

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- Transurethral excision of bladder cancers and transurethral excision of prostate.
- Hysterectomy using various methods.
- CSs.
- Alleviation of pain during vaginal birth and delivery.
- Urology cases.
- Anaesthesia-assisted examinations.

❖ **Complications**

Although spinal blocking difficulties are sometimes separated between major and small issues, the majority of serious issues are uncommon. Nonetheless, minor issues are frequent and should not be disregarded. SA failure rates have been reported to range from 1% to 17% [(4)].

● **Minor complications of SA**

N & V: After SA, the patient may have uncomfortable symptoms including nausea and vomiting, which might also make the surgeon's job more difficult. SA alone may induce IONV or PONV by a number of reasons, such as high block, hypotension, intrathecal additives, or insufficient block. Risk factors for IONV under spinal include a history of motion sickness, a baseline heart rate of 60 beats per minute or higher, a peak block height larger than T6, and prior hypotension following spinal block [(5)].

Hypotension: Predictable negative effects of a trustworthy spinal block include fetal acidity, reduced uteroplacental blood flow, and maternal hypotension that causes nausea and vomiting. A 20% decrease from baseline blood pressure is the most widely accepted definition of spinal-induced hypotension, with reports of a frequency of 70–80% [(6)].

Shivering: GA, as well as spinal and epidural anesthesia, can cause shaking. Although it is challenging to determine due to the variety of research, the incidence of shivering caused by neuraxial block is around 55% [(7)].

Itch: The well-known adverse effect of opiates is pruritus, which is more frequent when administered through the spinal route (46%) as opposed to the epidural (8.5%) and systemic routes. Neuraxial opioid-induced pruritus frequently affects the face and nose. The opioid receptor antagonist naloxone can be used to treat pruritus, even if symptoms may not be mediated by opioid receptors [(8)].

Postdural puncture headache (PDPH): Following SA and accidental dural puncture during epidural anesthesia, PDPH is a serious neuraxial anesthesia complication. This disorder is thought to be more common in obstetric patients due to their sex, age, and the frequent use of neuraxial blocks. A dull, throbbing ache that is distributed frontally and occipially is the initial symptom of PDPH. The headache usually becomes worse when you sit or stand up and gets better when you lie down. If the headache does not include a postural component, the diagnosis should be questioned. The patient should get at least some alleviation when they lie down. The ICHD criteria for diagnosing PDPH state that a headache starts five days after a dural puncture and goes away on its own within a week, or up to 48 hours following an epidural blood patch. Stiff neck, tinnitus, hypoacusia, photophobia, and nausea may accompany the headache [(9)].

● **Major complications of SA**

Meningitis: Following SA, meningitis, either bacterial or aseptic, may develop. The anesthesiologist's oral flora, patient illness, and contaminated spinal trays and medicine are among the sources of infection. Nonsteroidal anti-inflammatory medications, certain antibiotics, radiography agents, and muromonab-CD3 are examples of pharmaceuticals and chemicals that can cause meningitis. Additionally, there seems to be a connection between the development of hypersensitivity-type responses and underlying rheumatologic, vascular, and collagen disorders [(10)].

Vertebral canal hematoma: After SA, vertebral canal hematoma development is an uncommon yet deadly consequence. A few instances have identified subarachnoid hemorrhage as the source of neurologic impairments, despite the fact that the majority of spinal hematomata occur in the epidural space because of the large epidural venous plexus. Either a damaged vein or an injured artery may be the cause of the bleeding [(11)].

Spinal cord ischemia: A pial plexus and three longitudinal arteries—the anterior spinal artery and two posterior spinal arteries—make up the spinal cord's superficial vascular system. Numerous anastomoses shield the posterior chord from ischemia to a considerable extent. Because the core region of the anterior spinal cord depends on the anterior spinal artery, it is more vulnerable to ischemia. A vertebral canal hematoma compressing the arterial supply, adding vasoconstrictors to LAs, and persistent hypotension are some of the hypothesized causes of spinal cord ischemia resulting from spinal blocking [(12)].

Peripheral nerve injury: Injury to peripheral nerves may be an indirect consequence of SA. Normal defensive responses are momentarily eliminated by the sensory block caused by SA. As a result, proper placement, avoiding tight plaster casts, and monitoring distal circulation all require caution. Therefore, proper nursing care of limbs rendered insensate by SA is essential [(13)].

Total SA: Total SA results in circulatory dysfunction, respiratory depression, and unconsciousness. This may be preceded by upper limb weakness, numbness, or paresthesia, dyspnea, nausea, or anxiety [(14)].

ONDANSETRON

A carbazole derivative called ondansetron hydrochloride dihydrate is sold as a racemic combination. The empirical formula has a molecular weight of 365.9 and is $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$. It can be administered intravenously or intramuscularly

and comes in tablet, oral solution, oral disintegrating tablet, and suppository form. Reduced solubility in aqueous solution and a weak lipophilic base (pKa=7.4, logD=2.28 at pH7.4) characterize it. Reviewing ondansetron's function for PONV is the aim of this paper [15].

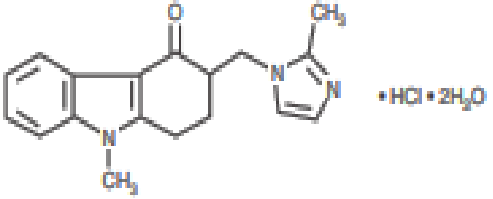
Drug name	Ondansetron hydrochloride
Phase	Launched
Indication	Postoperative and chemotherapy induced nausea and vomiting
Mechanism of action	5-Hydroxytryptamine 3 antagonist
Route of administration	Intravenous, intramuscular, orally and per rectum
Chemical structure	
Pivotal trial(s)	[46-48]

Figure (1): Drug summary [15].

❖ Indications

Doctors in emergency rooms and basic care clinics frequently meet patients complaining of nausea and vomiting on a regular basis. Ondansetron is included on the WHO list of essential medicines, which is a list of drugs that are thought to be safe and effective in addressing a health care system's fundamental requirements. Ondansetron is included among other antiemetics such as metoclopramide and dexamethasone. The brand-name form of ondansetron was the 20th best-selling brand-name medication in the US in 2006 (the last year of its patent), and its appeal is still present today. As an antiemetic medication, ondansetron is widely used and works well for a variety of nausea and vomiting conditions [16].

The FDA has authorized the following indications: Prevention of chemotherapy-induced nausea and vomiting (CINV) and PONV. When treating radiation-induced and chemotherapy-induced INV, it is regarded as first-line therapy. Usage outside of the prescribed medication to avoid pregnancy-related nausea and vomiting. Motion sickness-induced nausea and vomiting, which are mediated by many control centers and pathophysiologic processes, are not well treated by ondansetron. Little information is known on pediatric populations. The effectiveness of ondansetron in treating cyclic vomiting syndrome is not well understood, however it is utilized in pediatric populations for acute therapy. When neuroendocrine tumors (Carcinoid syndrome) cause severe refractory diarrhea, ondansetron is administered off-label [16].

❖ Adverse effects

Headaches, exhaustion, dry mouth, malaise, and constipation are the most often reported adverse effects, affecting over 10% of people. Less frequent side effects include local injection site responses, itching, and central nervous system symptoms including fatigue and sedation. There has also been a brief rise in liver function tests. Rarely, there may be clinically evident acute liver damage or jaundice, however the pattern of elevated liver enzymes is often hepatocellular. EKG interval alterations such as QTc elongation can be observed, however they are usually clinically inconsequential. Usually, these alterations take place one to two hours after administration, and they revert to normal within twenty-four hours. There is a risk of Torsade de Pointes and other arrhythmias, much like with any drug that lengthens the QTc. The FDA does not advise a single dose of more than 16 mg IV because of the increased risk of arrhythmias associated with IV delivery [17].

Additionally, isolated occurrences of a systole and sinus bradycardia have been documented. Intestinal blockage brought on by impaired gut motility has been documented. There have been reports of Stevens-Johnson syndrome in people with many comorbidities [18].

❖ Drug-drug interactions

Because pimozide and ondansetron might cause QTc prolongation, it is best to avoid taking both at the same time. Monitoring is necessary with ondansetron dosing since amiodarone may also lengthen the QTc interval. Concurrent use of ondansetron and other serotonergic drugs may result in serotonin syndrome [19].

❖ Contraindications

In individuals who are hypersensitive to ondansetron or any of its ingredients, the medication should not be administered. There have been reports of severe hypersensitivity responses, including anaphylaxis. Patients who are taking apomorphine at the moment should not take ondansetron. Because ondansetron intensifies apomorphine's hypotensive effects, using ondansetron and apomorphine together can result in severe hypotension and unconsciousness. Because the dissolving tablet formulation may include phenylalanine, which can cause irreparable brain damage in PKU patients, patients with PKU should exercise caution [20].

PREGABALIN

For the treatment of neuropathic pain (NeP), pregabalin is one of the first-line medications that has been authorized. Even though pregabalin helps a lot of patients, many of them receive inadequate dosages, maybe because doctors are not comfortable with prescripting the medication or because up-titration adverse effects might happen [21].

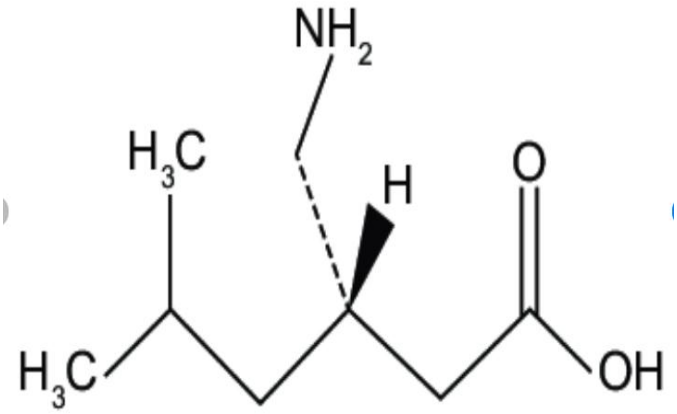


Figure (2): Chemical structure of pregabalin [21].

❖ **Indications**

Pregabalin was authorized by the USA FDA in 2004. Pregabalin is used to treat NeP and seizures [22].

FDA-approved indications [22]:

- NeP linked to spinal cord damage.
- Diabetes-related peripheral neuropathy and NeP.
- NeP that results from post-herpetic neuralgia.
- Adults with epilepsy who experience partial-onset seizures might benefit from adjunctive therapy.
- Therapy for fibromyalgia.

According to EULAR guidelines, those who have significant pain or sleep disturbances should think about using pharmaceutical therapy. When treating severe pain and sleep disturbances at the same time, pregabalin may be the most suitable medication [23].

Off-label uses [21]:

- The disorder of generalized anxiety.
- For example, social anxiety disorder.
- Sleeplessness.
- Conditions involving chronic pain.
- Urinary pruritus.
- A persistent cough.
- Uncomfortable legs syndrome.
- The syndrome of complex regional pain.
- The prevention of migraines.
- The trigeminal nerve pain.

❖ **Pregabalin antiemetic effect**

It does inhibit voltage-gated calcium channels by decreasing the production of excitatory neurotransmitters that lower postoperative inflammation, albeit its exact mode of action in preventing PONV is unknown. It may assist lower intraoperative and postoperative opioid use because of its inhibitory impact in the postrema region. Pregabalin dosages, use guidelines, and surgical procedures vary widely. This might help to explain why its use has shown inconsistent outcomes and point to the need for more research on the topic. Pregabalin dosages have varied, ranging from 50 mg to 600 mg daily. Certain individuals have taken pregabalin either before or after surgery, or one dosage before surgery and another twelve hours afterward [24]. **Grant *et al.*** [25] found that pregabalin lowers the incidence of nausea and vomiting, as well as the need for rescue antiemetics during the first twenty four hours following GA surgery.

The results of two other studies that assessed pregabalin's ability to prevent PONV in patients having hysterectomy were inconclusive [26]. It is important to emphasize that PONV was handled as a secondary outcome in every study they included. Pregabalin was shown to be effective in suppressing PONV by **Wang *et al.*** [27] although they stressed that their study was limited by the heterogeneity of the trials and the various pregabalin dosages utilized.

❖ **Adverse effects:** The majority of pregabalin-related side effects that were described were mild to moderate in severity, dose-dependent, and happened during the first two weeks after starting medication [21].

- The unfavorable effects that affected the central nervous system were the most frequent. The most prevalent side events that resulted in the cessation of pregabalin were somnolence and dizziness.
- According to premarketing studies, the most frequent side effects of pregabalin are sleepiness, light headedness, blurred vision, trouble focusing or paying attention, dry mouth, edema, and weight gain. These side effects affect more than 5% of patients and are twice as prevalent as those of a placebo.
- Pregabalin-induced weight gain is dose-dependent and can happen in as many as 14% of individuals taking 600 mg per day.
- Some individuals experienced anxiety, nervousness, irritability, headaches, nausea, diarrhea, and sleeplessness when stopping pregabalin suddenly or quickly.
- Pregabalin misuse is dangerous, particularly for individuals taking opioid medications or with a history of drug addiction, and prolonged usage can lead to physical dependency [21].

❖ **Drug-drug interactions**

Because of its low metabolism, lack of plasma protein binding, and mostly renal excretion, pregabalin's pharmacokinetics are unlikely to be impacted by other substances. Research indicates that pregabalin and popular antiepileptic medications do not significantly interact pharmacokinetically. No interactions between pharmacokinetics and pharmacodynamics were found. It is best to avoid coadministration of pregabalin with CNS depressants such as ethanol, benzodiazepines, and opioids since they work in concert [(28)].

❖ **Contraindications**

Patients who have a history of pregabalin hypersensitivity should not use pregabalin. There have been reports of angioedema and other hypersensitivity responses [(29)].

❖ **Warning and precautions:**

Studies have shown that pregabalin usage by mothers during the first trimester is not linked to a considerably higher risk of congenital abnormalities, but a little increase in risk cannot be ruled out, raising the possibility that pregabalin may harm the fetus. A limited sample size and residual confounding or chance findings are probably to blame for the previously documented significant increase in the incidence of malformations linked to first-trimester pregabalin use. Breastfeeding is not advised, and an alternate medicine is suggested, as pregabalin has been found in breast milk [(21, 30)].

Pregabalin has been linked to rhabdomyolysis, according to an examination of the FDA Adverse Event Reporting System (FAERS) database. If myopathy is suspected or creatine kinase levels are noticeably increased, patients should stop medication and report any unexplained muscular problems as soon as possible [(22)].

❖ **Pregabalin and PONV**

Pregabalin is licensed to treat partial seizures, but it has also been used to treat fibromyalgia, diabetic neuropathy, and even severe postoperative pain. While gabapentin has been studied as a PONV preventive medication, pregabalin has not received as much attention. Non-opioid options have been progressively included to perioperative improved recovery regimens in an effort to encourage early patient recovery. Many of these drugs have several functions, such as reducing postoperative inflammation, preventing PONV, limiting the need of opioids, and anxiolysis. As a result, drugs like gabapentin and pregabalin, which have been demonstrated time and time again to lessen postoperative pain and the need for opioids, now have a wider market [(31)].

Although, gabapentin's antiemetic properties have also been evaluated, not much information on the possible effectiveness of similar medications like pregabalin has been published to yet. Preoperative pregabalin treatment has been demonstrated to decrease nausea, vomiting, and rescue antiemetic therapy within 24 hours following surgery conducted under GA, according to a prior review of studies [(31, 24)].

Like gabapentin, the exact mechanism of action behind pregabalin's antiemetic effects is yet unknown. The α2/δ subunits of voltage-sensitive calcium channels are probably responsible for the effects, which, depending on the signalling pathway involved, produce a variety of downstream consequences. According to studies, gabapentinoids may prevent nausea and vomiting by reducing postoperative inflammation, inhibiting the postrema region, or lowering tachykinin neurotransmission. Others contend that postoperative opioid decrease is the cause of pregabalin's function in preventing PONV. Research revealed that individuals who got pregabalin had significantly lower narcotic administration rates than controls after surgery as compared to those who did not [(32)].

CONCLUSION

The most popular empirical application of ondansetron is for the treatment of nausea and vomiting. The most frequent usage of this medication is to stop post-operative nausea and vomiting. It is a 5-hydroxytryptamine receptor 3 antagonist that inhibits serotonin's action and has strong anti-emetic properties. Numerous populations have utilized pregabalin to treat a variety of pain conditions, including epilepsy, chronic pain, and anxiety disorders.

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