

Propofol with Varied Functions: A Potential Therapeutic Opportunity for Postoperative Nausea, Vomiting and Pruritus—A Narrative Review

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Abstract

Background: Despite the advances in anesthetics and non-pharmacological techniques, the prevalence of postoperative nausea and vomiting in all patients remains high. It is one of the most common distressing symptoms that cause dissatisfaction among patients after anesthesia and surgery. A sub-hypnotic dose of propofol has been shown to reduce morphine-induced postoperative nausea, vomiting, and pruritus. This review article will provide sufficient knowledge on the role of propofol in minimizing opioid-induced postoperative nausea, vomiting, and pruritus by providing detailed information on propofol antiemetic and antipruritic effects, as well as discussions based on empirically available data. **Method:** We conducted a narrative review of the literature published between 1990 and 2023 from a range of databases; PubMed, BioMed Central, Biosis Previews, Nature, International Pharmaceutical Abstracts, Springer-Link, and Elsevier. **Discussion and Conclusion:** The literatures reviewed in this study have demonstrated that propofol may have diverse therapeutic effects including antiemetic and antipruritic. The antiemetic effect of propofol may be an effective therapeutic approach for the prevention of postoperative nausea and vomiting. The literature also demonstrated that the use of propofol for sedation during surgery may as well ameliorates opioids induced postoperative pruritus, which may be beneficial

to surgical patients. Also, it was demonstrated that prophylactic use of propofol may be an effective way of preventing nausea and vomiting and pruritus during opioid use.

Keywords

Propofol, Nausea, Vomiting, Antiemetic, Antipruritic, Surgery

1. Background

Postoperative nausea and vomiting (PONV) are one of the most common distressing symptoms that cause dissatisfaction among patients after anesthesia and surgery. The etiology of postoperative nausea and vomiting is multifactorial and involves factors associated with the patient, surgery, and anesthesia (drugs, pregnancy, gastrointestinal pathology, migraine, vestibular disease, and motion) [1]. Despite the growing fear of pain among surgical patients, PONV is considered a major concern or complication of anesthesia and surgery [2]. When no antiemetic is provided, the incidence of PONV is estimated to be 20% - 70% for general surgical patients and 70% - 80% for high-risk patients [3]. Adverse effects of PONV include risk of aspiration of gastric contents, increased pain, bleeding, wound dehiscence, increased intracranial pressure, and distress [4]. Prolonged PONV can lead to electrolyte imbalance and dehydration which can result in delayed recovery and discharge from the hospital and hence increased healthcare cost.

Despite the advances in anesthetics and non-pharmacological techniques, the prevalence of PONV in all patients remains high [5]. Several antiemetics such as metoclopramide and ondansetron have been tested and found to be effective in the prevention of PONV in surgical procedures by 15% - 30%. [6]. Even though prophylaxis for PONV seems appropriate, the choice of antiemetic agents is wide, whereas some are too expensive for regular use.

Propofol (2,6-diisopropylphenol) is a short-acting intravenous general anesthetic agent that exhibits a favorable pharmacokinetic profile. It works primarily to induce and maintain an anesthetic state. However, it is reported to have antiemetic, antipruritic, and bronchodilator effects. Evidence shows that patients anesthetized with propofol experience low antiemetic scores [7]. Numerous studies have also demonstrated that a sub-hypnotic dose of propofol is equally effective in reducing the incidence of PONV associated with chemotherapy and surgical discomfort [8] (**Table 1**). This emerging piece of evidence suggests that propofol use may be an effective therapeutic approach for the prevention or management of PONV among surgical patients.

Conventionally, intrathecal opioids including morphine are frequently administered to patients undergoing major general, thoracic, orthopedic, urologic, and gynecological surgeries to provide postoperative analgesia. Perhaps, the most common adverse effect of intrathecal administration of opioids especially

Table 1. Effects of propofol on postoperative PONV and pruritus.

Surgical procedures	Induction agents	Propofol used	Effects on PONV	Effects on pruritus
Cesarean Section	Bupivacaine and Morphine then, Propofol	Prophylaxis		
		Subhypnotic dose Induction and anesthesia maintenance	* Reduced (20, 21, 22, 24, 34, 48, 49, etc.)	* Reduced (13, 34, etc.) * Did not reduce (44)
Lower abdominal surgery	Propofol	Induction and Anesthesia maintenance	* Reduced (23)	
Gynecological Surgery (Daycare)	Propofol	TIVA	* Reduced (19, 50)	
Laparoscopic cholecystectomy	Propofol then, epidural morphine and Ropivacaine	Induction	* Reduced (28)	* Reduced (53)
Palliative care	Propofol	Prophylaxis	* Reduced (16)	

morphine is pruritus. This is because, abundant in the spinal trigeminal nucleus are opioids-dependent serotonin (5-HT₃) receptors, which are hypothesized to function as an itch center [9]. If this occurs, it is often difficult to treat and respond poorly to conventional antihistamine treatment. Several studies have demonstrated that a sub-hypnotic dose of propofol also attenuates morphine-induced pruritus. This review aimed at reviewing published literature on the antiemetic and antipruritic effects of propofol.

2. Methods

Review of the literature

We conducted a review of the literature published between 1990 and 2023 from a range of databases; PubMed, BioMed Central (BMC), Biosis Previews, Nature, Open Access Journals, International Pharmaceutical Abstracts, Springer-Link, and PubMed Central. Boolean or advanced search operators were used to restrict, narrow, or broaden our searches. Given the diversity of propofol use, we chose the combinations of the following search terms for our literature search which helped us to have only restricted information on the topics; propofol; antiemetics; antipruritic; propofol AND antiemetic; propofol OR antiemetic; propofol NOT antiemetic; propofol AND antipruritic; propofol OR antipruritic; propofol NOT antipruritic; propofol AND postoperative nausea and vomiting; propofol OR postoperative nausea and vomiting; propofol NOT postoperative nausea and vomiting; propofol AND pruritus; propofol OR pruritus; propofol NOT pruritus; therapeutic effects of propofol on postoperative nausea and vomiting; therapeutic effects of propofol on pruritus; antiemetic effects of propofol on morphine-induced postoperative nausea and vomiting; antipruritic effects of propofol on morphine-induced pruritus; a sub-hypnotic dose of propofol attenuate postoperative nausea and vomiting; a sub-hypnotic dose of propofol attenuate morphine-induced pruritus; a low dose of propofol AND postoperative nausea and vomiting; a low dose of propofol OR postoperative nausea

and vomiting; a low dose of propofol NOT postoperative nausea and vomiting; a low dose of propofol AND pruritus; a low dose of propofol OR pruritus; a low dose of propofol NOT pruritus. For this review, the inclusion criteria for the type of published articles were original articles. We excluded review articles, news articles, and letters to the editor regarding some publications on the topic.

We retrieved 212 published articles that dealt with one or two of our search terms. However, many of these articles dealt with other uses of propofol such as induction of anesthesia and sedation, and were deemed irrelevant to our review. After the elimination of these articles, and also going through the abstracts of the remaining ones, we identified 53 articles that had the potential for our consideration. Another 10 articles were eliminated because they were no full text available. Based on our inclusion criteria, we identified 43 articles that were appropriate for our narrative review.

3. Antiemetic Effect of Propofol

One of the common adverse effects of anesthesia is the development of PONV. The high incidence of PONV is associated with patient characteristics, prior exposure to anesthesia and surgery, and any condition linked to gastroparesis. The prevalence has remained considerably high despite numerous attempts to address this issue [10].

In recent years, propofol has been used as an alternative way of reducing postoperative nausea and vomiting due to its antiemetic and anticonvulsant therapeutic properties [11] [12]. Due to its quick plasma clearance, it acts quickly but only lasts a short time [13] [14]. Rosillo-Menesesa *et al.* demonstrated that propofol primarily acts on GABA receptors by increasing chloride ion conduction. Although the precise mechanism by which Propofol acts as an antiemetic remains elusive, it has been hypothesized that its antiemetic effects may be a result of the 5-HT₃ receptor antagonist in the postrema region by gamma-aminobutyric acid (GABA) [15]. This makes it potentially effective for treating nausea and vomiting in the context of palliative care [10]. The antiemetic effect may result from inhibition of smooth muscle calcium channels, and also as an agonist of dopaminergic receptors. It is generally acknowledged, according to Kim *et al.*, that propofol-based anaesthesia reduces PONV more than volatile Anaesthesia [16].

The use of propofol for induction and maintenance of anesthesia was associated with a lower incidence of postoperative nausea and vomiting (PONV) [17] when compared to any other anesthetic drug or technique. According to Soppitt *et al.* (2000), there is strong evidence for its antiemetic efficacy following anesthesia maintained by a propofol infusion, as well as its use in the post-anaesthesia care unit (PACU) [18]. In addition, Soppitt *et al.* reported that the majority (84%) of anaesthesiologists sampled said they used propofol for its antiemetic effect: To achieve an antiemetic effect, 63% of those used propofol for induction only for cases lasting < 1 hour. Furthermore, 37% used a “sandwich” technique, introducing propofol at the beginning and end of a case for a similar

purpose (**Table 1**).

When given in sub-hypnotic doses, the novel total intravenous anesthetic propofol has been shown to have antiemetic properties. In comparison to placebo for lower abdominal surgery and metoclopramide or placebo for middle ear surgery, sub-hypnotic doses of propofol have been linked to a lower incidence of PONV [19]. Also, propofol at a subhypnotic dose ($1.0 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$) could provide significantly better prevention of emetic episodes than a placebo during the early hours after a cesarean section performed under spinal anesthesia with 0.5% hyperbaric bupivacaine [20]. According to Borgeat *et al.*, patients who received 10 mg of IV propofol noticed a greater reduction in nausea and vomiting than those who received a placebo. Their study realized 81% reduction in nausea and vomiting among those who received propofol as compared to 35% reduction among the placebo group (**Table 1**).

Spinal anesthesia for cesarean sections has grown to be the most popular option with a high safety profile, but it is linked to intraoperative nausea and vomiting (IONV) [21] [22] [23]. The immediate diaphragmatic contractions that accompany IONV may cause the patient discomfort as well as abdominal viscera protrusion, which may increase the risk of visceral injuries. The sudden contraction increases the risk of aspiration and needs to be avoided, especially in patients who have a full stomach [21]. Medications such as droperidol and metoclopramide can be used to accomplish this, but they also have negative side effects like agitation, extrapyramidal symptoms, and dystonic reactions. According to Rasooli *et al.* compared to the propofol and midazolam groups, the incidence of nausea, retching, and vomiting postoperatively was significantly higher in the control group. A comparison of PONV rates between the propofol and midazolam groups showed that neither group experienced any appreciable hemodynamic changes. Additionally, it has been suggested that benzodiazepines may help prevent nausea and vomiting by lowering anxiety and reducing dopaminergic input to the chemoreceptor trigger zone (CRTZ) [21]. Our recent study of a sub-hypnotic dose of propofol as antiemetic prophylaxis has shown to be just as effective as metoclopramide in preventing PONV in pregnant patients undergoing cesarean section under spinal anesthesia with intrathecal morphine [24] (**Table 1**).

Postoperative nausea and vomiting have become a common complication worldwide following the induction of anesthesia and a major concern for the surgical team due to their increased incidence rates with even higher rates recorded among higher-risk patients. This has a significant impact on patient outcomes such as prolonged hospital stays and increased cost of treatment. The use of 5-hydroxytryptamine 3-antagonists such as Ondansetron has become the gold standard for the prevention of postoperative nausea and vomiting [12]. According to previous studies, propofol which belongs to the alkylphenol family is the most widely used intravenous anaesthetic and has been demonstrated to have antiemetic properties. The mechanisms of antiemetic effects are not fully understood. Many researchers have conducted numerous studies to determine the

mechanism. According to Ostman *et al.*, the antiemetic effect of propofol is not due to the lipid emulsion used to solubilize the drug [25] and does not have vagolytic properties [26]. Hammas *et al.* argued that propofol reduces the intensity of retching after oral administration of ipecacuanha syrup, which releases 5-hydroxytryptamine [27].

In patients anesthetized with Propofol as opposed to Sevoflurane, the incidence of PONV during the first 24 postoperative hours was significantly lower, according to a study by Shinn *et al.* [28]. According to Yirmer *et al.*, numerous studies have also demonstrated that 30 mg of intravenous propofol can reduce the incidence of PONV without causing any noticeable side effects [15] (**Table 1**). In addition, Celik *et al.* found that 1 mg/kg/h of infusion of propofol is equally effective as dexamethasone for preventing PONV in patients undergoing laparoscopic cholecystectomy during the first 24 hours [29]. Appropriate dosages for propofol's antiemetic action have been determined by numerous investigations. In a group of patients receiving cisplatin chemotherapy, Borgeat *et al.* employed a 17 g/kg/min propofol infusion. According to Schulman *et al.*, 197 ng/ml of propofol is required in the plasma to treat PONV which is refractory [30]. For the treatment of PONV in the recovery room, Borgeat *et al.* used a bolus of propofol (10 - 20 mg). However, a patient who is awakening can find the discomfort from a propofol infusion distressing. According to Erdem *et al.*, 20 g/kg/min of propofol intraoperatively had a preventive antiemetic effect. Best *et al.* noted an incidence of PONV in 5% versus 35% of patients receiving propofol and methohexital respectively for micro laryngeal surgery [31]. Comparing the incidence of PONV after ambulatory surgery to that of enflurane, desflurane, or Isoflurane resulted in a significant reduction. The incidence of PONV, the need for antiemetics, and the likelihood of an unexpected hospitalization following daycare gynecological surgery were all reduced while using TIVA with propofol [32].

4. Antipruritic Effect of Propofol

Itching is an extremely bothersome side effect that frequently appears after epidural and intrathecal administration of opioids. Pruritus in intrathecal administration of opioids is reported in about 20% - 100% of patients in the perioperative period [33]. This typical adverse effect may be so intense that the patient equates it with, or even surpasses the actual pain. The therapeutic management of these patients still faces difficulties with both prevention and treatment [26]. Around 83 percent of obstetric patients experience pruritus on average, compared to 69 percent of non-pregnant patients, both men and women. Compared to other populations, pregnant women tend to be more vulnerable to pruritus after nitric oxide treatment [7].

Pruritus begins shortly after analgesia, with a variable onset depending on the type, route, and dose of opioids used. Highly lipophilic opioids like fentanyl and sufentanil can elicit short-lived pruritus, and using the lowest effective dose and

adding local anesthetics to the mix appears to lessen the frequency and intensity of itching. Intrathecal morphine-induced pruritus is more persistent and challenging to treat due to its higher hydrophilicity [34]. Chung-Hyun reported that a high incidence of pruritus is linked to the use of spinal opioids, especially morphine. After a cesarean section, this pruritus occurs more frequently than usual. According to Ganesh & Maxwell, pruritus may also be caused by serotonin and dopamine D2 receptors, prostaglandins, and spinal inhibitory pathways.

Because opioid antagonists and histamine blockers have drawbacks, researchers have been looking for additional medications that can effectively treat pruritus [35]. Propofol has been shown to produce marked spinal depression and probably exerts its antipruritic action through inhibition of posterior horn transmission [36]. Additionally, propofol has been demonstrated to have inhibitory effects on cyclooxygenase, which may contribute to the antipruritic effects noted in some investigations [37].

Some researchers have discovered that 10 mg of propofol effectively treats neuraxial morphine-related pruritus in surgical patients [38]. Subhypnotic propofol dose, according to Borgeat *et al.*, is an effective treatment for intrathecal morphine-induced pruritus. Similarly, in our recent study, a sub-hypnotic dose of propofol significantly reduces the incidence of postoperative pruritus after intrathecal morphine use [24] (Table 1). However, Warwick *et al.* found that subhypnotic propofol dose is ineffective for preventing intrathecal morphine-induced pruritus in caesarian section patients. Borgeat *et al.* discovered an 84% treatment success rate in the propofol group versus the placebo group (16%) in a prospective randomized double-blind study comparing IV 10 mg propofol with placebo. Bujedo also demonstrated the efficacy of propofol at sub-anesthetic doses, midazolam, and prophylaxis with mirtazapine and oral gabapentin [26].

In addition to the numerous anesthetic benefits, propofol has recently been found to have several non-anesthetic effects. For instance, it is found to constitutively stimulate Nitric oxide production while inducible nitric oxide production is suppressed by the medication [39]. The anxiolytic effects of propofol may be related to several neuromediator systems [39] [40]. Additionally, it has anti-inflammatory, analgesic, antiemetic, immunomodulatory, antioxidant, and neuroprotective effects. According to Vasileiou *et al.*, propofol also has direct inhibitory effects on recombinant cardiac sarcolemmal KATP channels which inhibits platelet aggregation, and increases intracellular calcium in response to thrombin or ADP [39].

Histamine (H1) blockers and other conventional treatments do not work very well for treating pruritus, which is unfriendly and frequently disturbing [26]. Even though pruritus is not a life-threatening condition [9], it is an inconvenient and common neuraxial opioid side effect that aggravates the urge to scratch and may reduce patient satisfaction, particularly in pregnant women [9] [10] [38]. The mechanism by which opioid-induced pruritus occurs is not fully understood, although there is growing evidence that opioid receptors play a significant

role, especially after neuraxial administration [9].

Unmyelinated C fibers and the anterolateral spinothalamic tract play a major role in the neural conduction of the itch sensation from free unmyelinated nerve endings to the central nervous system. Many dermatological or systemic diseases exhibit pruritus as a common symptom, but little is understood about how this condition develops [10]. Several medications have been used to treat and prevent pruritus but the most consistent agent effective at reducing opioid-induced pruritus is opioid receptor antagonists. However, they have dosage and administration issues [9]. Ganesh & Maxwell added that other medications, such as mixed opioid receptor agonist-antagonists such as Nalbuphine, butorphanol, serotonin 5-HT₃ receptor antagonists, propofol, NSAIDs, and D₂ receptor antagonists, are effective.

Even in severe cases, Beilin *et al.*, reported that naloxone effectively reduces pruritus, but doing so may compromise its analgesic effects. According to Borgeat, *et al.*, histamine blockers typically only relieve mild cases of pruritus, and their sedative effects may be the only reason for this.

According to a previous study, the simultaneous use of propofol and midazolam has a synergistic effect on their sedative properties [41], however, the combination of midazolam and propofol is less effective than midazolam alone in preventing pruritus [42]. According to Kostopanagiotou *et al.*, a single injection of 3 mg of epidural morphine combined with varying dosages of ropivacaine causes less pruritus when administered under propofol-based general anesthesia as opposed to thiopental-sevoflurane-based anesthesia [43]. This was because pruritus after a single epidural injection of morphine 3 mg seemed to last for <12 h and appeared to have a low incidence in the first 2 hrs in all patients. When pruritus was present, at 4 and 8 hrs after the injection, the group receiving propofol had a lower incidence.

5. Conclusion

The literatures reviewed in this study have demonstrated that propofol may have diverse therapeutic effects including antiemetic and antipruritic. The antiemetic effect of propofol may be an effective therapeutic approach for the prevention of postoperative nausea and vomiting. The sedation use of propofol during surgery may as well ameliorates opioids induced postoperative pruritus, which may be beneficial to surgical patients. The literatures reviewed have also demonstrated that prophylactic use of propofol may be an effective way of preventing nausea and vomiting and pruritus during opioid use. The review has also shown that the mechanism by which propofol prevents postoperative nausea and vomiting is not well understood, and the mechanism by which it prevents pruritus also remains unknown. More researches are needed to describe the molecular role or biological mechanisms that is involved in using propofol as an agent for preventing nausea and vomiting and pruritus. This may lead to better quality healthcare and patient outcomes during surgery.

Declarations

Availability of Data and Materials

All datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' Contributions

TWA and SK conceived and designed the study. TWA and DZK were responsible for the supervision and coordination of this study. SK, FB, DZK, TKD and JBZ conducted the data collection. SK led the data analysis with inputs from TWA, FB, DZK, TKD and JBZ. TWA and SK wrote the first draft of the manuscript, and then FB, DZK, TKD and JBZ contributed to revising and reviewing the article. All authors read and approved the final article before submission.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

PONV—Postoperative Nausea and Vomiting
CRTZ—Chemoreceptor Trigger Zone
PACU—Post-Anaesthesia Care Unit
GABA—Gamma-Aminobutyric Acid
CIVA—Continuous Intravenous Anaesthesia