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COMPARATIVE EFFICACY OF PALONOSETRON–DEXAMETHASONE AND ONDANSETRON–DEXAMETHASONE IN LAPAROSCOPIC CHOLECYSTECTOMY: INSIGHTS FROM CLINICAL STUDIES

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Abstract
Post operative nausea and vomiting is a frequent, unproductive complications of laparoscopic cholecystectomy, which leads to delayed recovery, unexpected hospital admissions, and higher healthcare expenses. Prophylaxis is critical, especially when it comes to high-risk patients detected through the use of risk stratification instruments. The study is a synthesis of available evidence comparing palonosetron-dexamethasone and ondansetron-dexamethasone combinations in the prevention of postoperative nausea and vomiting. In randomized controlled trials and comparative studies, both regimens are highly effective in the immediate postoperative period, but palonosetron has more effective control in the late postoperative period because of its longer half-life and longer receptor occupancy. The combination also minimises the use of rescue antiemetics and results in more patient satisfaction scores, with no augmentation of the cases of adverse effects. The results favour the utilisation of palonosetron with dexamethasone as a component of a multimodal prophylaxis approach, especially in patients undergoing laparoscopic surgery and who have several risk factors for emesis. The wider implementation of such a regimen could lead to improved recovery (omit measures), pre-emption of discharge, and better perioperative measures.

Keywords: Palonosetron, Ondansetron, Dexamethasone, Postoperative Nausea and Vomiting, Laparoscopic Cholecystectomy, Antiemetic Prophylaxis

Introduction

One of the most prevalent and uncomfortable complications with regard to general anaesthesia is post operative Nausea and Vomiting (PONV). Although there has been great advancement in anaesthetic methods, PONV is still very prevalent, especially following laparoscopic cholecystectomy. Increased intra-abdominal pressure, pneumoperitoneum, and irritation of the diaphragm are some of the factors

that increase the emetogenic response of this procedure [1]. PONV occurs in about 30 % of surgical patients, all the way to 70 to 80 % of patients with multiple risk variables, such as female sex , nonsmoking, prior PONV or motion sickness, and postoperative use of opioid use. It not only adds to the overall healthcare costs but also causes the existence of PONV to delay the recovery process, extend post-anaesthesia care unit length of stay, and raise the rate of unexpected hospital stay [2]. Prevention of PONV is one of the elements of perioperative care. Prophylaxis is associated with a more comfortable patient experience, enhanced oral intake, and easier reduction of complications, including dehydration and aspiration, and Enhanced Recovery after Surgery (ERAS), since effective prophylaxis allows the patient to walk early and discharge on time. A combination of multimodal approach involving the use of agents with varying mechanisms of action is advised for patients with moderate or high risk, to achieve a high complete response rate and reduce the incidence of rescue antiemetic therapy [3]. Comparative analysis of 5-HT_3 receptor antagonists with dexamethasone has received a lot of attention. Ondansetron is an antagonist of 5-HT_3 receptor with a short half-life, which was useful in the early postoperative period, but in the late period of recovery, it caused a tendency to relapse. Second-generation 5-HT_3 antagonist palonosetron has a long half-life and distinctive receptor-binding potential that provides extended coverage and enhanced control of late postoperative vomiting. It has been demonstrated that a mix of dexamethasone and palonosetron offers better prophylaxis, lessens the incidence of nausea and vomiting during the first 24 hours following surgery., reduces the number of rescue medications used, and increases the level of patient satisfaction [4].
The study aims to summarize the existing evidence on the comparison of palonosetron-dexamethasone and ondansetron-dexamethasone combinations in preventing PONV in patients undergoing laparoscopic cholecystectomy in terms of their efficacy, safety, and clinical relevance.

Pathophysiology of PONV

PONV is a complex phenomenon that is caused by the combination of humoral, neural, and central nervous system pathways. Emetogenic input is combined in the central vomiting center, which is found in the medullary reticular formation. The Chemoreceptor Trigger Zone (CTZ) of the area postrema is important because it is close to the blood-brain barrier, and it can detect emetogenic substances in circulation, including anesthetic agents, opioids, and metabolic by-products [5]. The CTZ expresses serotonin (5-HT_3), dopamine (D_2), opioid, acetylcholine, and substance P (NK_1) receptors, which have the potential to induce neuronal discharge and transmit the impulse to the vomiting center. The peripheral input also plays an important role; gastrointestinal tract enterochromaffin cells secrete serotonin to surgical stress, mechanical stimulation, or chemotoxic agents, which stimulates vagal afferents that synapse in the nucleus tractus solitarius. Vestibular input through the cranial nerve VIII pathway is involved in motion-related nausea and vomiting that is mediated through histaminergic and cholinergic receptors. The anticipatory nausea is regulated by cortical and limbic inputs, especially in predisposed individuals [5]. Several cranial nerves are involved in the efferent part of vomiting and facilitate the contraction of the diaphragm, abdominal wall, and glottis closure. The neurohumoral factors also modulate the process, and there are at least seven important neurotransmitters, i.e., serotonin, dopamine, histamine, acetylcholine, substance P, Gamma-aminobutyric Acid (GABA), and opioids.
Laparoscopic cholecystectomy is regarded as one of the most emetogenic surgical operations as it is affected by the effects of pneumoperitoneum, raised intra-abdominal pressure, and expansion of the visceral peritoneum that enhance vagal stimulation. This danger is amplified by inhalational anesthetics and the administration of perioperative opioids. Predictive scoring systems like the simplified score by Apfel have been used to stratify the risk based on four independent predictors: female gender, nonsmoking status, having experienced motion sickness or having experienced PONV, and postoperative opioid requirement to enable risk stratification at an individual level. The presence of all four factors results in a risk of more than 70 % and prophylaxis using several agents that operate on different emetogenic pathways is justified [6].

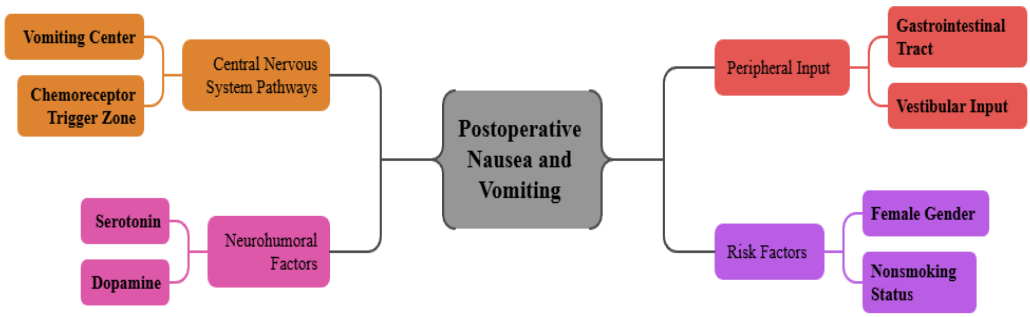

Figure 1: Mechanisms Involved in Postoperative Nausea and Vomiting

Figure 1 shows the essential central, peripheral, and neurohumoral pathways in PONV. It illuminates the functions of the vomiting center, chemoreceptor trigger zone, neurotransmitters, and patient-related risk factors.

Pharmacological Overview

a) Palonosetron

Palonosetron is a second-generation 5-HT_3 receptor antagonist characterized by strong binding affinity, allosteric receptor interaction, and long elimination half-life (approximately 40 hours). These pharmacodynamic properties lead to the receptor occupancy and prolonged antiemetic action that is carried into the delayed postoperative period. Palonosetron, in contrast to first-generation antagonists, is positively cooperative at the receptor site and can inhibit the process of receptor internalization, which adds to its prolonged action. Randomized controlled trials have shown that it can decrease early and late PONV, and the proportion of early and late antiemetic rescue decreases significantly up to the time 72 hours postoperative. Side effects are not severe, and the most common are headache and constipation, and no substantial QT prolongation at prophylactic dosage [7].

b) Ondansetron

The most commonly used 5-HT_3 receptor antagonist is Ondansetron. It has an onset of action that is fast and is successful in preventing nausea and vomiting in the early stages after surgery. Its half-life is relatively short (3–5 hours) and as such, its duration of protection is limited, and some recurrent symptoms are usually experienced after more than 6-8 hours unless more doses are used. During surgery, intravenous administration of 4 mg is the norm towards the end of surgery. The adverse events may involve mild headache, constipation, and infrequent cases of QT prolongation, which may be a cause of concern in patients with cardiac conduction abnormalities [8].

c) Dexamethasone

Dexamethasone is a potent long-acting glucocorticoid, commonly used as multimodal antiemetic prophylaxis. Its antiemetic effect consists of the inhibition of prostaglandin production, inhibition of serotonin release from enterochromaffin cells, and inhibition of the nucleus tractus solitarius. Induction of anesthesia with a single intravenous dose of 4-8 mg of propofol lasts up to 24 hours. Safety profile is positive with a single dose and fewer effects on the glucose homeostasis and wound healing in the perioperative environment [7].

d) Combination Therapy

Multimodal prophylaxis with medicines with complementary effects is recommended for patients with a moderate to high risk of PONV. A 5-HT_3 antagonist in combination with dexamethasone improves the overall antiemetic response, boosts complete response rates, and decreases the use of the rescue antiemetics. There is some evidence that palonosetron-dexamethasone regimens demonstrate better protection against late-phase vomiting than ondansetron-dexamethasone regimens,

which is consistent with the guideline employing second-generation antagonists in the high-risk groups. Opioid use combined with other pain management techniques also leads to an increase in patient satisfaction ratings and the ability to comply with the new standards of recovery [10].

Evidence from Clinical Studies

In several Randomized Controlled Trials (RCTs) and meta-analyses, clinical assessment of prophylaxis antiemetic schedules in laparoscopic cholecystectomy has compared palonosetron-dexamethasone with ondansetron-dexamethasone. The results are regular incidences of nausea, vomiting, the necessity of rescue antiemetics, patient contentment, and undesirable event profile.

a) Early Postoperative Phase (0–6 hours)

The two combinations are both shown to be highly effective at minimizing early postoperative nausea and vomiting (PONV). Comparisons at single intravenous dosages of palonosetron (0.075 mg) combined with dexamethasone (8 mg) with ondansetron (4 mg) combined with dexamethasone have shown similar frequency of complete response in the first six hours of post extubation. In a single prospective comparative study, about 6-8 % of all patients who were given palonosetron-dexamethasone experienced nausea within the first 2 hours, and 10-12 % of patients who received ondansetron-dexamethasone experienced nausea within the first 2 hours ($p > 0.9$), making no significant difference in the immediate prophylaxis. The incidences of vomiting during the same period were uncommon in both arms. These findings have been supported in meta-analyses, which indicate that the advantage of palonosetron increases during the later stages following the initial period because of its longer half-life and its occupancy of receptors [11].

b) Late Postoperative Phase (6–24 hours)

The difference between the two regimens is more evident in the late postoperative phase. Comparative studies have shown a marked decrease in cumulative vomiting with palonosetron-dexamethasone, with reported incidences of 22-25 % versus 39-40 % of ondansetron-dexamethasone at 24 hours ($p \approx 0.10$ -0.12). Although not all findings had reached a definite statistical significance, the clinical trend was favorable to palonosetron, especially in preventing delayed vomiting. The same tendencies have been exhibited by several RCTs in the gynecologic and laparoscopic populations with full response rates (no emesis, no rescue medication) of palonosetron-based prophylaxis of 75-85 %, as opposed to 60-70 % when ondansetron combinations are used. This high efficacy is explained by the extended elimination half-life and longer receptor occupancy of palonosetron that spans the time intervals during which the first-generation antagonists become ineffective [12,13].

c) Rescue Antiemetic Requirement

Reduction in the use of rescue antiemetics is a clinically relevant outcome, since it represents both the burden of breakthrough symptoms and exposure to further drugs. Fewer patients who needed rescue therapy have been reported to have been documented in the palonosetron-dexamethasone arm, with the range ranging between 20 and 30 % as compared to those in ondansetron-based regimens. This reduction helps to achieve better patient comfort and cost reduction related to the decreased drug intake and nursing care [14].

d) Patient Satisfaction

Patient-reported outcomes show that palonosetron-containing regimens are more satisfactory because of the reduced recurrence of late-phase symptoms and overall well-being in the postoperative period. When vomiting episodes are reduced, the early ambulation and discharge readiness are also enhanced.

e) Safety and Adverse Effects

Palonosetron and ondansetron have positive safety profiles at the recommended doses. Mild headache and Constipation were listed as the most frequent side effects, and the incidence of each group did not differ in any clinically meaningful way. Further studies of electrocardiographic monitoring have not demonstrated significant increases in QTc with palonosetron at prophylactic doses, whereas ondansetron has a rare though known risk of QT prolongation, particularly when taken at higher doses or with repeated doses. Side effects of dexamethasone, like hyperglycemia, are temporary, of little clinical consequence following a single dose of preoperative dexamethasone [15].

f) Synthesis of Evidence

All of this evidence favors the use of palonosetron-dexamethasone as a better option in providing lasting PONV prophylaxis, particularly in individuals at high risk having a laparoscopic cholecystectomy. Although the early postoperative protection is similar with the two regimens, palonosetron provides more assured protection in the late postoperative period, a reduction in the need for rescue antiemetic, and satisfaction as stated by patients. The combination is also consistent with consensus guidelines on PONV management on multimodal prophylaxis [16].

Clinical Implications

Prophylactic measures to prevent PONV are effective in improving the outcome of perioperative outcome. The particular use of combination regimens that address multiple emetogenic pathways would be of particular benefit in high-risk groups, including laparoscopic cholecystectomy patients. The comparative evidence suggests the use of palonosetron with dexamethasone as an option of choice in such an environment because of its long receptor occupancy and better coverage of late-phase emesis [17]. Integration of such a regimen into the perioperative practices could enhance patient comfort, reduce unexpected admissions, and enable the adoption of ERAS programs. The choice of prophylactic agent must be personalized according to risk assessment tools like the Apfel score, and palonosetron–dexamethasone preferential use among individuals who have three or more risk variables, who have ambulatory procedures, or who are expected to be discharged early [18].

Limitations of Available Evidence

The available evidence is mostly based on single-center studies and trials that have small samples, and hence, it may not be very extensive. The heterogeneity of studies is due to variability in dosing schedules, timing of administration of a drug, and the definition of complete response. Not all trials had the power to find differences in rare adverse events, so it was uncertain whether there were variations in long-term safety profiles in particular groups of patients. There is a lack of economic analyses that provide a direct comparison of the cost-effectiveness of palonosetron-based combinations with ondansetron-based regimens. Besides this, the majority of studies concentrate on the 24-hour post-operative period, which does not give sufficient information about the emesis after the 24-hour point, which can also impact recovery rates and patient satisfaction [19].

Future Directions

To ensure the superiority of palonosetron in combination with dexamethasone between various groups of surgical patients, future studies must involve large, multicenter randomized controlled trials. The endpoints and reporting criteria would need to be standardized, and this would increase the comparability and permit meta-analysis with more statistical power. Additional studies are needed on the incorporation of palonosetron-based regimens with other classes of antiemetic agents, including NK_1 receptor antagonists, in very high-risk populations. A study evaluating the pharmacoeconomic implications, quality of life, and impact on ERAS outcomes should be done. Developments in pharmacogenomics could permit patient-specific PONV prophylaxis based on polymorphisms of receptors, and this would be effective and economical [20].

Conclusion

The combinations of palonosetron and dexamethasone prove to be more successful in avoiding PONV when compared to ondansetron-dexamethasone, especially during the late postoperative time. The combination has decreased the rate of emesis, improved patient satisfaction and decreased the need for rescue antiemetics but has not changed the favorable safety profile. It has a high recommendation in multimodal prophylaxis levels in patients with moderate to high risk during laparoscopic cholecystectomy. Further study on the implementation of the regimen in larger and more diverse groups, and its ongoing use to improve perioperative recovery and resource use, can further improve perioperative recovery and resource use.

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