REVIEW ARTICLE

An overview of treatment options for postoperative nausea and vomiting after laparoscopic surgical procedures

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SUMMARY

Background: Postoperative nausea and vomiting (PONV) is a well-known entity following surgical procedures and may result in serious complications include aspiration of gastric contents, prolonged recovery period, impaired surgical wound healing. Laparoscopic surgery alone is a known risk factor for PONV and different treatment options with various agents are preferred for PONV prophylaxis and treatment.

Aim: We aimed to review advantages and disadvantages of various drugs and combination regimens for prophylaxis and treatment of PONV after different types of laparoscopic procedures.

Methodology: We made a comprehensive PubMed search using search terms PONV, laparoscopic surgery, prophylaxis, treatment, drug, without considering publication time period.

Findings: Relatively traditional anti-emetics, including anticholinergics, antihistamines and phenothiazines, have more prominent side effect profiles. Using different receptor antagonists (serotonin 5-HT3, neurokinin, dopamine receptor antagonists) especially when combined with agents of same group or from various different groups, e.g. dexamethasone - a strong corticosteroid, naloxone - an opioid receptor antagonist, or propofol – an intravenous anesthetic and hypnotic, effective anti-emesis can be achieved.

Conclusion: Combinations of antiemetic agents of different groups is more effective in prevention of postoperative nausea and vomiting.

Key words: PONV; Laparoscopic Surgery; Serotonin; Neurokinin; Opioid, Receptor Antagonist; Corticosteroid; Propofol; Anesthesia, Inhalation

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common complication of surgery and anesthesia protocols and reported incidence of PONV ranges between 12 and 38%.[1] However, in special patient populations, incidence may be as high as 70%.[2] PONV results in important undesirable clinical conditions such as prolonged hospital stay with patient discomfort, increased intracranial pressure, provoked bleeding, dehydration, electrolyte imbalance, impaired wound healing and stretching surgical sutures as well as aspiration of gastric contents that may result in serious pulmonary complications.[3] Early PONV is described as nausea and vomiting in first two hours at postoperative period while late PONV is nausea and vomiting in first 24 hours postoperatively.[4] There are many different agents and protocols in literature regarding PONV prophylaxis and treatment. However, there is no consensus on any one or more treatment modalities.

RISK FACTORS FOR PONV

Several risk factors for PONV have been identified such as female gender, previous PONV and/or motion

sickness history, non-smoking status, certain agents used in perioperative period (volatile anesthetics, nitrous oxide, opioids, ketamine, parasympathomimetic drugs (neostigmine >2.5 mg), longer operating time, intraabdominal surgeries including gynecologic and laparoscopic surgeries.[5-7]

PHYSIOLOGICAL MECHANISMS

Central or peripheral emetogenic signals are generted by various receptors which are primary targets of anti-emetic drugs.[8-10] Chemoreceptor trigger zone (CTZ) is placed at area postrema under the 4th ventricle and important for identifying noxious chemicals like volatiles, opioids and other emetogenics in body fluids, e.g. blood and cerebrospinal fluid. Serotonin type-3 (5-HT3), histamine type-1 (H1), muscarinic cholinergic type-1 (M1), dopamine type-2 (D2), neurokinin type-1 (NK1), and opioid receptors are located in CTZ. Toxins or drugs cause strong impulses at CTZ and, as an afferent center, newly generated afferent impulses from CTZ arrive nucleus tractus solitaries (NTS) in the brainstem. NTS is a key center for PONV and receives vagal impulses generated in vestibular and gastrointestinal system.[11] And finally activated central pattern generator for vomiting center in lateral reticular formation of medulla oblongata results in vomiting.

Serotonin is the key neurotransmitter in gastrointestinal system and binds visceral 5-HT3 receptors at gastrointestinal canal activates vagal impulses result in CTZ activation and nausea vomiting.[11] These receptors are primary targets of 5-HT3 receptor blocking agents.

Physiological Changes during Laparoscopic Surgery

Laparoscopic surgery has gained popularity among several surgical approaches and has many advantages, including less postoperative pain and hospital stay with early mobilization. Minimal wound size results in early wound healing with lower complication rates.[12] In order to have a sufficient surgical sight and manipulation pneumoperitoneum is essential in laparoscopic surgery. However, various systemic changes occur dependent to the type of gas used and level of the intraabdominal pressure. Cardiopulmonary effects, systemic carbon dioxide absorbtion and venous gas embolism are major problems in laparoscopic surgery.[13]

Physiological changes occur related to pneumoperitoneum and patient position. Carbon dioxide (CO_2) is the most commonly used gas and several chemical effects of CO_2 may emerge during laparoscopic surgery.

In cardiovascular system increased sympathetic discharge, hypercarbia and decreased venous return lead to tachycardia. Additionally, sympathetic stimulation emerges secondary to decreased venous return and peritoneum stretching. Hypercarbia and acidosis lead to cardiac rhythm disturbances, including premature ventricular contractions, ventricular tachycardia and fibrillations. Vagal stimulations may lead to bradyarrhythmias. This vagal stimulation due to pneumoperitoneum, in addition to risk factors related to surgery itself, may cause PONV.

Physiological changes in respiratory system are primarily related with increased intraabdominal pressure. Elevated diaphragm and collapsed lung bases result in decreased functional residual capacity (FRC), ventilation perfusion mismatch and intrapulmonary shunting. Clinical outcomes of these physiological changes are hypoxemia and increased alveolar arterial oxygen gradient.

TREATMENT CHOICES FOR PONV

Various drug regimens are effective modalities in PONV. Its important to keep in mind that more than one receptors, serotonin (5-HT3), dopamine (D2), Mu (M1), histamine (H1) and NK1 (neurokinin), play integral role in PONV so that an agent blocks a special type of receptor may be inadequate for PONV prevention and treatment.[14-16]

Anticholinergics and Antihistamines

Anticholinergic agents (most commonly used agent is scopolamine) block muscarinic receptors and inhibit cholinergic impulses from the vestibular nuclei to the vomiting center [17]. Anticholinergic agents have unfavorable adverse event profile that limits their use. Anti-cholinergic side effects include dry mouth and drowsiness, disorientation, memory disturbances, dizziness and hallucinations.[18]

Gan et al[19] compared transdermal scopolamine and ondansetron combination with ondansetron alone in outpatient laparoscopic surgery or breast augmentation and showed less PONV incidence with decreased side effects in combination therapy.

Histamine-1 (H1) receptors induce nausea and vomiting via NTS. Antihistamines, such as cyclizine, dimenhydrinate, diphenhydramine, hydroxyzine, meclizine and promethazine, inhibit acetylcholine at vestibular apparatus and H1 receptors in NTS. Similar to anticholinergics, antihistamines have common side effects including dry mouth, constipation, and less commonly mental changes such as confusion; also secondary to muscarinic inhibition blurred vision and urinary retention.[18]

In a combination therapy investigation metoclopramide plus dimenhydrinate regimen resulted in effective PONV protection in laparoscopic gynecologic surgery although

the findings of this study are questionable because of non-randomized and uncontrolled study design.[20]

Phenothiazines

Chemoreceptor trigger zone (CTZ) is rich in D2 receptors and receptor antagonists include the phenothiazines (e.g. chlorpromazine, fluphenazine), benzamides (e.g. domperidone, metoclopramide) and butyrophenones (e.g. droperidol, haloperidol) inhibit D2 receptors in CTZ.[18] Serious and common adverse effect profiles of phenothiazines caused limited usage area for these drugs; while benzamides (especially metoclopramide) have extensive usage. Most common side effects of benzamides are sedation, restlessness, diarrhea, CNS depression and agitation. On the other hand several uncommon but serious side effects of these drugs, e.g. hypotension, supraventricular tachycardia, extrapyramidal side effects and neuroleptic malignant syndrome, have been reported.

Metoclopramide is the most commonly used agent in this group and various studies reported different results when compared with different agents in protection PONV during perioperative period of laparoscopic surgeries. In a study, similar protection rates for PONV with metoclopramide and ondansetron have been reported in laparoscopic cholecystectomy (LC).[21] In contrast, Naguib et al[22] showed adequate protection with ondansetron while no protection with metoclopramide at postoperative period of LC. In another study similar PONV protection rates were reported with metoclopramide 20 mg versus ondansetron 8 mg administered just before end of LC.[23] Ko-Iam et al[24] showed better protection rates with metoclopramide 5 mg plus dexamethasone 4 mg than metoclopramide 10 mg alone administered at 30 minutes before anesthesia induction. In accordance with previous study Nesek et al[25] reported significantly effective protection profile with metoclopramide 10 mg + dexamethasone 8 mg than metoclopramide 10 mg alone.

Serotonin receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron, and ramosetron)

Serotonin receptors are found in CTZ and/or vomiting center, thus serotonin plays important role in PONV.[26] The most involved and effective receptor type is the 5-HT3 subtype that agents that work via receptor antagonism have significant effectiveness both for PONV protection and treatment.[26] Usefulness of these drugs is particularly important in PONV due to their action profile, because the effectiveness is significant during early phase of PONV. In this group of anti-emetics ondansetron, granisetron, dolasetron, ramosetron and tropisetron are available. Particularly granisetron and dolasetron are highly specific for 5-HT3 receptor. All the agents in this group except granisetron are metabolized by the cytochrome P-450 (CYP) enzyme 2D6. And so patients with more than three CYP2D6 gene and/or ultra-metabolizer genotypes are resistant to ondansetron prophylaxis for PONV.[27,28] Side effects of drugs in this group include headache, somnolence, ataxia, asymptomatic QTc interval prolongation, constipation, diarrhea, muscle pain and dizziness.[26]

Various studies investigating 5-HT3 RAs concluded different results in terms of PONV prophylaxis and treatment. In a study comparing various 5-HT3 receptor antagonists and metoclopramide in LC showed better PONV protection with ondansetron 4 mg than metoclopramide 10 mg while similar effectiveness levels with tropisetron 5 mg, granisetron 3 mg when compared with metoclopramide 10 mg.[22] Similarly Farhat et al[29] showed better PONV prophylaxis with ondansetron 4 mg than metoclopramide 10 mg administered at anesthesia induction in LC. In contrast two different placebo controlled studies showed equal efficacy with different doses of ondansetron and metoclopramide during LC.[21,23] Another study showed better PONV prophylaxis with ondansetron 8 mg plus dexamethasone 8 mg than ondansetron alone in LC.[30] In a prospective randomized and double blinded study three different 5-HT3 RAs (ondansetron 4 mg, ramosetron 0.3 mg and palonosetron 75 μg) were compared and better protection was found with palonosetron 75 μg.[31] Bhattacharjee et al[32] reported higher effectiveness levels with palonosetron 75 μg than granisetron 2.5 gr when administered before anesthesia induction in LC. Another study showed continuous infusion of ramosetron at postoperative period of laparoscopic gynecologic surgery was superior than single doses of either palanosetron or ramosetron.[33] Ryu et al[34] investigated different administration protocols of ramosetron and concluded that combination of oral and intravenous (0.1 mg and 0.3 mg respectively) administration provided better PONV protection. Also there are various studies reporting different results with 5-HT3 RA and corticosteroid regimens in PONV protection after different laparoscopic protocols.[35-37.]

Opioid Receptor Antagonists

Opioids have important modulatory effects on gastrointestinal system, including both inhibitory and excitatory effects. Opioids are not neurotransmitters in gastrointestinal system but there are at least 3 different opioid receptors – μ, δand δ[8] Morphine and other exogenous opioid receptor agonists primarily effects intestinal motility via cholinergic transmission while decrease gastrointestinal motility and gastric emptying via Mu receptors.[39]

Reduced nausea and vomiting with lowered additional anti-emetic usage has been shown with low-dose naloxone

(0.25 μg/kg/h) compared with placebo in adult patients,[40] and significantly decreased opioid-related adverse effects such as nausea and vomiting in children and adolescents.[41] In a study conducted in adult patients undergoing laparoscopic gynecological surgery two different combination regimens – naloxone+droperidol and naloxone+dexamethasone - were found significantly more effective than naloxone alone.[42]

Corticosteroids

There are increasing number of studies investigating the role of corticosteroids on PONV. Although the exact mechanism is unknown, anti-inflammatory or membrane-stabilising effects, both peripherally and/or centrally, are thought to be possible pathways on PONV protection.[43] In summary decreasing available neurotransmitter levels[44] and reducing the release of prostaglandin E,[45] both well-known effects of corticosteroids, are possible steps induced by corticosteroids at cellular level. Increased gastric acid secretion, gastrointestinal distress, psychiatric disturbances, hyperglycemia with increased insulin resistance, immunosuppression, flushing and osteoporosis are common side effects of corticosteroids.

Bisgaard et al[46] showed effective protection of PONV in LC with preoperatively administered dexamethasone 8 mg plus 4 mg ondansetron combination compared with placebo. Similarly in another study 8 mg dexamethasone added to 4 mg ondansetron provided more effective PONV protection compared with 4 mg ondansetron alone,[30] In a study comparing palonosetron 0.075 mg + 8 mg dexamethasone with palonosetron alone in LC, combination therapy was found significantly more effective than palonosetron alone.[35] However, another study couldn't find any difference between 0.075 mg palonosetron+8 mg dexamethasone and palonosetron alone in LC.[36]

Amer et al[47] compared metoclopramide 10 mg with metoclopramide 5 mg + dexamethasone 4 mg (administered 30 minutes before anesthesia induction) and concluded that combination therapy resulted significant PONV protection after LC. Similarly dexamethasone 8 mg added metoclopramide 10 mg was found more effective than metoclopramide alone for PONV after LC [25]. Another study compared dexamethasone 8 mg with metoclopramide 10 mg alone has shown better PONV prophylaxis with dexamethasone after LC [48]. In addition to listed treatment options above, various agents were investigated in different studies. Daabiss et al [49] showed that dexamethasone 5 mg plus ephedrine 0.5 mg/kg IM given ten minutes before the end of the LC was superior than control (saline) and dexamethasone 5 mg alone in protection PONV. Another randomized and placebo controlled study showed that methylprednisolone (125 mg iv) and methylprednisolone + etoricoxib (125 mg iv +120 mg orally) combination significantly reduced the incidence and severity of PONV [50].

Neurokinin (NK) Receptor Antagonists

The peptides belong to tachykinin family are widely distributed in different locations in the body and are excitatory neurotransmitters that have important roles within intercellular signaling pathways. Substance P is a well-known member of this family and has important role in afferent pathways of emesis.[10] Enterochromaffin cells in gastrointestinal system and sensory neurons are thought to be the sources of substance P.[10] Tachykinin peptides exert their activity via G-protein-coupled receptor subtypes found in the peripheral or central nervous tissue – NK1, NK2 and NK3. The NK1 receptors are distributed in the area postrema so that suspected roles of NK1 receptors in PONV (especially secondary to surgical trauma) are being investigated. In addition to NK1, NK2 receptors are located in gastrointestinal system and have important roles in visceral sensitivity, inflammation, regulation of motor functions and secretions. However, the exact mechanism of NK receptor antagonists in protection of PONV has not been identified.[10] One of the potential advantage that the NK1 receptor antagonists have -compared with 5-HT3 receptor antagonists- is the protection of both acute and delayed emesis.[10] Several studies conducted in laparoscopic gynecological surgery showed significant PONV protection with orally administered aprepitant (a novel NK1 receptor antagonist) compared with 5-HT3 RAs or controls.[51-53]

Propofol

Propofol is primarily an anesthetic agent with strong narcotic and hypnotic properties; however, clinical usage area is gradually increasing that includes antiemesis. Although the mechanisms of antiemetic properties has not been completely understood, a serotonin antagonistic effect and/or a blocking effect of glutamate and aspartate (excitatory amino acids in central nervous system) secretion are potential anti-emetic effects of propofol.[54, 55]

There are various studies comparing anti-emetic properties of propofol in combination with different agents or alone in laparoscopic surgery. Kim et al[54] showed better PONV protection with low dose propofol infusion (0.5 and 1 mg/kg) 15 minutes before the anesthesia cessation compared with placebo in laparoscopic assisted vaginal hysterectomy. In contrast Scuderi et al[55] showed equal PONV control with 0.1 mg/kg bolus administration followed by 0.1 mg/kg/hr propofol infusion compared with placebo in laparoscopic gynecological surgery. In another study conducted in laparoscopic prostatectomy, lower PONV incidence with profopol compared with

desflurane was reported.[56] Song et al[57] investigated anti-emetic effects of propofol in two different inhalation anesthesia protocols and showed better PONV control with propofol (0.5 mg/kg) administered at the end of the LC in sevoflurane + N_2O group than that in desflurane + N_2O group. In another study sub-hypnotic dose of propofol (1 mg/kg/hr during operation) and dexamethasone (8 mg before anesthesia induction) were found equally effective compared to control (10% intralipid) in LC.[58] Arslan et al[59] compared sub-hypnotic dose (0.5 mg/kg) of propofol bolus combined with dexamethasone 8 mg versus propofol plus metoclopramide (0.2 mg/kg) at the end of the LC. They found better PONV protection with propofol + dexamethasone rather than propofol + metoclopramide administration. Also protective and anti-oxidant role of propofol has been shown against hypoperfusion–reperfusion phenomenon occurs in laparoscopic surgery.[60]

DIFFERENT ANESTHESIA PROTOCOLS & PONV

TIVA vs. Inhalation Anesthetics

Total intravenous anesthesia (TIVA) is a relatively new protocol for anesthesic management of patients. TIVA is generally accepted as a well-tolerated technique with rapid and early recovery with minimal residual anesthesia effects. Beyond its advantages listed above, low incidence of PONV, as compared to inhalational agents, have been reported in numerous studies. Propofol with remifentanil is the most common technique however various combinations of other drugs (dexmedetomidine, ketamine, midazolam) may be preferred. In a study conducted in laparoscopic gynecologic surgery, propofol + remifentanil combination was compared with sevoflurane + N_2O + palonosetron 75 μg. Despite anti-emetic prophylaxis with palonosetron in second study group the authors reported similar PONV incidence between groups.[56] Similar results were achieved when ondansetron was used for PONV protection.[61] Another study comparing TIVA (propofol) vs. sevoflurane anesthesia indicated lower PONV incidence at postoperative first hour in TIVA group after laparoscopic gynecologic surgery.[62] Akkurt et al[63] showed better PONV protection with TIVA (propofol + alfentanyl (2-2.5 mg/kg and 20 μg/kg respectively) than inhalation anesthesia with desflurane + alfentanyl (4-6% and 20 μg/kg respectively).

CONCLUSION AND RECOMMENDATIONS

In this review we focused on PONV prophylaxis and treatment choices during laparoscopic surgical procedures. Based on different results regarding effectiveness of various anti-emetic agents presented in large number of different studies cited in the article, our investigation suggests that;

1. Antiemetic prophylaxis after laparoscopic surgery is ineffective when a single antiemetic drug is used.
2. Better antiemetic prophylaxis is achieved with combination regimens because different drugs act on different types of receptors and multi-receptor antagonism results in decreased PONV incidence and more effective treatment
3. There is insufficient evidence to recommend the most superior single antiemetic drug or a combination regimen for prophylaxis and treatment of postoperative laparoscopic surgery.
4. A favorable side-effect profile of the selected agent and additional risks related to laparoscopic procedure should be kept in mind when selecting an agent for PONV prophylaxis.

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