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## Prevention and treatment of postoperative nausea and vomiting

*Prevenção e tratamento de náuseas e vômitos no período pós-operatório*

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### ABSTRACT

Postoperative nausea and vomiting are common and can be prevented. Complications of this condition cause higher rates of morbidity and mortality. A review of literature was carried out on MEDLINE, with focus on controlled clinical trials. Pathophysiology is complex, with many afferent and efferent pathways, and its comprehension facilitate the choice of medication. Risk factors are presented, with a stratified score of chance to develop postoperative nausea and vomiting. An algorithm for identification of higher

risk patients was elaborated and classified the level of prevention/treatment recommended to avoid excessive use of drugs and their side effects. Postoperative nausea and vomiting must be prevented, because of the involved complications and discomfort for patients. A systematic approach with analysis of preoperative risk factors and prescription of medication can be effective for prevention.

**Keywords:** Postoperative nausea and vomiting/prevention & control; Postoperative Complications/prevention & control

### INTRODUCTION

Side effects of surgical procedures are frequent at postoperative, pain, nausea and vomiting are common. Although there is a major concern with prevention of pain, vomiting at postoperative occurs in about 30% of patients.<sup>(1)</sup>

Postoperative nausea and vomiting (PONV) are defined as development of episodes of nausea and emesis after a surgical act and before hospital discharge. Nausea is defined as subjective abdominal discomfort associated with an urge to vomit and may be caused by stimulation of mechanical receptors in the gastrointestinal tract and of the vestibular system. Also involved are the chemoreceptor trigger zone in the posterior area to the floor of the 4<sup>th</sup> ventricle, stimulated by dopamine receptors D 2 and 5-HT<sub>3</sub> receptors and upper cortical centers. Vomiting consists of forced ejection of gastric content by the neuromuscular complex with voluntary and involuntary components.<sup>(2)</sup> Center of vomiting is comprised by the solitary tract and by reticular formations of the bulbus, mediated by receptors H<sub>1</sub> and M<sub>1</sub> and parasympathetic activity.

Although PONV progresses in an auto-limited course, it may lead to dehydration, electrolytic disorders, dehiscence of the suture, bleeding, bronchoaspiration and rupture of the esophagus.<sup>(3)</sup> The economic impact of this syndrome is underestimated, because costs associated to PONV may significantly increase with time of recovery after surgery.<sup>(4)</sup>

However the unrestrained use of antiemetic agents for universal prevention of PONV may be responsible for side effects and excessive cost. A better guidance of prophylaxis is required for those at higher risk of PONV and a stratified orientation for rescue treatment.

Our objective is to review relevant studies on the occurrence of PONV in adults and draw up an algorithm for prevention and treatment of the syndrome. A reference survey was made in the database PubMed using the keywords "postoperative nausea and vomiting", as Mesh terms, producing 1680 references. Survey limits were used to focus search on the more relevant articles: studies in humans, English or Portuguese language, in adults (over 19 years of age) and clinical studies of any kind (case reports or series, stage I,II, III or IV studies, comparative studies, controlled clinical studies with or without randomization). The search disclosed 741 articles (6 reviews) classified as: etiology (203), physiopathology (12), epidemiology (178), diagnosis (13), therapy (487) prevention and control (405) and economy (13).

## WHICH ARE THE RISK FACTORS?

Risks may be ranked in three categories: associated to the patient, to the surgical procedure and to the anesthesia performed.

### Factors associated to the patient

The main risk factor associated to PONV is the female gender.<sup>(4)</sup> Women before puberty may not present an increased risk for PONV, which suggests association with hormone factors.<sup>(5,6)</sup>

Other risk factors are former history of kinesiophobia and PONV.<sup>(7,8)</sup> Tobacco smoking seems to reduce the risk.<sup>(9)</sup> Evidence proves that age would also be an independent risk factor, because the highest incidence is in children and risk after each decade of life is reduced by 10%.<sup>(7)</sup> Other possible risk factors are: poorer evaluation in the American Society of Anesthesiology (ASA) score, migraine and postoperative anxiety.<sup>(8-10)</sup>

### Factors associated to surgical procedure

Surgery time is an independent risk factor for PONV (risk increases by 60% for each additional 30 minutes of surgery time).<sup>(7,8)</sup> Type of surgery is considered as an important risk factor.<sup>(9,11)</sup> It is known that intra-abdominal, laparoscopic, orthopedic, gynecological, plastic, otorhinolaryngologic surgeries, thyroid surgeries and breast surgeries have an increased risk in relation to other procedures.

## Factors associated to anesthesia

Multiple variables related to anesthesia were associated to higher risk of PONV incidence. Use of volatile anesthetics and nitrous oxide particularly increase the risk.<sup>(3,12,13)</sup> Use of high doses (above 2.5 mg) of neostigmine is also considered a risk factor.<sup>(14)</sup>

It is proven that opioids in the intra and preoperative periods increase risk of developing PONV. Venous, subcutaneous or spinal administration, is associated to occurrence of the syndrome.<sup>(15)</sup> There is a dose-response relation between opioids and risk of PONV.<sup>(16)</sup> Tramadol shows relative higher risk of PONV than other opioids, remifentanyl was temporarily associated to less risk, however there was no difference among use of remifentanyl, fentanyl and PONV in controlled studies.<sup>(12)</sup> Nevertheless, analgesic adjuvant drugs must be tried, aiming to reduce frequency of opioid use. General anesthesia is another risk factor if used in detriment to other forms of sedation and regional block.<sup>(7,9)</sup>

## HOW TO PREVENT AND/OR MANAGE PONV?

The identification of risk factors for PONV leads to the development of scores to quantify its probability. These scores are relevant in adults,<sup>(3)</sup> and use as parameters only risk factors associated to the patient and some have already been validated.<sup>(17)</sup> Accuracy was shown to be relatively low, improving prediction by 12% to 57%. Interventions oriented by scores significantly reduce PONV (23 to 71%) especially in high risk patients, while they avoid high costs and potential side effects in low risk patients.<sup>(18)</sup> Simplified risk scores (only preoperative risk factors) do not have a reduced accuracy and easy to use, accuracy is equivalent or superior in relation to other more complex systems.

### Preoperative strategies

Even at preoperative stages, there are strategies for prevention of PONV. Patient hypovolemia may increase incidence of PONV and generous hydration or more liberal conduct regarding zero diet may ease these effects.<sup>(19)</sup> Inhalation anesthetics increase risk of PONV, mainly nitrous oxide. In studies with animals, this agent may alter the pressure of the middle ear and cause intestinal distension, besides activating the dopamine system.<sup>(20-22)</sup> Effects of inhalation agents further depend on duration of anesthesia, and are greater in procedures of more than 3 hours duration. Regard-

ing anesthesia, propofol was associated to decreased risk, although its antiemetic mechanism has not been proven.<sup>(23)</sup> Maintenance of anesthesia with propofol, when compared to inhalation anesthetic agents, significantly reduces incidence of PONV, regardless of other risk factors, mainly if used in continuous infusion.<sup>(24)</sup> At the end of surgery, anticholinesteratic drugs are administered to antagonize the residual effect of neuromuscular blocking agents, however they increase gastrointestinal motility and gastric secretion, that are balanced by means of anticholinergic agents.<sup>(14)</sup> Administration of supplemental oxygen at high fractions is not beneficial when, compared to use of oxygen at 30% as previously suggested.<sup>(25,26)</sup> Gastric aspiration may reduce risk of PONV in surgeries with large blood accumulation in the stomach (oropharyngeal surgeries), because blood is a potent emetogenic in addition to the nauseating effect of gastric distension.<sup>(27)</sup>

### Pharmacological prophylaxis

Chart 1 shows the main drugs used for PONV prophylaxis. Several studies were carried out with antago-

nists of the 5-HT<sub>3</sub> receptors. Ondansetron is effective for treatment of PONV, more so against vomiting than nausea.<sup>(28)</sup> It was proven that 8mg of ondansetron at the end of surgery is not more efficient than 4 mg.<sup>(29)</sup> Dolasetron also proved efficient to prevent PONV, in a dose of 12.5 mg at the end of surgery.<sup>(30)</sup> Comparing ondansetron with dolasetron, no difference was found in the efficacy of PONV prophylaxis.<sup>(31)</sup> Granisetron is new antiemetic agent, however with no ideal dose defined.<sup>(32)</sup> The more common para-effects of these drugs are headaches, constipation and elevation of hepatic enzymes. Furthermore, electrocardiographic alterations may be found, although seldom and dose-dependent.<sup>(33)</sup>

Butyrophenones have an antiemetic effect due to blockade of dopamine receptors D<sub>2</sub> of the chemoreceptor trigger zone of the posterior area. They are more effective against nausea than vomiting. Studies show that there is no statistical difference in prophylaxis of PONV and occurrence of para-effects with droperidol (0.625mg or 1.25 mg) or ondansetron (4 mg).<sup>(34)</sup> In 2001, the Food and Drug Administration (FDA)

**Chart 1 – Drugs for prevention and treatment of postoperative nausea and vomiting**

Drugs	Class	Dose for prophylaxis	Time of prophylaxis	Dose for treatment	Comments
Scopolamine	Anticholinergic	Transdermal patch	Up to 4 hours before end of surgery	Not indicated	Wash hands after handling patch
Dimenhydrinate	Antihistamine	1-2 mg/kg or 50-100 mg IV or IM	Before induction of anesthesia	50-100 mg IV	-
Promethazine	Phenothiazine	12.5-25mg IV. IM or trans-rectal	At end of surgery	12.5-25 mg	The 6.25 mg dose is advised for patients at risk due to sedation
Droperidol	Butyrophenones	0.625-1.25 mg IV	At end of surgery	1.25-2.5 mg IV	Electrocardiographic monitoring is needed due to risk of prolongation of QT and of <i>torsades de pointes</i>
Ondansetron	Antagonist 5-HT <sub>3</sub> receptors	of 4 mg IV	At end of surgery	4 mg IV	Risk of dose-dependent alterations
Dolasetron	Antagonist 5-HT <sub>3</sub> receptors	of 12.5 mg	At end of surgery	25-50 mg IV	Risk of dose-dependent alterations
Granisetron	Antagonist 5-HT <sub>3</sub> receptors	of 5 ug/kg or 1mg	At end of surgery	0.1 – 1 mg IV	Risk of dose-dependent alterations
Dexametasona	Corticosteroids	4-10 mg IV	Before induction of anesthesia	Not indicated	Well tolerated in single dose
Metoclopramide	Benzamides	10-20 mg IV	At end of surgery	10-20 mg IV	Indicated in case of NV induced by opioid, its use is not considered in PONV prophylaxis

IV - intravenous; IM - intramuscular; NV – nausea and vomiting; PONV – postoperative nausea and vomiting.

ruled that droperidol should be restricted to patients who did not respond to or tolerate other treatments. [Due to the risk of triggering a prolonged QT interval and arrhythmias, patients must be submitted to cardiac monitoring before and after use of this drug.

Anticholinergic agents are antagonists of M1 receptors in the brain cortex and of H1 receptors in the hypothalamus and in the center of vomiting, in addition to suppressing the noradrenergic system, improving adjustment to vestibular stimulation and are often used in kinetosis management.<sup>(37)</sup> Transdermal scopolamine is efficient in PONV prophylaxis,<sup>(35,36)</sup> disclosing better results in patients with a history of kinetosis and nausea induced by opioids.<sup>(37)</sup> Its application is recommended on the night before surgery or up to four hours prior to end of anesthesia. More common side effects are visual disturbances and dry mouth.

Antihistamines have antiemetic qualities because of their ability to suppress the vestibular stimulus and due to anticholinergic and sedative effects. Dymenhydrinate is effective in prophylaxis of PONV, especially in patients of moderate or high risk although benefit has not been proven when compared to ondansetron.<sup>(38)</sup> The more common side effects are headache, sleepiness and vertigo.

Phenothiazines have antiemetic effects by blocking dopamine receptors D2 of the chemoreceptor trigger zone and the cortical centers of the central nervous system. Promethazine further presents antihistaminic and anticholinergic activity, and is more efficient than ondansetron in PONV prophylaxis in middle ear surgeries.<sup>(39)</sup> Prochlorperazine has a more rapid action than promethazine and has also sedative effect. Its administration was even more effective in reducing PONV when compared to ondansetron in hip and knee surgeries.<sup>(40)</sup> The more common side effects of phenothiazines are extrapyramidal symptoms.

Dexamethasone is an antiemetic routinely used for patients submitted to chemotherapy. Although its mechanism and ideal dose remain unknown<sup>(41,42)</sup> it is believed that dexamethasone may antagonize prostaglandins and release endorphins. In studies on prophylaxis for PONV, there was efficacy and there were no reports of adverse effects by administering a single dose.<sup>(43)</sup> Its effects on PONV prophylaxis are comparable to those of other classes of antiemetics, such as antagonists of the 5-HT<sub>3</sub> and D2 receptors. A dexamethasone dose of 8 mg before induction of anesthesia may reduce fatigue, pain and need of opioids as well as reduce the level of protein C reactive

at postoperative.<sup>(44)</sup>

Metoclopramide (group of benzamides) is prokinetic and antagonist of central dopamine D2 receptors. When administered in the habitual 10 mg dose, metoclopramide is not efficient in prevention of PONV. In a review of 66 randomized studies (626 patients) it was proven that use of metoclopramide does not prevent nausea at postoperative.<sup>(45)</sup> Its use for prophylaxis of postoperative vomiting, is efficient when compared to placebo, although there is no consensus about use.<sup>(1)</sup> However, metoclopramide manages nausea and vomiting efficiently when induced by paralytic ileum, due to high morphine does for control of postoperative pain.<sup>(46)</sup>

### Rescue treatment

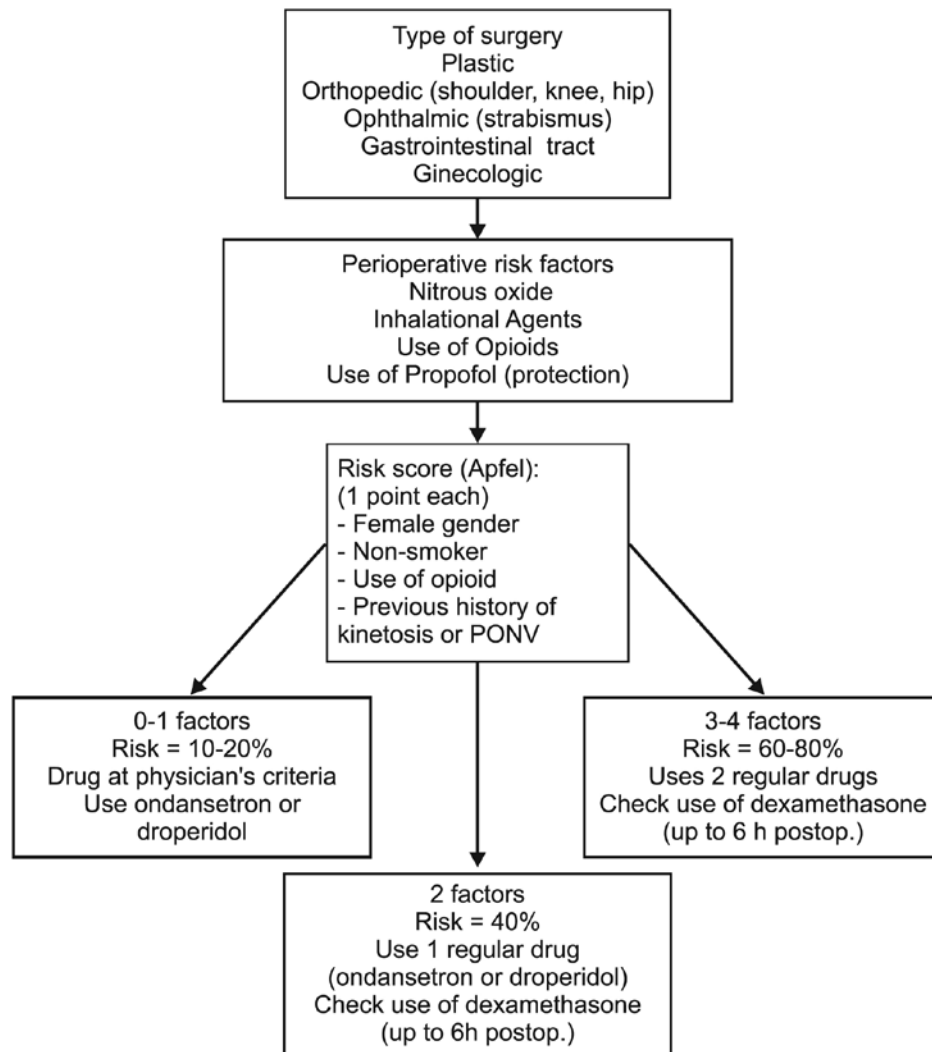
For rescue treatment, blockers of the 5-HT<sub>3</sub> receptors have been the most studied drugs. This class presents better results when treating vomiting than nausea episodes.<sup>(47)</sup> Scarce information is available on use of other classes of drugs for treatment of PONV, Rescue treatment of PONV must be begun with drugs of a different class than that used for prophylaxis.<sup>(48)</sup>

### Alternative and nonpharmacologic therapy

Studies disclose that nonpharmacological or alternative therapies may be beneficial for prophylaxis and treatment of PONV, such as acupuncture, transcutaneous nerve stimulation, hypnosis and aromatherapy.<sup>(49)</sup> Noteworthy is stimulus of the acupoint P6 (Nei-Guan), located on the median nerve, between the tendons of the flexor carpi radialis and palmaris longus muscles, that has proven efficient in comparison to antiemetics.<sup>(50)</sup>

## FINAL CONSIDERATIONS

Analysis of risk factors may be useful in the approach of postoperative PONV (Figure 1). Some types of surgery (plastic, orthopedic, ophthalmic, gastrointestinal and gynecological) predispose to PONV, as well as a longer surgery time, use of inhalation anesthetics and opioids, while continuous infusion of propofol is protective. When arriving at the intensive care unit, a risk score is calculated (female gender, tobacco smoking, history of kinetosis or PONV and use of opioids) and if there are two or more of these, prophylactic drugs should be administered. This approach may reduce discomfort and postoperative complications.



PONV – postoperative nausea and vomiting

**Figure 1 - Algorithm proposed for management of postoperative nausea and vomiting.**

## CONCLUSIONS

PONV are easily recognized and may be prevented. They entail complications and discomfort to patients, mainly after some specific types of surgery. Systematic approaches with analysis of preoperative risk factors as well as drug prescription may be efficient to prevent the undesirable PONV.

## RESUMO

Náuseas e vômitos pós-operatórios são comuns e podem ser evitados. Complicações provenientes deste problema acarretam aumento de morbi-mortalidade. Foi realizada revisão de literatura

no MEDLINE, com foco em estudos clínicos controlados. A fisiopatologia é complexa, com várias vias centrais aferentes e eferentes, e seu entendimento ajuda na escolha das medicações. Fatores de risco são apresentados, com escala de estratificação de chance para desenvolvimento de náuseas e vômitos pós-operatórios. Algoritmo para abordagem de pacientes com maior risco foi elaborado e estratifica nível de prevenção/tratamento a ser recebido, de modo a evitar uso excessivo de drogas e seus paraféitos. Náuseas e vômitos pós-operatórios devem ser prevenidos, pois acarretam complicações e desconforto nos pacientes. Abordagem sistemática com análise de fatores de risco per-operatórios e prescrição de medicações podem ser eficazes para sua prevenção.

**Descritores:** Náusea e Vômito pós-operatório/prevenção & controle; Complicações pós-operatórias/prevenção & controle

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