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REVIEW ARTICLE

# MANAGEMENT OF POSTOPERATIVE NAUSEA AND VOMITING (PONV) WITHIN THE ENHANCED RECOVERY AFTER SURGERY (ERAS) CONCEPT AND INTRAOPERATIVE NAUSEA AND VOMITING (IONV)

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## ABSTRACT

**Background**: Postoperative Nausea and Vomiting (PONV) occurs as a common adverse event subsequent to surgery with rates reported to reach 30% in patients undergoing surgery generally, with occurrence rates approaching 80% in those considered high risk. This occurrence impacts patient satisfaction, prolongs length of stay, and increases the risk of complications. PONV management under the Enhanced Recovery After Surgery (ERAS) framework includes risk factor identification, prevention strategies, multimodal prophylaxis administration, and therapeutic management based on different pharmacological classes. Intraoperative Nausea and Vomiting (IONV), particularly in cesarean section operations with regional anesthesia, has its own characteristics and risk factors, such as hypotension, peritoneal stretching, and uterotonic use.

**Aim**: This study reviews current evidence regarding pathophysiology, risk assessment systems, prevention strategies, and pharmacological and non-pharmacological therapeutic options for PONV and IONV, while discussing the application of these guidelines within the ERAS context.

Materials and Methods: A review was conducted to examine current evidence-based approaches for PONV and IONV management within the ERAS framework. Evidence from the Fourth Consensus Guidelines on PONV Management 2020, randomized controlled trials, meta-analyses, and case studies were synthesized to evaluate multimodal prophylaxis strategies and therapeutic interventions.

**Results**: A case report of a patient with severe aortic stenosis undergoing elective cesarean section with low-dose spinal anesthesia technique demonstrates that applying ERAS principles, including postoperative chewing gum use, can maintain hemodynamic stability, minimize PONV/IONV, and accelerate recovery.

**Conclusion**: The multimodal approach integrated within ERAS proves effective in reducing PONV and IONV incidence, improving patient comfort, and accelerating discharge time.

***Keywords*****:** Postoperative Nausea and Vomiting, Intraoperative Nausea and Vomiting, ERAS, Multimodal Prophylaxis, Cesarean Section.

## INTRODUCTION

Postoperative nausea and vomiting (PONV) are the two most frequently encountered complications occurring after surgery, with reported frequencies of approximately 30% in the general surgical population and up to 80% in high-risk categories.[1] It can contribute to lengthening the duration of PACU admission and increase the risk of postoperative complications.[2] An evidence-based framework for PONV management comprises risk assessment, multimodal risk reduction, preventive measures, and prompt therapeutic rescue.[1] PONV can prolong the length of stay in the post-anesthesia care unit and increase the risk of postoperative complications.[1]

Nausea and vomiting commonly occur in various surgical procedures, including during the intraoperative phase.[3] Various studies have been conducted to

investigate postoperative nausea and vomiting incidents, however, research on intraoperative nausea and vomiting (IONV) events has been limited.[4] Onset of nausea and vomiting during surgery, continuing after the procedure, adversely affects patient comfort, prolongs discharge, and raises overall treatment costs. This issue warrants greater attention due to potential consequences, including dehydration, electrolyte imbalance, wound dehiscence, venous hypertension and bleeding, esophageal rupture, airway obstruction, and aspiration pneumonia, must be considered.[5]

Enhanced Recovery After Surgery (ERAS) defines organized and thorough framework to perioperative care aimed at accelerating postoperative functional recovery by reducing surgical stress response.[6] This concept focuses on minimizing physiological disturbances after surgery while promoting practices that accelerate recovery.[7] While the application of perioperative nausea and vomiting management represents a core aspect of the ERAS protocol, the emergence of ERAS reinforces the importance of perioperative nausea and vomiting management and draws attention to various causative factors.[6] This review article will discuss the identification of risk factors, risk mitigation strategies, prophylaxis, and management, as well as IONV and PONV management within the ERAS concept.

## LITERATURE REVIEW

Optimal PONV and IONV management is a complex process. There are many antiemetics with varying pharmacokinetic profiles, efficacy, and side effects, so antiemetic choice will depend on the patient's clinical condition.[1] The benefits of PONV prophylaxis must also be balanced against the risk of side effects. From these various considerations and based on the Fourth Consensus Guidelines on PONV Management 2020[1], PONV management begins with identifying risk factors for PONV occurrence, determining interventions that can reduce the basic risk of PONV emergence, administering PONV prophylaxis to at-risk patients, and antiemetic treatment for patients with PONV, both those who did not receive prophylaxis and those with prophylaxis failure.

## PATHOPHYSIOLOGY OF PONV

The pathophysiology of PONV itself is complex and not fully understood to date. The coordination center for vomiting is centralized in the pons and medulla. Starting from the chemoreceptor trigger zone (CTZ) and nucleus tractus solitarius (NTS), stimuli that can cause nausea and vomiting are received. Stimuli from CTZ are then projected to NTS and trigger vomiting by transmitting stimuli to several other nuclei (rostral nucleus, ambiguous nucleus, ventral respiratory group, and dorsal motor nucleus of vagus).

CTZ receives stimuli from vagal afferents of the gastrointestinal tract. Additionally, since CTZ is located in the area postrema of the fourth ventricle (outside the blood-brain barrier), CTZ can also be stimulated by emetogenic drugs, toxins, and metabolites in blood and cerebrospinal fluid. NTS receives stimuli from vagal afferents, vestibular and limbic apparatus; therefore, NTS is also sensitive to motion sickness. Additionally, NTS also receives direct input from the cerebral cortex related to nausea caused by anxiety.

Several other neurotransmitter pathways are involved in stimulus transmission, including: 5-$HT_3$ is the main neurotransmitter for vagal afferents to CTZ, dopamine-2 transmits from CTZ to NTS, and the vestibular apparatus uses histamine-1 and acetylcholine as its neurotransmitters.

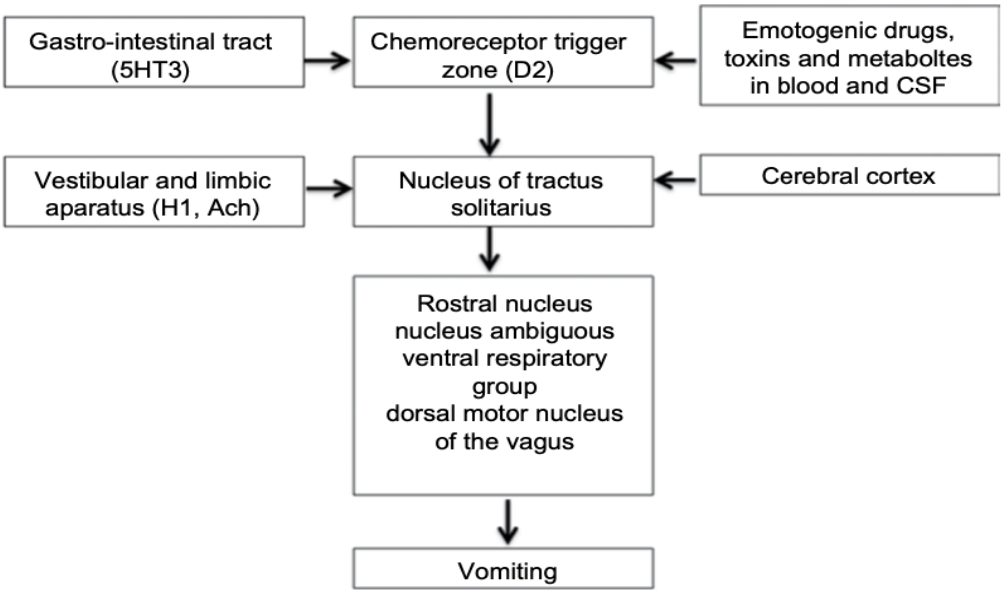


**Figure 1.** Pathophysiology of postoperative and anesthetic PONV[8]

PONV can be triggered by various stimuli acting on different neurotransmitter pathways, including anxiety, pain, medications, and movement. Several classes of antiemetic drugs are available to target these different pathways.[8]

**PONV RISK FACTOR IDENTIFICATION**

PONV risk factors are important to know from the beginning to serve as guidelines in PONV management.[8] Specifically, PONV risk factors for adult patients include female gender, history of PONV or motion sickness, non-smoker status, and postoperative opioid use, which can be analyzed through the Apfel and Koivuranta scoring system.[9,10]

| Risk Factors | Points |
|---|---|
| Female Gender | 1 |
| Non-Smoker | 1 |
| History of PONV and/or Motion Sickness | 1 |
| Postoperative Opioids | 1 |
| Sum of points | 0-4 |

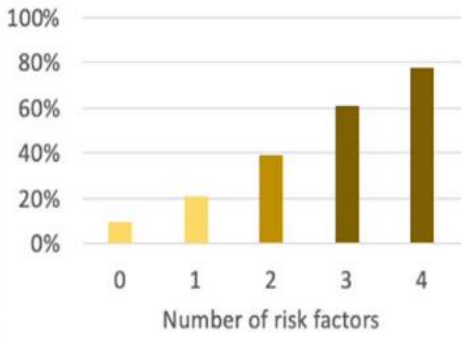


**Figure 2.** Apfel scoring system for assessing patient risk factors for PONV occurrence[1]

Consecutively, Apfel scores with values of 0, 1, 2, 3, 4 can predict 10%, 20%, 40%, 60%, and 80% PONV occurrence respectively.[1] If no or only one risk factor is present, PONV incidence can vary between approximately 10% and 21%, while if at least two risk factors are present, this figure can increase to between 39% and 78%.[9] In the Fourth Consensus Guidelines on PONV Management 2020, panelists classified patients with scores 0-1 as low risk category, score 2 as medium risk category, and scores 3 and above as high risk category.[1]

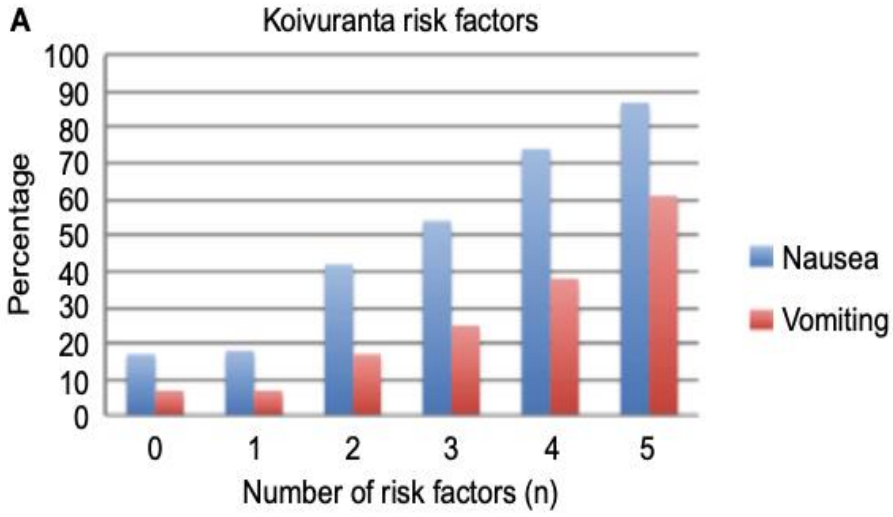


**Figure 3.** Koivuranta scoring system for assessing patient risk factors for PONV occurrence[8]

In the Koivuranta scoring system, the incidence (%) of postoperative nausea and vomiting in adult patients is divided into six risk score classes (0, 1, 2, 3, 4, and 5) based on five strongest predictors, including female gender, history of PONV, history of motion sickness, and surgery duration more than 60 minutes, each having equal score weight. Nausea incidence ranges from 17% to 87% and vomiting incidence from 7% to 61% based on six risk classes.[10]

**Table 1. Various scoring systems for assessing PONV risk factors[8]**

| Authors | Sex | Smoking Status | History of PONV | Opioids | Duration of Surgery | Motion Sickness | Type of Surgery | Age | Type of Anesthesia |
|---|---|---|---|---|---|---|---|---|---|
| Apfel et al. | + | + | + | + | - | + | - | - | - |
| Koivuranta et al. | + | + | + | - | - | + | - | - | - |
| Palazzo and Evans | + | - | + | + | - | + | - | - | - |
| Sinclair et al. | + | + | + | - | + | - | + | + | + |
| Sarin et al. | + | - | + | + | + | + | + | + | + |
| Junger et al. | + | + | - | + | + | - | _ | - | + |

Internationally agreed consensus guidelines recommend that clinicians assess each patient's PONV risk individually using validated risk scores based on independent predictors.[11] The Palazzo and Evans scoring system studied PONV risk factors specifically in patients undergoing minor orthopedic surgery and identified female gender, opioids, and previous nausea history as independent risk factors.[12] Junger et al. created an algorithm to predict PONV in the post-anesthesia care unit (PACU) using female gender, smoking status, age, surgery duration, intraoperative opioid use, N2O use, and intravenous anesthesia with propofol.[13]

Considering that PONV is likewise shaped by local practices from various healthcare centers, incorporating local data from each healthcare facility is important to produce predictive risk factor scores relevant to individual patient conditions. Useful risk factor score characteristics are clinical credibility, accuracy, generalization, and clinical effectiveness.[14] One study conducted by Apfel et al. (2004) proved that surgical location is actually not a strong predictor of PONV risk factors. However, generally, some specific surgical locations have been accepted to have higher PONV incidence.[15] Some types of surgery with PONV potential include laparoscopic operations such as cholecystectomy, bariatric (non-laparoscopic), and gynecological procedures. However, several other literature sources seem to show varied results.[15] Nevertheless, PONV is a multifaceted clinical issue, and the relative impact of one factor (surgical location) which requires consideration of confounding variables through multivariate analytical approaches.

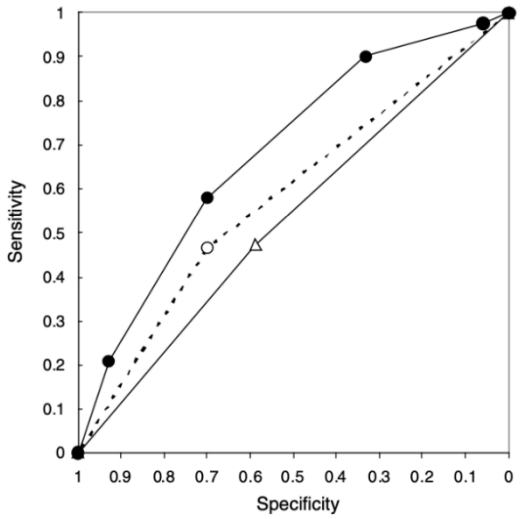


**Figure 4.** Comparison of Receiving Operating Characteristic (ROC) curves between surgical location curve (Δ), PONV history curve (O), and Apfel score curve (●). Areas Under the Curve (AUC) from surgical location 0.53 (95% CI 0.50–0.56), from PONV history 0.58 (95% CI 0.56-0.61), and from risk factor scoring system 0.68 (95% CI 0.66-0.71)

From the anesthesia perspective, the use of inhalational anesthesia, duration of anesthesia administration, and perioperative opioid administration contribute to PONV risk.[2] Inhalational anesthetic gas administration shows a prominent dose-dependent effect at 2-6 hours postoperatively.[1] Regardless of the specific type of opioid given, opioids increase PONV risk in a dose-dependent manner, and PONV seems to persist as long as opioids are used in the postoperative period.[16] PONV incidence was found to be lower in surgeries with total intravenous anesthesia (TIVA), multimodal pain management, opioid-free regional anesthesia (RA), and limited opioid consumption.[1]

**PREVENTION OF PONV RISK**

Several approaches are recommended by the Fourth Consensus Guidelines on PONV Management 2020 to suppress basic risk factors related to PONV potential. These efforts include:

1. Minimizing perioperative opioid use through multimodal analgesia regimens
2. Preference for regional anesthesia over general anesthesia
3. Preference for propofol as the primary intravenous anesthetic agent
4. Reducing inhalational anesthesia use
5. Adequate hydration for surgical patients

Minimizing perioperative opioid use eliminates the risk of opioid-related side effects, including PONV, as well as respiratory depression and ileus.[17] With advances in regional anesthetic techniques and non-opioid analgesia options, several authors have discussed the feasibility of opioid-free anesthesia or analgesia.[18] While both terms are often used interchangeably, the American Society for Enhanced Recovery and the joint Perioperative Quality Initiative Consensus define opioid-free anesthesia as "absolute avoidance of opioids from anesthesia induction to complete emergence"; and opioid-free analgesia as "absolute avoidance of opioids in the pre and postoperative periods." The benefits of absolute opioid avoidance must be balanced against issues such as the risk of block failure and unwanted motor block. Additionally, most available literature does not compare opioid-free anesthesia/analgesia with minimal opioid/opioid-sparing approaches. In the American Society for Enhanced Recovery and Perioperative Quality Initiative consensus statement, it was concluded that there is limited evidence that opioid-free approaches are superior to opioid-minimizing approaches.[19]

Regional anesthesia use has proven effective in reducing PONV incidence. A meta-analysis showed that epidural anesthesia significantly reduces PONV risk, while intrathecal opioids can increase PONV.[20] Several studies have proven that regional anesthesia application can reduce PONV incidence in various surgeries.

In gynecological surgery, epidural anesthesia administration may need to be continued after surgery and at sufficient concentration (e.g., lidocaine 10 mg/mL or equivalent) effectively reduces PONV incidence.[21]

In colorectal surgery, thoracic epidural anesthesia shows much better pain control compared to IV morphine administration and with fewer PONV incidents.[22] Bilateral transversus abdominis plane (TAP) block reduces postoperative opioid use and PONV incidence in abdominal surgical cases. In comparison between thoracic epidural anesthesia and TAP block, TAP block allows for shorter length of stay (LOS) without differences in PONV reduction effectiveness.[23] With continuous local anesthetic wound infiltration or epidural anesthesia for 48 hours after open gastrectomy surgery, it has proven to have lower morphine consumption rates, fewer PONV incidents, and shorter LOS than patient-controlled anesthesia (PCA) with morphine technique.[24]

A systematic review - meta-analysis of randomized controlled trial (RCT) research showed that PONV risk decreases with propofol TIVA compared to inhalational anesthesia techniques combined with single PONV prophylactic agents, namely 5-hydroxytryptamine 3 [5-HT3] receptor antagonists. When used in combination with prophylactic agents, propofol TIVA also reduces PONV risk.[25] Subhypnotic doses of propofol infusion, in combination with antiemetics, also significantly reduce PONV incidence.[26] Hakim and Wahba conducted research and found that propofol/dexmedetomidine TIVA anesthesia technique was associated with much lower antiemetic requirements than propofol/fentanyl anesthesia.[27]

Considering that laparoscopic procedures in gynecological surgery and N2O are independent predictors for PONV, ERAS Society Guidelines (ESG) explicitly recommend against using N2O as an inhalational anesthetic agent.[28] In colorectal surgery, ESG recommends total intravenous anesthesia (TIVA) technique with propofol and remifentanil in high-risk patients rather than inhalational anesthesia techniques in pancreaticoduodenectomy operations.[29] A randomized controlled trial (RCT) studied opioid-free TIVA technique versus general inhalational anesthesia with opioids in elective bariatric surgery found significantly less PONV in the opioid-free TIVA group.[30]

Perioperative fluid status is an important risk factor for PONV prevention development. Intraoperative fluid administration can affect PONV risk. Adequate hydration status is one effective strategy for reducing PONV risk.[1] This can be achieved by minimizing preoperative fasting time or using infusion fluids to maintain euvolemic status during the preoperative phase. However, due to the heterogeneity of included surgical procedures, there is no consensus on optimal intravenous fluid administration volume. A more recent meta-analysis by Xu et al. looking at laparoscopic cholecystectomy reported that preoperative carbohydrate drinks were associated with significantly lower PONV risk.[31] A recent review found that intraoperative crystalloid fluid administration of 10-30 mL/kg significantly reduces PONV risk and the need for antiemetics as PONV therapy.[32] A recent meta-analysis by Kim et al.

reported that compared to crystalloid fluid supplementation, colloids significantly reduce PONV risk in longer surgeries (>3 hours) compared to shorter surgeries (<3 hours).[33]

**PONV PROPHYLAXIS ADMINISTRATION IN AT-RISK PATIENTS**

There has been a paradigm shift toward using multimodal prophylaxis for PONV, namely the administration of multiple antiemetics, as the standard of care for patients.[2] One major change from the Fourth Consensus Guidelines on PONV Management 2020 is that multimodal prophylaxis is now recommended for patients with one or more risk factors. Before providing PONV prophylaxis to at-risk patients, it is important to perform risk stratification as a guide for antiemetic therapy administration. In patients without risk factors, one or no prophylactic agents can be given; in patients with one to two risk factors, two prophylactic agents can be given, while in patients with more than two risk factors, three to four prophylactic agents can be given.[2] Reasons for this prophylaxis use paradigm shift include: 1) PONV risk scores only provide risk stratification estimates, 2) patients identified as low risk still have PONV potential, 3) PONV risk factor scoring systems do not account for factors such as emetogenic risks arising from surgical procedures, and 4) antiemetic effectiveness varies in each patient.[1]

In recent years, evidence has emerged for new therapeutic options for PONV prophylaxis. Several drug classes are recommended as PONV prophylactic agents, including 5-$HT_3$ receptor antagonists, NK1 receptor antagonists, corticosteroids, antidopaminergics, antihistamines, and other antiemetic drugs such as gabapentin, midazolam, and ephedrine.

**5-HT3 Receptor Antagonists**

1. Ondansetron

Ondansetron is widely utilized and investigated first-generation 5-HT3 receptor antagonist and is considered the "gold standard" in PONV management. Ondansetron has anti-nausea and vomiting effects when used as a single drug or combination for prophylaxis or treatment with a dose of 4 mg IV or 8 mg tablet with 50% bioavailability.[34]

Compared to other 5-HT3 receptor antagonists, ondansetron is considered to have lower effectiveness compared to ramosetron 0.3mg IV, granisetron 1-3mg IV, palonosetron 0.075mg. Compared to NK-1 receptor antagonists, ondansetron is also considered to have lower effectiveness compared to aprepitant 80mg orally and fosaprepitant 150mg IV. However, compared to metoclopramide 10mg IV, ondansetron is considered to have higher effectiveness. Ondansetron is considered to have the same effectiveness as antiemetic agents from the corticosteroid class, namely dexamethasone 4-8mg and antidopaminergic class namely haloperidol.[1]

2. Granisetron

Granisetron is one of the first-generation 5-HT3 receptor antagonist drugs that has effectiveness comparable to drugs from the same class and corticosteroid class, dexamethasone 8mg; granisetron at 0.3mg IV dose proved more effective than ondansetron at 4mg IV dose.

In patients undergoing middle ear surgery, granisetron produces less PONV than ondansetron up to 24 hours postoperatively.[1] In patients undergoing laparoscopic cholecystectomy, granisetron is comparable to palonosetron in the first 24 hours postoperatively but less effective in 24-48 hours postoperatively.[35]

3. Ramosetron

Ramosetron is one of the second-generation 5-HT3 receptor antagonist drugs used in Japan and Southeast Asian countries as medication for nausea, vomiting, and diarrhea. The most effective dose for adult patients for PONV prevention and treatment is 0.3 mg IV, where this dose proved more effective compared to ondansetron 4mg administration.[36]

4. Palonosetron

As a second-generation 5-HT3 receptor antagonist drug, palonosetron has characteristics of 40-hour half-life and 5-$HT_3$/neurokinin 1 (NK1) receptor antagonist.[37] In several meta-analysis studies related to PONV prevention, palonosetron 0.075 mg is more effective compared to other 5-HT3 receptor antagonist drugs such as ondansetron 4 and 8 mg, granisetron 1 mg, and ramosetron 0.3 mg, as well as corticosteroid class, dexamethasone 5 and 8 mg.[38] Palonosetron can be combined with sevoflurane inhalational anesthetic agents or N2O and can still reduce PONV incidence comparable to total TIVA techniques.[39] Combining palonosetron with TIVA techniques can reduce PONV incidence compared to applying TIVA techniques alone.[40]

**NK1 Receptor Antagonists**

*Aprepitant & Fosaprepitant*

Aprepitant is a competitive Neurokinin (NK)-1 receptor antagonist that was also initially approved for treating chemotherapy-induced nausea and vomiting. Aprepitant is given orally and is equivalent to the intravenous form, namely Fosaprepitant.[2] Aprepitant has a half-life of 9-13 hours, and it has been studied that its duration of action may last up to 40 hours.[41] All doses (40, 80, and 125mg) have proven more effective in reducing postoperative vomiting incidence than nausea.[1] Aprepitant 40mg orally has the same PONV prevention effect as palonosetron 0.075 mg IV.[1] Aprepitant 40 and 80 mg orally are more potent than ondansetron.[42] Fosaprepitant (aprepitant prodrug) 150 mg IV is more potent than ondansetron.[1]

Evidence from Cochrane network meta-analysis by Weibel et al. showed that NK1 receptor antagonist monotherapy has similar efficacy to several combination therapies.[43] Similar to palonosetron, aprepitant also proves beneficial in outpatient surgery due to its long duration of action and lower risk of post-discharge nausea and vomiting.[2] NK1 receptor antagonists could be beneficial as prophylactic antiemetics when postoperative emesis events are highly avoided, such as in gastric surgery and neurosurgery.[1]

**Corticosteroids**

*Dexamethasone*

The use of glucocorticoids during the perioperative period has long been applied to reduce PONV incidence. Currently, recommended dexamethasone doses range from 4 to 10mg.[1] Dexamethasone prophylaxis produces comparable PONV incidence compared to 5-HT3 receptor antagonists (especially ondansetron). One exception, in comparison between dexamethasone and 5-HT3 receptor antagonists, is palonosetron, which at 75 mcg dose shows superiority compared to dexamethasone 8 mg for PONV reduction in the 0-24 hour postoperative interval.[44]

Further, as an added advantage compared to 5-$HT_3$ receptor antagonists, dexamethasone reduces analgesic requirements in many studies, including cases with neuraxial anesthesia.[45] Dexamethasone also improves respiratory parameters, reduces fatigue, provides better recovery quality, and reduces hospital length of stay.[1]

Although dexamethasone safety is often questioned in many studies, it appears that dexamethasone given in single doses has few side effects.[1] An additional review of 56 trials showed that corticosteroids, especially dexamethasone, do not increase rates of wound infection, anastomotic leakage, wound healing, bleeding, or clinically significant hyperglycemia.

There is some evidence that repeated dexamethasone prophylaxis administration is more effective than single intraoperative administration, so interval administration allows for application in very long surgical procedures. However, increased risk of corticosteroid-related complications (such as infection, bleeding, and hyperglycemia) with repeated corticosteroid administration still needs investigation.

*Other Corticosteroids*

Other corticosteroids appear to have similar efficacy to dexamethasone in terms of PONV reduction and analgesic effects. Low-dose (40 mg) and high-dose (125 mg) methylprednisolone have proven effective in reducing PONV. However, not all steroids appear to have the same relative efficacy for PONV prevention.[1] In trials using betamethasone 8mg in patients undergoing elective breast cancer surgery, there was only little effect in reducing PONV compared to placebo.[46]

**Antidopaminergics**

*Amisulpride*

Amisulpride is a dopamine D2, D3 receptor antagonist. The antiemetic dose for prophylaxis is 5mg IV and 10mg IV for rescue treatment, while the antipsychotic dose is 50-1,200mg/day orally. A clinical trial has reported that, compared to placebo, amisulpride significantly reduces PONV incidence and rescue antiemetic requirements.[2] Additionally, at doses used for PONV prophylaxis, amisulpride poses no meaningful risk of QT interval prolongation or extrapyramidal side effects.[2]

*Metoclopramide*

The antiemetic effectiveness of 10mg metoclopramide dose is uncertain. A large study involving 3,140 patients receiving PONV prophylaxis with dexamethasone 8mg compared to metoclopramide at doses of 10, 25, or 50 mg, only doses of 25 and 50 mg achieved a meaningful reduction in PONV.[1] Extrapyramidal symptoms rarely occur but are significantly higher in the 25 and 50 mg groups compared to the metoclopramide 10 mg group. Metoclopramide may be useful in institutions where other dopamine antagonists are not available, but otherwise may not be very potent.

**Non-pharmacological Prophylaxis**

*Acupressure/Acupuncture*

Pericardium 6 (PC6) is an acupuncture point located on the palmar aspect of the forearm, between the palmaris longus and flexor carpi radialis tendons, approximately 6cm proximal to the wrist. A clinical trial and 2015 Cochrane review concluded that acupuncture point stimulation with various instruments (including needle acupuncture, acupressure devices, nerve stimulators, electrical stimulation needles, and lasers) is effective in reducing PONV risk and antiemetic requirements.[47] The review also included comparisons of PC6 point stimulation with 6 different types of antiemetic drugs (metoclopramide, cyclizine, prochlorperazine, droperidol, ondansetron, and dexamethasone), and found no differences in nausea, vomiting, or need for antiemetic therapy between PC6 point stimulation and pharmacoprophylaxis.[47]

*Chewing Gum*

Chewing gum shows promise for PONV treatment, with 1 small pilot study in 2017 showing that chewing gum is not inferior to ondansetron for PONV treatment in female patients undergoing laparoscopy or breast surgery under general anesthesia. Another new study in 2021 proved that patients who chewed gum experienced 5.09 times fewer vomiting incidents 0-6 hours after surgery compared to those who did not chew gum. Therefore, chewing gum is recommended to regulate digestive system function after surgery.[48] Chewing gum can be suggested as an early oral feeding

alternative and is crucial in preventing risks that are associated with inadvertent early enteral feeding. Chewing gum reduces the time to first consumption after surgery as well as the return of bowel function and hence semblance.[48] Chewing gum is considered a form of sham feeding, where nutrition is chewed, but nothing enters the stomach.[48]

Chewing gum is easily accessible therapy, with low cost and no special storage considerations. It is also familiar to patients and can be done independently by patients. On the other hand, requirements for equipment and training in some non-pharmacological techniques (e.g., acupressure or transcutaneous electrical nerve stimulation) are potentially limited in application for most anesthesiologists.[2]

In the latest PONV management guidelines, recommendations regarding the use of combination antiemetics both as therapy and prevention remain unchanged, that the use of 2 or more antiemetics in patients with higher PONV risk has more advantages than single agent administration in various studies.[1] The use of combination therapy for PONV prevention in adults is now commonly found in current anesthetic practice.

**The Use of New Therapies as Part of Multimodal Prophylaxis Regimens**

5-HT3 receptor antagonists are usually used alone or in combination with dexamethasone 4 or 8 mg, and are the foundation of antiemetic prophylaxis for surgery. Results from a 2016 meta-analysis stated that combination ondansetron and dexamethasone administration significantly reduces PONV risk and lower antiemetic therapy requirements compared to single 5-HT3 receptor antagonist use.[49]

New antiemetic combination therapies have been studied, namely the use of palonosetron 0.075 mg and dexamethasone 4 or 8 mg combination. One study by Cho et al. found that palonosetron combined with 8 mg dexamethasone achieved higher significance for prevention and lower PONV incidence compared to palonosetron alone[50], while other research reported no significant difference compared to palonosetron alone. However, what should be underlined is that palonosetron combined with dexamethasone has lower PONV incidence than ondansetron combined with dexamethasone, and palonosetron combined with aprepitant has lower PONV than combinations of other 5-HT3 receptor antagonists with aprepitant.

As an NK-1 receptor antagonist, aprepitant can be used in combination with 5-HT3 antagonists and other antiemetics.[2] Vallejo et al. conducted clinical trials on 150 patients with moderate to high risk undergoing outpatient plastic surgery, and found that aprepitant combination with ondansetron was associated with significantly lower PONV incidence and severity than ondansetron alone.[51] Similarly, Lee et al. studied 84 low-moderate risk female patients presented for gynecological surgery and concluded that compared with ramosetron alone, aprepitant plus ramosetron was associated with significantly lower incidence and severity of PONV.[36]

Aprepitant also has potential for use in combination with dexamethasone. While aprepitant monotherapy is more effective than ondansetron, its benefits as part of combination therapy are unclear. Habib et al. conducted clinical trials on 104 low to moderate risk patients undergoing craniotomy procedures and reported that aprepitant combination with dexamethasone significantly reduced PONV incidence compared to ondansetron combination with dexamethasone.[52] On the other hand, Bilgen et al. conducted clinical trials on 67 moderate to high risk patients undergoing laparoscopic surgery and reported that aprepitant combination with dexamethasone was not associated with a meaningful decrease in PONV incidence or rescue antiemetic therapy requirements compared to ondansetron and dexamethasone.[53]

In contrast, Yoo et al. performed clinical trials on 100 moderate risk female patients undergoing moderate to high risk surgery, and affirmed that aprepitant combination with palonosetron did not significantly reduce PONV incidence or rescue antiemetic requirements compared to palonosetron alone. One possible explanation is that because palonosetron is intrinsically more effective than other 5-HT3 antagonists, the advantage of adding aprepitant provides less significance.[2]

In summary, while new drugs are considered more effective for monotherapy use, consensus guidelines on PONV management still recommend using multimodal prophylaxis. This allows for the use of lower single antiemetic doses, thereby further reducing the risk of adverse reactions. In this regard, these new drugs still require further study.

**ANTIEMETIC TREATMENT FOR PATIENTS WITH PONV, BOTH THOSE WHO DID NOT RECEIVE PROPHYLAXIS AND THOSE WITH PROPHYLAXIS FAILURE**

Failure of PONV prophylaxis warrants the use of an antiemetic agent from a different drug class than the PONV prophylactic drug. Repeated administration of antiemetics from the same class within 6 hours provides no additional therapeutic benefit compared to placebo. If more than 6 hours have passed, a second dose of 5-HT3 receptor antagonist may be considered if no other alternatives are available.

In patients who do not receive PONV prophylaxis, 5-HT3 receptor antagonists become first-line pharmacotherapy to treat occurring PONV. Recommended antiemetic drugs as therapeutics include ondansetron at 4 mg dose given orally or IV, ramosetron at 0.3 mg IV, and granisetron 0.1 mg IV.[1]

Palonosetron administration produces higher PONV resolution rates compared to placebo.[2] However, in patients who have previously received ondansetron prophylaxis, palonosetron administration only produces significant response in 25% of patients. This is not much different from additional ondansetron dose administration as therapy. Therefore, repeated administration of 5-HT3 receptor antagonists is not recommended if the previous dose was given within 6 hours.[2]

Multiple studies indicate that combination therapy using more than one antiemetic agent may offer superior efficacy in managing established PONV. For example, ondansetron + droperidol + dexamethasone combination is more effective than ondansetron + droperidol[54]; and palonosetron + dexamethasone is more effective than palonosetron alone.[54] Additionally, additional midazolam 30 mcg/kg administration to ondansetron is superior to ondansetron administration alone.[55]

Amisulpride may also be effective for treating established PONV. In patients who do not receive PONV prophylaxis, 5 mg (and 10 mg) amisulpride produces significantly higher complete response rates compared to placebo.[56] A 2019 multicenter study reported that, compared to placebo, 5 mg amisulpride produces significantly lower vomiting episode rates, so a 10 mg dose is recommended.[57]

Currently, evidence regarding optimal combination therapy for established PONV is quite limited, therefore practitioner discretion is highly expected, and antiemetics used in combination therapy should be selected from different classes.[1] In addition to providing rescue antiemetics to patients experiencing PONV, patients should be evaluated for reversible PONV causes, such as excessive opioids, mechanical intestinal obstruction, or blood in the pharynx.[12]

## APPLICATION OF PONV GUIDELINES IN THE ENHANCED RECOVERY AFTER SURGERY (ERAS) CONCEPT

Enhanced Recovery After Surgery is a currently developing perioperative care concept. In 2016, the American Society for Enhanced Recovery (ASER) released an expert opinion statement and concluded that "All patients should receive PONV prophylaxis during the perioperative period." The number of drugs used for treatment and prophylaxis should be adjusted to the number of modifiable and non-modifiable risk factors; drugs used should represent different mechanisms of action in an effort to achieve multimodal benefits.

PONV prevention and management persist as fundamental components of the ERAS framework. This practice includes gastrointestinal system recovery, prevention of postoperative physiological stress, and increased patient comfort to enter the rehabilitative phase such as mobilization, physical therapy, and enteral intake. Several other ERAS components, namely, multimodal analgesia, are also important in definitively reducing PONV risk. PONV prevention in ERAS patients requires identification of risk factors in patients who potentially require secondary additional antiemetic therapy[6]. Components within the ERAS concept that support PONV management practice can be seen in Figure 5

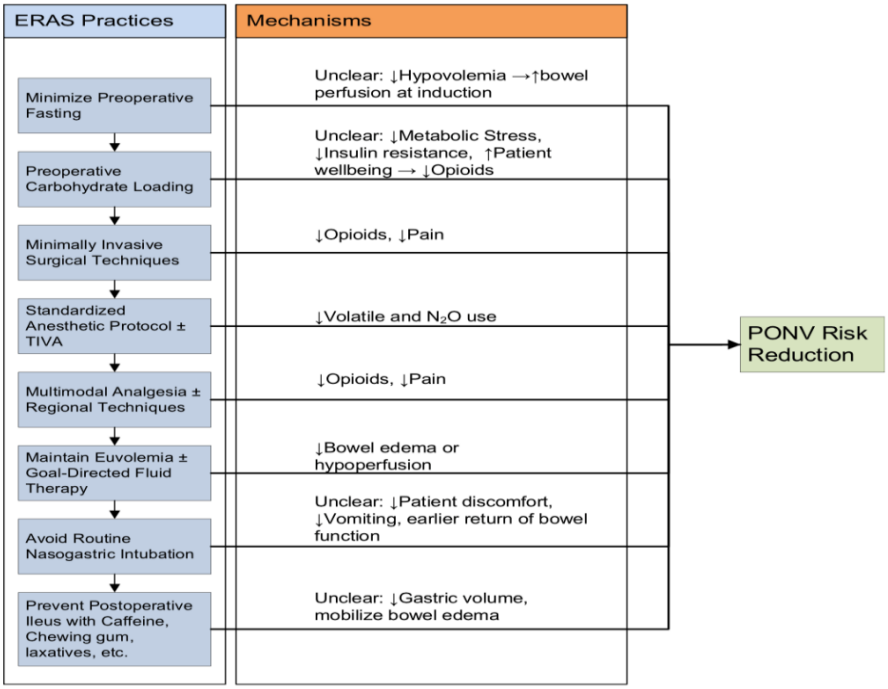


**Figure 5.** Components in the ERAS concept that support reducing PONV risk factors[6]

Since the emergence of the ERAS concept in 2001, particularly in the colorectal surgery subspecialty, this concept has been widely adapted by other surgical subspecialties for their respective patient populations, adjusted to indication and contraindication considerations in each field.[6] For each type of surgery, the emetogenic potential of each procedure, availability of effective regional anesthetic techniques, and expected postoperative recovery should be considered to optimize PONV management.[1] The following are applications of PONV guidelines in the ERAS concept for each type of surgery.

**Breast Surgery**

ESG focuses on 5-HT3 antagonist administration and TIVA use for general anesthetic techniques as PONV prevention.[6] Nonsteroidal anti-inflammatory drug (NSAID) administration supports as part of multimodal analgesia, with consideration of not significantly increasing bleeding risk. Additionally, a 2015 RCT study found significant reduction in intraoperative fentanyl consumption and lower PONV in PACU when PECS type II nerve block was added to general anesthesia for breast cancer surgery.[58]

**Caesarean Section Surgery**

For caesarean section surgery, specific risk factors include hypotension related to neuraxial anesthetic techniques, decreased cardiac output due to aortocaval compression, surgical stimulation, uterotonic use, and neuraxial opioid use. PONV risk reduction measures, particularly for caesarean section surgery, include intravenous fluid administration, and ephedrine use to prevent hypotension, and should be given as additional to PONV prophylaxis.[59]

**Gynaecological Surgery**

Multimodal PONV prophylaxis is recommended; regional analgesic techniques such as transversus abdominis plane/TAP block can reduce opioid use and postoperative pain, which can indirectly be interpreted as an advantage in PONV management in all cases.[2]

**Gastrointestinal Surgery**

In colorectal surgery, postoperative pain is significantly associated with high opioid requirements. Additionally, postoperative ileus incidence is also a common side effect. Postoperative pain can be effectively managed through epidural analgesic techniques, TAP blocks, and bupivacaine infiltration analgesic techniques. Postoperative ileus risk may be mitigated through the use of minimally invasive surgical techniques when possible, as well as maintaining euvolemic status and early patient mobilization.[60] The ERAS concept in radical cystectomy surgery can also be applied with minimally invasive surgical technique implementation, early oral intake provision, antiemetics, chewing gum, prokinetic agents, and opioid-sparing analgesia to minimize PONV and postoperative ileus. The ERAS concept in colorectal surgery can also be adapted to other gastrointestinal surgical procedures, such as esophageal, gastric, pancreatic, and hepatic surgeries.

**Head and Neck Surgery**

Head and neck surgery is considered high risk for PONV occurrence, and recent clinical trials have shown that preoperative assessment and multimodal prophylaxis are effective in reducing PONV risk.[2] Vomiting incidence after free-flap reconstruction in head-neck surgery can cause suture dehiscence, wound infection, fistula formation, and flap failure. ESG for major head and neck surgery recommends corticosteroids with other antiemetics as first-line prophylaxis.

**Orthopedic Surgery**

In orthopedic surgery, pain is the primary postoperative manifestation encountered and can increase opioid requirements. Effective analgesic techniques include spinal anesthesia, peripheral nerve blocks, and bupivacaine infiltration. In one study, introduction of multimodal analgesia and opioid-sparing analgesia, multimodal PONV prophylaxis significantly reduced PONV risk.[60]

The ERAS concept for several other surgical procedures includes multimodal PONV prophylaxis as part of PONV management components. Therefore, it can be summarized that multimodal PONV prophylaxis applies to most ERAS implementations. On the other hand, special surgical considerations related to emetogenic effects of each procedure, postoperative pain and ileus risk, specific regional anesthetic technique implementation should be adjusted accordingly.[2]

**INTRAOPERATIVE NAUSEA AND VOMITING (IONV)**

Reviews related to PONV management have been extensively discussed, but regarding IONV complications, research is still limited, as IONV events specifically occur in obstetric anesthesia in cesarean operations.

Regional anesthesia has proven effective, safe, and is the anesthetic technique of choice for elective and emergency cesarean operations. Despite major advances in spinal, epidural, and combined spinal-epidural techniques, IONV remains prevalent among many patients.[3]

From the incidence perspective, IONV in cesarean operations varies greatly; several studies have compared IONV incidence can reach 80% depending on the chosen regional anesthesia type (spinal, epidural, or combined spinal-epidural anesthesia).[3]

Pathophysiologically, IONV emergence is not different from PONV. However, specifically in

cesarean operations, increased intra-gastric pressure, hypotension related to regional anesthetic technique impacts, peritoneal stretching (uterine exteriorization), excessive surgical manipulation and visceral stimulation, opioid use, uterotonic agent use, and patient mental status play roles and place patients at high risk for IONV. [61]

In obstetric patients, physiological changes during pregnancy contribute to nausea and vomiting susceptibility. This is caused by esophageal, gastric, and small intestinal motility disturbances as a result of smooth muscle relaxation caused by increased hormone levels, especially progesterone during pregnancy. Additionally, changes in lower esophageal sphincter competence are also caused by hormonal changes during pregnancy.

A 2017 study by Semiz et al. found risk factors for IONV occurrence in cesarean operations.

**Table 2.** Risk factors for intraoperative nausea occurrence[61]

| | p | OR | 95% CI for OR | |
|---|---|---|---|---|
| 1st TM nausea/vomiting | <0.001 | 6.75 | 3.03 | 15.05 |
| Motion sickness | <0.001 | 12.02 | 4.62 | 31.30 |
| Absence of PMS | 0.068 | 3.41 | 0.91 | 12.75 |

**Table 3.** Risk factors for intraoperative vomiting occurrence[61]

| | p | OR | 95% CI for OR | |
|---|---|---|---|---|
| 1st TM nausea/vomiting | <0.001 | 7.36 | 2.47 | 21.96 |
| Foetal sex (female) | 0.045 | 3.80 | 1.03 | 14.01 |

It can be concluded that IONV risk factors in cesarean operations are history of nausea or vomiting in the first trimester of pregnancy, history of motion sickness before pregnancy, and female gender of the newborn baby. The study recommends providing antiemetic prophylaxis to patients with the above risk factors.[61]

As IONV preventive measures during intraoperative period, several previous studies recommend strict blood pressure monitoring, opioid use should be kept to a minimum, surgical techniques should be gentle with minimal uterine exteriorization (not exiting through the incision), and uterotonic and antibiotic administration in diluted form and slow infusion.[61]

IONV represents a complex clinical issue with etiologies linked to anesthetic and non-anesthetic factors. Anesthetic causative factors of IONV include hypotension, increased vagal activity, opioid administration both parenteral and neuraxial. Non-anesthetic causative factors of IONV include surgical stimulation, uterotonic drugs, and positional changes occurring at the end of surgery. Both anesthetic and non-anesthetic causes can cause IONV individually or in combination, so IONV management is adjusted to the cause of occurrence.

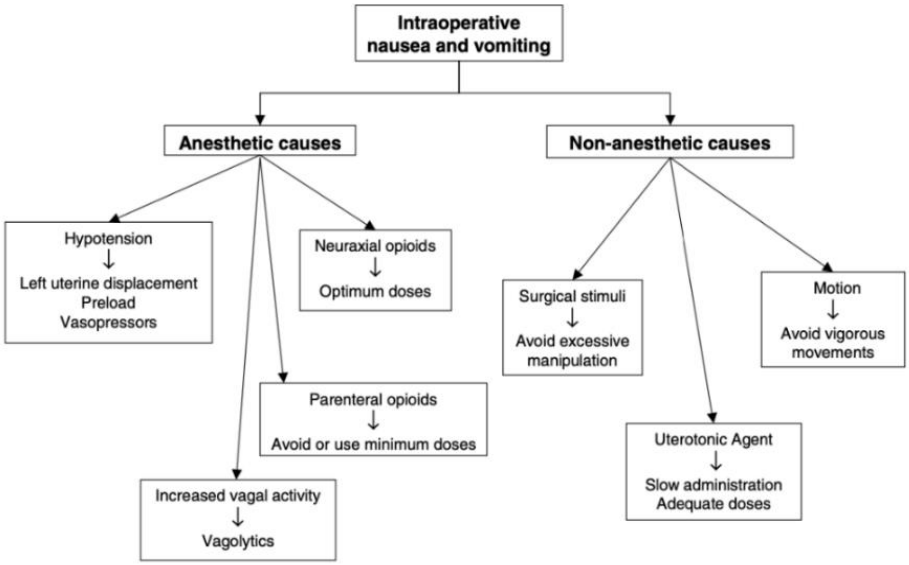


**Figure 6.** Causative factors and IONV management for cesarean section surgery with regional anesthesia[61]

IONV management appropriate to the triggers as previously stated, is likely to offer superior prophylaxis for IONV in the context of cesarean section.

The use of antiemetic agents in IONV management during cesarean surgery is still not clearly proven. According to Semiz et al. routine prophylactic antiemetic administration for cesarean section surgery with regional anesthesia is not indicated.[61] Rescue antiemetic drugs should be available for treating patients where multimodal approaches for IONV prevention have failed. The use of these drugs should be consistent with safety for mother and baby. Metoclopramide has become the most widely used intraoperative drug[62] and therefore should be offered as first-line treatment. Dimenhydrinate can be used as second-line treatment as it has been safely used in hyperemesis gravidarum management.[63] Ondansetron or granisetron should be the last choice, due to limited data on the use of these drugs during pregnancy.[64]

## CASE REPORT

### PREOPERATIVE

**Patient Identity**

Name: Mrs. I
Age: 31 years
Medical Record No.: 12985xxx
Room: Merpati
Admission Date: 05/09/2023

**Anamnesis**

Current Medical History:

1. January: Patient experienced delayed menstruation, patient checked pregnancy herself with positive results. Patient had control check-up at Prima Husada Hospital with Dr. Amik Yuliati, Sp.O.G, ultrasound examination performed (results not provided) and blood pressure ranged 110-120/70-80 mmHg. Pregnancy was said to be good and pregnancy vitamins were given.

2. February - July 2023: Patient had pregnancy control at Prima Husada Hospital with Dr. Amik Yuliati, Sp.OG twice, Dr. Istanti Siti Rahmawati, Sp.OG three times, ultrasound examinations performed and blood pressure ranged between 110-120/70-80 mmHg. Because the patient has a history of congenital heart disease (Aortic Stenosis), patient was referred to RSDS for further examination.

3. August 2, 2023: Patient's first pregnancy check-up at RSDS Pregnancy Clinic Currently no major congenital abnormalities found.

4. September 1, 2023: Patient returned for pregnancy control, no complaints, good fetal movement. Patient arrived at RSDS emergency room, complaining of reduced shortness of breath.

*Conclusion*

a. True-Severe Aortic Stenosis, Low Flow, High Gradient, Normal EF
b. Mild Aortic Regurgitation
c. Recommendation: -

*Cardiology Consultation Results 23-08-2023*

A: True severe AS without signs of acute heart failure, Gravida GIIP0101 GA 34/35 weeks

P:

a. Furosemide 1x40mg as needed for shortness of breath
b. Routine cardiology clinic control

*Discussion with Cardiology Specialist*

a. Patient with Severe AS, we have performed echo
b. Disease worsens pregnancy, with mWHO class IV (severe symptomatic AS). Pregnancy can worsen disease
c. We gave patient Furosemide 1x40mg if short of breath. Abnormality can be corrected with Aortic valve replacement after delivery
d. Patient can become pregnant again after valve abnormality is corrected
e. Pregnancy can be maintained as term as possible, with timing consideration of pregnancy termination according to obgyn specialist
f. Avoid using hormonal contraceptives with estrogen derivatives related to increased thromboembolic risk
g. Patient with mWHO class IV, contraindication to bearing down

*Based on considerations*

a. Severe Aortic Stenosis
b. Patient currently has no signs of acute heart failure
c. Patient with mWHO class IV, contraindication to bearing down

5. September 5, 2023: Patient checked at pregnancy clinic for surgery preparation

*Treatment History:* Lisinopril, urdafalk, lansoprazole

*Delivery History:*

a. 8 months/SC due to Congenital Heart Disease (Aortic Stenosis)/RSDS/Female/2300 grams/4 years ago
b. Current pregnancy

*Past Medical History:* No Diabetes Mellitus, No Hypertension, No Allergies, No Asthma.

6. 2007: Patient experienced left chest pain, then sought

treatment at RSDS Cardiology Clinic and was told Aortic Stenosis. Patient was given bisoprolol 1 x 2.5 mg for 3 months, after that did not consume any medication until now. Patient did not regularly control to Cardiology Clinic because there were no complaints.

**Physical Examination**

Respiratory System: Free airway, spontaneous breathing RR 20-22 times per minute SpO2 98% with room air. Symmetrical vesicular breath sounds, no rhonchi and wheezing.

Cardiovascular System: Warm extremities, Blood Pressure 129/83 mmHg (MAP 98), HR 85 x/minute

Cardiac auscultation examination:

a. Parasternal line ICS 2-3 left: systolic murmur grade 3/6 (maximum heard)
b. Parasternal line ICS 2-3 right: systolic murmur grade 1-2/6
c. Parasternal line ICS 3-4 left: systolic murmur grade 2/6
d. Midaxillary line ICS 3-4: no murmur heard

DASI METS Score: 6.58

Nervous System: Glasgow Coma Score 4-5-6

Urogenital System: Spontaneous urination with frequency 4-5 times, clear colored urine

Abdominal System: Gravid abdomen appropriate for gestational age

Musculoskeletal System: No extremity edema, temperature 36.7°C

Obstetric Status:

a. Fundal Height 28 cm, Presentation: Head
b. Fetal Heart Rate 148 x/minute, Contractions: none

**Supporting Examinations**

Laboratory 1/9/2023:

a. Hb 11.0/HCT 33.4/WBC 9,660/PLT 195,000
b. PPT/APTT 13.2/28.9
c. HBsAg NR
d. SGOT/SGPT 18/9
e. BUN/Creatinine 4.4/0.7
f. Na/K/Cl 136/3.5/109.0
g. Albumin 3.5
h. Random Blood Sugar 148
i. COVID PCR Swab: Negative

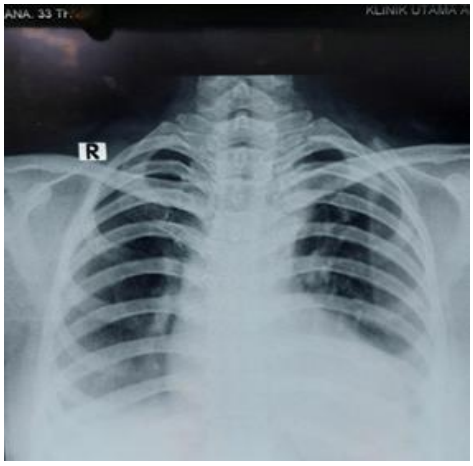


**Figure 7.** CXR results dated August 23, 2023Lungs: no abnormalities, Heart: cardiomegaly CTR 57%

**Diagnosis and Plan**

GII P0101 36/37 weeks, THIU, Cephalic Presentation, Severe Aortic Stenosis (without signs of acute heart failure), Mild Aortic Regurgitation, Trivial Tricuspid Regurgitation, Trivial Mitral Regurgitation, Concentric LVH, BSC, Estimated Fetal Weight 2350 g

Procedure: Caesarean Section (SC)

Assessment: ASA Physical Status 3

a. Severe aortic stenosis, mild AR
b. Gravida

Anesthesia Plan: Regional Anesthesia SAB Marcaine 7.5mg and fentanyl 50mcg

**Intraoperative**

Patient arrived in the operating room, premedication with Midazolam 2 mg IV was given, monitors were attached and positioned laterally, while SAB was performed, ABP was inserted and connected to mostcare. When SAB was given, Marcaine 7.5mg 0.5% and Fentanyl 50mcg were administered.

Results:

Caesarean section / Male / 2650 g / 48 cm / Apgar score 8–9

Gestational age: 36 weeks

Fetal size: p50–75

Clear amniotic fluid

Baby breathing spontaneously

Operation duration: 2 hours (Sign-in at 11:00–13:00)

Input: Crystalloid (RL 400cc)

Output:

a. Blood loss: 300 cc
b. Urine: 100cc

**Postoperative**

Patient arrived in the recovery room at 13:30 with good conscious condition.

Condition in RR:

a. Respiratory System: Free airway, spontaneous breathing. Respiratory rate 20 times per minute. Oxygen saturation 99% with room air. No rhonchi and wheezing.
b. Cardiovascular System: Warm extremities, Blood Pressure 131/79 mmHg (MAP 92), HR 76 x/minute

Cardiac auscultation examination:

a. Parasternal line ICS 2-3 left: systolic murmur grade 3/6 (maximum heard)
b. Parasternal line ICS 2-3 right: systolic murmur grade 1-2/6
c. Parasternal line ICS 3-4 left: systolic murmur grade 2/6
d. Midaxillary line ICS 3-4: no murmur heard

Neurological System: Glasgow Coma Scale 4-5-6

Urogenital System: Urination via catheter, urine production 100 cc during 2-hour operation, yellow colored.

Gastrointestinal System: Post-operative abdomen, good uterine contraction, no active bleeding, surgical wound not oozing.

Musculoskeletal System: No edema, temperature 36.8 degrees

Postoperative Orders:

a. RL infusion 500 cc plus 20 units oxytocin in 24 hours
b. Fasting until fully conscious, start eating and drinking gradually 3 hours postoperatively
c. Chewing gum 2 hours postoperatively
d. If nausea and vomiting occur, turn head to side and report to on-call doctor
e. Monitor vital signs every 15 minutes
f. Paracetamol infusion 1gr every 8 hours for 2 days
g. Metoclopramide injection 10mg every 8 hours if nausea and vomiting occur for 1 day

Patient returned to the ward at 16:00, during recovery room stay patient did not complain of pain, nausea, or vomiting. The next day, patient did not complain of pain, nausea, or vomiting. Patient was planned for discharge the following morning.

## CONCLUSION

Fundamentally, the selection of anesthetic techniques and doses for caesarean section in pregnancy with severe aortic stenosis depends heavily on patient hemodynamics. Low-dose SAB selection produces fairly stable hemodynamics, with adequate fasting treatment 2 hours preoperatively given sugar water drink, resulting in calm patient during surgery, no complaints of nausea and vomiting or hemodynamic fluctuations. Postoperative chewing gum is useful for training intestinal peristalsis to prevent paralysis. Patients can also return home quickly and meet family quickly using the ERACS method.

## DECLARATIONS

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable.

**Competing interests**

There are no conflicts of interest to report.

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