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Postoperative Nausea and Vomiting in Regional Anesthesia

A Review

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ANESTHESIA has become remarkably safe, and while death and permanent damage have become rare occurrences, other sequelae of anesthesia are gaining more importance. Postoperative nausea and vomiting (PONV) still is the most troublesome adverse event encountered in the recovery room, despite advances in prevention and treatment.[1] The incidence of PONV has remained high and has a major negative impact on patient satisfaction about the overall surgical experience.[2] Furthermore, the ongoing trend toward ambulatory procedures has increased the focus on PONV as its occurrence may delay discharge[3] or cause unanticipated hospital admission.[4]

General anesthesia has long been considered as causing a greater frequency and severity of PONV than regional anesthetic techniques. Recent studies investigating this time-honored dictum in a controlled manner mostly, but not unanimously, confirmed it.[5–8] Accordingly, considerable effort has been invested to examine etiology, define patients at risk, and outline preventive and therapeutic strategies in patients undergoing general anesthesia. Reviews dealing with PONV have discussed almost exclusively general anesthesia and largely ignored regional anesthesia.[9,10] This contrasts with the increasing popularity of regional anesthesia. A survey in Europe showed that one third of patients are undergoing regional anesthesia for their operative procedure.[11] In France, the proportion of regional anesthesia increased from 15 to 25% of all anesthetics administered from 1980 to 1996.[12]

The number of local anesthetic and analgesic agents available for regional anesthesia has increased over the last two decades. Since the introduction of intrathecal and epidural morphine in 1979, a multitude of medications, such as synthetic opioids, α_2-agonists, and cholinesterase inhibitors, have been introduced in an attempt to enhance the action of local anesthetics. The decision about their usefulness will not only rely on their effects on nerve blockade and pain relief, but also on their influence on side effects such as PONV.

This review focuses on PONV in the setting of perioperative regional anesthesia. General aspects of PONV, such as physiology, patient, and perioperative factors involved are discussed. Few studies regarding these issues have been specifically devoted to regional anesthesia. Therefore, much information must be derived from investigations of general anesthesia. Specific regional anesthetic techniques and the influence of adjunctive medications on PONV are also presented. Combined general–regional anesthesia is purposefully excluded, avoiding the many variables introduced by general anesthesia. A final section is devoted to continuous peripheral nerve blocks and their possible impact on PONV.

General Aspects of Postoperative Nausea and Vomiting

The Relevance of Postoperative Nausea and Vomiting

Patients often express fear about PONV when questioned before surgery. Its importance compared with other possible postoperative sequelae varies but is generally high.[13] When questioned about issues of concern, 22% of 800 patients gave PONV the highest level of concern, compared with 34% for postoperative pain and 24% for waking up during surgery.[14]

The Difficulty of Studying Postoperative Nausea and Vomiting

The investigation of PONV has not proved to be an easy task. Outlines for adequate methodology have been published,[15] but several aspects make generalization or comparison of results difficult.

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There is a wide array of patient, anesthetic, and surgical factors that influence incidence and severity of PONV.[9–10] Methods of determining whether a patient suffers PONV vary. Patients may be asked repeatedly about nausea, or only complaints offered spontaneously may be registered. The occurrence of vomiting may be known from patient interrogation or derived from nurses' notes, which have been shown to underreport emesis events by 50%.[16] Some studies distinguish between nausea, retching, and vomiting, whereas others use a single term. The incidence may refer to the number of patients experiencing PONV or the number of events. The severity is either not differentiated or reported in categories (mild–severe), in visual analog scale scores or elaborate nausea scores, or implied by the need for antiemetic medications. Another source of confusion is the observation time. Intraoperative nausea and vomiting and PONV are sometimes not reported separately. The postoperative recording may end with the discharge of the patient from the postanesthetic care unit, the first analgesic administration after a regional anesthetic, or the passing of anywhere between 12 and 72 h after a defined "time zero."

Few studies are specifically designed to investigate PONV associated with regional anesthesia. Usually the main observation is centered on factors describing the block, such as intensity or duration. PONV, if reported at all, is only a secondary endpoint. This implies that the number of patients studied is tailored to the need to show statistical significance regarding the primary endpoint. When such studies report no difference in PONV rates between groups, the risk of a type II error should be kept in mind.[17] One way to satisfy the need for high patient numbers is to conduct a multicenter study. But despite using strict protocols, marked variations in the rate of PONV across hospitals were found, which were not explained by the case mix of patients.[16] Equally striking are the differences in results among countries reported in multinational investigations.[18] Metaanalysis as another means to achieve larger numbers of patients is not only hampered by differences in study designs, but also by the high rate of double-reporting patients, estimated to occur up to 25% in some PONV studies.[19] The same problem may also occur in a review article.[20].

Mechanisms of Postoperative Nausea and Vomiting in Regional Anesthesia

Several different mechanisms may play a role in causing PONV in patients who receive regional anesthesia. In a retrospective analysis, Crocker and Vandam[21] found that hypotension (systolic blood pressure < 80 mmHg), a block higher than the fifth thoracic segment, and the anesthetic mixture (*e.g.*, addition of vasoconstrictors to the local anesthetic) increased the incidence of nausea and vomiting during spinal anesthesia. The prospective work of Carpenter *et al.*[22] in a similar setting confirmed these findings. It appears that not one single mechanism is responsible for causing PONV. Several mechanisms may be active simultaneously, and the importance of each in a particular case may remain speculative.

Nausea and vomiting are not among the cardinal signs and symptoms of toxicity of the currently used local anesthetics when infused systemically, although they may occur in the context of general cerebral toxicity.[23] Consequently, they are usually not considered as emetogenic.

The addition of other medications to local anesthetics for regional anesthesia has become increasingly popular. When administered intrathecally, hydrophilic substances (*e.g.*, morphine) tend to remain in the cerebrospinal fluid for prolonged periods of time and can move rostrally by diffusion or bulk movements of cerebrospinal fluid, reaching the area of the chemoreceptive trigger zone. Morphine concentrations in the medulla oblongata reach significant levels within 5–6 h, as evidenced by the onset of trigeminal analgesia.[24] This time coincides with the peak time of nausea observed after spinal administration of morphine.[25] Lipophilic opioids are taken up quickly into the spinal cord. Nonetheless, about 10% of a dose of fentanyl administered in the lumbal intrathecal space can be recovered in the cervical cerebrospinal fluid as early as 30 min after injection, demonstrating rapid ascension.[26] Baricity of the solutions will influence drug kinetics in the cerebrospinal fluid. In fact, hyperbaric neostigmine was shown to cause lower PONV rates than an isobaric formulation, an effect attributed to decreased rostral spread.[27]

Epidural administration of drugs leads to rapid vascular uptake that provides access to the chemoreceptive trigger zone *via* the bloodstream. Peak plasma concentrations may be achieved within 5–15 min,[28] and systemic concentrations often approach those obtained after a similar intramuscular dose.

In the case of peripheral perineural administration, adjuvant drugs are absorbed into the systemic circulation, thereby reaching the chemoreceptive trigger zone. Centripetal intraneural transport of substances like opioids has been documented,[29] but this mechanism is considered insignificant in drug distribution.[30] Femoral perineural application or intramuscular administration of morphine leads to the same low morphine concentrations in cerebrospinal fluid.[31]

Hypotension is a common occurrence during neuraxial anesthesia. Low blood pressure may lead to brain stem ischemia, which is thought to activate the circulatory, respiratory, and vomiting centers grouped together in the medulla.[32] Consequently, supplemental oxygen can relieve nausea in such circumstances.[33] Other investigators have speculated that hypotension rather leads to gut ischemia and the release of emetogenic substances (*e.g.*, serotonin) from the intestines.[34] These different hypotheses linking hypotension and PONV still need to be clarified and the mechanism linking hypotension to nau-

sea and vomiting defined.[32,35] Strategies avoiding hypotension were shown to be effective in reducing emesis.[36,37] Many of these investigations were limited to patients undergoing cesarean section, and most used ephedrine as a pressor agent, which is suspected to possess antiemetic activity unrelated to its hemodynamic action.[38]

Neuraxial anesthesia also changes the function of the gastrointestinal tract.[39] Sympathetic blockade by local anesthetics creates unopposed vagal action, resulting in gastrointestinal hyperactivity. The efficacy of vagolytic agents to relieve nausea during spinal anesthesia has been taken as evidence of the importance of this mechanism.[33]

Patient Factors

Considerable effort has been invested to identify patients at increased risk of PONV. These studies often involve the use of elaborate statistics, and they vary in patient characteristics as well as surgical and anesthetic case mix.[16,22,40,41] Unfortunately, because most do not analyze a regional anesthesia group separately, there is little information available on the influence of specific patient risk factors on PONV in the context of regional anesthesia.

Age. Younger age was shown to be a risk factor for PONV in the studies by Apfel *et al.*,[40] Sinclair *et al.*,[41] and Cohen *et al.*[16] No significant correlation, however, was found by Larsson *et al.*[42] or Koivuranta *et al.*[43] Quinn *et al.*[44] reported results of 3,850 inpatients and analyzed separately the 606 patients undergoing regional anesthesia. Younger age was significantly associated with nausea or vomiting in both general and regional anesthesia groups. Standl *et al.*[8] interviewed 217 patients 4 days after spinal anesthesia for lower extremity orthopedic surgery. Patients younger than 20 yr complained most often of PONV (20%), while only 4% of patients between 40 and 60 yr of age did so. For patients older than 60 yr, the risk increased again to 9%. This increase at older age was also observed by Kalso[45] in 50 cases of spinal anesthesia for orthopedic surgery, but older patients had more complex surgeries and more hypotensive episodes.

In conclusion, the role of age remains unclear in view of these results in general as well as mixed and regional anesthetic groups. It might be safe to speculate, therefore, that any influence of age on PONV that exists in regional anesthesia patients may be limited, but the impact of the wake state—stress—needs to be clarified. Finally, awake patients would be more likely to respond to certain medications (*e.g.*, opioids) with nausea and vomiting.

Gender. There is more consistency regarding the influence of gender. Female patients were found to be at significantly higher risk of PONV in the studies of Apfel *et al.*,[40] Cohen *et al.*,[16] Sinclair *et al.*,[41] Larsson *et al.*,[42] and Koivuranta *et al.*[43] The latter also specified this relation for their regional anesthetic group, where they found PONV rates of 48% for females and 26% for males. The same results were found by Quinn *et al.*[44] In the regional anesthesia group, they reported postoperative nausea in 28% of women and 14% of men, and vomiting in 17% and 7%, respectively.[44] A relation of nausea and vomiting to the menstrual cycle was pointed out in an investigation of 68 women with epidural anesthesia for lower extremity surgery, with the peak incidence during days 25 to the end of cycle.[46] These studies indicate that female gender is a significant risk factor for PONV in patients receiving general and regional anesthesia, while the influence of the menstrual cycle needs further study.

Other factors, such as previous history of PONV or motion sickness, smoker–nonsmoker status, or obesity have not been sufficiently investigated in patients undergoing regional anesthesia.

To summarize, patient factors linked to increased risks of PONV in patient undergoing general anesthesia need to be further clarified those undergoing in regional anesthesia.

Systemic Anesthetic Factors

Premedication. The role of premedication in regional anesthesia remains largely uninvestigated, and there is no information that any difference exists as compared with general anesthesia. Therefore, no conclusion can be drawn from the various premedication given, with the exception that opioids remain a risk.

Intraoperative Sedation. In addition to premedication, many patients receive intraoperative sedation to supplement regional anesthesia, to improve patient acceptability and comfort, and to reduce stress and anxiety. A wide variation exists in the frequency of use of sedation and the agents administered.[47] While clonidine is considered not to influence the incidence of PONV,[48] methohexital,[49] γ-hydroxybutyrate,[50] or etomidate[51] have shown to cause significantly more nausea and vomiting compared with midazolam or propofol sedation, respectively. From these data, it is evident that the decision to administer adjunctive sedation must be followed by a careful evaluation of what agents to use, as the consequences of PONV might well be significant. The sedatives most often given to supplement regional anesthesia are midazolam and propofol. Both drugs may have a positive impact on PONV. Midazolam has been shown to be as effective as droperidol in preventing PONV after strabismus surgery in outpatient children.[52] The same group found similar results after tonsillectomy in children.[53] Propofol has been claimed to possess antiemetic effects at sedative doses,[54] but these results were not confirmed by Lacroix *et al.*[55] However, it is accepted that propofol should be part of the intraoperative management in a patient with PONV.[56] The mechanism of action of any antiemetic effect of propofol has not been elucidated,

but Cechetto *et al.*[57] recently showed that propofol decreases the concentration of both serotonin and 5-hydroxyindoleacetic acid within the central nervous system of the fourth ventricle at the level of the area postrema. Although the positive effects of either midazolam or propofol on PONV has not been specifically studied in the context of regional anesthesia, these two drugs appear most appropriate to supplement a central or peripheral block. Propofol has the advantage of having better pharmacokinetic properties,[58] making its titration easier than midazolam or other sedatives.[59]

Hydration. Another factor that has been implicated in negative postoperative outcome is dehydration. The administration of extra fluid is standard practice, especially in neuraxial techniques, and the amount is usually titrated to blood pressure. Correspondingly, Carpenter *et al.*[22] found no correlation between intraoperative amount of fluid administration and intraoperative nausea as long as no hypotension occurred during spinal anesthesia. Fluid administration for the purpose of blood pressure stabilization is rarely an issue in peripheral nerve blocks, but data regarding the impact of different regimens of hydration regimens on PONV are not available.

Postoperative Factors

Pain. The possible influence of postoperative pain management on PONV remains incompletely understood. While there is no doubt that opioid administration can provoke nausea, opioid analgesia relieved PONV in 80% of patients who experienced both pain and PONV concomitantly in the study by Andersen *et al.*[60] Some investigators used analgesic regimens with nonopioid adjunctive medications. Opioid consumption was thereby reduced, but PONV rates did[61,62] or did not[63,64] diminish. Opioid reduction was[65,66] or was not[67,68] followed by reduced PONV rates during use of regional techniques. Opioid-free intraoperative and postoperative regimens are rare, but could provide insight into the complex issue of pain, pain medication, and PONV. Callesen *et al.*[69] compared three groups of patients undergoing hysterectomy receiving either opioid-free epidural–spinal anesthesia, general anesthesia with continuous epidural bupivacaine, or continuous epidural bupivacaine and morphine, respectively. Despite poorer pain control, patients in the opioid-free group experienced significantly less PONV in the postoperative period. Similar findings were published by Wajima *et al.*[70] In a series of investigations in patients undergoing arm surgery with brachial plexus anesthesia continued postoperatively by catheter infusion, the investigators observed that complete omission of opioids led to the lowest incidence of PONV despite more frequent need for nonopioid rescue pain medication, while the route of administration of opioids (systemically or by brachial plexus catheter) did not matter. Such findings would, contrary to the conclusions of Andersen *et al.*,[60] lend support to the statement that it is opioid-based pain management rather than pain itself that provokes PONV. In this context, the application of continuous regional anesthesia and the subsequent opioid-sparing effect is most likely beneficial in reducing the incidence of PONV.

The impact of other factors such as movement on PONV and oral intake have not yet been investigated in patients undergoing regional anesthesia.

To summarize, operative and postoperative factors that have been identified as risk factors for PONV after general anesthesia have not been thoroughly investigated in the context of regional anesthesia and cannot be automatically extrapolated from one technique to the other. Further studies are warranted to specify the impact of these factors on PONV in the context of regional anesthesia.

Specific Regional Anesthetic Techniques and Postoperative Nausea and Vomiting

It is clear that PONV is a complex, multifactorial problem. To design and complete a study with sufficient size, controlling for all factors influencing PONV, represents a monumental task. Furthermore, the published studies differ in design in a way that makes comparison often difficult or impossible.[71] Heterogeneity is a recognized weakness of systematic reviews and metaanalysis and may therefore weaken the impact of the results, particularly when dealing with regional anesthesia and PONV, since the latter has rarely been a primary endpoint.

Spinal Anesthesia. The reported incidence of PONV associated with spinal anesthesia varies widely.[22,72,73] Carpenter *et al.*[22] studied 952 patients undergoing all types of procedures. They found an intraoperative rate of nausea of 18% and vomiting of 7%, but it must be noted that 12% of their patients received additional inhalational anesthesia. Older prospective studies reported postoperative retching and vomiting in 11.1%[74] or nausea and vomiting in 21.1%[75] of patients after spinal anesthesia. Perioperative rates of 0–21% have been noted in patients younger than 21 yr.[76,77] Comparatively high rates have been repeatedly observed in the context of major orthopedic (*i.e.*, joint replacement) surgery and cesarean section.

Choice of Local Anesthetics. Clinical experience would indicate that the choice of local anesthetic used for intrathecal injection does not influence PONV. Most investigations found no difference when comparing local anesthetics, but the number of patients involved was usually small.[78,79] However, the 78 patients receiving procaine in the study by Carpenter *et al.*[22] suffered significantly more nausea and vomiting than those given other local anesthetics despite similar degrees of hypotension. The investigators could not explain this finding. A more recent study by Hodgson *et al.*[80] comparing

lidocaine to procaine for ambulatory surgery confirmed this result as the incidence of PONV did not differ between groups. It therefore appears that the agent used is of little importance.

Similarly, the dose of drug does not seem to influence the occurrence of PONV, as long as hypotension is avoided. Sheskey *et al.*[81] administered bupivacaine in doses of 10, 15, or 20 mg to 60 patients undergoing transurethral resection of the prostate, with no difference in nausea between groups, while hypotension was treated with vasopressors. Povey *et al.*[82] reported no case of nausea or vomiting in 30 patients given either 25 or 30 mg bupivacaine, resulting in a mean sensory block height of T4 and T3, respectively, when blood pressure was maintained with ephedrine. Similarly, there was no difference in emetic sequelae following 60 *versus* 80 mg of mepivacaine.[83] The influence of the baricity of the solutions has not been investigated in the context of PONV, but one has to remember that hyperbaric solutions usually have a greater spread.

Intrathecal Epinephrine. The addition of epinephrine to local anesthetics caused more nausea and vomiting in the patients studied by Carpenter *et al.*[22] This occurred despite no difference in the rate of hypotension. This result would corroborate the finding of a retrospective analysis from 1959, in which Crocker and Vandam[21] also associated intraoperative emesis with the use of epinephrine, but the investigators attributed the effect to a higher level of block. More recently, the combined use of procaine and epinephrine resulted in significantly more PONV in 60 patients undergoing short procedures when compared with procaine alone (30 *vs.* 10%).[72] Block heights did not differ between groups, but patients administered epinephrine required more vasopressors.

Other, mostly small investigations comparing various subarachnoid solutions with or without epinephrine in different settings have found higher PONV rates in patients receiving epinephrine[84,85] or no difference.[86–89] These data indicate that epinephrine may be a significant factor in PONV. The mechanism of the action in the absence of hemodynamic or block height differences remains unclear, but systemic epinephrine has been linked to increased serotonin release[34] as well as to effects on the chemoreceptive trigger zone mediated by α-adrenergic receptors.[90]

Intrathecal Morphine. Intrathecal morphine causes a dose-dependent increase in vomiting in volunteers.[91] However, when dealing with patients undergoing painful surgery, the picture becomes less clear. Several dose-finding studies investigated the efficacy and side effects of intrathecal morphine. Kalso[45] found, over 48 h, a slight but not statistically significant difference in nausea or vomiting after adding 0, 0.2, or 0.4 mg morphine to bupivacaine for orthopedic surgery (40 *vs.* 50 *vs.* 55%, respectively). Jacobson *et al.*[92] reported PONV rates of 60 *versus* 50 *versus* 100% after 0, 0.3, and 1 mg morphine, respectively, used in joint replacement surgery. In a study involving 181 patients scheduled for transabdominal hysterectomy with tetracaine spinal anesthesia, patients receiving 0.1 mg morphine had significantly more emetic sequelae than those administered doses between 0.03 and 0.08 mg.[93] Weber *et al.*[94] conducted a large investigation involving 300 patients undergoing major orthopedic surgery of the lower extremities, comparing bupivacaine to bupivacaine with 0.2 mg morphine. There was no statistically significant difference between groups with regard to subjective feeling or consumption of antiemetics (60 *vs.* 56.6%). These data suggest that, at least in more extensive surgery where effective postoperative pain relief is warranted, intrathecal morphine is not associated with higher PONV rates than opioid-based systemic analgesia, especially if a dose of less than 0.1 mg is chosen. Use in minor surgical procedures has not been well studied, but reports about significantly higher PONV incidence after 0.2–1.0 mg intrathecal morphine for transurethral resection of the prostate compared with a morphine-free solution should produce caution.[95,96]

Similarly, early studies dampened the enthusiasm for subarachnoid morphine to ease labor pain secondary to nausea and vomiting rates consistently exceeding 50%, although morphine doses were usually high (0.5–2 mg).[97,98] A reduced dose of 0.25 mg also caused significantly more nausea and vomiting than a morphine-free epidural regimen when 59 parturients were studied by Caldwell *et al.*[99] In a recent investigation in 95 women, however, Yeh *et al.*[100] compared a fentanyl–bupivacaine solution with or without 0.15 mg morphine and found no difference in nausea or vomiting.

When morphine was added to local anesthetics to provide spinal anesthesia for cesarean section, an increase of nausea or vomiting was observed postoperatively but not intraoperatively.[89,101,102] This is in accordance with an investigation showing the peak incidence of nausea and vomiting between 4 and 6 h after completion of surgery when intrathecal morphine was administered.[25] Furthermore, the PONV rates were higher after larger doses (0.2 or 0.25 mg) of morphine were administered compared with 0.1 mg.[103,104] Using even smaller amounts, Cardoso *et al.*[105] showed a trend toward lower emetic sequelae with smaller doses of 0.05 and 0.025 mg *versus* 0.1 mg morphine in a study involving 120 term parturients. A metaanalysis confirmed a dose-dependent increase in PONV when morphine is used.[106]

Intrathecal Fentanyl. The highly lipophilic synthetic opioids, fentanyl and sufentanil, produce intense but shorter-lasting analgesia than morphine when applied intrathecally. The administration of intrathecal fentanyl to volunteers by Liu *et al.*[107] did not provoke nausea. Studies comparing varied doses of intrathecal fentanyl with opioid-free solutions in patients undergoing lower

extremity revascularization procedures[108] found no difference in PONV incidence among groups. Several studies showed rather low rates of vomiting in the immediate perioperative period in patients receiving intrathecal fentanyl *versus* control patients, although the sample sizes were notoriously small.[109,110] Michaloudis *et al.*[111] administered a spinal anesthetic to 48 patients (American Society of Anesthesiologists status II–IV) undergoing various surgical procedures and continued a bupivacaine–fentanyl mixture *via* the intrathecal route for 5 days postoperatively, and none of their patients complained of nausea or vomiting. This contrasts with the 30% PONV rate reported by Niemi *et al.*[112] after 24 h of intrathecal fentanyl infusion, but almost all of their patients received additional intramuscular morphine.

Two dose-finding studies evaluated the use of intrathecal fentanyl for treatment of labor pain. While Herman *et al.*[113] reported not a single occurrence of nausea and vomiting in 90 parturients administered up to 25 μg fentanyl, Palmer *et al.*[114] gave up to 45 μg in 84 women and stated that this side effect was "uncommon in all groups, occurring too infrequently for any meaningful comparisons to be made."

Earlier studies in patients undergoing cesarean section have also shown that intrathecal fentanyl led to no greater frequency of nausea or vomiting than when local anesthetics alone were used,[84,115,116] a finding confirmed by metaanalysis.[106] Several investigators found lower rates of nausea or vomiting during surgery when using intrathecal fentanyl,[117,118] and 20 μg added to bupivacaine recently proved more effective than 4 mg ondansetron given immediately after spinal placement.[119] This beneficial effect of fentanyl was ascribed to improved control of visceral pain during surgery.

Intrathecal Sufentanil. The intrathecal injection of sufentanil has led to emetic sequelae in volunteers.[120,121] A dose-finding study in patients scheduled for extracorporeal shock wave lithotripsy found no increase in PONV at the highest dose of 20 μg, but the fact that patients administered lower doses required significantly more propofol because of inadequate analgesia might have confounded the results.[122] The comparison of sufentanil to lidocaine in a similar setting[123] showed no increase in nausea or vomiting in patients receiving sufentanil. Similarly, the direct comparison of sufentanil *versus* fentanyl in 42 patients after hip surgery revealed a similar incidence of PONV.[124]

Sufentanil has gained widespread popularity for intrathecal use in the treatment of labor pain. Many small investigations evaluated different doses from 0 to 10 μg sufentanil, mostly finding overall low figures for nausea and vomiting with no dose relation.[125–127] A recently published study in 170 women reported significantly higher rates of both nausea and vomiting, however, when a dose of 10 μg sufentanil was compared with the control group (24 *vs.* 3% for nausea and 15 *vs.* 0% for vomiting), but most nausea was rated as mild.[128] When compared with fentanyl, no difference in PONV was found with sufentanil.[129,130]

Little information has been published regarding sufentanil use during cesarean section. Dahlgren *et al.*[131] administered 2.5 or 5 μg sufentanil with bupivacaine and found significantly less intraoperative vomiting compared with the placebo group. There was no difference compared with the group that received fentanyl (10 μg) intrathecally, confirming results of an earlier report by Pan *et al.*[132]

Meperidine as an Intrathecal Agent. Meperidine possesses local anesthetic as well as opioid properties.[133] It can therefore be administered alone or in combination with local anesthetics to provide operative spinal anesthesia. Some studies have shown no difference in vomiting or PONV when meperidine was compared with local anesthetic agents,[134,135] but several investigators noted higher rates after meperidine use, especially during the intraoperative phase.[136]

This side effect has also been observed when meperidine was used in laboring women. Honet *et al.*[130] registered significantly higher nausea scores with meperidine compared with fentanyl or sufentanil, similar to an earlier investigation.[137] Recently, a study designed to compare fentanyl–bupivacaine with meperidine was terminated early because of significantly more nausea and vomiting in the meperidine group.[138]

For cesarean section, meperidine has not gained great interest, especially because the duration of anesthesia is often inadequate. PONV rates of 29% and 32% have been reported after its use, but controlled studies are absent.[139,140]

Overall evidence points out that, although all intrathecal opioids have the potential to increase the risk of PONV, they are not "created equal" in their tendency to do so. Meperidine appears to be the most harmful. Morphine, especially at higher doses, follows next. The lipophilic opioids, fentanyl and sufentanil, seem to carry the lowest risk.

Intrathecal Clonidine. The addition of clonidine to intrathecal solutions to prolong the action of local anesthetics results in no increase in PONV. There is no evidence after multiple studies, often involving patients undergoing orthopedic surgery, that the risk of PONV increases after addition of clonidine to various local anesthetics or opioids.[141–143]

Similarly, a dose–response study in laboring patients in which clonidine was given as a single agent in a dose up to 200 μg showed no nausea or vomiting as a side effect.[144] Also, the addition of clonidine to sufentanil,[145] sufentanil–bupivacaine,[146] or fentanyl–bupivacaine[147] did not result in a significant change in the incidence of PONV in this setting.

Clonidine administered with local anesthetics for cesarean section equally lacks emetic side effects. In con-

Table 1. Pure Local Anesthetic Epidural Blockade and PONV

Study	Patients, n	Type of Surgery	PONV, %	Comments
Jorgensen[158]	371	General	20	Vomiting in 14%
Brockway *et al.*[159]	120	General	14	Vomiting in 2%
Morrison *et al.*[160]	91	Hernia, varices	11	Vomiting in 2%
Wood and Rubin[161]	44	Abdominal gynecologic	9	
Finucane *et al.*[162]	116	Abdominal hysterectomy	68	Vomiting in 26%, 28% also general anesthesia
Wolff *et al.*[163]	126	Orthopedic	8	
Niesel *et al.*[164]	44	Orthopedic	18	
Bjornestad *et al.*[165]	122	Cesarean section	18	Intraoperative, postoperative 4%
Bader *et al.*[166]	63	Cesarean section	40	Vomiting in 10%

PONV = postoperative nausea and vomiting.

trast, Pan *et al.*[148] documented significantly higher rates of nausea and vomiting when 150 μg of clonidine was added to bupivacaine (30 *vs.* 10%), but this may have been because of an increased incidence of hypotension in the clonidine group (70% *vs.* 40%). It seems that the potential of clonidine to influence PONV may not be related to the drug itself, but to the balance between hypotensive and sedative effects.

Intrathecal Neostigmine. Neostigmine has recently been investigated as an adjuvant medication for spinal anesthesia. In volunteer studies, a dose-dependent increase in nausea and vomiting was observed after neostigmine administered either alone[27] or in combination with a local anesthetic.[149] This emetogenic effect of spinal neostigmine also became evident in patient studies. In a dose-finding study, 92 women undergoing vaginal hysterectomy were given a bupivacaine spinal anesthetic with neostigmine (0–75 μg). Even the 25-μg group required significantly more treatment for nausea in the recovery room than patients given bupivacaine alone (54 *vs.* 29%), while significantly higher nausea scores were documented in the 75-μg group.[150] Other investigations confirm the high frequency of this side effect.[151,152] An additional problem seems to be the poor efficacy of antiemetics in neostigmine-induced nausea and vomiting.[153,154]

Little information exists regarding use of neostigmine for labor analgesia. Nelson *et al.*[155] reported severe nausea and vomiting after 20 μg neostigmine but observed no significant difference when comparing 9 μg sufentanil with 6 μg sufentanil plus 10 μg neostigmine.[155] However, Owen *et al.*[147] found a significantly higher rate of nausea when neostigmine (10 μg) was added to a bupivacaine–fentanyl–clonidine solution (33 *vs.* 0%).

The same picture emerges when neostigmine is administered as an adjunct in spinal anesthesia for cesarean section. A dose-dependent increase in nausea and vomiting was found in a small dose–response study, with an incidence of 100% after a 100-μg dose of neostigmine.[156] A dose of 50 μg increased the rate from 10% in control patients to 79% in another study.[148] A high rate of severe nausea was found by Chung *et al.*,[157] and even a dose of 10 μg given with bupivacaine led to an increase in the occurrence of nausea requiring treatment from 3% of patients in the control group to 38% in the neostigmine group.[157] Clinical experience demonstrates that the increased incidence of PONV associated with the application of spinal neostigmine outweighs its possible beneficial effect.

Epidural Anesthesia. There is a wide range of PONV incidences reported when epidural anesthesia was administered for surgery (tables 1 and 2).[158–174] The epidural injection of only local anesthetics is associated with a very low risk. Only a single case of nausea was registered when 37 male volunteers were given up to 660 mg ropivacaine or 550 mg bupivacaine.[175] The anesthetic chosen appears to be of little influence, although only controlled trials comparing the closely related local anesthetics ropivacaine and bupivacaine were published recently.[165–166]

Local anesthetics alone are sometimes used for labor pain relief *via* epidural catheter. The incidence of nausea and vomiting reported in this setting varies from less than 10%[176] to more than 50%.[177] The severity is also

Table 2. Effects of Adjunctive Medications on PONV After Epidural Anesthesia

Study	Patients, n	Type of Surgery	Epidural Control	PONV, %	Medication Added	PONV, %	Comments
Lanz *et al.*[167]	139	Orthopedic	Bupivacaine	29	Morphine	35	P = NS
Gürel *et al.*[168]	79	Anorectal	Prilocaine	0	Morphine	2	P = NS
Rucci *et al.*[169]	80	Hernia/prostate	Bupivacaine	10	Fentanyl	17	P = NS
Engel *et al.*[170]	60	Orthopedic	Ropivacaine	<10	Clonidine	<10	P = NS
Laishley *et al.*[171]	80	Cesarean section	Bupivacaine	45	Epinephrine	35	Intraoperative, P = NS
Eisenach *et al.*[172]	30	Cesarean section	Bupivacaine	72	Epinephrine	53	Intraoperative, P = NS
Noble *et al.*[173]	45	Cesarean section	Bupivacaine	33	Fentanyl	30	Intraoperative, P = NS
Vincent *et al.*[174]	60	Cesarean section	Lidocaine	62	Fentanyl	32	Intraoperative, $P < 0.05$

NS = not significant; PONV = postoperative nausea and vomiting.

variable, with reports ranging from low nausea scores[178] to vomiting rates of 52%.[179]

The same variability is described in reports of epidural anesthesia for cesarean section. Overall frequencies of PONV range between 0%[180] and more than 70%.[175] Chestnut *et al.*[181] reported on the repartition of emetic events during the course of anesthetic induction and surgery, with an incidence of nausea of 21% and vomiting of 0% before delivery, 36% and 15% after delivery, and 36% and 36%, respectively, during the first 4 h postoperatively.[181]

Other investigators differed in their findings, either emphasizing the intraoperative predelivery[182] or postdelivery[177] period as the one at highest risk. Possibly, the use of other medications, such as sodium citrate or uterotonic agents, is responsible for at least part of these differences.

Epidural Epinephrine. The epidural injection of epinephrine alone did not cause nausea or vomiting in a study of 15 volunteers.[183] When added to epidural morphine, however, Bromage *et al.*[184] observed "markedly intensified and prolonged" nausea and vomiting in three volunteers, and Collier[185] confirmed this finding by reporting twice the rate of vomiting when epinephrine was combined with epidural morphine in patients undergoing gynecologic surgery. However, this effect could not be duplicated in women undergoing cesarean section.[186] There are many, mostly small, studies conducted in different patient populations where varying epidural solutions were compared with or without epinephrine. The majority did not find a significant difference in PONV whether epinephrine was added or not,[171,173,177,187] although some investigators reported a higher[188,189] or lower[190] incidence with epinephrine admixture. The role of adding epinephrine to epidural local anesthetics is controversial. However, clinical experience suggests avoiding its use whenever possible.

Epidural Morphine. Initially, reports of rates of PONV lower than with intravenous morphine stirred enthusiasm for the epidural administration of morphine.[191] However, in a volunteer study using a crossover design, 10 mg morphine administered epidurally caused nausea in 6 of 10 participants, compared with only 1 case when the same dose was given intravenously.[192] A relation to the morphine dose was suggested in another investigation in volunteers, where 1 of 5 participants experienced nausea after 2 or 4 mg epidural morphine and 5 of 5 participants after a 10-mg dose.[193] In dose–response studies involving patients receiving operative epidural anesthesia, there were no differences in rates of PONV when different morphine doses up to 5 mg were administered.[167,194] Higher doses either did[195] or did not[196] lead to an increased incidence of PONV. Similarly, studies comparing epidural morphine with parenteral opioid analgesic regimens did not show significantly different frequencies of emetic complications, although the reported incidences vary between 10% and more than 50%.[168,197]

The addition of morphine to local anesthetics for epidural labor analgesia was found to have no clinical advantages. In a trial by Lirzin *et al.*,[198] 11 of 85 parturients given local anesthetics alone (13%) complained of nausea, while the incidence increased to 27 of 83 women (33%) when 4 mg morphine was added. Macdonald *et al.*[199] studied 124 parturients given 0, 2, or 4 mg morphine in addition to bupivacaine for vaginal delivery, with vomiting occurring in 5%, 23%, and 28%, respectively.

Morphine administered epidurally for post–cesarean section pain control led to nausea and vomiting in 39.9% of 4,880 patients studied retrospectively by Fuller *et al.*[200] The incidence of PONV after epidural morphine in patients undergoing cesarean section is usually not different when compared with conventional parenteral opioid analgesia.[201] A significant correlation between morphine dose and PONV incidence has not been established.[180,202]

Epidural Fentanyl. The use of lipophilic opioids for operative epidural anesthesia is not very common. Furthermore, recent research questions the advantage of their epidural as compared with systemic administration.[203] Fentanyl injected epidurally in volunteers did provoke nausea in 2 of 12 participants, with no dose-dependent effect observed.[204] In a dose–response trial, Rucci *et al.*[169] studied 80 patients undergoing hernia or prostatic surgery with single-shot epidural anesthesia. Fentanyl (up to 200 μg) was added to bupivacaine, and an overall PONV rate of 15% with no difference between groups was observed. Other investigators equally reported no significant differences regarding PONV when fentanyl was added to local anesthetics for operative epidural anesthesia compared with local anesthetics alone,[205,206] a finding also confirmed by metaanalysis.[207] When compared with morphine, epidural fentanyl use was associated with a significantly lower PONV incidence after orthopedic surgery.[208] It is obviously difficult to compare the quality of analgesia reported in the aforementioned studies, but control of pain—when assessed—was rated by the investigators as good to very good.

The addition of fentanyl to local anesthetics for labor pain relief has no significant consequences regarding nausea or vomiting. Some studies show slightly lower[209] or higher incidences, but the difference usually does not reach statistical significance.

Fentanyl administered epidurally during cesarean section had no influence on nausea and vomiting in many trials.[173,210] However, Vincent *et al.*[174] demonstrated a significant decrease in intraoperative postdelivery nausea and vomiting when 100 μg fentanyl was given after umbilical clamping. On the contrary, Thomas *et al.*[211] found significantly more nausea when the same amount of fentanyl was administered at induction of epidural anesthesia, but this increase was limited to cases of mild

nausea requiring no treatment. The dose of fentanyl injected was not related to the incidence of emetic sequelae when different amounts up to 100 μg were given by Naulty *et al.*[212] or when 25- and 50-μg doses were used by Yee *et al.*[213] Compared with epidural morphine, fentanyl given at induction was followed by significantly less vomiting.[214] Similarly, the use of fentanyl postoperatively reduced the incidence of PONV compared with either local anesthetics alone,[215] epidural morphine,[216] or parenteral morphine.[217]

Epidural Sufentanil. Epidural sufentanil can cause nausea in volunteers to a similar degree than fentanyl, with no clear effect of dosage.[204] Doses of sufentanil up to 50 μg added to epidural lidocaine for knee surgery in 50 patients led to no difference in PONV between groups.[218] Given at the conclusion of surgery in the presence of local anesthetic epidural blockade, the incidence of PONV was similar between groups receiving sufentanil up to 75 μg,[219] although sufentanil had only variable success in reducing PONV compared with epidural morphine in this setting.[220]

Sufentanil used for labor does not lead to increased emetic sequelae. Vertommen *et al.*[176] reported nausea in 4% and vomiting in 4% of 344 parturients given 10 μg sufentanil in addition to bupivacaine, an incidence not different from the one observed in 318 control subjects given bupivacaine alone. Dose-range studies found no relation between PONV and sufentanil dose when up to 30 μg sufentanil was administered.[221] Not surprisingly, there is also no difference in the incidence of PONV when sufentanil is compared with fentanyl as an adjuvant to local anesthetic for epidural labor analgesia.[220]

When sufentanil is administered in the context of cesarean section, there appears to exist no difference in the frequency of PONV as compared with local anesthetics alone.[222] Madej *et al.*[223] observed a significant increase in emetic sequelae, however, when sufentanil doses greater than 20 μg were administered at the onset of anesthesia compared with lower doses or 100 μg fentanyl.[223] This effect could not be observed when different doses of sufentanil were used at the end of surgery for initial postoperative pain control.[224] Compared with intraoperative morphine, the application of sufentanil was followed by significantly less PONV.[214] When given at the end of surgery, however, no difference was observed.[225]

Meperidine as an Epidural Agent. In contrast to spinal anesthesia, epidurally applied meperidine did not increase the incidence of PONV in joint replacement surgery.[208] In parturients, its use was associated with a trend to higher rates of nausea and vomiting.[226] In women undergoing cesarean section, epidural meperidine is not followed by undue nausea and vomiting, although a dose of 100 mg was found to cause more nausea than lower doses.[227] Meperidine also compared favorably with other epidural opioids in this context, resulting in less PONV than morphine use[228] and a similar incidence to fentanyl.[229]

In conclusion, volunteer studies and clinical evidence confirm the potential of epidural opioids to induce nausea and vomiting. Morphine appears to carry the highest risk, while fentanyl or sufentanil have fewer emetic sequelae. Because of little available data, it is difficult to position meperidine in this regard, but it seems to lie closer to the lipophilic opioids than to morphine.

Epidural Clonidine. Epidural clonidine does not provoke nausea or vomiting in volunteers.[183,230] The experience in patients with chronic pain, where clonidine is infused over weeks, also suggests that it is not the cause of such side effects.[231] In a dose-range trial, Engel *et al.*[170] studied the addition of up to 150 μg clonidine to ropivacaine epidural anesthesia for elective hip replacement surgery in 60 patients and could not document a difference in PONV between groups.[170] When added to local anesthetic at the end of hip surgery during epidural blockade for postoperative pain control, clonidine actually lowered PONV rates in another trial.[232] Overall, there is no evidence to date that could implicate epidural clonidine as a significant cause of PONV.

This observation is also made when clonidine is added to various solutions to provide labor pain relief[233] or administered for post–cesarean section pain management.[234]

Epidural Neostigmine. Experience with epidural neostigmine is limited. Observations in patients with cancer pain showed promise that its use might be followed by less nausea and vomiting than the intrathecal application.[235] In an investigation randomizing 48 patients to receive 0, 1, 2, or 4 μg/kg epidural neostigmine in addition to a bupivacaine spinal anesthetic for minor knee surgery, no case of intraoperative nausea or vomiting was observed, and postoperative nausea scores did not differ between groups.[236] These results need to be corroborated by further studies before epidural neostigmine can be recommended for everyday practice.

Spinal *versus* Epidural Anesthesia. Several aspects distinguish epidural and spinal anesthesia. Among others, the slower onset of epidural anesthesia might favor better hemodynamic control. On the other hand, the higher density of spinal anesthetic blockade potentially provides superior anesthetic quality with less need for additional neuraxial or systemic medications. These factors potentially influence the frequency of emetic events.

The direct comparison of the two approaches has led to mixed results.[237–239] In a trial involving 192 patients undergoing general surgery, single-shot spinal anesthesia with plain bupivacaine resulted in similar less PONV as lidocaine epidural anesthesia (17 *vs.* 22%).[238] When regional anesthesia was continued into the postoperative period using local anesthetics without additives in a study of 102 patients after hip surgery, significantly fewer patients experienced nausea after continuous spi-

Table 3. Peripheral Nerve Blockade *versus* Other Anesthetic Techniques and PONV

Study	Patients, n	Type of Surgery	Block	PONV, %	Comparison	PONV, %	Comments
Pusch *et al.*[6]	86	Breast	Paravertebral	9	General	29	Vomiting only, $P < 0.05$
Klein *et al.*[246]	245	Breast	Paravertebral	19	General	39	Treatment only, $P < 0.05$; retrospective
Szmuk *et al.*[247]	250	Circumcision	Penis block	6	General	27	Adult patients, *P* value not shown
Vloka *et al.*[248]	68	Varicose veins	Femoral	3	Spinal	6	$P = NS$
Patel *et al.*[249]	90	Knee arthroscopy	3 in 1	3	General	17	$P = NS$
Chilvers *et al.*[250]	185	Hand	IVRA	0	General	5	Vomiting only, $P < 0.05$

IVRA = intravenous regional anesthesia; NS = not significant; PONV = postoperative nausea and vomiting.

nal *versus* epidural anesthesia (41 *vs.* 76%).[240] In women undergoing cesarean section, spinal or combined spinal–epidural anesthesia was followed intraoperatively either by a higher need for antiemetics,[241] no difference in PONV,[242] or less nausea and vomiting[239] than epidural anesthesia in different investigations.

The role of intrathecal compared with epidural administration of opioids regarding PONV is not clear. Trials in different patient populations found no significant differences,[243] but many studies suffer from retrospective design or the use of nonequivalent opioid doses. When Hallworth *et al.*[244] administered diamorphine in an equipotent dose (0.25 mg intrathecally or 5 mg epidurally) to patients undergoing cesarean section, they found significantly less PONV in the spinal group compared with the epidural group (4 *vs.* 24%), which the investigators explained by higher systemic opioid uptake after epidural injection.[244]

In laboring women, the use of intrathecal opioids alone has also been compared with epidural analgesia. While spinal morphine[245] was found to cause a significantly higher incidence of nausea and vomiting than epidural local anesthetics, intrathecal sufentanil compared favorably to different epidural analgesic regimens.[246]

Peripheral Nerve Blockade. Combining various block and surgery types, older prospective studies found an incidence of nausea and vomiting of 4.3[77] to 8.8%[78] after peripheral regional anesthesia. Such blocks often compare favorably with alternative methods of anesthesia regarding PONV (table 3).[246–250] In current practice, peripheral blocks are often used for minor surgery in outpatients, and follow-up time in studies is frequently limited. Furthermore, it is common that these patients are given additional systemic medications for sedation, among those benzodiazepines, opioids, or propofol. It is not surprising, therefore, that the frequency of nausea and vomiting, if reported at all, varies considerably in different investigations.

Blocks for Upper Extremity Surgery. Blockade of the nerves to the upper extremity can be achieved at different levels, such as the interscalene, supraclavicular, infraclavicular, or axillary location. The incidence of PONV is usually very low after pure local anesthetic block. Hickey *et al.*[251] administered systemic morphine and midazolam to their patients and reported an incidence of nausea of 10% and vomiting of 6% within 3 h after block completion.

The addition of other medications to the local anesthetic block solution has increased in popularity (table 4).[252–256] Different opioids have been used, and their administration was usually not followed by higher PONV rates. Nonetheless, prolonged infusion by means of a plexus catheter led to a significantly higher incidence of nausea compared with local anesthetic infusion alone.[73] Also, Bouaziz *et al.*[254] observed a tendency for a dose-related increase in nausea after the addition of sufentanil to mepivacaine in 92 patients receiving an axillary plexus block, although they rated all episodes as mild and of short duration. Clonidine added to local anesthetics is usually devoid of emetic side effects. Episodes of nausea have been reported, however, secondary to bradycardia and hypotension attributed to systemic absorption after injection of clonidine into the plexus diffusion space.[257] Bouaziz *et al.*[256] compared the effects of 500 μg neostigmine given with the local anesthetic or given systemically with a control group. The frequency of all side effects of gastrointestinal origin was similar between the groups in which neostigmine was given locally or systemically and was significantly higher than

Table 4. Medications Added to Brachial Plexus Anesthesia and PONV

Study	Patients, n	Control	PONV, %	Medication Added	PONV, %	Comments
Racz *et al.*[252]	40	Lidocaine–bupivacaine	11	Morphine	19	$P = NS$
Gormley *et al.*[253]	60	Lidocaine	0	Alfentanil	4	$P = NS$
Bouaziz *et al.*[254]	92	Mepivacaine	5	Sufentanil	17	$P = TNS$
Erlacher *et al.*[255]	40	Ropivacaine	0	Clonidine	0	$P = NS$
Bouaziz *et al.*[256]	69	Mepivacaine	0	Neostigmine	17	$P < 0.05$

NS = not significant; PONV = postoperative nausea and vomiting.

in the control group. Nausea and vomiting occurred only in patients receiving neostigmine.

For short procedures of the upper and, rarely, lower extremity, intravenous regional anesthesia remains popular. Limited surgery, short operating times, and quick recovery after tourniquet release are also factors leading to low PONV risk. Consequently, reported rates of nausea and vomiting are low, ranging between 0 and 10% after injection of local anesthetic alone. There is no evidence that the choice of local anesthetic would influence PONV rate.[258–259] The addition of opioids to the solution to be injected has been repeatedly followed by increased nausea after tourniquet deflation, and their indication is questionable.[260,261] Similarly, the substitution of local anesthetic with meperidine caused a significantly higher incidence of PONV in volunteers.[262] When different doses of meperidine were added to mepivacaine, a dose-dependent increase in PONV was observed.[263] Clonidine admixture, on the other hand, seems devoid of such consequences, at least as long as hemodynamic stability is not compromised after cuff release.[264]

Blocks for Truncal Surgery. Breast surgery with general anesthesia is known to pose a high risk of PONV.[265] Therefore, alternative techniques have been tried, such as intercostal nerve blocks and multiple- or single-injection paravertebral blocks. Problems, including time-consuming performance or considerable failure rates, are common. Furthermore, most patients require additional intraoperative sedation. Nonetheless, the results regarding PONV are encouraging. Several investigators reported significantly lower rates of PONV when comparing regional and general anesthetic techniques.[6,246] Klein *et al.*[246] achieved nausea scores after paravertebral blockade that were less than half of those seen after general anesthesia. Lumbar paravertebral blockade used for inguinal herniorrhaphy was accompanied by nausea in 15% and vomiting in 5% of patients.[266]

Blocks for Lower Extremity Surgery. Surgical anesthesia of the lower extremity by peripheral blockade usually requires the blockade of multiple nerves and is therefore often considered cumbersome and time-consuming to perform. Nonetheless, combinations such as femoral–sciatic or saphenous–popliteal block have regained interest, especially for ambulatory surgery.

These blocks are generally followed by low rates of nausea and vomiting. Mansour *et al.*[267] reported very low emetic scores after major knee surgery using a combination of lumbar plexus and sciatic nerve block, with more than 96% of patients symptom-free at any observation time. In vein-stripping surgery, a femoral plus genitofemoral nerve block resulted in a PONV rate of 3%, which compared favorably with the 6.3% rate observed in a comparable spinal anesthesia group.[248] Similar experience has been published when sciatic–femoral blockade was compared with spinal anesthesia for knee arthroscopy.[268] For foot surgery, Singelyn *et al.*[269] used a femoral–popliteal block and continued the popliteal block into the postoperative period by means of a catheter. The incidence of nausea and vomiting of 5% was significantly lower than in a historical control group that received general anesthesia followed by morphine patient-controlled analgesia (49%). A similar approach also proved advantageous for short saphenous vein stripping, although no difference in PONV was seen compared with spinal anesthesia.[270] The use of adjunctive medications added to the local anesthetic has not been well studied in lower extremity anesthesia. Low doses of fentanyl mixed with local anesthetic neither increased efficacy nor side effects.[271] Clonidine, on the other hand, was reported to be beneficial without an obvious increase in nausea or other adverse events.[272]

Continuous Peripheral Nerve Blockade for Postoperative Analgesia. Continuous peripheral nerve blocks have not found the same widespread use as continuous epidural blocks. For postoperative epidural analgesia, however, it has been noted that PONV rates were significantly lower over several days compared with morphine-based patient-controlled analgesia.[273] Furthermore, the concept of opioid-free epidural regimens have shown additional benefit, and the same holds true for continuous peripheral nerve blocks (table 5).[70,274–279]

In upper extremity analgesia, Wajima *et al.*[70] showed that operative axillary plexus blockade with postoperative continuous opioid-free plexus analgesia can result in complete absence of emetic sequelae. Borgeat *et al.* compared different opioid-free interscalene analgesic regimens with nicomorphine patient-controlled analgesia after shoulder surgery with combined interscalene and propofol-based general anesthesia. They consistently found significantly lower PONV rates in the regional analgesia groups.[274–276] Other investigators reported higher incidences of PONV in similar settings, but differences in study design might account for this. For example, Singelyn *et al.*[277] administered an inhalational general anesthetic and used a sufentanil-containing solution for plexus analgesia. The use of inhalational general anesthesia and the small study size could explain why Lehtipalo *et al.*[278] were unable to demonstrate a difference in PONV rates comparing opioid-free interscalene analgesia with morphine patient-controlled analgesia.

For analgesia after surgery of the lower extremity during inhalational general anesthesia, Capdevila *et al.*[65] used a continuous femoral nerve block with a lidocaine–morphine–clonidine mixture and found a significantly reduced the incidence of PONV at 24 h compared with morphine patient-controlled analgesia. Similarly, Schultz *et al.*[280] reported a significant decrease in PONV rates when postoperative analgesia was administered after knee surgery by a bupivacaine continuous lumbar plexus block instead of epidural morphine. Singelyn *et al.*[269] could reduce PONV by 90% providing analgesia after foot surgery by means of a popliteal catheter instead of

Table 5. Effects of Continuous Peripheral Nerve Blockade for Postoperative Analgesia on PONV

Study	Patients, n	Type of Surgery	Operative Anesthesia	Postoperative Peripheral Blockade	PONV, %	Postoperative Control	PONV, %	Comments
Wajima *et al.*[70]	23	Arm	Axillary plexus	Axillary plexus Mepivacaine	0	Axillary plexus Butorphanol	50	$P < 0.05$
Borgeat *et al.*[274]	35	Shoulder	Interscalene plexus ITN (propofol)	Interscalene plexus Ropivacaine	3	PCA Nicomorphine	35	$P < 0.05$
Borgeat *et al.*[275]	60	Shoulder	Interscalene plexus ITN (propofol)	Interscalene plexus (PCIA) Ropivacaine	10	PCA Nicomorphine	46	$P < 0.05$
Borgeat *et al.*[276]	40	Shoulder	Interscalene plexus ITN (propofol)	Interscalene plexus (PCIA) Bupivacaine	15	PCA Nicomorphine	30	P = NS, vomiting 0 *vs.* 25%, $P < 0.05$
Singelyn *et al.*[277]	40	Shoulder	Interscalene plexus ITN (inhalation)	Interscalene plexus (PCIA) Bupivacaine–sufentanil–clonidine	10	Interscalene Bupivacaine–sufentanil–clonidine	25	P = NS
Lehtipalo *et al.*[278]	20	Shoulder	ITN (inhalation)	Interscalene plexus Bupivacaine	20	PCA Morphine	30	P = NS
Capdevila *et al.*[65]	39	Knee	ITN (inhalation)	Femoral block Lidocaine–morphine–clonidine	5	PCA Morphine	21	$P < 0.05$ (at 24 h postoperatively)
Singelyn *et al.*[279]	30	Knee	Lumbar plexus ITN (inhalation)	Lumbar plexus Bupivacaine–sufentanil–clonidine	33	PCA Morphine	40	P = NS
Singelyn *et al.*[269]	105	Foot	Popliteal block ITN (control group)	Popliteal block	5	PCA Morphine	49	$P < 0.05$ Historic controls

ITN = intubation general anesthesia; NS = not significant; PCA = patient-controlled analgesia; PCIA = patient-controlled interscalene analgesia; PONV = postoperative nausea and vomiting.

by morphine patient-controlled analgesia. In contrast, Ganapathy *et al.* could not detect a significant difference in PONV whether a continuous femoral block with bupivacaine or morphine patient-controlled analgesia were used after knee arthroplasty during spinal anesthesia, but the patients in the regional group required as much systemic morphine in the first day as the patients in the patient-controlled analgesia group.[281]

In conclusion, continuous peripheral nerve blocks provide a promising tool to reduce PONV compared with standard analgesic techniques. Further investigations are warranted to define the appropriate indications and to find the optimal anesthetic solution to be used.

Conclusion

Postoperative nausea and vomiting remains a significant problem for both patients and clinicians. Most investigations of PONV have been conducted in the context of general anesthesia, but there is no evidence that fundamental differences exist regarding mechanisms and patient-related risk factors when regional anesthesia is considered. We have to admit that in the majority of the studies dealing with this question, PONV has rarely been the primary outcome variable, which is a shortcoming of this review.

The common assumption that regional anesthesia is associated with less PONV than general anesthesia is generally correct, although newer general anesthetic agents (*e.g.*, propofol) have narrowed the gap. However, some procedures such as cesarean section or major orthopedic surgeries are followed by high PONV rates after regional anesthetic techniques. While nausea and vomiting are very rarely life-threatening, their impact on patients is negative enough to impose a deliberate search for the most appropriate anesthetic technique and to justify antiemetic strategies in high-risk patient groups.

The choice of agents for premedication and intraoperative sedation may significantly impact on the incidence of PONV and should be made with this aspect in mind. Avoidance of hypotension, adequate hydration, and the administration of supplemental oxygen are part of an antiemetic plan. The addition of adjunctive medications to the local anesthetic can increase, decrease, or leave unchanged the rate of emetic sequelae and should be considered accordingly. While clonidine appears harmless, neostigmine must be cautioned against. Opioids have to be differentiated according to type and setting. In spinal anesthesia, meperidine should be avoided, as should morphine in lesser surgeries where little postoperative pain is expected. Morphine for epidural anesthesia should be replaced by fentanyl or sufentanil, as these substances appear to carry the lowest PONV risk of the opioids in neuraxial anesthesia. The use of opioids in patients undergoing peripheral regional anesthesia remains controversial, but their potential to cause PONV should be taken into consideration. A quantitative analysis of the risk of PONV when opioids are added to local

anesthetics would have been interesting to evaluate, but was not realistic in this review because of the large protocol heterogeneity.

At least in more extensive surgical cases, regional administration of opioids does not seem to increase PONV compared with the use of systemic opioids. In some instances, such as cesarean section, regional opioids may even lower PONV rates. Furthermore, the continuation of regional analgesia into the postoperative period by means of catheter techniques offers a possibility of reducing PONV compared with opioid-based analgesic regimens. Indeed, in appropriate settings, these techniques can provide excellent pain control without the administration of opioids offering the best conditions to prevent PONV.

In the ether era, nausea and vomiting were considered almost unavoidable companions of anesthesia. While a carefully planned regional anesthetic will not completely banish them, it offers to date the best chance not to cross their path and to avoid the "big little problem" of anesthesia.[282]

In summary, early and efficient rehabilitation are the new requirements of modern surgery, especially in orthopedics. This evolution has resulted in a renewed interest in regional anesthesia. The development of the continuous perineural catheter in particular has led to better postoperative pain control associated with a large reduction of the incidence of PONV. To take advantage of these techniques, future research needs to identify the risk factors for PONV that are specifically linked to regional anesthesia and to find the most appropriate adjuvants and sedative regimens to supplement neural or peripheral block to reduce as much as possible the systemic use of opioids.

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