

Post Operative Effects: Anesthesia

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Abstract

Anesthesia result in a variety of metabolic and endocrine responses, but conventional wisdom maintains that anesthetic technique has little long-term effect on patient outcomes. There is accumulating evidence that, on contrary, anesthetic management may in fact exert a number of longer-term effects in postoperative outcome. Here, we review the most topical aspects of anaesthetic management which may potentially influence later postoperative outcomes. Overall, there is insufficient evidence to confirm the ability of postoperative outcomes. This is primarily due to typically insufficient subject numbers to detect differences in currently low incidences of postoperative complications.

Keywords: Anesthesia; Postoperative outcome

Introduction

Anesthesia is commonly classified into two main techniques: general anesthesia in which drugs achieve central neurologic depression, and regional anesthesia, in which drugs are administered directly to the spinal cord or nerves to locally block afferent and efferent nerve input [1]. After surgery, the risk of fatal or life threatening events like deep vein thrombosis, pulmonary embolism, myocardial infarction, transfusion requirements, pneumonia and renal failure are increased several fold, but there is debate about whether the type of anesthesia has any substantive effect on these risks. Neuraxial blockade has several physiological effects that provide a rationale for expecting to improve outcome with this technique [2]. It is logical to hypothesize that a "stress-free" perioperative period may attenuate or prevent detrimental physiologic responses and decrease resultant morbidity [3].

Method

Medline, Pubmed, Embase and the Cochrane library were searched using the term's type's anesthesia and postoperative outcomes. Articles are restricted to the English language. A manual search for papers that may pertinent to the study was also performed. All reports were then considered and relevant papers were included in the review that follows. A formal assessment of quality was not made although to avoid duplication of data, papers from the same unit or hospital were included only once if data were being updated in a later publication. We prioritized evidence from well designed randomized controlled trials, when available. A meta-analysis was not performed because heterogeneity in the studies cited in the review precluded this.

Cancer Recurrence

Surgery is the most efficient method for treatment of many types of cancer, but residual micrometastases are inevitable. Whether minimal residual disease results in clinical metastases depends on the balance between host immune defence and tumour survival and growth. Surgery and anesthesia result in a variety of metabolic and endocrine responses, which result in a generalised state of immunosuppression has been implicated in the development of postoperative septic complications and tumor metastasis formation [4]. Postoperative pain, an inevitable consequence of cancer surgery, has itself been shown to facilitate metastatic spread of cancer in a live animal model [5]. Opioid analgesia, the mainstay of treatment of postoperative pain and cancer pain,

inhibits cellular immune function in humans, increases angiogenesis and promotes breast tumour growth in rodent [6]. Regional anaesthesia and analgesia attenuates each of these adverse effects by preventing the neuroendocrine surgical stress response, reducing the need for general anaesthesia and minimizing opioid requirement [7]. A review of 225 patients who underwent open radical prostatectomy for invasive prostate carcinoma found that those who received general anaesthesia plus epidural analgesia had an estimated 57% lower risk of recurrence compared with general anaesthesia plus opioid analgesia [8]. Animal studies indicate that regional anaesthesia and optimum postoperative analgesia reduces the metastatic burden in animals inoculated with breast adenocarcinoma cells following surgery [9].

Nitrous oxide reduces DNA and purine synthesis and suppresses neutrophil chemotaxis, facilitating cancer spread. However, a FARCT (Follow-Up Analysis of a Previous Randomized Controlled Trial) of 204 patients undergoing colon resection for bowel cancer, in which patients were randomly assigned to nitrous oxide or air found no statistically significant difference in cancer recurrence rates [10].

Cardiovascular Effects

Approximately 100 million adults worldwide undergo noncardiac surgery annually, and nearly half of the patients are estimated to have cardiac risk factors [11]. As such, it is estimated that nearly 500,000–900,000 patients will suffer a perioperative cardiovascular complication [11]. Reported incidences of perioperative cardiovascular complications vary depending on surgical procedure and patient population.

Cardiac morbidity is the primary cause of death after anesthesia and surgery with reported incidences ranging from 2% to 15% in high risk surgical population [12]. So anesthesia techniques that reduce car-

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diac morbidity should have greatest effect on improving surgical outcomes. Stress induced activation of the sympathetic nervous system may be partially responsible for perioperative cardiac events. Blockade of cardiac sympathetic innervation (T1-T5) by thoracic epidural local anaesthetics could reduce myocardial oxygen demand, ischemia and coronary vessel constriction [13]. If it is to be of cardiac benefit, postoperative epidural analgesia may need to be continued for at least 48-72 h [14]. Compared with standard anaesthesia, a highly significant decrease in incidence of cardiovascular failure has been documented in patients undergoing high risk surgery who received epidural anaesthesia and analgesia [15]. According to a meta-analysis by Svircevic et al. [16] epidural anaesthesia during cardiac surgery reduces postoperative supraventricular arrhythmias and respiratory complications, but definitive conclusions regarding mortality, myocardial infarction, and stroke were precluded due to the diversity of data, although a reduced risk of cardiopulmonary complications was estimated. Hypercoagulability occurs in association with surgical procedures with resultant risk of formation of deep Venous Thrombosis (DVT) and potentially fatal Pulmonary Embolism (PE). Older data in patients without thromboprophylaxis reported incidences for DVT of 0.4%–4% for general surgery, 1%–5% for urological surgery, 5%–36% for joint replacement, and 23%–30% for hip fracture surgery. Incidences for fatal PE were 0.1%–0.4% for general surgery, 0.5% for urological surgery, 0.1%–2% for joint replacement, and 2.5%–7.5% for hip fracture surgery [17]. The effects of neuraxial regional anaesthesia on platelet function are well known [18-21]. Recent publications show that epidural anaesthesia also prevents perioperative venous stasis [22]. The incidence of perioperative venous thrombosis can be significantly reduced, as shown by a Cochrane meta-analysis from Parker et al. [16]. With regard to the influence of various regional anaesthetic techniques on blood coagulation, local anaesthetics do have a direct effect on platelet function [23-25]. Thus, a combination of indirect and direct mechanisms for regional anaesthesia effects on blood coagulation seems to be responsible for the antithrombotic effects of regional block.

Pulmonary Outcomes

After surgery, respiratory complications play major role for determining hospital stay, morbidity and mortality [26,27]. Actually respiratory complications may cause at least 50% more costs than cardiac complications after adjustment for patient characteristics [28]. Pathophysiological changes that occur under anesthesia and/or following surgery, can interact thereby contributing to respiratory complications. The reduction of lung inflation is one of the basic mechanisms of postoperative pulmonary complications. The body position change from upright to supine itself reduces resting lung volume by around 1 litre [29]. As well as during induction of anesthesia, most of the general anesthetics, except for ketamine, produce a further reduction of Functional Residual Capacity (FRC) [30,31]. So FRC and vital capacity are affected after anesthesia, indicating the presence of a restrictive process. In patients undergoing abdominal surgery, there is a marked reduction of inspiratory and expiratory reserve volume during the first days, with 40% reduction in functional residual volume [32,33]. The reduction of FRC cause V/Q mismatch and contributes to the development of atelectasis and hypoxemia.

Respiratory complications seem to be related to a disruption of the normal activity of respiratory muscles starting from the induction of anesthesia. The impairments are primarily a decrease in phrenic nerve activity. Decreasing phrenic nerve activity results decrease in diaphragmatic function and increase in intercostal and abdominal muscle tone. Adequate pain control is important for avoiding than worsening of

pulmonary dysfunction associated with surgery and general anesthesia. Wahba et al. directly measured the effects of TEA on FRC and CC after upper abdominal surgery [34]. 22% decrease in FRC was documented in the immediate postoperative period prior to TEA. After institution of TEA with local anesthetics, FRC increased by 27%. In addition to restoration of FRC, the benefits of EAA on pulmonary function may also be related to preservation of phrenic nerve activity.

In several studies, when EAA is used in thoracotomy or abdominal surgery, an improvement in pulmonary function tests were demonstrated; but this improvement doesn't always correlate with clinical outcome [35-37].

In patients with reactive airway disease, endotracheal intubation increases the risk of bronchospasm. Wang et al. reported that 64% of asthmatics develop wheezing during general anesthesia with intubation versus 2% with general anesthesia without intubation or with regional anesthesia [38].

In a study, Cassasole et al. assessed that 462 surgical cancer patients who underwent major surgeries of the abdomen, thorax or both, found that patients managed with EAA required less ventilatory support than those in the general anesthesia / IV-PCA group. Patients in the EAA group also spent less time in the ICU [39]. This shows the most significant pulmonary outcome advantage of EAA.

Gastrointestinal Effects

Postoperative ileus is an important morbidity and mortality factor. Postoperative ileus is very common after abdominal surgery (90% in many series) and may increase resource utilization [40]. Several series in patients undergoing noncardiac surgery have observed that ileus was the most common issue in delaying hospital stay beyond 7 (51% of patients) and 10 days (42% of patients) [40]. Although the pathophysiology of postoperative ileus multifactorial, primary mechanisms include neurogenic (spinal, supraspinal adrenergic pathways), inflammatory (i.e., local inflammatory responses initiate neurogenic inhibitory pathways), and pharmacologic (e.g., opioids) mechanisms [41]. The preventions and treatment of postoperative ileus are multifactorial and should include the avoidance of opioids, use of epidural block, use of a nasogastric tube, and correction of electrolyte imbalance [42]. Epidural analgesia provides pain control superior to systemic opioids (including IV PCA) and allows marked sparing of opioid consumption [43]. Sympathetic block from epidural local anesthetics may help attenuate postoperative reflex inhibition of GI motility. Suppression of the surgical stress response and systemic absorption of epidural local anesthetics may reduce the inflammatory response to attenuate postoperative ileus [44,45]. Consistent with these mechanisms, experimental data consistently indicate that epidural analgesia with local anesthetics shortens time of intestinal paralysis, increases the strength of colonic contractions, and does not impair anastomotic healing or increase risk of anastomotic leakage [46].

Anaesthesia and Postoperative Cognitive Dysfunction

The role of anaesthesia in the development of postoperative cognitive complications remains unclear. It is remarkably common, especially in the elderly, to experience a varying degree of cognitive dysfunction post-operatively, which can vary from mild and short-lived to severe and permanent. Such manifestations are described as Postoperative Cognitive Dysfunction (POCD) which is described a range of abnormalities, one of which is Postoperative Delirium (POD).

There is in-vitro and animal model evidence that neurotoxic effects

of anaesthetics are not confined to the developing brain. Isoflurane has been shown to activate the membrane-bound IP3 receptor producing excessive calcium release and triggering apoptosis in cells [47]. In-vitro experiments suggest that some anaesthetics act in the processing of amyloid b-peptide providing a possible link between the effects of anaesthetics and postoperative cognitive sequelae. Clinical concentrations of isoflurane cause altered processing of amyloid precursor protein and increase amyloid b-peptide production in both human neuroglioma and mice brain cell lines [48]. There is also enhancement of Ab oligomerization that is thought to be responsible for synaptic dysfunction and neurodegeneration [49].

A meta-analysis of 21 studies on POCD and POD found no effect of anaesthesia type on the OR of developing Postoperative Delirium POD (50). In a small subgroup analysis of a prospective, randomized controlled trial [General Anaesthesia vs. Local Anaesthesia (GALA) study], 40 patients undergoing Carotid Endarterectomy (CEA) were randomized to receive either local anaesthesia (n¼17) or general anaesthesia (n¼23) [51]. Despite carotid clamping times being longer in the local anaesthesia group [mean 24 min (SD 10) vs. 15 min (SD 8), P¼0.003] and less patients in the local anaesthesia group receiving a shunt [5 (9%) vs. 9 (39%), P¼0.001], information processing, during psychometric testing, was found to be significantly slowed in the general anaesthesiagroup at 5 and 29 h but not at 77 h postoperatively, as compared to their preoperative baseline tests. There was no significant difference between the preoperative and postoperative results in the local anaesthesia group at any of the time points. This is the first prospective, randomized, albeit small, clinical study to show a beneficial effect of local anaesthesia on early postoperative cognitive function in CEA patients.

In an effort to discover a dose-response relationship between anaesthesia and POCD, a prospective observational study of 70 patients over 60 years of age undergoing elective noncardiac surgery measured depth of anaesthesia using a cerebral state monitor and compared the measured Cerebral state index (CSI) to the performance of the patients on neuropsychological testing 1 week after surgery (98). The mean CSI was 40 and 43 in patients with (n¼49) and without (n¼56) POCD, P¼0.41. The cumulated time of both deep anaesthesia (CSI<40) and light anaesthesia (CSI>60) did not differ significantly, and no significant correlation was found between the mean CSI and risk of POCD.

Persistent cognitive decline may be attributable to underlying undiagnosed neurological disease or other comorbidities rather than to surgery or to anaesthesia per se. There are other perioperative influences to which elderly people are more susceptible such as altered environment and sleep disturbance. Further large-scale prospective studies are required to investigate the possible prolonged effects of even short-acting anaesthetics on the elderly brain.

Postoperative Nausea and Vomiting

Nausea and vomiting that develops within 24 hours post operation is known as Postoperative Nausea and Vomiting (PONV) [53]. It is the second most common complaint after pain in the postoperative period. While occurrence is about 30% in all patients, that increases to 70% in high risk patients [54,55]. Children are affected twice as often compared to adults [55]. PONV in patients may cause morbidity due to aspiration pneumonia, airway obstruction, dehydration, and suture tightening or rupture [54,55]. It prevents early discharge of patients and increases costs [55,56].

Though PONV's etiology is unknown it is thought to be multi-

factorial. Since the 1990's the factors increasing PONV incidence have been investigated and different risk factors identified. According to the Society for Ambulatory Anesthesia (SAMBA) 2007 Guidelines for the Management of PONV, factors which increase PONV incidence can be grouped under three main headings; patient characteristics, anesthesia technique and surgical characteristics [57].

The first set of factors is Patient-specific risk factors; [53,54,57-61] female sex, nonsmoking status history of PONV/motion sickness. The second group of factors is anesthetic risk factors [53,54,57,58,61,62]; use of volatile anesthetics, nitrous oxide, use of intraoperative and postoperative opioids. Surgical risk factors [57,60,61] include; duration of surgery (each 30-min increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased by 16% after 30 min), and type of surgery (laparoscopy, laparotomy, breast, strabismus, plastic surgery, maxillofacial, gynecological, abdominal, neurologic, ophthalmologic, urologic) [57].

Several scoring systems examining these risk factors have been published. The most accepted system was published in 1999 by Apfel et al., the Apfel scoring system [57,58]. Four risk factors were identified; female sex, patient history of PONV or motion sickness, not smoking and intraoperative and/or postoperative opioid use. Every factor is given 1 (one) point to quantify risk. With no risk factors the chance of PONV occurrence is 10%, in this system each factor increases the possibility of PONV by 18-22%. With 1, 2, 3, and 4 risk factors present the chances of PONV developing become 21%, 39%, 61% and 79%, respectively [57,58].

In the Apfel Scoring system, 0 and 1 points are low risk, 2 is moderate risk and 3 and 4 are high risk groups. In the low risk group the procedure adopted is wait and see. For the moderate risk group prophylactic treatment (1-2 interventions in adults, 2 or more interventions for children is recommended). High risk patients are given more than 2 interventions (multimodal approach). Moderate and high risk prophylactics require antiemetic administration. In the postoperative period moderate risk should be given 1 or 2, high risk patients should be given more than 2 antiemetic medications [57].

Preference should be for regional anesthesia for moderate to high risk patients, if general anesthesia is necessary induction should be with propofol, and strategies to minimize the baseline risk of PONV should be adopted. Prophylaxis should be combined pharmacologic and nonpharmacologic prophylaxis in order to reduce baseline risk. Combine drug therapy should be applied with drugs that affect different mechanisms. In this risk group prophylaxis should be one of the 5-HT3 receptor antagonists, steroids, phenothiazines, ephedrine, butrophenones, antihistamine or anticholinergics. Small dose of 5HT3 receptor antagonists may be the first drug of choice. 4 mg ondansetron, 1.25 mg droperidol and 4 mg dexamethasone have equal effect but are known to reduce the incidence of POVN by 25% [57,63,64]. If prophylaxis is insufficient another class of antiemetic should be added. Except for dexamethasone and scopolamine drug doses may need to be repeated after 6 hours by the PACU.

One approach would be to reduce baseline risks for POVN [57]; avoidance of general anesthesia by use of regional anesthesia [57,60], use of propofol for induction and maintenance of anesthesia [57,63,65,66], avoidance of nitrous oxide [57,58,63,64,66], avoidance of volatile anesthetics [57,62], minimization of intraoperative and postoperative opioids [58,62-65,67-69], minimization of neostigmine [57,70] and use of adequate hydration [71].

Studies are available in the literature showing general anesthesia

has 11 times higher risk of PONV compared to regional anesthesia [60,64]. It is also possible to reduce opioid use to a minimum with regional anesthesia [64]. High dose opioid use increases the risk of PONV to nearly double [58,63,72].

Use of nitrous oxide, inhalation agents and emetogenic induction agents such as etomidate and ketamine should be avoided for patients at high risk of PONV [57]. Maintenance of anesthesia can be continued with propofol and TIVA (Total Intravenous Anesthesia with propofol) [57]. To reduce perioperative opioid use analgesia should be supported by NSAID and local anesthesia.

Use of high doses of anticholinesterases such as neostigmine should be avoided, adult doses need to be limited to 2.5 mg. Studies are available in the literature showing neostigmine increases PONV incidence and should be avoided at high dose (>2.5 mg) [57,70]. However the clinical importance of neostigmine and its effects on PONV are still debated [73].

Though some studies suggest perioperative supplemental oxygen may reduce PONV incidence [73,74] other studies show it has no effect [53]. SAMBA guidelines from 2007 do not recommend extra oxygen use during operations [57].

Another approach would be prophylactic antiemetic treatment with the proviso that pharmacological prophylaxis may only be reasonable in risky patients. Not all patients should receive PONV prophylaxis. This score might be useful for patient selection in antiemetic trials [55,56,58].

Drugs for PONV prophylaxis for adults should be considered in monotherapy or in combination for patients at moderate risk for PONV. In general, combination therapy is superior to monotherapy for PONV prophylaxis. Antiemetic rescue therapy should be administered to patients who have an emetic episode after surgery [56].

Serotonin (5-HT₃) receptor antagonists exert their effects in the chemoreceptor trigger zone and on vagal afferents in the gastrointestinal tract. First-generation serotonin receptor antagonists are ondansetron, granisetron, dolasetron, and tropisetron. If a patient has received no prophylaxis, therapy with small dose 5-HT₃ receptor antagonists should be initiated on the first sign of PONV. Ondansetron is comparatively more effective and has fewer side effects compared with all previous antiemetics. The US Food and Drug Administration (FDA) approves 12.5 mg as the minimum effective dose for the prevention of PONV [53-55,57].

Dexamethasone, a potent synthetic glucocorticoid, prevents PONV. Notwithstanding early studies were conducted with 8-10 mg of dexamethasone, the newest studies convince that 2.5-5 mg can be considered minimum effective dose [53-56]. Dexamethasone appears to be most effective when administered before the induction of anesthesia rather than at the end. It also effectively prevents opioid-induced nausea and vomiting [77].

Droperidol exerts its antiemetic effect by blocking central D₂-receptors in the CTZ and area postrema. It should be given at the end of surgery at the lowest effective dose of 0.625 mg to minimize potential sedative side effects. Droperidol can cause hypotension, anxiety, restlessness and Extra Pyramidal Symptoms (EPSs), such as akathisia and dystonia. In 2001, the FDA issued a "black box" warning about droperidol, stating that it may cause death associated with QT prolongation and torsades de pointes. This action by the FDA makes it very difficult to advocate droperidol as a first-line antiemetic. In addition, haloperi-

dol has also been reported to prolong the QT interval and cause torsades de pointes [53-55].

Metoclopramide exerts its antiemetic effect by blocking central D₂-receptor antagonists in the CTZ and vomiting centre. It also shortens bowel transit time and in high doses blocks serotonin receptors. A dose of 50 mg intravenous metoclopramide has been shown to significantly reduce late PONV [53,54]. Promethazine and prochlorperazine belong to a group of drugs known as phenothiazines, which exert an antiemetic effect by blocking D₂-receptors in the CTZ and other areas of the brain. Their role in the control of PONV is still poorly understood [53-55].

Aprepitant was the first Neurokinin-1 (NK-1) receptor antagonist approved for the treatment of PONV. Aprepitant is an antiemetic chemical compound that belongs to a class of drugs called Substance P Antagonists (SPA). This drug blocks NK1 receptors in the central and peripheral nervous systems, thus preventing emesis. Its acquisition cost is relatively high, making it less appealing as a first line agent [53].

Scopolamine is very effective for prevention of PONV in the first 24 hours after surgery [53,57,77]. With a four-hour onset of action, a scopolamine patch (Transdermal Scopolamine-TDS) should be applied the night before surgery or before induction of anesthesia when it is anticipated that at least four hours will elapse before anesthesia ends. TDS was associated with an increased prevalence of visual disturbances at 24 to 48 hours [77].

Nonpharmacologic therapies, such as acupuncture, acupressure, transcutaneous electrical nerve stimulation, or acupoint stimulation, and aromatherapy have shown antiemetic efficacy when used before surgery [53,54,78]. Hypnosis has been found to be effective when compared with placebo [78,79].

Conclusion

There is accumulating evidence that anaesthetic management may indeed exert a number of influences on longer term postoperative outcomes. Further prospective, randomized, large scale, human trials with long-term follow-up are required to clarify the association between anaesthesia technique and postoperative outcome.

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