Review

Does anaesthesia care affect the outcome following craniotomy?

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Keywords: neurosurgery, craniotomy, brain tumour, anaesthesia

INTRODUCTION

Most neurosurgeons could list the qualities of a good neuroanaesthetic: the patient is well prepared for anaesthesia, the technical aspects of the anaesthetic proceed swiftly and smoothly, operating conditions are good, cerebral haemodynamics are well controlled and the brain is protected against ischaemic and traumatic insults, post-operative complications are few and the patient awakens promptly, ready for neurological assessment to confirm the success of the operation.3 However, what is the evidence that any of these qualities makes a difference to the outcome from neurosurgery?

Anaesthesia per se has had a tremendous impact on the scope and outcome of neurosurgery. Before the introduction of ether anaesthesia in 1846, neurosurgery was largely confined to urgent operations following intracranial haemorrhage. After 1846, and with improvements in antisepsis and diagnostic techniques, neurosurgery entered the modern era of precise, anatomical treatment of neurological conditions. Nevertheless, anaesthesia for neurosurgery was a hazardous undertaking.

A neurosurgeon, Harvey Cushing, did a lot to improve the safety of neuroanaesthesia,2 introducing regular monitoring and recording of heart rate, respiratory rate and temperature; routine estimation of arterial blood pressure, and more extensive use of local anaesthetics. He also employed a full-time physician anaesthetist. Cushing cited improved anaesthesia care as one reason for his peer-less operative results.4 However, what is the evidence that any of these qualities makes a difference to the outcome from neurosurgery?

The intra-operative period

Choice of anaesthetic agents

Newer available anaesthetic agents often have theoretical advantages over older agents (such as faster onset and offset times), but unfortunately comparisons of drugs in neurosurgical patients looking at long-term neurologic outcomes are uncommon.

Propofol

Propofol has many of the properties of an ideal agent for neuroanaesthesia, with its beneficial cerebral haemodynamic effects, potential for neuroprotection, favourable pharmacokinetics and high-quality recovery profile despite prolonged duration of infusion. Propofol results in decreased MAP and ICP, but CPP and cerebral autoregulation are maintained even in doses that produce an isoelectric EEG.4–7 In addition, CO2 reactivity is maintained over a wide range during propofol anaesthesia.8,9 Although thiopentone is the traditional choice for brain protection, its advantage over propofol is (if anything) small, especially when delayed emergence is taken into account. Propofol may provide brain protection via a variety of mechanisms, but only its ability to decrease CMRO2 is confirmed in humans.

An exciting pilot study was published recently comparing propofol/morphine sedation with morphine sedation alone in intubated head-injured patients.20 Despite a higher incidence of poor prognostic indicators in the propofol/morphine group, ICP therapy was less intensive, ICP was lower on the third day, and long-term outcome was similar to that of the morphine group. The authors concluded that propofol-based sedation may be superior to an opiate-based sedation regimen in intubated head-injured patients. The results of the full randomised trial are awaited with interest.

Inhaled agents

Inhaled agents are preferred by some neuroanaesthetists because of the ease of their administration, the availability of end-tidal

Accepted 4 May 2001

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Received 27 March 2001

agent monitoring and lack of evidence that outcome is adversely affected compared with intravenous hypnotics. Recently, attention has been focused on the newer agents, sevoflurane and desflurane, which, due to their physical properties, have more rapid onset and offset, and titratability during anesthesia than older agents.

Like all volatile anaesthetics, sevoflurane causes cerebral vasoconstriction in the clinical dose range, but the increase in CBF is not as great as for equipotent doses of isoflurane. Sevoflurane does not affect cerebral autoregulation and maintains cerebrovascular reactivity.

The literature on the cerebral haemodynamic effects of desflurane is conflicting. When desflurane was compared with isoflurane, neither agent altered CBF or reactivity to CO2 at clinically relevant doses, whereas when desflurane was compared with sevoflurane, desflurane significantly increased MAP and cerebral blood flow velocity. Differences in measurement methods and baseline anaesthesia may have influenced these results. Sevoflurane may be the volatile agent of choice during neurosurgery, but a direct clinical comparison looking at outcome has not been published.

Although inhaled anaesthetics are thought to impair cerebral autoregulation more than intravenous agents, there are few controlled studies in humans. Strebel et al. randomised patients to isoflurane, desflurane or propofol anaesthesia. Low-dose isoflurane delayed, but did not reduce the autoregulatory response. Low-dose desflurane delayed and reduced the response. High-dose isoflurane or desflurane ablated autoregulation. In contrast, autoregulation was preserved during low- or high-dose propofol.

The neuroprotective effects of the new volatile agents have similar status to propofol: suggested in animals but unproven in humans. Both decrease CMRO2 but transient increases in intracranial pressure (ICP) may occur as a result of dose-dependent decreases in mean arterial pressure (MAP). Studies comparing fentanyl, sufentanil and alfentanil reveal similar conditions during surgery and recovery from anaesthesia. For example, in a double-blind, randomised trial of these agents, From et al. reported that intraoperative hypnotic and anti-hypertensive requirement, induction hypotension, operating conditions, recovery times and discharge neurologic status did not distinguish one agent from the other.

A new ultra-short acting opioid, remifentanil, has become very popular because of its superb titratability during anaesthesia. Remifentanil has similar effects on ICP and cerebral perfusion pressure (CPP) to fentanyl and alfentanil, and cerebrovascular reactivity is similar during remifentanil and fentanyl anaesthesia. When remifentanil and fentanyl were given in equi-analgesic doses, neither agent altered CBF or reactivity to CO2 at clinically relevant doses, whereas when desflurane was compared with sevoflurane, desflurane significantly increased MAP and cerebral blood flow velocity. Differences in measurement methods and baseline anaesthesia may have influenced these results. Sevoflurane may be the volatile agent of choice during neurosurgery, but a direct clinical comparison looking at outcome has not been published.

Control of intraoperative hypertensive responses

Critical periods occur during neurosurgery where hypertensive responses are expected and need to be controlled: laryngoscopy, endotracheal intubation, the insertion of the pins, opening of the dura and extubation. These noxious stimuli may provoke a significant increase in arterial blood pressure, and the rapidity of this increase may allow insufficient time for autoregulation. Consequently, ICP may increase, particularly in areas of the brain where autoregulation is impaired.

Intraoperative and early post-operative hypertension may be associated with an increased incidence of post-operative intracranial haemorrhage. Basali et al. conducted a retrospective case-control study of intracranial haemorrhage in their hospital. Sixty-two percent of intracranial haemorrhage patients had intraoperative and early post-operative hypertension compared with only 34% of controls. That is, for every 60 patients with perioperative hypertension, there will be one extra post-operative haemorrhage compared to the control group. Hospital stay and mortality were significantly greater in the cases than controls. Whilst hypertensive episodes may reflect the severity of intracranial pathology rather than inadequate blood pressure control, these data suggest that efforts to control hypertensive episodes may be justified. A randomised trial would be unethical and a prospective study very time-consuming as the incidence of intracranial haemorrhage is < 1%.

Simple precautions will often be sufficient to prevent pressor responses. As adequate anaesthesia and muscle relaxation are essential in anticipation of noxious stimulation, good communication between surgeon and anaesthetist is vital. Pressor responses are often greatest during intubation and are proportional to the
duration of laryngoscopy. Prompt extubation of the trachea if coughing occurs at the end of surgery is also important.55

Numerous studies have investigated the relative merits of additional pharmacological interventions to prevent hypertension. Dosage and timing of agents is critical. For example, an additional bolus of propofol was more effective than a bolus of thiopentone in attenuating intubation hypertension, although neither prevented tachycardia. This was best achieved with fentanyl, 2 μg/kg.56 In another study, fentanyl, 5 μg/kg, at least 2.5 min prior to intubation prevented the hypertensive response, and 2 μg/kg significantly attenuated it.57 Similarly, alfentanil, 15 μg/kg, prevented the hypertensive response, but 30 μg/kg was required to prevent tachycardia.58 Intravenous lignocaine is also an option, either intra-venously or intra-tracheally.59

The problem with additional doses of these anaesthetic agents, however, is that recovery may be prolonged. The short-acting opioid, remifentanil, may be the answer. Remifentanil, 2 μg/kg, completely ablates the pressor response to intubation but is associated with a significant decrease in MAP and heart rate,60 whereas 1 μg/kg significantly attenuates the response without causing as much hypotension.61 Remifentanil also effectively ablates responses on emergence.62

In unstable patients, a β-blocker or α2-agonist may be a better choice. The ultra-short acting β-blocker, esmolol may be useful in doses of 0.5–1.0 mg/kg i.v.63 or clonidine, a centrally-acting α2-agonist, can be given as a premedication (3 μg/kg p.o.). Clonidine has the additional advantage of providing pre-operative anxiolysis and reducing anaesthetic requirement.64

Hypothermia

Deliberate mild hypothermia is often induced during neurosurgery in an effort to provide brain protection. Most neurological patients develop ≤ 3°C of hypothermia within an acceptable time-frame during surgery, as nearly all commonly-used anaesthetics impair thermoregulation.65 However, obese or febrile patients, or those treated with vasodilators (such as nimodipine), may become sufficiently hypothermic, as the gradient for redistribution of body heat following induction of anaesthesia is not great enough.66,67 Forced-air cooling may be useful in these patients.58

Unfortunately, however, there is still only limited evidence of brain protection by hypothermia in humans.68,69 At the same time, large studies reporting the potential for serious complications accumulate, including delayed recovery,11 wound infection and delayed wound healing,70 coagulopathy71 and morbid cardiac events.72 A result from the IHAST trial is therefore eagerly awaited (Intraoperative Hypothermia during Aneurysm Surgery Trial; Principal Investigator: Michael M. Todd, Professor of Anaesthesia, University of Iowa). This is an NIH funded, prospective, randomised, multi-centre trial intended to determine whether intraoperative hypothermia affects the outcome of surgery for ruptured cerebral aneurysm. A pilot study from this group reported that mild hypothermia was safe in these patients and suggested a potential protective effect, as fewer patients remained intubated in the hypothermic group 24 h after surgery.70

THE POST-OPERATIVE PERIOD

The immediate post-operative period is a critical time for neurological patients and prompt detection and management of complications has the potential to improve outcomes. However, the literature on post-operative complications following craniotomy is tiny: neither adequate audits of post-operative complications in neurological patients nor large randomised comparisons of treatment options are available. In addition, there is little information about the effect of anaesthesia care on post-operative outcomes. In one of the few published studies, Manninen et al.73 reported the results of a prospective survey of early post-operative complications following neurosurgery in their unit. Forty-seven percent of intracranial tumour surgery patients suffered one or more complications in the first 4 post-operative hours; a higher incidence than in the general surgical population.74 The most common complications were post-operative nausea and vomiting (PONV) (28%), shivering (11%) and neurological deficits (10%). Re-intubation of the trachea occurred in 3.2%, and haemodynamic instability in 4.8%, of patients. No data on the anaesthetic technique used, the incidence of uncontrolled pain or events after the first 4 h were reported. Therefore, further audit of the incidence of post-operative complications in neurosurgical patients is warranted.

Seizures

Early post-operative seizures may affect overall outcome adversely by producing respiratory complications and neurological deterioration. Whether the use of propofol affects the incidence of post-operative seizures remains controversial. On one hand, case reports describe seizures after propofol anaesthesia75 and animal studies report activity at excitotoxic receptors,76 whilst on the other hand, a body of evidence suggests that propofol is anticonvulsant or has no proconvulsant activity.77–80 Recently, Hewitt et al. studied the electrocorticographic effects of propofol and thiopentone in patients undergoing temporal lobectomy.52 Both agents caused activation and extension of epileptiform discharges. However, Hewitt et al. argued that anaesthetic drugs may produce these changes by promoting EEG synchrony, rather than by a proconvulsant action (particularly as thiopentone is a known anticonvulsant). In an accompanying editorial, Sneyd83 recommended avoiding the use of propofol in epileptic patients who hold a driving license and present for non-neurological surgery (on pragmatic grounds), whilst choosing propofol if indicated in other situations.

The cloud hanging over atracurium, with regard to seizure causation by its metabolite laudanosine, has dispersed somewhat. Although animal evidence continues to appear about the proconvulsant effects of supra-clinical concentrations of laudanosine,84,85 no further case reports of seizures attributed to atracurium in patients have been published,56 despite extensive use of atracurium worldwide.86

Pain

Craniotomy patients usually describe mild-to-moderate post-operative pain, which may be less severe than after other types of surgery.87,88 However, there is substantial intra- and inter-individual variation.96–92 For example, De Benedictis et al. reported that whilst 15 of the 37 patients in their study experienced no post-operative pain whatsoever, eight experienced mild pain and 14 experienced moderate-to-severe pain up to 48 h after the operation. It is unclear from their report, however, what post-operative analgesia was available to their patients.91

Inadequate treatment of post-operative pain may result in adverse physical and psychological outcomes.88 Indeed, neurological post-operative pain is widely perceived as being under-treated, largely due to the prevalent use of codeine phosphate.90,93,94 The lack of efficacy (and apparent safety) of codeine phosphate may be due to inadequate dosing, unreliable absorption after intramuscular injection and slow bio-activation to morphine in a significant proportion of patients.87,88 Meanwhile, intramuscular, intravenous and patient-administered morphine have been established as safe and efficacious in small randomised trials.95,96,97

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As the opioids share many undesirable side-effects, other analgesic options have been sought for neurosurgical patients. Tramadol, a weak μ-receptor agonist that inhibits neuronal reuptake of serotonin and noradrenaline, lacks respiratory depressant, sedative or myotropic effects. However, when compared with intramuscular codeine phosphate in a randomised, double-blinded trial, intramuscular tramadol was associated with higher pain scores, more frequent dosing, more sedation and more post-operative nausea and vomiting. In addition, seizures have been reported after rapidly-administered intravenous boluses. Tramadol, therefore, does not appear to be the answer.

Non-steroidal anti-inflammatory drugs are widely used as adjuvant drugs in general surgical patients. The opioid-sparing ability of ketoprofen was compared with paracetamol in a small randomised trial in neurosurgery patients: ketoprofen was more efficacious than paracetamol, but equi-potent doses were probably not administered. Whilst there were no haemorrhagic complications in this study, non-steroidal anti-inflammatory drugs should be used with caution neurosurgical patients at risk of bleeding.

A recent set of Clinical Practice Guidelines published by the National Health and Medical Research Council (NHMRC) made specific recommendations for neurosurgery patients, which we endorse: carefully-titrated, individualized doses of intravenous morphine, along with regularly administered paracetamol. Scalp infiltration with bupivacaine during surgery also decreases post-operative pain scores. The NHMRC also emphasised the need for careful monitoring of sedation and pain scores in neurosurgical patients. If patient-controlled analgesia is employed, management by an Acute Pain Service may result in significant practice differences and fewer side effects compared with primary service physician care.

Nausea and vomiting

Post-operative nausea and vomiting (PONV) is common in patients undergoing craniotomy, despite the universal use of dexamethasone, an effective anti-emetic. Younger patients, women, and those having infratentorial surgery, are more likely to suffer PONV. The data suggest a protective effect of propofol-based anaesthesia, although confirmation of this finding awaits a suitably-designed trial.

Routine use of prophylactic anti-emetics therefore may be warranted. However, the data supporting one agent over another are inadequate and conflicting. When metoclopramide (10 mg i.v.) was compared with ondansetron (8 mg i.v.) in 60 patients undergoing intracranial surgery, significantly less PONV was reported in the metoclopramide group than the ondansetron group (44% vs 30%; P = 0.038). However, ondansetron patients received more codeine phosphate: either a chance finding or due to ondansetron-induced headache. In contrast, when ondansetron (4 mg i.v.) was compared with placebo in 40 patients having infratentorial surgery, significantly less PONV was reported in the ondansetron group than the placebo group (50% vs 10%; P = 0.05). Post-operative sedation was more common in the ondansetron group. Finally, Fabling et al. compared ondansetron (4 mg i.v.) with droperidol (0.625 mg i.v.) and placebo in 60 patients undergoing supratentorial surgery. Ondansetron and droperidol halved the incidence of nausea compared to placebo (40% vs 40% vs 70%; P = 0.02), but only droperidol decreased the incidence of vomiting (45% vs 20% vs 55%; P = 0.004). There were no differences in pain or sedation scores. Further evidence is required before a recommendation about antiemetic prophylaxis in neurosurgical patients can be made.

Patient satisfaction

Many of our yardsticks for ‘success’ are irrelevant to patients, who have a different perspective on what constitutes high-quality care.

CONCLUSIONS

We started with the question: ‘what is the evidence that anaesthesia care makes a difference to the outcome from neurosurgery?’. We have identified differences between anaesthetic agents in terms of pathophysiology and intermediate outcomes, such as quality of recovery, but have found no evidence that the choice of anaesthetic affects the neurologic outcome. Based on current evidence, therefore, carefully administered anaesthesia with any of a variety of agents is acceptable. There is a paucity of information in the literature about the prevention of post-operative pain and nausea and vomiting in neurosurgical patients. These problems need to be addressed with properly-designed clinical trials.

REFERENCES


