Purpose of review
In this review, we present an update on the relationship between anesthesia and intraoperative hemodynamic complications, early postanesthesia recovery, postoperative pain and postoperative nausea and vomiting after craniotomy. We also review latest advances in education and research in neuroanesthesia for brain surgery.

Recent findings
Insights from clinical reports published from January 2012 to April 2013 on anesthesia for craniotomy will be summarized. Recent findings address the need for a tight intraoperative hemodynamic monitoring – that should include aggressive prevention of arterial hypotension and cardiac arrhythmias – and a careful management of fluids and electrolytes balance. Data on the relationship between anesthesia (selection of anesthetics used intraoperatively) and early recovery demonstrate a limited benefit when ultra-short acting drugs (as remifentanil vs fentanyl) are used. Evidence on postoperative pain and postoperative nausea and vomiting contribute to define how to better prevent and treat these complications. Latest guidelines on training and research in neuroanesthesia define unique end points in this subspecialty.

Summary
Neuroanesthesia for craniotomy should be aimed to ensure intraoperative loss of consciousness (unless awake craniotomy is the selected anesthesiological approach), pain control and an uneventful postoperative recovery, but should also be addressed to manipulate physiological variables including cerebral blood flow and to obtain optimal surgical exposure.

Keywords
craniotomy, neuroanesthesia, neuroanesthesiology training, neurosurgery, traumatic brain injury

INTRODUCTION
The practice of anesthesia for craniotomy is evolving along with evidences from the literature, changes in the types of patients treated, available drugs and monitoring techniques [1,2]. In neuroanesthesia, patient’s safety and well-being are established priorities as is surgical field exposure, and these objectives often have, as a prerequisite, an appropriate patient positioning [3]. The practice of anesthesia for craniotomy encompasses different clinical scenarios – traumatic brain injury (TBI), intracranial tumors, brain neurovascular surgery – that require to be addressed in a dramatically different way [1,4].

In this review, we present an update of published evidence on anesthesia for craniotomy with results from intraoperative and postoperative management studies – used end points include: time to extubation, recovery of physiological variables, time to discharge from the operating room, postoperative pain and postoperative nausea and vomiting (PONV) – and insights on education and research.

INTRAOPERATIVE MANAGEMENT
Latest evidence on intraoperative management of hemodynamic, fluid/electrolytes balance and coagulation, in patients undergoing anesthesia for craniotomy, are reported in this chapter [5–12,13*, 14,15*,16–23].

Appropriate management of hemodynamic variables is a cornerstone of anesthesia for craniotomy and includes manipulation of cardiac output, arterial blood pressure, cardiac rhythm and cerebral blood flow [1,5,6]. In patients with TBI the severity of the primary insult is the major factor determining the outcome, secondary damage to brain tissue can
Arterial hypotension and cerebral hypoperfusion are among the most important risk factors for secondary brain damage and are independently associated with increased morbidity, mortality and worsening of long-term outcome after TBI [5,6].

Intraoperative arterial hypotension, defined as SBP less than 90 mmHg, has been reported to complicate the course of anesthesia for craniotomy in 36–42% of the cases [6–8]. In a retrospective cohort study [6], data from 113 patients with TBI were revised and occurrence of intraoperative arterial hypotension was recorded in 65% of the patients. The high prevalence of intraoperative arterial hypotension recorded in this study – attributed to accuracy of monitoring technologies – is alarming and underlines the need for continuous clinical alertness and aggressive prevention [6]. Several risk factors for intraoperative arterial hypotension can be predicted by preoperative CT scan – that is presence of multiple brain lesions and presence and thickness of hemorrhage – and it highlights the importance of including anesthesiologist’s evaluation of preoperative CT scans in patients with TBI [6]. The role of lidocaine, injected along with rapid sequence anesthesia induction drugs, in preventing postintubation arterial hypotension – defined as MAP less than 70 mmHg – has been assessed in a retrospective cohort study in which data from 101 patients with TBI were revised [9]. In this study, the use of lidocaine (mean-injected dose 1.38 mg/kg) was not associated with increased rate of postintubation arterial hypotension [9].

Cardiac rhythm disturbances, and especially asystole and bradycardia, can be evoked during anesthesia for craniotomy by various mechanisms: parasympathetic stimulation, as intracranial pressure (ICP)-mediated vagus nerve stimulation or trigeminal cardiac reflex (TCR) and local anesthetic toxicity [10–12,13]. Isolated bradycardia during skull pin fixation with sudden heart rate (HR) decrease from 80 bpm to 44 bpm has been described in a 21-year-old patient electively scheduled for craniotomy to remove an intraventricular ependymoma [10]. In this case, withholding pin application temporarily normalized HR, but a subsequent attempt to fasten the pins again caused a drop in HR to 45 bpm. The patient was effectively treated by head elevation, hyperventilation and an additional 50 mg of propofol was administered, and pin fixation was accomplished without inducing further cardiovascular complications [10]. Intraoperative asystole, during monitored anesthesia for awake craniotomy, has been described in a 50-year-old patient [11]. In this patient, sudden asystole associated with signs of parasympathetic stimulation – including hypotension, nausea and vomiting, interpreted as TCR – occurred during skin closure [11]. Asystole was successfully treated with cessation of the stimulus and the authors conclude that vigilant monitoring throughout the procedure can avoid catastrophic consequences [11,12]. Complete ativoventricular block during awake craniotomy has been reported in a 53-year-old patient who underwent awake craniotomy for a supratentorial brain lesion adjacent to the primary language area [13]. In this patient, after selective block of sensory branches of trigeminal nerve with ropivacaine (40 ml of ropivacaine 0.75%) and infiltration of the surgical field with lidocaine (irrigation with 20 ml of lidocaine 2% and infiltration with 5 ml of lidocaine 2%) before dura opening, complete ativoventricular block – associated with spontaneous idioventricular rhythm (HR <30 bpm) and severe arterial hypotension (MAP 40 mmHg) – developed. Bradycardia did not improve after atropine bolus injection (0.5 mg). Local anesthetic toxicity was suspected, and 20% intralipid was infused (100 ml bolus followed by 20 min continuous infusion) in association with phenylephrine (10 mg) bolus effectively inducing the restoration of

KEY POINTS

- During anesthesia for craniotomy multiple patient-based and disease-based needs should be addressed. Latest evidence underlines the importance of appropriate management of systemic and cerebral hemodynamic that includes: tight monitoring and control of mean arterial pressure (MAP) and cardiac rhythm.
- Intracranially, the fluid and electrolytes balance and coagulation profile need to be kept within normal limits – to the larger possible extent – both in elective and emergency cases.
- There is a tight relationship between anesthesia, quality of postoperative recovery and complications rate after craniotomy. Latest evidence highlights that the use of shorter acting opioid anesthetics (remifentanil) is not associated with earlier recovery of physiological variables.
- Appropriate management of postoperative pain is strictly recommended and effectively associated with pain control.
- Dedicated training, education and research are necessary and can extensively contribute to improve the quality of patient care in anesthesia for craniotomy.

be caused by perturbations of physiologic variables and can contribute to determine the outcome [5,6].
its safety and to reduce related complications [15]. After restoration of sinus rhythm, intralipid 20% solution was continuously infused for 20 min to avoid local anesthetic redistribution. Surgical excision of the lesion was completed, and the patient had an uneventful postoperative course [13*].

During craniotomy, intraoperative fluids and electrolytes balance is dramatically affected by the use of diuretics administered to decrease ICP and to facilitate intracranial dissection [14,15*,16–18]. Effects of administration of mannitol-alone (1 g/kg) or combined with furosemide (0.3 mg/kg) on surgical brain relaxation has been prospectively assessed in 23 patients who underwent craniotomy for tumor surgery [14]. The use of mannitol alone induced large volume diuresis, the adjunct of furosemide increased urine output (from 1533 ± 335 to 2561 ± 611 ml, P < 0.001) [14]. In this study [14], the increase in urine output was not associated with significant differences in electrolyte derangements or hypovolemia in the two groups. Effects on electrolyte excretion are different when mannitol therapy, with repeated infusions, is established [15*,16]. In a prospective study [15*] in 56 neurocritical care patients treated for cerebral edema, mannitol therapy (0.5 g/kg at 4 h interval) was associated with a significant increase in potassium urinary excretion. The adjunct of a potassium sparing diuretic (canrenone 200 mg daily) effectively blunted the increase in potassium urinary excretion [15*]. The potential harm related to mannitol therapy – that includes volume and electrolyte shift, higher risk of cardiac arrhythmias – led to question its role in the treatment of cerebral edema [14,16–18]. The adjunct of potassium sparing diuretics to mannitol therapy can contribute to increase its safety and to reduce related complications [15*].

Perioperative blood loss can be associated with intraoperative coagulopathy and anemiaization that are especially dangerous in neuroanesthesia [1,4,19,20]. In pediatric neurosurgical patients, intraoperative transfusion of fresh frozen plasma effectively preserves whole blood coagulation as demonstrated by thromboelastometry analysis [20]. In patients undergoing craniotomy, normal blood coagulation is essential and perioperative fluid therapy should not alter this homeostasis [21]. Artificial colloids and mannitol, because of dilutional effect, decrease whole blood clot strength and increase the risk of bleeding [22,23].

In conclusion, anesthesia for craniotomy should address multiple patient-based and disease-based needs, in the elective and emergency setting. Latest evidence underlines the importance of appropriate management of systemic and cerebral hemodynamic, fluid and electrolyte balance and coagulation profile.

**POSTOPERATIVE MANAGEMENT**

In patients undergoing craniotomy, the relationship between intraoperative anesthesia, early postoperative recovery and postoperative complications rate has been extensively studied [24–26]. Hereafter, we report an update on the relationship between anesthesia and early postoperative recovery (measured as time to extubation, recovery of physiological variables and discharge from the operating room) and length of hospital stay (LHS) after craniotomy [27**,28,29]. We also report recent evidence on postoperative pain management with patient-controlled analgesia (PCA), on the safety of NSAIDs and on the risk of PONV after craniotomy [30–34].

The anesthetic regimen used to maintain general anesthesia during craniotomy has modest clinical impact on early postoperative recovery [27**,28,29]. Limited relevance of the anesthetic regimen used to maintain general anesthesia, and the time necessary to postoperative recovery of physiological variables (using Aldrete score as a quantitative measure to compare the three study groups) has been demonstrated by the Neuromorfoe trial [27**]. In this study, 400 patients were prospectively and randomly assigned to three study groups – total intravenous anesthesia with propofol and remifentanil, or sevoflurane with either remifentanil or fentanyl – and time necessary to reach an Aldrete of at least 9 after extubation did not differ among recruited patients [27**]. Similarly, there was no relevant clinical difference in time to extubation and time to discharge from the operating room when isoflurane or propofol were used to maintain general anesthesia in patients undergoing craniotomy for brain tumor excision [28]. Although in this retrospective analysis in 159 cases a statistical difference has been reported (39 vs. 29 min and 67 vs. 53 min, P < 0.001), the related clinical difference seems to be trivial [28]. The effects of remifentanil-based general anesthesia on LHS and in hospital mortality have been evaluated in a retrospective study of 3692 patients undergoing craniotomy or colorectal surgery [29]. Data led to controversial results: among patients undergoing craniotomy (936 pairs) those who received remifentanil had shorter LHS and lower in-hospital mortality as compared with the control group, these figures were not confirmed in patients undergoing colorectal surgery (2.756 pairs) [29].

Postoperative analgesia therapy is a cornerstone of optimal postoperative management after craniotomy, because inadequate pain control can cause discomfort and may lead to increased postoperative complications and prolonged hospital stay [30]. In the latest years, clinical practice have
focused on challenging and more aggressive treatment of pain following craniotomy, but no firm recommendations are available also because of the lack of large randomized clinical trials that investigate postcraniotomy pain [30]. Current practice is based on a multimodal approach that should include scalp block with local anesthetics and the use of NSAIDs and opioids [30]. Efficacy of PCA after craniotomy, for posterior fossa surgery, has been proven in 31 patients prospectively randomized to receive PCA as compared with 34 patients treated with nurse-administered as-needed fentanyl [31]. In spite of the promising results, larger studies are needed to assess the safety of this approach. Furthermore, because of the potential effects of opioids on neurological function and cognitive abilities and the need for a full clinical evaluation in order to immediately detect changes in the clinical status – when intracranial hemorrhage complicates the postoperative period – sedative opioids should be used cautiously after craniotomy but a good pain therapy is also essential to avoid hypertension [30]. In a retrospective nested case–control study [32] in which data from 1571 patients treated with ketorolac (50 ± 15 mg/die) after craniotomy are described, the adjusted estimate for risk of symptomatic bleeding requiring emergency redo surgery is close to the null effect when compared with 2515 patients of the control group. Nevertheless, reported evidence is not a conclusive witness of the safety of ketorolac after elective craniotomy.

Occurrence of PONV is distressing, undesirably complicated and potentially dangerous after neurosurgical procedures also because of the effects on intracranial pressure and cerebral intravascular pressure, that can result into brain swelling, intracranial hemorrhage and hematoma formation [33,34]. Incidence of PONV and the effects on length of stay in the postoperative recovery room were reported in a retrospective case–control study, in which data from 117 patients undergoing elective microvascular decompression or acoustic neurinoma resection were compared with 185 control patients who have undergone craniotomy [33]. In patients undergoing neurinoma resection, the risk for PONV is higher than after craniotomy for other tumor resection, patients who experienced PONV required longer stays in the recovery room [33]. Effectiveness of transcutaneous electrical acupoint stimulation at the P6 meridian point as adjunct to the standard antiemetic drug therapy for preventing PONV after craniotomy has been successfully tested in 119 patients [34].

In conclusion, in patients undergoing craniotomy, there is a tight relationship between anesthesia and the quality of postoperative recovery and complications rate. Latest evidence highlights that the use of shorter acting opioid anesthetics (remifentanil) is not associated with earlier recovery of physiological variables and that appropriate management of postoperative pain is effectively associated with pain control.

EDUCATION AND RESEARCH

Adequate education for the practice of neuroanesthesia, should include a dedicated fellowship training and continuing medical education (CME) and a tight link between daily practice and clinical research are prerequisites for qualified and evidence-based patient care [35**].

The Society for Neuroscience in Anesthesiology and Critical Care has recently released curricular guidelines to standardize accreditation criteria for neuroanesthesiology fellowship training through the American College of Graduate Medical Education [35**]. According to these guidelines, the director of the neuroanesthesiology fellowship program should be board certified by the appropriate institution, should devote the majority of his/her time to clinical neuroanesthesia, should have a documented record of scholarly activity in neuroanesthesiology in the past 5 years and should be an active member of neuroanesthesia or neurocritical care societies [35**]. Curricular guidelines, intended to be minimal rather than optimal standards for training, are built upon 10 modules of 4-week units and include: six modules of clinical neuroanesthesia (including adult and pediatric cases); one module of neurocritical care; one module of neuroradiology; one module of neuromonitoring and; one module of neuroscience scholarship [35**]. These guidelines represent a milestone for high quality medical education in neuroanesthesia, additional initiatives for CME in this subspecialty – including meeting lectures, refresher courses, website supported activities and dedicated journals – can further contribute to increase the quality of provided care [36,37].

Advancements in neuroanesthesia are also related to well designed – and well conducted – studies in which qualified end points are selected [26,38,39]. The importance of using appropriate end points is related to the fact that in neuroanesthesia patients, differences can become apparent a long time after the procedure – up to months – and that used scales are not adequately sensitive. Especially, detecting differences in long-term outcome can be demanding and expensive [26,38,39]. Several treatments supported by positive preclinical results failed to confirm the related benefits when challenged into clinical practice thus creating a mismatch between bench and bedside tools [38]. To strengthen
the ability of clinical trials in providing robust evidence for advanced science and improve clinical practice in brain-diseased patients, the neurocritical care society has promoted and published a research conference dedicated to clinical trial design in neurocritical care patients [39].

In conclusion, adequate training, education and research can extensively contribute to improve the quality of patient care in neuroanesthesia.

**CONCLUSION**

Anesthesia for craniotomy is significantly evolved over time. Among the key issues for this discipline is the harmonious management of pharmacological, clinical and physiological variables. Intraoperative management encompasses to address multiple patient-based and disease-based needs in the elective and emergency setting. Quality of post-anesthesia recovery and the rate of postoperative complications are affected by efficacy in physiological variables manipulation, by the anesthetic strategy adopted intraoperatively (that should include appropriate patient positioning, management of systemic and cerebral hemodynamic, fluid and electrolyte balance and coagulation) and by postoperative care (including prevention and treatment of pain and PONV).

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest

II of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 632–633).


Detailed guidelines that originally address the need for a specific training in neuroanesthesia.


