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Incidence and predicting factors of perioperative complications during monitored anesthesia care for awake craniotomy

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Abstract

Study objective: to assess incidence and predicting factors of awake craniotomy complications

Design: Retrospective cohort study

Setting: Operating room and Post Anesthesia Care unit

Patients: 162 patients who underwent 188 awake craniotomy procedures for brain tumor, ASA I to III, with monitored anesthesia care.

Measurements: We classified procedures in 3 groups: major event group, minor event group, and no event group. Major events were defined as respiratory failure requiring face mask or invasive ventilation ; hemodynamic instability treated by vasoactive drugs, or bradycardia treated by atropine, bleeding more than 500 ml, transfusion, gaseous embolism, cardiac arrest; seizure, cerebral edema, or any events leading to stopping of the cerebral mapping. Minor event was defined as any complication not classified as major. Multivariate logistic regression was used to determine predicting factors of major complication, adjusted for age and ASA score.

Main results: 45 procedures (24%) were classified in major event group, 126 (67%) in minor event group, and 17 (9%) in no event group. Seizure was the main complication (n = 13). Asthma (odds ratio: 10.85 [1.34; 235.6]), Remifentanil infusion (odds ratio: 2.97 [1.08; 9.85]) and length of the operation after the brain mapping (odds ratio per supplementary minute: 1.01 [1.01; 1.03]) were associated with major events.

Conclusions: Previous medical history of asthma, remifentanil infusion and a long duration of neurosurgery after cortical mapping appear to be risk factors for major complications during AC.

Key words: Awake craniotomy; monitored anesthesia care; neurosurgery.

1. Introduction

Complete brain tumor resection of glioma is associated with better outcome [1] . However, the risk of post-operative neurological deficit may be high in cases of tumors located near functional areas. Awake craniotomy (AC), known since the beginning of the 20th century, allows intraoperative mapping of the functional areas in order to optimize brain tumor resections [2,3]. This procedure allows the surgeon to localize motor-, language- or cognitive-related areas, known to have important inter-individual variations, in order to try to avoid neurological deficits [4,5].

Anesthesia for AC may be challenging [6,7]. Active participation of the patient during the cortical mapping is mandatory. This requires a fully conscious patient, but also comfort, analgesia and security during other phases, such as skull and dura-mater incision or closing. Several anesthetic protocols have been described [7–9]. In the “asleep-awake-asleep” protocol, the patient is under general anesthesia before and after the cortical mapping. The “awake-awake-awake” protocol includes intravenous analgesia and local anesthesia of the scalp without planned hypnotic drug infusion [8]. The “monitored anesthesia care” (MAC) is the association of different levels of sedation according to surgical phases, with spontaneous breathing throughout the procedure. The incidence of perioperative complications during AC probably differs among anesthetic protocols [10]. Impossibility of completing cortical mapping or the need to stop the surgery and to convert to General Anesthesia (GA) have been described in up to 6.4% of cases [10]. However, there is lack of data concerning the incidence and predicting factors of perioperative complications during AC using MAC for brain tumor resection.

The main objective of this study was to determine the incidence and predicting factors of major or minor complications during brain tumor resection using MAC throughout the surgical procedure and the early postoperative phase in the postoperative anesthesia care unit (PACU). The second objective was to compare MAC and general anesthesia for the incidence of complications.

2. Material and methods

2.1. Study design

This monocentric retrospective study was approved by the local ethics committee (Comité d'éthique regional, Reference Number 121016). According to this committee and French law, no written consent was required, but patients were informed that their data could be used anonymously for scientific reports.

2.2. Inclusion and exclusion criteria

All patients who had undergone AC for scheduled brain tumor resection between January 2009 and April 2016 in French University Hospital (Purpan Hospital, University Toulouse 3-Paul Sabatier, Toulouse) were included. Anesthesia, intraoperative and postoperative reports were reviewed.

These patients were matched with a group of patients who had undergone neurosurgery for brain tumor resection under GA in our center. This group was extracted from a database provided by a national study focusing on postoperative complications after neurosurgical procedure published elsewhere [9].

2.3. Definitions of major and minor events

Major events were defined as:

- Respiratory failure during procedure or in the postoperative anesthesia care unit (PACU) stay requiring face mask ventilation, laryngeal mask or orotracheal intubation;
- Hemodynamic instability during procedure or PACU stay treated by vasoactive drugs or bradycardia treated by atropine, bleeding with blood loss of 500 mL, transfusion, gaseous embolism with hemodynamic instability, cardiac arrest;
- Neurologic complications defined by seizure during procedure leading to stopping of the cortical mapping or during PACU stay, or cerebral edema treated with osmotherapy;
- Any events leading to the cerebral mapping being stopped, for example agitation or anxiety requiring sedation;

Minor events were defined as:

- Respiratory complications: hypoxemia defined by a pulse oximetry lower than 95%, hypercapnia defined by end-tidal CO₂ greater than 45 mmHg, polypnea with respiratory rate higher than 30 bpm or bradypnea with respiratory rate lower 10 bpm, and airway obstruction treated by oropharyngeal (Guedel) or nasopharyngeal cannula during procedure or PACU stay, with no need for face mask ventilation, laryngeal mask or orotracheal intubation.
- Hemodynamic complications: arterial hypotension defined by a systolic arterial pressure (SAP) lower than 90 mmHg, arterial hypertension defined by a SAP higher than 160 mmHg, bradycardia with a heart rate (HR) lower than 50 bpm, tachycardia defined by an HR higher than 120 bpm, any other cardiac arrhythmia or conduction disorders during intraoperative time or PACU stay, without need for any drugs (intravenous fluids excepted).
- Neurologic complication: Transient loss of patient participation but with full completion of the cerebral mapping, either with or without use of anxiolytic drugs.

We classified procedures in 3 groups: major event group, minor event group, and no event group.

A procedure with at least one major event was classified in the major event group. A procedure with at least one minor event and no major event was classified in the minor event group. Otherwise, the procedure was classified in the no event group.

2.4. Data collection

One authorized person collected all the data from the medical record of each patient. Demographic data collected were age, gender, weight, height, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, native language, and the handedness of the patient.

Previous medical history was recorded:

- Neurologic data: history of previous intracranial surgery, stroke or intracranial bleeding, epilepsy, preoperative cerebral motor or sensory impairment, dysphasia;
- Cardiologic data: history of high blood pressure, coronary insufficiency, dyslipidemia, chronic cardiac failure, venous thromboembolism;
- Respiratory data: asthma, chronic obstructive pulmonary disease (COPD), smoking, obstructive apnea sleep syndrome;

- Diabetes mellitus or chronic renal failure.

Preoperative medications were also recorded with particular interest in steroids, antiepileptic and benzodiazepine drugs.

The following data were collected from the procedure record: the use of propofol and remifentanyl with target-controlled infusion; the time before the cerebral mapping, defined as the time between the beginning and first discontinuation of anesthesia; the time during cerebral mapping, defined as the time between the discontinuation of anesthetic drug and the restart of anesthetics infusion; the time after cerebral mapping defined the time between the restart of anesthetics infusion and the end of surgery; the total time of the procedure ; **patient discomfort reported to the surgeon or anesthesiologist during postoperative period** and the hospital length of stay.

From patients who underwent brain surgery under general anesthesia, the following patients' characteristics were collected: age; gender; ASA physical status; medical history and treatment; anesthetic drug used per operatively.

For both groups were collected hypertensive episode, defined by systolic arterial pressure (SAP) higher than 160 mmHg at any moment; hypotensive episode, defined by SAP lower than 90 mmHg at any moment; norepinephrine infusion; osmotherapy; red blood cells (RBC) transfusion; hypothermia, defined by body temperature lower than 36 °C; intra- or postoperative seizure; postoperative nausea and vomiting (PONV); revision **defined by reoperation during hospitalization for any reason**; PACU and Hospital length of stay (LOS); and death.

2.5. Selection of patients

All patients underwent standardized, intraoperative language tests (by a speech therapist) as follows: visual naming using the DO80 test (this test was also performed postoperatively in all patients, between 2 days and 2 weeks after the operation), written, auditory and visual comprehension abilities, oral fluency, reading, dictation, repetition, written transcription, and object handling [9]. Briefly, the DO80 test is a French version of the Boston Naming test based on 80 basic items that the patient has to name. Dysphasic patients (with more than 10% of errors in the DO80 naming test) were excluded. Patients with chronic cardiac failure, chronic pulmonary failure, obstructive sleep apnea, predicted or known difficult airway,

American Society of Anesthesiologists (ASA) status of 4, major preoperative anxiety, or age less than 14 years were also excluded.

2.6. Surgical protocol

One hour before admission to the operating room, a patch containing a eutectic mixture of prilocaine (2.5 mg/g) and lidocaine (2.5 mg/g) (EMLA[®]) was applied in the supraorbital and auriculotemporal regions. Lidocaine 1% with epinephrine 1:100000 was infiltrated to block the supraorbital, auriculotemporal, and occipital nerves. Additionally, the Mayfield head holder (Ohio Medical, Cincinnati, OH) pin site and the surgical skin incision line were infiltrated. Sedation with spontaneous respiration was stopped during the dural opening (around 10 mn before brain mapping). A neuronavigational system was used in all patients to guide tumor resection and intraoperative cortical stimulations were used to localize areas of functional cortex. Anatomical structures (gyri and sulci) were identified according to these neuronavigational data and the visual identification of the shape of gyri and sulci (i.e. 3D anatomy of the circumvolutions). Before starting a direct cortical stimulation procedure, we chose a substantial number of sites on the brain surface. Each site was separated from the others by 3 mm. The number of stimulation sites varied from one patient to another depending on the size and the location of the craniotomy. Once the cortical mapping procedure was completed, patients were put back under sedation using the same protocol for the rest of the operation.

2.7. Anesthesia protocol

AC was performed with MAC, with the association of propofol and remifentanil by target-controlled infusion. At the discretion of the anesthesiologist in charge of the patient, remifentanil might be replaced by sufentanil **continuous infusion with intermittent bolus if needed, and propofol infusion can be stopped if needed**. In the majority of cases, propofol effect-site concentration was between 1 and 2 µg/ml and remifentanil effect-site concentration was between 1 and 2 ng/ml. When used, sufentanil was titrated on a 5 µg basis. In all cases, the regimen was adapted to obtain unconsciousness with spontaneous breathing without airway instrumentation (laryngeal mask or endotracheal tube). Sedation was stopped after dura mater opening, restarted after cerebral mapping and thereafter continued until scalp closure.

Cardiac rhythm was continuously monitored. Arterial blood pressure was monitored in all cases via a non-invasive sphygmomanometric method with or without invasive intra-arterial monitoring. Oxygen supply was administered through a facial mask and end-tidal carbon dioxide waveform and pressure was continuously monitored using a Capnomask™ (Mediplus, UK) connected to the ventilator carbon dioxide analyzer during the entire procedure.

GA was induced by intravenous 0.2 µg/kg sufentanil, 2 to 2.5 mg/kg propofol and 0.15 mg/kg cisatracurium, and maintained with sevoflurane with an objective of 0.8 to 1.2 minimal alveolar concentration (MAC) adjusted for age. In few cases, GA was maintained with Target-controlled infusion (TCI) of propofol. During procedure, anesthesiologist had as objectives to maintain mean arterial pressure superior to 65 mmHg, SpO₂ superior to 95%, and adjust ventilation to maintain end-expiratory carbon dioxide pressure between 30 and 35 mmHg. Sevoflurane (or propofol) was stopped at the end of the procedure, and patient was extubated and transferred to PACU.

2.8. Statistical analysis

Statistical analyses were performed with the R software (R Core Team (2014). (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>). Student's t test or Welch's t test (when Student's t test was not appropriate) was used to compare quantitative variables, and the Chi-squared test to compare binomial variables. Data were expressed as median with first and third interquartile, mean +/- standard deviation, or percentage. Univariate logistic regression was performed in order to find factors associated with major events. Factors with p-values lower than 0.2 were included in the multivariate logistic regression, with the backward stepwise selection method, adjusted by age and ASA score. For the comparison with general anesthesia, we used a propensity score with nearest neighbor matching ("MatchIt" package). Multiple imputation with the "mice" package was used to deal with missing values [12]. A two-sided p value of less than 0.05 was considered to be statistically significant.

3. Results

One hundred and ninety-seven procedures were screened, and 9 were excluded due to insufficient data (**Figure 1**). Overall, data from 188 procedures performed on 162 patients (26 patients had more than one surgery) were analyzed. Forty-five procedures (24%) were classified in the major event group, 126 (67%) in the minor event group, and 17 (9%) in the no event group. **Table 1** summarizes the demographic characteristics of the population, and **Table 2** procedures data.

3.1. Major event group (**Figure 2**)

We found 9 procedures with hemodynamic events (4.8%). Ephedrine was the only vasoactive drug used. We also found 9 procedures with respiratory events (4.8%). The only intubation retrieved occurred during PACU stay for status epilepticus.

Overall, one neurologic event occurred in 26 procedures (13.8%), with 2 procedures having more than one major neurologic. Of notice, 2 procedures were stopped for major bleeding in intraoperative time and 4 for complete loss of patient's cooperation. One patient received osmotherapy for cerebral edema in the PACU. During the first postoperative week, 4 patients needed further surgical procedures: 2 patients for external ventricular drainage for hydrocephalus, one for subdural hygroma, and one for extradural hematoma. For 6 procedures (3.2%), the patient's ICU stay was prolonged (more than 24h).

We found 38 procedures with at least one major event associated with at least one minor event, and 34 associated with more than one minor event: 54 minor hemodynamic events (4 bradycardia, 2 tachycardia, 13 hypotension, 14 hypertension episodes in intraoperative time, 5 bradycardia, 5 tachycardia, 3 hypotension, 8 hypertension episodes during PACU stay), 53 minor respiratory events (19 episodes of bradypnea, 2 of polypnea, 10 of hypoxemia, 3 of hypercapnia, and 3 airway obstructions treated by oropharyngeal cannula in intraoperative time; and 10 episodes of bradypnea, 1 of polypnea, 4 of hypoxemia during PACU stay), 1 transient loss of patient participation during cerebral mapping, 11 post-operative nausea and vomiting episodes and 12 accidental hypothermia in PACU.

3.2. Minor events group (**Figure 2**)

We found 83 procedures with a least one *minor* hemodynamic event (44.1%), including 35 procedures with more than one minor hemodynamic event: The rhythm trouble retrieved was

a paroxysmal atrial fibrillation and the conduction trouble was a second degree atrioventricular block without hemodynamic disturbance in intraoperative time.

We found 104 procedures with a *minor* respiratory event (55.3%), including 38 with more than one minor event. Airway obstructions were treated 4 times by oropharyngeal cannula and 3 times by nasopharyngeal cannula

We found 3 procedures with a *minor* neurologic event (1.6): No patient discomfort was reported.

There were 86 procedures in which more than one minor event was detected.

3.3. Factors associated with major events (Table 3)

Multivariate logistic regression included 3 univariate significant variables (asthma, remifentanyl infusion and morphine infusion in PACU stay) and 1 univariate variable with a p-value of less than 0.2 (time after cerebral mapping). We chose not to include estimated blood loss (p=0.06) because of too many cases of missing data (135 missing data among the 188 procedures). We adjusted the analysis to age and ASA score. *Asthma* (odds ratio: 10.85 [1.34, 235.6]), *Remifentanyl infusion* (odds ratio: 2.97 [1.08, 9.85]) and *prolonged operation duration after mapping* (odds ratio per supplementary minute: 1.01 [1.01, 1.03]) were significantly associated with major events in multivariate logistic regression.

3.4. Comparison with procedures under GA

One hundred and twenty-six patients who had brain tumor surgery under GA were screened. Their characteristics are summarized in **Table 4**. Patients were matched by age, ASA score, gender, preoperative motor deficit, dysphasia, epilepsy, previous neurosurgery, arterial hypertension, diabetes mellitus, cardiac insufficiency, tumor localization, preoperative antiepileptic drugs or corticosteroids. After matching by propensity score, 60 patients from each group were included.

AC was associated with *fewer patients experiencing hypotensive episodes* (21 vs 53, p < 0.001), *hypothermia* (10 vs 29, p < 0.001), and *postoperative vomiting and nausea* (7 vs 18, p = 0.013). AC was associated with *a reduced length of stay (LOS) in hospital* - 5 days vs 8 days, p<0.001, **Table 5**.

4. Discussion

In the present cohort of 188 AC performed with the MAC procedure, minor events were the type of complications most commonly encountered (two thirds of the procedures). Nevertheless, major events were found in approximately 25% of the procedures, associated with 3 significant factors: a medical history of asthma, the use of remifentanyl and the operation duration after mapping. Compared with strictly matched procedures under GA, the MAC procedure was significantly associated with fewer episodes of hypotension, hypothermia and PONV. Furthermore, the hospital LOS was also significantly shorter in the AC group.

With the MAC procedure, anesthesiologists pay particular attention to airway management. In our study, we found very few laryngeal mask insertions (1.1% of all procedures) or face mask ventilation (3.2%). We believe that this low level of events was in relation with the experience of the team and patient selection. With the agreement of the neurosurgical team, patients with severe pulmonary disease or known for difficult airway management were not candidates for awake surgery. These data are in complete accordance with other studies. Using a similar MAC protocol over 27 years, Hervey-Jumper et al. noted only 1% laryngeal mask insertion to treat respiratory complications [13]. Other authors have reported an airway obstruction rate of 7% with MAC protocol and systematic nasopharyngeal cannula insertion [14]. Although hypoxemia occurrence was not reported, face mask ventilation was performed in several cases. The MAC procedure seems superior in some respects to the asleep-awake-awake protocol used by others. In a prospective study using asleep-awake-awake protocol with systematic laryngeal mask insertion, Conte et al. reported 5% of emergency intubations and 7% of vomiting in their 238 cases [15]. We observed no intraoperative emergency intubation or vomiting for any procedure in our series of patients.

On the other hand, hypertension and hypotension occurred frequently in the present study (respectively 34.6% and 20.7%). Other authors using asleep-awake-awake protocol with 135 patients, found rather similar rates of hypertension (27%) and hypotension (10%) [15]. This contrasts with the retrospective study of 46 patients by Sarang et al. using MAC protocol, who detected no blood pressure abnormalities [14]. A similar study of 17 patients reported no hypotension episodes but a hypertension rate of 24% [16]. These discrepancies could be related to the definition of blood pressure abnormalities, which has not been the same across studies, and to the number of cases studied.

In the present study, the incidence of seizure was 6.9%, which was rather lower than previously reported. Some other studies reported a rate of 3 to 16%, and seizure was a major cause of procedure cessation [13,15,17–20]

. In our experience, cold saline solution applied in the operating field stops seizure in the vast majority of cases, with few consequences on the patient's ability to participate in the cerebral mapping. Clonazepam was never used in the present cohort.

A better outcome is suggested by the present result when AC was compared to GA, with a reduced hospital length of stay. This was consistent with results previously published by our team for supratentorial tumor resection [19]. There is only one randomized controlled trial comparing GA and AC [20]. In this study, in which only 53 patients with intrinsic lesions of eloquent cortex were included, no improvement in neurological outcome, extent of resection or length of hospitalization was found. In contrast, in a retrospective study with cohort matched comparison of patients treated for supratentorial glioma, Peruzzi et al. found a shorter length of stay with AC [21]. Furthermore, several studies found that AC was well tolerated by patients (with, for instance, less pain and less PONV) [14,22–24]

In our institution Dexmedetomidine was not the standard of care for several reasons. First, at the time of the study, the European Medicine Agency recommended cautious with the use of dexmedetomidine in neurosurgical patient due to the lack of data. They recently revised their warning in 2018 [25]. Several authors define propofol-remifentanil association as the gold standard and dexmedetomidine as an alternative. In their review, Kulikov and Lubnin wrote in their review that “a combination of propofol and remifentanil has been the standard approach for sedation during the preawake phase of awake craniotomy for more than 2 decades [26]. They also emphasized interindividual variability of sedative effect and the risk of bradycardia with the use of dexmedetomidine. In their editorials, Lobo et al. conclude that “... the ability to perform intra operative mapping was similar between the groups” when referring to the study of Goettel et al. comparing dexmedetomidine to propofol- remifentanil association [6,27]. Our team use this association for many years and have experience with it.

One aim of the current study was to identify the independent risk factors associated with major events during AC. History of asthma, remifentanil use, and a prolonged operation time after mapping have been found to be associated with major events. To the best of our knowledge, asthma had never been reported to be associated with major events during awake surgery. In the present cohort, 6 patients had asthma, and 5 of them had a major event (2 face mask ventilation, 1 hypotension requiring use of vasopressor and 2 surgical revisions), and all

presented at least one minor respiratory event. Two patients were treated successfully by intraoperative inhaled β 2-mimetic. Stress and anxiety are known to trigger attacks in asthmatic patients: a lower level of sedation than required could lead to asthma attack, and higher to hemodynamic event or apnea requiring airway management. We could not retrieve asthma status of those patients, but its preoperative assessment seems to be as important as for GA according to our study. Remifentanyl is known to induce bradypnea, bradycardia and hypotension, especially when associated with propofol. Two studies have compared the association of propofol-remifentanyl to the propofol-dexmedetomidine association in AC, for epilepsy surgery in one study, and dexmedetomidine alone in the other, which concerned AC for brain tumor, both with the MAC protocol [27,28]. Both studies reported more respiratory complications in the propofol-remifentanyl group, even though better sedation was observed with this association. In our study, all major respiratory events and vasopressor uses occurred with remifentanyl infusion. We could not retrieve the dosage infused when events occurred, but we can hypothesize that it was higher than required.

In addition, prolonged operation duration after mapping reflects procedural issues found by either the surgeon or the anesthesiologist. Also, more time under sedation can, itself, increase the risk of complications, especially in PACU.

Two procedures have been stopped for bleeding. For one, the tumor was near to the middle cerebral artery, which was injured during the procedure. Procedure was stopped after control of the bleeding and removal of one third of the tumor. Neurologic status was normal at emergence. The patient had a second awake craniotomy two month later without complication. For the other, the tumor was highly vascularized and to completely remove it due to bleeding. At emergence, the patient was first hemiparetic, but returned two normal neurologic status without any revision after 2 days. The patient had a second surgery 1 year later under GA without complication.

4.1. Limits

This study may have some limits. Its design was retrospective. Some events, dealt with quickly, may not have been reported in the anesthesia charts and, therefore, may have been underestimated. Moreover, the definitions of major or minor events can be challenged, as no consensual definition is available. This could have conducted to overestimate the incidence minor complications. Finally, even if matching was performed according to best practice, a

selection bias cannot be excluded for the comparison of procedures performed with AC or GA.

4.2. Conclusion

Previous medical history of asthma, remifentanil use, and a prolonged operation duration after mapping have been found to be associated with major perioperative complications during awake craniotomy. A strict selection of patients and the experience of the team are probably key-factors for safety.

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Table 1. Demographic data; patients were classified in the “major event” category if they had at least one procedure with at least one major event, in the “minor event” category if they had at least one minor event with no major event, otherwise in “no event”. md: missing data; n: number of cases; \$: data expressed in mean; *: data expressed in median [1st quartile, 3rd quartile]

	Major event	Minor event	No event	Total
Patients n(%)	42 (25.9)	104 (64.2)	16 (9.9)	162(100)
ASA*	2 [1 – 2]	2 [1 – 2]	2 [1 – 2]	2 [1 – 2]
ASA 1, n(%)	13 (31)	32 (31)	5 (31)	50 (31)
ASA 2, n(%)	22 (52)	61 (59)	10 (63)	93 (57)
ASA 3, n(%)	7 (17)	11 (11)	1 (6)	19 (12)
ASA 4, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age, years (min-max) \$	46.7 (14-81)	49.0 (13-78)	47.4 (23-83)	48 (13-83)
Male n(%)	23 (54.8)	62 (59.6)	10 (62.5)	95 (58.6)
Weight, kg (min-max) \$	72.2 (48-110)	71.0 (48-105)	72.3 (55-98)	71.4 (48-110)
Height, cm (min-max) md=5 \$	169.3 (156-187)	170.5 (150-187)	172.1 (159-189)	170.3 (150-189)
Body Mass Index, kg/m² (min-max) n=5 \$	25.1 (18.1-34.0)	24.2 (17.9-35.9)	24.4 (19.5-33.2)	24.4 (17.9-35.9)
Mother language French, n (%)	41 (98)	103 (99)	16 (100)	160 (99)
Left handed, n (%) (md=2)	38 (91)	95 (91)	14 (88)	147 (91)
Previous Medical history				
Neurologic				
Stroke, n(%)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.6)
Intracranial bleeding, n(%)	1 (2)	4 (4)	0 (0.0)	5 (3)
Partial Epilepsy, n(%)	18 (43)	33 (32)	7 (44)	58 (35)
General Epilepsy, n(%)	16 (38)	41 (39)	4 (25)	61 (38)
Motor deficit, n(%)	10 (24)	24 (23)	4 (25)	38 (23)
Facial paralysis, n(%)	2 (5)	8 (8)	0 (0.0)	10 (6)
Dysphasia, n(%)	11 (26)	28 (27)	1 (6)	40 (25)
Sensory deficit, n(%)	3 (7)	13 (13)	1 (6)	17 (10)
Neurosurgery, n(%)	14 (33)	34 (33)	6 (38)	54 (33)
Cardiologic				
Arterial hypertension, n(%)	11 (26)	23 (22)	1 (6)	35 (22)
Coronary artery disease, n(%)	2 (5)	2 (2)	0 (0)	4 (2)
Dyslipidemia, n(%)	5 (12)	11 (11)	2 (13)	18 (11)
Venous thromboembolism, n(%)	2 (5)	3 (3)	1 (6)	6 (4)
Pulmonary				
Obstructive sleep apnea, n(%)	0 (0)	0 (0)	0 (0)	0 (0)
Asthma, n(%)	5 (12)	1 (1)	0 (0)	6 (4)
Chronic Obstructive Pulmonary Disease, n(%)	1 (2)	0 (0)	0 (0)	1 (0.6)
Smoking, n(%)	15 (36)	37 (36)	7 (44)	59 (36)
Diabetes mellitus, n (%)	1 (2)	4 (4)	0 (0.0)	5 (3)
Chronic renal failure, n (%)	2 (5)	0 (0)	0 (0)	2 (1)

Table 2. Procedure data. Procedures were classified in the “major event” group if at least one major event occurred, “minor event” group if at least one minor event and no major event occurred, and “no event” group if there was no event during the procedure; n: number of cases; md: missing data; min: minutes; *: data expressed as median [1st quartile; 3rd quartile]

	Major event	Minor event	No event	Total
Procedures n (%)	45 (24)	126 (67)	17 (9)	188 (100)
Corticosteroids				
Before surgery, n (%)	31 (69)	52 (41)	6 (35)	82 (44)
Day of the surgery, n (%)	29 (64)	81 (64)	9 (53)	119 (63)
antiepileptic drugs				
Before surgery, n (%)	24 (53)	78 (62)	9 (53)	118 (63)
Only for the surgery, n (%)	14 (31)	48 (38)	8 (47)	70 (37)
Benzodiazepine				
Before surgery, n (%)	6 (13)	16 (13)	4 (24)	26 (14)
Premedication, n(%) md = 2	4 (9)	10 (8)	2 (12)	16 (9)
Technique				
Propofol with Target-controlled infusion, n (%) md = 4	45 (100.0)	121 (96)	16 (94)	182 (99)
Remifentanil with Target-controlled infusion, n(%)	40 (89)	95 (75)	10 (59)	145 (77)
Time before cerebral mapping, min * md = 21	90 [75 – 103.75]	30 [80 – 100]	95 [88.75 – 110]	90 [80 – 105]
Cortical mapping time, min * md = 23	30 [22.5 – 45]	33 [25 – 45]	32.5 [20 – 43.75]	30 [25 – 45]
Time after cerebral mapping, min * md = 26	87.5 [60 – 110]	75 [55 – 105]	72.5 [65 – 80]	75 [56.25 – 105]
Total time, min * md = 26	215 [167;5 – 245]	202.5 [180 – 236.25]	195 [175 - 218.5]	205 [180 – 240]
Patient discomfort, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Estimated blood loss, ml * md=135	225 [150 – 250]	150 [100 – 200]	175 [100 -250]	150 [100 – 250]
Hospital length of stay, day *	6 [5 - 10]	5 [4 - 6]	5.0 [5 - 7]	5 [5 - 7]
Glasgow outcome Scale at 6 months	5 [4 - 5]	5 [4 - 5]	5 [4 - 5]	5 [4 - 5]

Table 3. Factors associated with major events in univariate and multivariate analysis.

All medical history, preoperative and preoperative variables were tested. Variables with p-value lower than 0.2 were included in the multivariate logistic regression, with a backward stepwise selection method, adjusted by age and ASA score. A two-sided p value less than 0.05 was considered to be statistically significant. ASA score: American Society of Anesthesiology score; PACU: postoperative anesthesia care unit.

	Univariate analysis		Multivariate analysis		P
	odds ratio	p	odds ratio	P	
Age	0.99 [0.97, 1.02]	0.47	0.99 [0.96, 1.02]	0.42	
ASA score	1.18 [0.67, 2.09]	0.55	1.58 [0.80, 3.20]	0.2	
History of Asthma	16.08 [2.49, 313.3]	0.01	10.85 [1.34, 235.62]	0.04	
Remifentanil use	3.17 [1.24, 9.79]	0.02	2.97 [1.08, 9.85]	0.04	
Morphine in PACU	2.13 [1.04, 4.43]	0.04	NA	NS	
Time after cerebral mapping	1.01 [1.00, 1.02]	0.05	1.01 [1.01, 1.03]	0.03	

Table 4. Comparison between awake craniotomy and general anesthesia groups, on variable used for propensity score matching, before and after matching. A p value below 0.05 was defined as significant; n: number of cases; *: data expressed as median [1st quartile, 3rd quartile]

	Before matching			After matching		
	Awake craniotomy n = 188	General anesthesia n = 126	p value	Awake craniotomy n = 60	General anesthesia n = 60	p value
Age *	47 [35 – 59]	60 [51 – 68]	<0.001	56 [46 - 64]	54 [42 - 67]	0.623
Female n (%)	77 (41)	73 (58)	0.003	33 (55)	31 (51.7)	0.714
Body Mass Index (mean (sd))	24.29 (3.46)	26.35 (5.68)	<0.001	25.02 (4.08)	25.27 (3.63)	0.725
ASA, n (%)			0.001			0.492
1	53 (28.2)	21 (16.7)		12 (20.0)	11 (18.3)	
2	112 (59.6)	67 (53.2)		41 (68.3)	38 (63.3)	
3	22 (11.7)	36 (28.6)		7 (11.7)	9 (15.0)	
4	1 (0.5)	2 (1.6)		0 (0.0)	2 (3.3)	
Motor deficit, n (%)	48 (25.5)	35 (27.8)	0.755	15 (25.0)	16 (26.7)	1
Dysphasia, n (%)	44 (23.4)	16 (12.7)	0.027	14 (23.3)	11 (18.3)	0.653
Neurosurgery, n (%)	77 (41.0)	30 (23.8)	0.003	23 (38.3)	18 (30.0)	0.441
Epilepsy, n (%)	122 (64.9)	50 (39.7)	<0.001	35 (58.3)	33 (55.0)	0.854
Hypertension, n (%)	38 (20.2)	43 (34.1)	0.009	16 (26.7)	19 (31.7)	0.688
Diabetes mellitus, n (%)	6 (3.2)	12 (9.5)	0.034	1 (1.7)	2 (3.3)	1.000
Cardiac insufficiency, n (%)	0 (0.0)	22 (17.5)	<0.001	0 (0)	0 (0)	NA
Antiepileptic drug, n (%)	180 (95.7)	84 (66.7)	<0.001	53 (88.3)	57 (95.0)	0.322
Corticosteroid, n (%)	119 (63.3)	62 (49.2)	0.018	25 (41.7)	31 (51.7)	0.360
Supratentorial surgery, n (%)	188 (100.0)	113 (89.7)	<0.001	60 (100.0)	60 (100.0)	NA

Table 5. Comparison of intra- and postoperative events between patients who underwent awake craniotomy and general anesthesia, after matching by propensity score; n: number of cases; SAP: systolic arterial pressure; RBC: red blood cells; PONV: postoperative nausea and vomiting; PACU: postoperative anesthesia care unit; LOS: length of stay. *: data expressed as median [1st quartile, 3rd quartile].

	Awake craniotomy n = 60	General anesthesia n = 60	p value
Propofol use, n (%)	60 (100)	7 (11.7)	<0.001
Remifentanil use, n (%)	48 (80)	6 (10)	<0.001
SAP > 160 mmHg, n (%)	23 (38.3)	22 (36.7)	0.85
SAP < 90 mmHg, n (%)	21 (35)	53 (88.3)	<0.001
Norepinephrine use, n (%)	0 (0)	3 (5)	0.244
Osmotherapy use, n (%)	2 (3.3)	8 (13.3)	0.095
RBC transfusion, n (%)	0 (0)	2 (3.3)	0.496
Hypothermia, n (%)	10 (16.7)	29 (48.3)	<0.001
Seizure, n (%)	4 (6.7)	2 (3.3)	0.679
PONV, n (%)	7 (11.7)	18 (30)	0.013
Revision, n (%)	0 (0)	1 (1.7)	1
PACU LOS *	1 [1 - 1]	1 [1 - 1]	0.397
Hospital LOS * (days)	5 [5 - 6]	8 [6 - 12]	<0.001
Death, n (%)	0 (0)	0 (0)	NA

Figure 1. Flow chart of the study

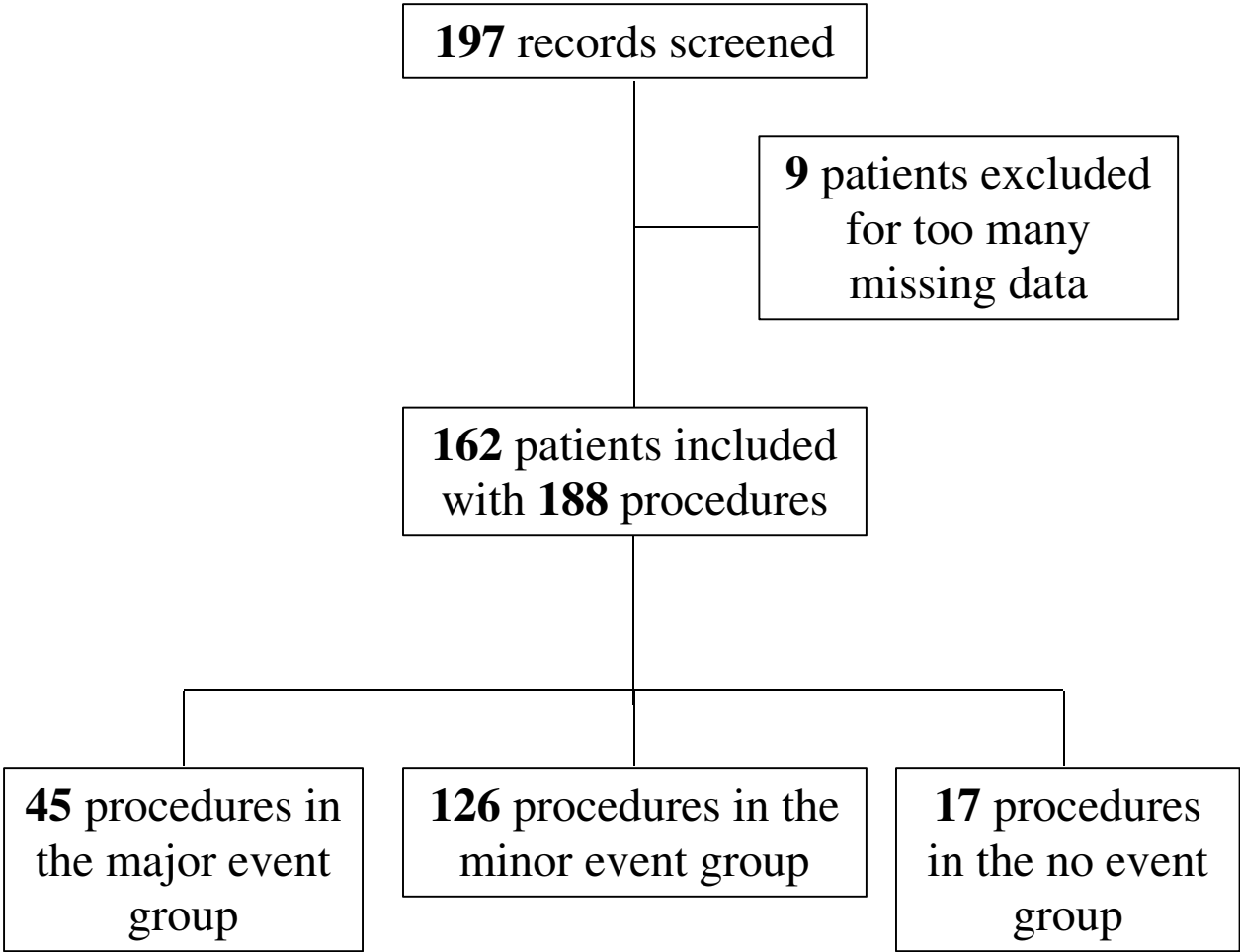


Figure 2. Number of major events (A) and minor events (B) among all procedures. Although seizures represented the most frequent event, they were rather rare i.e. 13 over 188 procedures (6.9%). All of them were rapidly treated by brain irrigation with cold saline. No brain mapping procedure was stopped because of seizures. PONV: postoperative nausea and vomiting.

