

Anesthetic management for awake craniotomy applied to neurosurgery

Grazia D'Onofrio^{1,*}, Antonio Izzi^{2,†}, Aldo Manuali², Giuliano Bisceglia², Angelo Tancredi², Vincenzo Marchello², Andreas Recchia², Maria Pia Tonti², Nadia Icolaro³, Elena Fazzari³, Vincenzo Carotenuto³, Costanzo De Bonis³, Luciano Savarese³, Leonardo Pio Gorgoglione³, Alfredo Del Gaudio²

¹ Clinical Psychology Service, Health Department, Fondazione IRCCS Casa SollievodellaSofferenza, San Giovanni Rotondo, Foggia, Italy; g.donofrio@operapadrepio.it

² Complex Unit of Anaesthesia - 2, Fondazione IRCCS Casa SollievodellaSofferenza, San Giovanni Rotondo, Foggia, Italy; A.I.: antonioizzi1201@gmail.com, A.M.: a.manuali@operapadrepio.it, G.B.: giulianobisceglia@live.it, A.T.: angelotancredi2@virgilio.it, V.M.: vincenzomarchello@libero.it, A.R.: a.recchia@operapadrepio.it, M.P.T.: mariapiatonti@alice.it, A.D.G.: a.delgaudio@operapadrepio.it

³ Complex Unit of Neurosurgery, Fondazione IRCCS Casa SollievodellaSofferenza, San Giovanni Rotondo, Foggia, Italy; N.I.: nadia.icolaro@gmail.com, E.F.: elena.fazzari87@gmail.com, V.C.: kino.23@virgilio.it, C.D.B.: costanzo.debonis@operapadrepio.it, L.S.: l.savarese@operapadrepio.it, L.P.G.: l.gorgoglione@operapadrepio.it

* Correspondence: g.donofrio@operapadrepio.it; Tel. and Fax: +39 0882-410271.

† Contributed equally to this work with the first author.

Abstract: An anesthetic technique proposed for awake craniotomy is the Monitored Anesthesia Care (MAC), with the patient in sedation throughout the intervention. Our protocol involves an algo-sedation by administering Dexmedetomidine and Remifentanyl in continuous intravenous infusion, allowing the patient to be sedated and in comfort, but contactable and spontaneously breathing. During pre-surgery, patient is premedicated with intramuscular clonidine (2 µg/ kg), it acts both as an anxiolytic and an adjuvant in pain management and improves hemodynamic stability. In operating setting, Dexmedetomidine in infusion and Remifentanyl in Target Controlled Infusion (TCI) for effect are started. The purpose of the association is to exploit the pharmacodynamics of Dexmedetomidine which guarantees the control of respiratory driving and the pharmacokinetics of Remifentanyl characterized by insensitivity to the contest. Post-operative management: at the end of the surgical procedure, the infusion of drugs was suspended. Wake-up craniotomy is associated with reduced hospital costs compared to craniotomy performed in general anesthesia, mainly due to reduced costs in the operating room and shorter hospital stays. Greater patient satisfaction and benefits of avoiding hospital stay have led to the evolution of outpatient intracranial neurosurgery.

Keywords: Awake craniotomy; Monitored Anesthesia Care; Dexmedetomidine; Remifentanyl.

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1. Introduction

The neurosurgical approach practiced on an awake patient, or awake craniotomy, was developed as early as the nineteenth century for the removal of epileptic foci under local anesthesia [1]. More recently, thanks largely to the improvement of monitoring methods and the availability of new anesthetic agents [2], the indications of this operative modality were extended to the execution of stereotaxic biopsies, to the treatment of vascular lesions [3], to the resection of tumor lesions involving areas of language [4] and to the exeresis of supratentorial neoformations localized in different cortical areas [5]. The neurosurgical interventions carried out with this purposes include, in the in-

traoperative phase, the cognitive mapping [6] and administering ad hoc neuropsychological tests while the patient is fully awake and cooperating [7], in order to preserve his cognitive capacity and, at the same time, to obtain the maximum neurosurgical excision [8]. The anesthetic techniques proposed for awake craniotomy are the Monitored Anesthesia Care (MAC), with the patient in sedation throughout the intervention [9]; the Asleep-Awake-Asleep technique, which involves a phase of general anesthesia with orotracheal intubation, or laryngeal mask (LMA), followed by an awakening phase and, once the mapping is finished, by a final stage of general anesthesia [10]; the two-step anesthesia technique: Asleep-Awake (AA) anesthesia. The latter mode involves a phase of general anesthesia followed by awakening for mapping, after which, it can be a subsequent sedation is planned for the completion of the intervention [11].

Our protocol consists of an MAC technique, which involves analgo-sedation by administering Dexmetomidine and Remifentanyl in continuous intravenous infusion, allowing the patient to be sedated and in comfort, but contactable and spontaneously breathing [12].

2. Materials and Methods

2.1. Ethical consideration

Informed consent given include approval for the procedure. Further details can be obtained in the protocol which also includes a description of protection of data.

2.2. Critical issues

- Patient selection: adult patients of both sexes were considered to undergo resection of neoplasms near the Broca area, in particular low and high grade gliomas. The only absolute exclusion factor considered was the refusal by the subjects to undergo the awake procedure. Other relative exclusion criteria could be: ASA class (≤ 3), difficult airway assessment, risk of intraoperative complications (e.g. risk of epilepsy), failure risk of sedation assessment, neurological disorders and treatment, psychic and / or psychiatric disorders, abuse of alcohol, drugs and other psychotropic substances, chronic pain and opioid use for the treatment, low pain tolerance.

- Preoperative: the management of the strategy to be adopted in a multidisciplinary manner is essential. In addition, the anesthetic visit and the interview with the patient guarantee an adequate preliminary assessment of the clinical and anesthetic conditions. Finally, correct anxiolysis allows greater compliance with the procedures to be performed in the operating room.

- Locoregional anesthesia: regardless of the anesthetic and surgical techniques used in all the studies carried out on awake craniotomy, the use of local anesthetics at the scalp level is essential [13]. Reason why their use is one of the important points of this discussion

- Management of analgo-sedation: the anesthetic technique used is a MAC (monitored anesthesia care) in which we tried to tailor the dosage and pharmacological infusion as much as possible by exploiting the synergy between the $\alpha 2$ -agonists and remifentanyl thanks to their pharmaceutical characteristics [14].

- Management of any complications: despite the low incidence in this procedure, acute conditions may arise which lead to the failure of the anesthetic technique or which in any case involve the need to intervene to avoid serious neurological sequelae. In particular, we are talking about all that which involves the need to intubate the patient and therefore conditions of cognitive decline, the onset of worsening dyspnea, haemodynamic alterations, the appearance of epileptic seizures, etc.

2.3. Procedure	92
2.3.1. Pre-operative phase	93
Case discussion in a multidisciplinary context with the involvement of a neurosurgeon, an anesthetist and a psychologist followed by the anesthetic visit and the interview with the patient (Table 1).	94 95 96
As part of the preoperative assessment, the neuropsychological framework is essential for:	97 98
- Assessing the degree of collaboration; - Evaluating cognitive impairments; - Presenting the tests to be submitted to the patient in the operating room.	99 100 101 102
From an anesthetic point of view, the patient undergoes an accurate clinical evaluation about a week before surgery. A thorough medical history and physical examination allow us to obtain useful information to better frame clinical cases. The data are confirmed by blood chemistry and instrumental tests based on the need for further study according to the current guidelines and by any specialist consultations that best outline the pathophysiological contexts to be highlighted. Any potential risky situations to be faced in the operating room are prevented through the necessary precautions (presence of the cart for difficult intubations in cases where such an eventuality can be envisaged, high risk of onset of epileptic seizures in subjects suffering from this condition or in which the area to be operated on is particularly at risk, etc.). [15] The evening before the surgery and half an hour before arriving in the operating block, the patient is premedicated with intramuscular clonidine (2 µg/ kg), it acts both as an anxiolytic and an adjuvant in pain management and improves hemodynamic stability [16].	103 104 105 106 107 108 109 110 111 112 113 114 115 116
2.3.2. Management in the operating room	117
Preparatory phase: the patient is re-evaluated upon arrival in the operating room, in the event that new morbid conditions may have arisen in the meantime (fever, haemodynamic changes, etc.). The last doubts or concepts that can transmit anxiety or fear to the patient are clarified and then the patient is placed on the operating table. The monitoring of vital parameters is carried out by means of a standard monitor that allows the display of the values of SpO ₂ , T °, NiBp, Fc, RR and state of consciousness. Arterial lines or urinary catheters were not routinely inserted. On the other hand, at least two large-caliber peripheral vascular accesses (16-18G) are found. The continuous manual infusion of Dexmetomidine at low doses (0.7-1 µg/kg/h) and of Remifentanyl via Target Controlled Infusion (TCI) to effect with the Minto model (0.5-1 ng / ml) are started by means of an infusion pump. All patients breathed spontaneously and received supplemental oxygen at 4 l/min (inducing a FiO ₂ of about 36%) through nasal cannulae, increasing the inspiratory reserve, improving tissue oxygenation and reducing the risk of accidental desaturations. Thereafter, analgesic blocks of the nerves of the scalp were performed with Levobupivacaine or Ropivacaine without exceeding the maximum dosage allowed for the patient's weight and in relation to age. The blocks in particular were performed at the level of the six cranial nerves that innervate the scalp, hence the name scalp block, bilaterally distributing the local anesthetic [17]. Overall management of the anesthetic with respect to drug infusion adjustments was left to the anesthetist present. Afterwards, the most appropriate decubitus for the procedure is taken, taking into account both the surgical needs but above all the comfort of the patient who, due to the long stay in the same position, could complain of pain, fidget and move during the surgery causing problems for the surgeon and even leading to lesions of brain structures, invalidating the procedure. Furthermore, anti-decubitus devices are placed in the areas most at risk of injuries of this type. Approximately 10 minutes later with local anesthetic agent (2% lidocaine	118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142

with 1: 200,000 epinephrine) the pin placement sites of the Manfield fixator were infiltrated and then placed by the neurosurgeon to keep the head immobile during the procedure. It should be noted that this would not be possible after locoregional analgesia of the affected area, as the bone tension caused would be too painful [18]. At any time during the procedure, when excessive pain was expected or if the patient complained of pain or discomfort, the infusion rates of Dexmedetomidine and/or Remifentanyl were increased.

Awake craniotomy phase: once the craniotomy is performed, the dura mater is opened and the neurosurgeon begins with exposed tumor excision. As previously mentioned during skin incision and dura mater manipulation an increase in drug dosages may be necessary, especially Remifentanyl. Afterwards it may be necessary to reduce the doses of drugs in continuous infusion as the brain parenchyma has a poor innervation of pain sensitivity and the patient must remain awake and cooperating in order not to invalidate the tests that allow the cognitive-motor evaluation. The infusion rates are adjusted not only according to the needs of the procedure but also according to the patient's requests and vital parameters constantly monitored. Pain assessment is done through the Numerical rating scale (NRS) (Figure 1). During the surgical excision the patient is awake, spontaneously breathing and perfectly cooperating. The mapping of the affected brain areas takes place through the placement of stimulating electrodes on the cortical surface by the neurosurgeon. Thanks to this, it is possible to minimize lesions in areas not affected by the neoplasm, allowing the assessment of cognitive abilities and in particular the integrity of the areas of language and association. [19] Intraoperative neuropsychological testing is conducted by administering to the patient the cognitive tests already performed previously in the pre-operative phase. In addition to the administration of the tests, an overall neuropsychological evaluation is carried out by the psychologist and the neurosurgeon determines the positive areas that will allow to establish the limits of the lesion resection. During the intervention, the neuropsychologist and the anesthetist remain next to the patient until the neurosurgical intervention is completed.

Post excision phase: after removing the tumor mass and having checked for any bleeding, the reconstruction and suturing phase begins. In this phase, the algogenic stimuli of the skin and brain membranes are considerable. Anesthetic management provides the dosages of the infusion drugs are again increased according to the clinical and respiratory haemodynamic parameters to prevent the pain.

2.3.3. Post-operative phase

Postoperative management: at the end of the surgical procedure, the infusion of drugs was suspended and the patient was placed back in the supine position and transported to the recovery room. The vital parameters are constantly monitored and the GCS (Glasgow coma scale) (Figure 2) and the Aldrete scale (Figure 3) are evaluated. If there is an onset of side effects (vomiting, nausea, shivering, pain, anxiety, epileptic seizures, breathing difficulties, haemodynamic changes, etc.) they are resolved immediately. Patients stay for about an hour in this room and after a final evaluation of vital and cognitive parameters they are discharged and transported to the departments of origin. Post-operative pain is treated with paracetamol 1g every 8h max 4g/day. Ondansetron 4 mg or metoclopramide 20 mg and / or dexamethasone 4 mg i.v. were administered for postoperative nausea and vomiting when needed. In the ward, the patient is monitored by the staff and reassessed at least once every hour. Discharge unless complications occur within 1-2 days of surgery.

3. Outcome measures

- Width of the tumor area removed
- Reduction of intra and post procedural pain
- Patient gradation
- Grade of the surgeon
- Reduction of costs
- Fewer hospital stays
- Reduced complications compared to general aesthesia
- Reduced side effects

3.1. Figures, Tables and Schemes

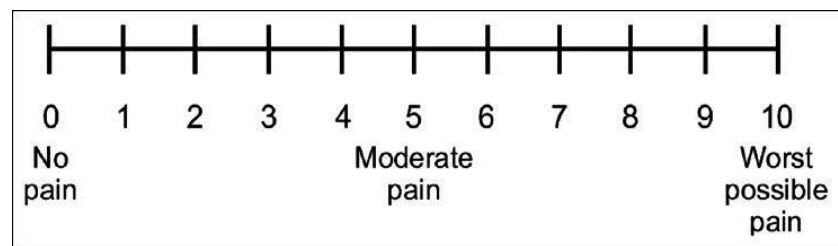


Figure 1. Numeric rating scale.

Feature	Response	Score
Best eye response	Open spontaneously	4
	Open to verbal command	3
	Open to pain	2
	No eye opening	1
Best verbal response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Best motor response	Obeys commands	6
	Localising pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1

Figure 2. Glasgow coma scale.

Parameters	Description of the patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respiration	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mmHg > preanesthetic level	2
	Is 20 to 50 mmHg > preanesthetic level	1
	Is 50 mmHg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level > 90% when breathing room air	2
	Requires supplemental oxygen to maintain level > 90%	1
	Has level < 90% with oxygen supplementation	0

*Maximum total score is 10; a score of ≥ 9 is required for discharge.

Figure 2. Aldrete score.

Table 1. Patient selection criteria

Age >18
ASA class (≤ 3)
Airway assessment
Risk of intraoperative complications (e.g. risk of epilepsy)
Failure risk of sedation assessment
Neurological disorders and treatment
Psychic and/or psychiatric disorders
Abuse of alcohol, drugs and other substances psychotropic
Chronic pain and opioid use for the treatment
Low pain tolerance

4. Discussion

The neurosurgical interventions conducted with the awake craniotomy approach applied to the treatment of tumor lesions allow to safeguard the patient's cognitive abilities.

However, for the success of the technique, close collaboration is required between the various professionals involved (neurosurgeon, anesthetist, neuropsychologist and nurse). With reference to anesthetic management, the anesthesiologist's challenge is to develop a technique that allows you to safely obtain an awake state, to ensure that the patient is able to cooperate and perform neuropsychological tests.

Consequently, it is mandatory to refer to a detailed anesthetic protocol, making the most of the pharmacokinetic / dynamic characteristics of the drugs used and the operating methods of the drug administration and anesthesia monitoring systems [20].

We can consider a clear advantage in using an anesthetic management of this type, the possibility of communicating with the patient and keeping in contact with him during all phases of the procedure is an invaluable factor, compared to a management in which in some moments the patient is not contactable. Surely all of this is guaranteed by the synergism of Dexmedetomidine in infusion and Remifentanyl in TCI for effect. The purpose of the association is to exploit the pharmacodynamics of Dexmetomidine which

guarantees the control of respiratory driving and the pharmacokinetics of Remifentanyl characterized by insensitivity to the contest. [21] Conscious sedation with dexmedetomidine has several advantages over the use of propofol in continuous infusion, including less demand for vasoactive agents, reduced opioid consumption, better compliance with intraoperative tests, and shorter duration of surgery and hospital stay [22]. Sedation with dexmedetomidine is particularly useful in high-risk patients or when surgery is likely to be prolonged. due to its ability to reduce postoperative delirium and cognitive impairment, postoperative cognitive dysfunction (POCD) [23]. Fundamental research suggests that dexmedetomidine converges on a natural sleep pathway to exert its sedative effect. This unique state of sedation, also called "collaborative" sedation, can be useful for AC, which requires a deep level of sedation during painful and stimulating operating procedures on the one hand and sufficient patient cooperation during eloquent function mapping on the other [24]. In this scheme, the use of Clonidine in premedication contributes not only to the preoperative control of surgical stress through anxiolysis, in perfect compliance with the ERAS protocol [25], but also to a condition of preemptive analgesia, favoring opioid sparing and the action of local anesthetics during execution of nerve blocks of the scalp [26]. Precisely on this point there is a greater need, namely that local anesthesia avoids not only pain during the surgical cut but above all the distress during the positioning of the pins of the Mayfield clamp which certainly involves strong bone tension. There is a large variation in the occurrence of postoperative pain and the need for analgesic drugs in neurosurgical patients [13]. The experience of the surgeons naturally reduces the risks associated with excessive bleeding and therefore significant cardiovascular alterations and conditions related to triggers of epileptic seizures and altered epileptic foci that necessarily involve the use of drugs that can modify the anesthetic plan. The psychologist's support in this type of patient who already has a dramatic family and social condition and experience is very important. Psychologically preparing a patient for all the phases of a surgical procedure of such invasiveness or simply for everything that involves being in an operating room with all its lights, sounds, noises, smells, in the midst of surgery can be a nightmare. This is why the presence of a professional figure who can minimize stress and discomfort both pre and intra procedural is fundamental if not impossible to eliminate. In addition, it is necessary to consider any tests aimed at the patient during the resection phase of the area adjacent to Broca's, in which an evaluation of the results is required to consider the integrity of language, visual association and data processing skills. Intraoperative monitoring is essential as alterations in vital parameters help prevent any ongoing decompensation before clinical events of instability. The efficacy of intraoperative seizure prophylaxis with anticonvulsants remains questionable, Levetiracetam may be superior to other drugs for this purpose [27] [28]. Awake craniotomy is associated with a shorter length of hospital stay compared to craniotomy under general anesthesia, potentially reducing the risks of nosocomial infection and thromboembolic complications and shortening the intervals between surgery and initiation of chemotherapy and / or radiotherapy if required. Wake-up craniotomy is associated with reduced hospital costs compared to craniotomy performed in general anesthesia, mainly due to reduced costs in the operating room and shorter hospital stays. Greater patient satisfaction and benefits of avoiding hospital stay have led to the evolution of outpatient intracranial neurosurgery [29] [30].

5. Conclusions

To conclude, I would first like to underline how much work it takes to be able to formulate a valid and complete protocol in the peri-operative management of a patient to undergo awake craniotomy. This in fact requires a well-oiled and trained sector of work to better deal with any adverse conditions and possibly modify the previously agreed conduct and opt for the best one that can solve the problem in progress. The coordination of the team and the preoperative preparation of the management of each patient is the

key to obtaining the best result both from an anesthetic and surgical point of view. Furthermore, it must be said that it is not easy to be able to recruit a patient to undergo this type of procedure who agrees to stay awake, just think that the first request that any type of patient normally makes is that he wants to sleep and not see and feel anything and wake up only after the fact. The correct execution of the nerve blocks of the scalp is necessary to obtain a valid start of the intervention without having to convert the anesthetic management to a technique in which the patient is asleep. Although the optimal anesthesia for this type of intervention is questionable and depends on the experience of the team from our point of view, we can affirm that the synergy between opioid drugs and alpha2 agonists has a valid efficacy in allowing the necessary comfort of the patient and the correct mapping of the area to be treated. The problem of optimal anesthetic support of awake craniotomy at high risk patients with somatic or neurological disorders is central to future research. Although brain tumor surgery remains the most common indication for awake craniotomy, the technique is finding use in other neurosurgical procedures.

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1. Sahjpaul, R.L. Awake craniotomy: Controversies, indications and techniques in the surgical treatment of temporal lobe epilepsy. *Can J Neurol Sci* **2000**, 27 Suppl 1, S55-S63. 330
 2. Bilotta, F.; Guerra, C.; Rosa, G. Update on anesthesia for craniotomy. *Curr Opin Anaesthesiol* **2013**, 26(5), 517-522. 332
 3. Gamble, A.J.; Schaffer, S.G.; Nardi, D.J.; Chalif, D.J.; Katz, J.; Dehdashti, A.R. Awake Craniotomy in Arteriovenous Malformation Surgery: The Usefulness of Cortical and Subcortical Mapping of Language Function in Selected Patients. *World Neurosurg* **2015**, 84(5), 1394-1401. 333
 4. Brown, T.; Shah, A.H.; Bregy, A.; Shah, N.H.; Thambuswamy, M.; Barbarite, E.; Fuhrman, T.; Komotar, R.J. Awake craniotomy for brain tumor resection: the rule rather than the exception? *J Neurosurg Anesthesiol* **2013**, 25(3), 240-247. 336
 5. Blanshard, H.J.; Chung, F.; Manninen, P.H.; Taylor, M.D.; Bernstein, M. Awake craniotomy for removal of intracranial tumor: Considerations for early discharge. *Anesth Analg* **2001**, 92(1), 89-94. 337
 6. Duffau, H. Awake Mapping with Transopercular Approach in Right Insular-Centered Low-Grade Gliomas Improves Neurological Outcomes and Return to Work. *Neurosurgery* **2022**, 91(1), 182-190. 338
 7. Tomasino, B.; Guarracino, I.; Ius, T.; Maieron, M.; Skrap, M. Real-Time Neuropsychological Testing Protocol for Left Temporal Brain Tumor Surgery: A Technical Note and Case Report. *Front Hum Neurosci* **2021**, 15, 760569. 339
 8. Paldor, I.; Drummond, K.J.; Awad, M.; Sufaro, Y.Z.; Kaye, A.H. Is a wake-up call in order? Review of the evidence for awake craniotomy. *J Clin Neurosci* **2016**, 23, 1-7. 340
 9. Taylor, M.D.; Bernstein, M. Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: A prospective trial of 200 cases. *J Neurosurg* **1999**, 90(1), 35-41. 341
 10. Huncke, K.; Van de Wiele, B.; Fried, I.; Rubinstein, E.H. The asleep-awake-asleep anesthetic technique for intraoperative language mapping. *Neurosurgery* **1998**, 42(6), 1312-1316. 342
 11. Attari, M.; Salimi, S. Awake craniotomy for tumor resection. *Adv Biomed Res* **2013**, 2, 63. 343
 12. Eseonu, C.I.; ReFaey, K.; Garcia, O.; John, A.; Quinones-Hinojosa, A.; Tripathi, P. Awake craniotomy anesthesia: A comparison between the monitored anesthesia care versus the asleep-awake-asleep technique. *World Neurosurgery* **2017**, S1878875017307520. 344
 13. Potters, J.W.; Klimek, M. Local anesthetics for brain tumor resection: current perspectives. *Local Reg Anesth* **2018**, 11, 1-8. 345
 14. Root-Bernstein, R. Biased, Bitopic, Opioid-Adrenergic Tethered Compounds May Improve Specificity, Lower Dosage and Enhance Agonist or Antagonist Function with Reduced Risk of Tolerance and Addiction. *Pharmaceuticals (Basel)* **2022**, 15(2), 214. 346
 15. Kulikov, A.; Lubnin, A. Anesthesia for awake craniotomy. *Curr Opin Anaesthesiol* **2018**, 31(5), 506-510. 347
 16. Dahmani, S.; Brasher, C.; Stany, I.; Golmard, J.; Skhiri, A.; Bruneau, B.; Nivoche, Y.; Constant, I.; Murat, I. Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. *Acta Anaesthesiol Scand* **2010**, 54(4), 397-402. 348
 17. Zetlaoui, P.J.; Gauthier, E.; Benhamou, D. Ultrasound-guided scalp nerve blocks for neurosurgery: A narrative review. *Anaesth Crit Care Pain Med* **2020**, 39(6), 876-882. 349
 18. Osborn, I.; Sebeo, J. "Scalp block" during craniotomy: a classic technique revisited. *J Neurosurg Anesthesiol* **2010**, 22(3), 187-194. 350
 19. Chacko, A.G.; Thomas, S.G.; Babu, K.S.; Daniel, R.T.; Chacko, G.; Prabhu, K.; Cherian, V.; Korula, G. Awake craniotomy and electrophysiological mapping for eloquent area tumours. *Clin Neurol Neurosurg* **2013**, 115(3), 329-334. 351
 20. Sewell, D.; Smith, M. Awake craniotomy: anesthetic considerations based on outcome evidence. *Curr Opin Anaesthesiol* **2019**, 32(5), 546-552. 352
 21. Chabot-Doré, A.J.; Schuster, D.J.; Stone, L.S.; Wilcox, G.L. Analgesic synergy between opioid and α_2 -adrenoceptors. *Br J Pharmacol* **2015**, 172(2), 388-402. 353
 22. Lee, S. Dexmedetomidine: present and future directions. *Korean J Anesthesiol* **2019**, 72(4), 323-330. 354
 23. Tasbihgou, S.R.; Barends, C.R.M.; Absalom, A.R. The role of dexmedetomidine in neurosurgery. *Best Pract Res Clin Anaesthesiol* **2021**, 35(2), 221-229. 355
 24. Suero Molina, E.; Schipmann, S.; Mueller, I.; Wölfer, J.; Ewelt, C.; Maas, M.; Brokinkel, B.; Stummer, W. Conscious sedation with dexmedetomidine compared with asleep-awake-asleep craniotomies in glioma surgery: an analysis of 180 patients. *J Neurosurg* **2018**, 129(5), 1223-1230. 356
 25. Brindle, M.; Nelson, G.; Lobo, D.N.; Ljungqvist, O.; Gustafsson, U.O. Recommendations from the ERAS® Society for standards for the development of enhanced recovery after surgery guidelines. *BJS* **2020**, 4(1), 157-163. 357
 26. Rosero, E.B.; Joshi, G.P. Preemptive, preventive, multimodal analgesia: what do they really mean? *Plast Reconstr Surg* **2014**, 134(4 Suppl 2), 85S-93S. 358
 27. Yuan, Y.; Peizhi, Z.; Xiang, W.; Yanhui, L.; Ruofei, L.; Shu, J.; Qing, M. Intraoperative seizures and seizures outcome in patients undergoing awake craniotomy. *J Neurosurg Sci* **2019**, 63(3), 301-307. 359
 28. Roca, E.; Pallud, J.; Guerrini, F.; Panciani, P.P.; Fontanella, M.; Spina, G. Stimulation-related intraoperative seizures during awake surgery: a review of available evidences. *Neurosurg Rev* **2020**, 43(1), 87-93. 360
 29. Eseonu, C.I.; Rincon-Torroella, J.; ReFaey, K.; Quiñones-Hinojosa, A. The Cost of Brain Surgery: Awake vs Asleep Craniotomy for Periolandic Region Tumors. *Neurosurgery* **2017**, 81(2), 307-314. 361
 30. Dziedzic, T.; Bernstein, M. Awake craniotomy for brain tumor: indications, technique and benefits. *Expert Rev Neurother* **2014**, 14(12), 1405-1415. 362