

## Conscious Sedation with Dexmedetomidine in Awake Surgery

Roberto Altieri<sup>1\*</sup>, Francesco Zenga<sup>1</sup>, Antonio Melcarne<sup>1</sup>, Carola Junemann<sup>1</sup>, Emanuela Faccoli<sup>2</sup>, Alessandro Rivera<sup>2</sup>, Sante Atlante<sup>2</sup>, Andrea Lavorato<sup>1</sup>, Giuseppe Palmieri<sup>1</sup>, Massimiliano Minardi<sup>1</sup>, Fabio Cofano<sup>1</sup>, Alessandro Ducati<sup>1</sup>, Riccardo Savastano<sup>3</sup> and Diego Garbossa<sup>1</sup>

<sup>1</sup>Department of Neuroscience, Neurosurgical Unit, University of Turin, Turin, Italy

<sup>2</sup>Department of Intensive Care Unit, Unit of Anesthesiology, Città della Salute e della Scienza di Torino, Turin, Italy

<sup>3</sup>AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

\*Corresponding author: Roberto Altieri, Department of Neuroscience, Neurosurgical Unit, University of Turin, Turin, Italy, Tel: +39 3335740036; E-mail: roberto.altieri.87@gmail.com

Received date: March 10, 2018; Accepted date: April 09, 2018; Published date: April 13, 2018

Copyright: ©2018 Altieri R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Background:** It is well demonstrated that awake surgery for brain tumours is the gold standard to achieve the maximal safe resection. On the other hand, many surgeons prefer general anesthesia in order to avoid useless stress for patients. The aim of our paper is to investigate if there are clinical and biochemical findings demonstrating a different stress level in patients who underwent awake craniotomy compared to those who underwent totally asleep surgery.

**Methods:** We compared our awake craniotomy series performed with conscious sedation using Dexmedetomidine to a group of patients treated in general anesthesia settings in terms of patient stress, rated by blood pressure, heart rate, glycaemia, lactate values, post-operative ischemia or bleeding at the MRI. We also compared the duration of surgeries in the two groups and the relations between time and other parameters.

**Results:** We found that preoperative heart rate was higher in the awake group (63.00 (SD13.58) vs. 76.5 (SD 14.34) p value 0.025) together with preoperative systolic blood pressure 122 (SD 12.95 vs. 135.1 SD (11.78) p value 0.044). However there were no clinical, biochemical and radiological differences in post-operative period in the two groups, suggesting the efficacy of Dexmedetomidine in stress control. It is demonstrated a cause-effect relation between the duration of surgery and the raising of blood pressure, suggesting that conscious sedation can reduce useless anesthesiological time in the awake surgery setting.

**Conclusions:** We showed that the two anesthetic settings are similar in terms of stress parameters after surgery. This finding could be confirmed in a prospective study with a higher number of patients.

**Keywords:** Glioma; Awake craniotomy; Awake surgery; Dexmedetomidine; Extent of resection; Asleep awake asleep; Conscious sedation; Brain tumor; Low grade glioma; General anesthesia; Glioblastoma; Intubation; Brain mapping; Maximal safe resection; Surgical stress; Stress parameters

### Introduction

Brain tumours nearby the so called “eloquent areas” represent a surgical challenge since it is mandatory for Neurosurgeons to reach the best “onco-functional balance” [1-3].

Nowadays the evidences suggest that the best brain tumours treatment, in particular for gliomas located in eloquent regions, is the awake craniotomy associated with brain mapping [4]. It is well demonstrated in neurosurgical literature that the maximal safe resection improves overall survival (OS), progression-free survival (PFS) and retards malignant transformation in low-grade glioma (LGG) [5-7]. De Witt Hamer et al. conducted a meta-analysis and examined the usefulness of intraoperative brain mapping, revealing a rate of 58% of reduced mobility and improved extent of resection (EOR) with use of stimulating mapping compared with no use of intraoperative mapping [8,9]. On the other hand, it's important to consider that despite its demonstrated utility, awake craniotomy is

used only in a very low percentage of glioma surgery [10] and many surgeons prefer general anesthesia in order to avoid “useless stress” for patients.

In this scenario, anesthesiological care becomes fundamental. Different anesthesiological techniques have been described in literature for performing awake craniotomy [11-15] the “asleep-awake-asleep” (AAA), “conscious sedation” (CS) and “totally awake” (TA), in which the patient is always conscious and no kind of sedation is performed.

AAA setting provides general anesthesia before and after the testing phase; in particular, in the first stage the patient is under general anesthesia while the craniotomy is carried out, then the level of sedation is reduced to obtain a consciousness status that allows motor and/or speech mapping [16]. It is technically complex for the anesthesiologists that have to intubate the patients with a blocked head and in some cases there is the risk to not have the maximal collaboration by the patient during the awake phase. The TA setting performed only with locoregional scalp anesthesia [12], on the other hand, has the advantage to ensure the maximal collaboration during the mapping phase because of the lack of sedative drugs, although it could expose the patient to a more difficult management of intraoperative complication. Some of the patients reported “anxiety

and fears, due to terrifying noises, immobility, loss of control, and the feeling of helplessness and being left alone". In this context, the CS setting provides a mild sedation, minimizing the excess of awake time during the opening, dissection and closure phase but allows a right level of awareness during the mapping phase.

The recent acquisitions and results about this technique are based on the rising use of Dexmedetomidine (DEX), a potent highly selective  $\alpha_2$ -adrenoceptor agonist [17] with sedative, anxiolytic, analgesic, opioid-sparing [18] and sympatholytic effects. In contrast to other sedative agents, DEX is not associated with respiratory depression; this effect is clinically relevant as demonstrated in a prospective randomized study [19].

In this retrospective study we compare awake craniotomy for supratentorial tumors performed with CS (using DEX) and general anesthesia settings in terms of patient stress, rated by blood pressure, heart rate, glycaemia, lactate values, post-operative ischemia or bleeding at the MRI. We also compared the duration of surgeries in the two groups and the relations between time and other parameters.

## Materials and Methods

We retrospectively analyzed patients who underwent operations under CS conditions using DEX infusions with patients who underwent surgery in asleep condition using propofol-remifentanyl.

Between 1/1/2017 and 31/12/2017 we performed 10 awake surgeries for gliomas located near the "speech areas" (group 1) and 73 surgeries in general anesthesia with Neuromonitoring for the same pathology located in all the rest of supratentorial regions. The same surgical team operated all patients.

Group 1 underwent surgery under local anesthesia with a cortical and subcortical brain mapping achieved by direct electrical stimulation (DES). DEX (0.7-2.0  $\mu\text{g}/\text{kg}/\text{h}$ ) were used for sedation during the surgical procedure. Sedation was discontinued after the craniotomy

and prior to incision of the dura. The craniotomy was made to expose the tumor and up to 2-3 cm of surrounding cortical surface. DES was performed using bipolar electrodes separated by a distance of 5 mm. Electroencephalography was performed in every patient. We avoided stimulation-induced seizures by irrigating the exposed brain surface with cold saline solution. If seizures were refractory to cold irrigation, intravenous levetiracetam (1 g) was administered. We started with double task (contralateral arm movement and counting) in order to identify the Negative Motor Network (NMN) around the inferior frontal gyrus (IFG) and sensorimotor area. Once evoked a totally motor arrest (TMA), we followed the mapping with the same amplitude stimulus. DO80, PPT and REM were administered in order to identify language and mentalizing responses. We considered positive the point in which there are already 3 consecutive responses after DES.

The labeled mapping sites were recorded by digital photography prior to and after tumor resection. Tumor resection was performed using frameless navigational guidance based on the preoperative MRI.

We selected 10 patients operated in general anesthesia that was comparable with group 1 for age, sex, pathology, comorbidity and ASA score. These patients are in Group 2.

All patients performed a post-operative MRI within 48 h.

We have recorded heart rate and blood pressure values before and after surgery, together with glycaemia and lactate level after surgery in order to compare biochemical and clinical stress in the 2 groups. We have also recorded the surgical time and post-operative MRI in order to study the correlation between surgical time and patients' stress and to compare the neuroradiological results. The statistical analyses were performed using STATA v14 software.

## Results

All data of the Group 1 and Group 2 are summarized in Table 1 and Table 2.

Patient	Sex	Age	ASA Score	Surgical site	Dexmedetomidine bolus ( $\mu\text{g}/\text{kg}$ )	Dexmedetomidine infusion ( $\mu\text{g}/\text{kg}/\text{h}$ )	Remifentanyl bolus ( $\mu\text{g}/\text{kg}/\text{h}$ )	Remifentanyl infusion ( $\mu\text{g}/\text{kg}/\text{h}$ )	Preop. heart rate (bpm)	Postop. heart rate (bpm)	Preop. blood pressure (mmHg)	Average preop. blood pressure	Postop. blood pressure (mmHg)	Average postop. blood pressure	Postop. Lactate value (mmol/L)	Postop. glycaemia (mg/dL)	Surgical time (min)
1	M	36	II	(R) Temporo-insular lobe	0,2	0,4-06	0,05	0,05-0,08	80	60	160/100	120	140/70	93	1,5	186	300
2	M	55	II	(R) Temporal lobe	0,2	0,2-04	0,02	0,03-0,05	85	100	130/60	83	140/80	100	0,9	140	210
3	M	44	I	(R) Frontal lobe	0,15	0,4-0,8	0,05	0,01-0,05	80	75	130/80	97	140/80	100	0,8	125	240
4	F	38	I	(R) Frontal lobe + (L) parietal lobe	0,2	0,4-0,8	0,05	0,01-0,05	105	75	140/70	93	140/60	87	0,7	175	300
5	M	59	II	(L) Temporal lobe	0,1	0,1-0,5	0,01	0,01-0,05	80	95	130/80	97	80/40	53	2,5	156	150
6	M	70	II	(L) Frontal lobe	0,3	0,8	0,05	0,01-0,1	70	70	140/60	87	160/70	100	2,8	125	270
7	F	62	II	(L) Parietal lobe	0,2	0,6-0,8	0,5	0,02-0,1	50	45	120/80	93	110/70	83	2,6	241	210

8	F	49	II	(L) Frontal lobe	0,2-0,5	0,5-09	0,15	0,05-0,1	80	75	140/80	100	140/80	100	0,6	145	195
9	F	52	II	(L) Frontal lobe	0,1 -0,2	0,03- 0,07	0,02 - 0,03	0,6-1,1	70	75	140/75	97	140/80	100	3,8	119	300
10	M	46	II	(L) Temporal lobe	0,4-0,7	0,4-0,8	0,05	0,02-0,05	65	70	120/80	93	120/80	93	0,6	146	240

**Table 1:** Patients who underwent awake surgery (Group 1).

Shapiro wilk test was carried out and confirmed the normality of data.

glycaemia, lactate blood level, blood pressure, heart rate and duration time of surgery in the two groups.

T Student Test was conducted for all the variables analyzed in this study in order to compare the preoperative and postoperative

Patient	Sex	Age	ASA Score	Surgical site	Prop ofol bolus	Prop ofol infusion	Remifentanyl bolus (µg/kg/h)	Remifentanyl infusion (µg/kg/h)	Preop. heart rate (bpm)	Postop. heart rate (bpm)	Preop. blood pressure (mm Hg)	Average preop. blood pressure	Postop. blood pressure (mm Hg)	Average postop. blood pressure	Intraop. Lactate value (mmoI/L)	Postop. Lactate value (mmoI/L)	Intraop. Glycaemia (mg/dL)	Postop. glycaemia (mg/dL)	Surgical time (min)
1	F	45	1	(R) Temporal lobe	5-4	4,5	0,1-0,2	0,15-0,2	80	90	115/65	82	150/90	110	0,9	1	135	126	170
2	F	48	2	Posterior third of the falx	0,15		0,05-0,2	0,1-0,18	60	105	115/70	85	160/80	107	/	1	/	110	220
3	M	67	2	(R) Frontal lobe	0,2	2-5	0,1-0,2	0,05-0,08	50	60	110/50	70	120/40	67	/	2,5	/	107	98
4	F	67	2	(L) Temporal lobe	5-4	4,5-2	0,25	0,2-0,05	70	65	140/85	103	100/55	70	3,1	3	146	138	295
5	F	69	2	(R) Temporal lobe	0,14		0,2	0,05-0,2	50	75	140/80	100	140/70	93	/	1,2	76	188	130
6	F	76	2	(L) Fronto-temporal lobe	2	3-4	0,2	0,05-0,25	75	90	120/70	87	130/80	97	1,2	1,4	90	133	110
7	M	67	2	(R) Temporal lobe	3,5	4	0,2	0,15-0,2	45	60	130/60	83	120/60	80	1,1	1,3	101	95	240
8	F	74	2	(R) Frontal lobe	0,1		0,15	0,05-0,1	80	90	100/70	80	130/70	90	0,9	2	99	140	105
9	M	59	2	(L) Temporal lobe	3,5	4-4,2	0,05	0,3-0,05	50	70	120/70	87	120/60	80	/	1,8	/	143	290
10	M	30	2	(L) Fronto-basal lobe	2-3	3,2-4	0,2	0,05-0,25	70	90	130/85	100	110/80	90	1,5	2,3	94	125	330

**Table 2:** Patients who underwent asleep surgery (Group 2).

Blood pressure level was examined as systolic, diastolic and mean value.

Preoperative heart rate was statistically different in the two groups (63.00 (SD13.58) vs. 76.5 (SD 14.34) p value 0.025) with an higher frequency in the awake group. There were no differences in the postop.

There was also a difference between preoperative systolic blood pressure (122 (SD 12.95) vs. 135.1 (SD 11.78) p value 0.044) with an higher level in the awake group.

Correlation pearson test was conducted in order to test the relation between time of surgery and all of the rest of data recorded in the two

groups. This test showed a positive correlation between duration of surgery and postoperative systolic blood pressure level in the awake group (pearson coefficient correlation 0.683 p values 0.02).

A linear simple regression showed that there are a significant relation between duration time of surgery and post-operative systolic blood pressure level in the awake group ( $\beta=0.29$  p value 0.02). The graph 1 shows that for every minute the systolic blood pressure increases of 0.29 mmHg. No bleeding or ischaemia in postop MRI in the two groups.

## Discussion

Different anesthesiological techniques have been described in literature to perform awake craniotomy [11-15] the AAA setting provides general anesthesia before and after the testing phase; in particular, in the first stage the patient is under general anesthesia while the craniotomy is carried out, then the level of sedation is reduced to obtain a consciousness level that allows motor and/or speech mapping [16].

The second anesthesiological setting is the CS: in this case the patient is mildly sedated but respiratory independent for the all the duration of surgery. The last possible setting is the so called TA in which the patient is always conscious, and no kind of sedation is performed. Each setting has advantages and drawbacks widely described in literature, but currently there is no consensus on which method provides the best anesthesia management. The right surgical and anesthesiological planning derives from the balance of selecting a technique that provides sedation, anxiolysis and optimal analgesia during brain exposure. Immobility and comfort during mapping and resection of the tumor are equally fundamental as well as minimizing hypoxemia, hypercarbia, nausea, vomiting, seizures and hemodynamic instability. The AAA setting has the important advantage of an easier patient management in case of intraoperative complications and allows avoiding patient stress reactions in the first phases of the intervention with tachycardia, hypertension and increased levels of anxiety. Moreover, in case of relapsing glioma, the opening phase and the anatomical dissection could take long time with negative effects on patient's performance during the successive mapping phase.

In addition, there's the possibility that the tumor could involve also non eloquent region, so keeping the patient awake after mapping is useless [20]. A prospective study of 140 glioma surgery performed with the AAA setting demonstrated that no seizures, no swelling, no severe permanent neurological deficit and no mortality occurred [21] moreover the European Low Grade Glioma Network multicenter study with 105 patients used the AAA setting in the vast majority of cases [22]. However this setting is challenging for anesthesiologists because it is not simple a safe intubation in a patient with a blocked head. Moreover, there is the risk to have a sedated patient when a full collaboration is required.

The TA setting performed only with scalp nerves blockade [12], on the other hand, has the advantage to ensure the maximal collaboration during the mapping phase because of the lack of sedative drugs, although it could expose the patient to a more difficult management of intraoperative complication. Some of the patients reported "anxiety and fears, due to terrifying noises, immobility, loss of control, and the feeling of helplessness and being left alone". In this contest, the CS setting provides a mild sedation during the craniotomy and closure phase but allows a right level of awareness during the mapping phase.

The recent acquisitions and results about this technique are based on the rising use of DEX.

DEX is a lipophilic imidazole derivative drug which acts like an  $\alpha$ -2 agonist [23] stimulating central  $\alpha$ -2 adrenergic subtypes. It has demonstrable dose-reducing effects with inhalational anesthetics and opiates [24] and can also induce anesthesia thanks to its effect on the  $\alpha$ -2a receptor subtype. Acting as an  $\alpha$ -2 agonist, DEX has also dose-related cardiovascular effects, reproducibly reducing blood pressure and lowering heart rate values. It induces vasodilation of arterial vessels, renal diuresis, anxiolysis and sedation [24]. DEX has a rapid onset of action, and is highly biotransformed in the liver with 95% of its metabolites excreted in urine. Its volume of distribution is large with a consequent clinical effect half-life of about 6 min, and a clearance half-life of 2 h. It has almost no effect on respiration at clinically relevant doses [24] and allows arousal from a state mimicking sleep to permit cognitive engagement and facilitate communication during diagnostic and surgical procedures, which renders it uniquely useful in its sedative profile [25].

It has been used in a large variety of clinical situations including the provision of sedation within the ICU [24,26] for the active management of benzodiazepine and opiate withdrawal [27] and as a dose-sparing agent associated with concomitant analgesic and anesthetic use. In limited series, DEX has been used successfully for the provision of sedation in awake craniotomies [28-31].

Using DEX as sole sedative agent in awake craniotomies allows a more complete neurological evaluation of the surgical patient, avoiding the AAA passages and the effects of propofol on the Central Nervous System inhibition [31], thus permitting a more accurate assessment of neurological modification during the neurosurgical maneuvers.

On the other hand, a patient that remains conscious for a longer time in an operating room could be a more stressed patient, and not only from a psychologically point of view.

Souter et al. [25] describe the use of DEX as unique sedative agent in some of the six patients that underwent resection of epileptogenic foci for intractable seizures through awake craniotomies resection. Postoperatively, all patients who received DEX as the sole sedative agent were asked to evaluate their comfort and willingness in the future to undergo such sedation. In all cases it was not reported discomfort, all patients pointed to satisfaction with the sedation technique, and willingness to undergo a similar anesthetic technique in the future.

In our report, we used DEX as sole sedative agent during awake craniotomies for its rapid onset of action, anesthetic manageability and limited effect on respiration at clinically relevant doses [24]. In limited series, DEX has been successfully used for the provision of sedation in awake craniotomies [28,29,30]. We retrospectively recorded clinical and radiological outcomes of all the patients of the awake resection group and compared our data with a control group of patients who underwent neurosurgical resection in totally asleep sedation. In addition, we recorded some physiological and biochemical parameters (heart rate, blood pressure, glycemia, lactate levels) pre and postoperatively for all our patients of the case and control groups, in order to evaluate the effect of surgical stress on biochemical parameters before and after awake and asleep neurosurgical procedures.

We selected these four parameters because of their easy availability through pre and post-operative blood exams, hemogasanalysis and intraoperative measurements. Also, glycaemia is strictly related to

adrenergic response in physical and psychological stressing situations, with a rapid variability of its levels that can be easily recorded. Lactates levels are not just a useful parameter to register systemic hypoxia and organic fatigue: their blood concentration raises when glycolytic activity [32] increases, even without a proper lack of oxygen supply by tissues. It could be seen as a hormone related to stress enzymatic response [32] the higher are its levels, the clearer is the necessity for the patient to activate stress reaction mechanisms. Furthermore, heart rate and blood pressure are two easily recordable parameters that vary rapidly in stressful situations. During a surgical operation not all the phases are equally stressful for the patient (for example, painful *vs.* not painful maneuvers), so a rapid variable parameter is useful to understand which of the single phases is more trenchant in causing stress for the patient, even in the same surgical intervention. We combined the four single parameters data to understand how awake neurosurgical resections could be stressful for a patient compared with an asleep one. We also could identify in which phase the most important stress reaction is concentrate and how every single phase influences this response.

Surprisingly, the moment in which we have recorded a major stress reaction, confirmed by the statistically significant raising of pulse rate and blood pressure in the awake group *vs.* the asleep group, is the preoperative phase. From this point of view, we could justify these recordings with a patient's major psychological stress during his entrance in the operating room, with the awareness of taking an essential part in a neurosurgical resection during an awake sedation. The same parameters, together with glycaemia and lactate levels, have no statistically significant differences in the two groups. This could be related to the cardiovascular and psychological effects of DEX, reducing blood pressure (by inducing arterial vasodilatation) and heart rate [24] it induces renal diuresis, anxiolysis and sedation too [24]. It is significant that postoperative glycemic and lactate levels have no statistically relevant differences between the awake and asleep group. It is likely that the cardiovascular and anxiolytic effect of DEX nullifies even the preoperative difference of heart rate and blood pressure observed in the awake group. In this sense, from a biochemical point of view, the awake and the asleep sedation for neurosurgical resection had no postoperative differences on the stress parameters that we analyzed in the patients of this study [24]. Moreover, in our series, the vasodilatation effect of DEX has not influenced the surgical results with ischaemia or bleeding. It is also important underline that surgery duration is a crucial parameters and CS can reduce useless anesthesiological time.

## Conclusions

In our report we show that the two anesthetic settings are similar in terms of stress parameters after surgery, even when preoperative heart rate and blood pressure values are different between awake and totally asleep patients. The retrospectively analysis of this study is its most relevant limit, together with the poor number of patients sample considered. Against this background, this report paves the way for further prospective studies, to better evaluate the feasibility of awake surgeries even in other neurosurgical pathologies and clinical cases, in order to obtain a constant intraoperative neurological evaluation for better postoperative outcomes.

## References

1. Herholz K, Thiel A, Wienhard K, Pietrzyk U, von Stockhausen HM, et al. (1996) Individual functional anatomy of verb generation. *Neuroimage* 3: 185-194.
2. Ojemann G, Ojemann J, Lettich E, Berger M (1989) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 71: 316-326.
3. Ns G, Development C, Retardation M (1978) Language Localization. *J Neurosurg* 260: 239-260.
4. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, et al. (2003) Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. *J Neurosurg* 98: 764-778.
5. Altieri R, Hirono S, Duffau H, Ducati A, Fontanella M, et al. (2017) Natural history of de novo High Grade Glioma: first description of growth parabola. *J Neurosurg Sci*.
6. Altieri R, Agnoletti A, Quattrucci F, Garbossa D, Calamo Specchia FM, et al. (2014) Molecular biology of gliomas: present and future challenges. *Transl Med UniSa* 10: 29-37.
7. Altieri R, Zenga F, Ducati A, Melcarne A, Cofano F, et al. (2017) Tumor location and patient age predict biological signatures of high-grade gliomas. *Neurosurg Rev* 41: 599-604.
8. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS (2012) Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. *J Clin Oncol* 30: 2559-2565.
9. Altieri R, Zenga F, Fontanella MM, Cofano F, Agnoletti A, et al. (2015) Glioma Surgery: Technological Advances to Achieve a Maximal Safe Resection. *Surg Technol Int* 27: 297-302.
10. Chang SM, Parney IF, Huang W, Anderson FA Jr, Asher AL, et al. (2005) Patterns of Care for Adults With Newly Diagnosed Malignant Glioma. *JAMA* 293: 557-564.
11. Hansen E, Seemann M, Zech N, Doenitz C, Luerding R, et al. (2013) Awake craniotomies without any sedation: The awake-awake-awake technique. *Acta Neurochir (Wien)* 155: 1417-1424.
12. Hill CS, Severgnini F, McKintosh E (2017) How I do it: Awake craniotomy. *Acta Neurochir (Wien)* 159: 173-176.
13. Rajan S, Cata JP, Nada E, Weil R, Pal R, et al. (2013) Asleep-awake-asleep craniotomy: A comparison with general anesthesia for resection of supratentorial tumors. *J Clin Neurosci* 20: 1068-1073.
14. Shen SL, Zheng JY, Zhang J, Wang WY, Jin T, et al. (2013) Comparison of Dexmedetomidine and Propofol for Conscious Sedation in Awake Craniotomy: A Prospective, Double-Blind, Randomized, and Controlled Clinical Trial. *Ann Pharmacother* 47: 1391-1399.
15. Shen SL, Xie YH, Wang WY, Hu SF, Zhang YL (2014) Comparison of dexmedetomidine and sufentanil for conscious sedation in patients undergoing awake fiberoptic nasotracheal intubation: A prospective, randomised and controlled clinical trial. *Clin Respir J* 8: 100-107.
16. Sacko O, Lauwers-Cances V, Brauge D, Sesay M, Brenner A, et al. (2011) Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. *Neurosurgery* 68: 1192-1198.
17. Karol MD, Maze M (2000) Pharmacokinetics and interaction pharmacodynamics of dexmedetomidine in humans. *Bailliere's Best Pract Res Clin Anaesthesiol* 14: 261-269.
18. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ (2004) The Efficacy of Dexmedetomidine Versus Morphine for Postoperative Analgesia After Major Inpatient Surgery. *Anesth Analg* 98: 153-158.
19. Goettel N, Bharadwaj S, Venkatraghavan L, Mehta J, Bernstein M, et al. (2016) Dexmedetomidine vs propofol-remifentanyl conscious sedation for awake craniotomy: A prospective randomized controlled trial. *Br J Anaesth* 116: 811-821.
20. Duffau H (2013) The reliability of asleep-awake-asleep protocol for intraoperative functional mapping and cognitive monitoring in glioma surgery. *Acta Neurochir (Wien)* 155: 1803-1804.

21. Deras P, Moulinié G, Maldonado IL, Moritz-Gasser S, Duffau H, et al. (2012) Intermittent general anesthesia with controlled ventilation for asleep-awake-asleep brain surgery: A prospective series of 140 gliomas in eloquent areas. *Neurosurgery* 71: 764-771.
22. Beez T, Boge K, Wager M, Whittle I, Fontaine D, et al. (2013) Tolerance of awake surgery for glioma: A prospective European Low Grade Glioma Network multicenter study. *Acta Neurochir (Wien)* 155: 1301-1308.
23. Virtanen R, Savola JM, Saano V, Nyman L (1988) Characterization of the selectivity, specificity and potency of medetomidine as an  $\alpha$ 2-adrenoceptor agonist. *Eur J Pharmacol* 150: 9-14.
24. Maze M, Scarfini C, Cavaliere F (2001) New Agents for Sedation in the intensive care unit. *Crit Care Clin* 17: 881-897.
25. Souter MJ, Rozet I, Ojemann JG, Souter KJ, Holmes MD, et al. (2007) Dexmedetomidine sedation during awake craniotomy for seizure resection: Effects on electrocorticography. *J Neurosurg Anesthesiol* 19: 38-44.
26. Venn RM, Karol MD, Grounds RM (2002) Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. *Br J Anaesth* 88: 669-675.
27. Multz AS (2003) Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. *Anesth Analg* 96: 1054-1055.
28. Bekker AY, Kaufman B, Samir H, Doyle W (2001) The Use of Dexmedetomidine Infusion for Awake Craniotomy. *Anesth Analg* 92: 1251-1253.
29. Ard JL, Bekker AY, Doyle WK (2005) Dexmedetomidine in awake craniotomy: A technical note. *Surg Neurol* 63: 114-116.
30. Ard J, Doyle W, Bekker A (2003) Awake craniotomy with dexmedetomidine in pediatric patients. *J Neurosurg Anesthesiol* 15: 263-266.
31. Herrick IA, Craen RA, Gelb AW, Miller LA, Kubu CS, et al. Propofol Sedation During Awake Craniotomy for Seizures: Patient-Controlled Administration Versus Neurolept Analgesia. *Anesthesia & Analgesia* 84: 1285-1291.
32. Garcia-Alvarez M, Marik P, Bellomo R (2014) Stress hyperlactataemia: Present understanding and controversy. *Lancet Diabetes Endocrinol* 2: 339-347.