Department of Anesthesiology[1], Department of Emergency[2], The First Affiliated Hospital of Nanchang University, Nanchang, P.R. China

Effects of dexmedetomidine, propofol and etomidate on the intraoperative wake-up in the cerebral functional area under the guidance of entropy index

Zhao Xinyan[1,#], Hu Zhengbang[2,#], Zhang Xuekang[1,*], Hu Qian[1], Wu Qiong[1], Liang Sisi[1], Fang Xinhua[1], Shu Shi[1], Liu Zhiyi[1]

Received June 27, 2018, accepted July 30, 2018

**Corresponding author: Zhang Xuekang, Department of Anesthesiology, The First Affiliated Hospital of Nanchang University, Nachang, Jiangxi 330006, P.R. China*
kang7139@163.com
[#]These authors contributed equally to this work.

Pharmazie 73: 647–650 (2018) *doi: 10.1691/ph.2018.8613*

Objective: The study observed the efficacy and safety of dexmedetomidine, propofol and etomidate on brain functional areas in patients undergoing wake-up brain surgery under the guidance of entropy index. *Methods:* Sixty patients undergoing wake-up brain surgery on brain functional areas were enrolled, and randomly divided into three groups: dexmedetomidine group (group D), propofol group (group P) and etomidate group (group E), 20 in each. The vital signs, entropy indices of each time point, wake-up time, wake-up quality and adverse reaction in the wake-up period were observed and compared. *Results:* There were no differences in the duration of wake-up, duration of anesthesia, duration of surgery and postoperative wake-up time between the three groups (P> 0.05). The wake-up quality in group D was significantly better than group P and group E (P <0.05), group P was better than group E (P <0.05). The incidence of adverse events in group D was lower than that in groups P and E (P <0.05). The incidence of adverse events in group P was lower than that in group E (P <0.05). *Conclusion:* Under the guidance of entropy index, anesthesia induced by dexmedetomidine, propofol and etomidate combined with remifentanil can safely and effectively be used to the wake-up brain functional areas surgery, but the wake-up quality with use of dexmedetomidine is highest, and the incidence of adverse events is the lowest during wake-up period.

1. Introduction

Accurate localization of resection lesions while protecting normal nerve function is a challenge for surgery in brain functional areas. Cortical microcurrent stimulation (CES) is the most effective method, but CES requires awakening during surgery. At present, propofol or etomidate combined with remifentanil are often used for intraoperative awakening anesthesia, but there are shortcomings such as long awakening time, low quality of arousal, and not effectively inhibited arousal stress response (Fu et al. 2018). Dexmedetomidine is a highly selective α2-adrenoceptor agonist. It has been reported to be superior to propofol and etomidate in arousal quality during brain surgery for awakening (Hu et al. 2015) due to its unique kind of sedation, acting on the subcortical areas, which resembles natural sleep without respiratory depression, and without impairment of intraoperative CES electrophysiological monitoring (Brady 2010; Agarwal et al. 2014). This subject sets a fixed value of the entropy index as the standard for arousal, observes and compares the awakening time, arousal quality and adverse events of the three anesthetics, and objectively evaluates the efficacy of dexmedetomidine for intraoperative arousal in patients. It provides a theoretical basis for clinical application undergoing surgery in brain functional areas.

2. Investigations and results

The patient characteristics are summarized in Table 1. There were no statistically significant differences in patient's age, gender, BMI, duration of surgery initiation to preparation awakening (T_3), arousal duration, duration of anesthesia, duration of surgery, and postoperative awake time between the three groups (p>0.05).

The HR of T2 ~ T6 in group D was lower than that in T1 (P<0.05). Compared with group D, the HR in group P and E was significantly increased at T2 ~ T6 (P<0.05). There was no significant difference in other vital signs (p>0.05) (Table 2). Compared with group D, the wake-up times (T_3~T_A, T_A~T_4, and T_3~T_4) in groups E and P increased significantly (P<0.05), but wake-up quality decreased

Table 1: Comparison of patient characteristics and surgical data (n=20 $\bar{x}$±S)

Group	Age (years)	Sex ratio (male/female)	BMI (kg/m)	Time from beginning of surgery to T_3 (min)	Awakening time (min)	Anesthesia time (min)	Surgery time (min)	Postoperative awake time (min)
Group p	48.7±7.5	7/13	21.7±1.3	71.1±6.2	29.5±4.4	318.0±29.7	291.5±33.2	24.6±6.4
Group E	50.1±8.1	9/11	22.3±1.5	69.8±5.9	28.4±3.7	325.3±33.2	302.1±36.1	25.9±6.7
Group D	49.5±7.8	8/12	20.6±1.4	72.6±6.7	28.7±4.0	320.6±31.8	296.6±34.5	23.2±5.9

Values are expressed as the mean±standard deviation or number(n) of patients. BMI = body mass index.

Table 2: Comparison of three group's vital signs data in peri-awake period (n=20, $\bar{x}$±S)

Time point	Group	MAP (mmHg)	HR (bpm)	SpO_2 (%)	$P_{ET}CO_2$ (mmHg)	RE (%)	OAA/S (value)
T1	Group P	97.5±7.9	88.6±6.3	99.4±0.5	40.1±3.4	43.1±1.9	0
	Group E	98.6±8.3	89.7±6.8	99.5±0.5	40.5±3.6	44.4±2.8	0
	Group D	99.8±8.7	89.6±7.3	99.3±0.6	40.3±4.1	42.6±2.4	0
T2	Group P	92.7±6.9	79.8±6.9[a]	99.3±0.5	42.2±3.0	42.7±1.7	0
	Group E	93.1±7.3	83.4±7.5[a]	99.2±0.7	42.5±2.9	45.0±2.3	0
	Group D	91.6±7.1	61.4±5.6[*]	99.3±0.5	41.2±3.8	41.9±2.5	0
T3	Group P	95.5±8.3	81.2±7.1[a]	96.1±1.1	44.0±3.5	79.6±4.2	0
	Group E	96.2±8.8	85.4±6.9[a]	96.5±0.9	44.3±3.6	80.3±5.1	0
	Group D	94.7±7.5	64.5±6.0[*]	97.8±1.2	43.3±3.3	78.3±4.5	0
T4	Group P	99.2±8.4	87.8±6.7[a]	95.3±2.3	45.2±2.9	93.7±4.8	4.1±0.6
	Group E	100.3±8.9	91.3±8.5[a]	96.1±2.1	45.0±2.5	92.6±5.0	4.2±0.4
	Group D	98.0±7.8	71.8±6.2[*]	96.7±1.0	43.2±2.7	94.0±5.5	4.1±0.5
T5	Group P	99.7±8.0	84.7±6.3[a]	95.1±2.2	43.6±2.6	94.7±5.4	4.3±0.3
	Group E	101.3±8.7	89.3±8.0[a]	95.8±2.0	43.8±2.3	93.6±5.2	4.4±0.1
	Group D	98.3±7.6	69.5±5.9[*]	96.0±1.8	42.1±2.8	95.3±5.7	4.1±0.5
T6	Group P	100.2±8.3	79.7±6.7[a]	95.0±2.3	42.9±3.0	93.9±4.9	4.1±0.6
	Group E	101.5±7.8	84.1±7.7[a]	95.4±1.9	43.1±2.6	92.3±4.6	4.2±0.5
	Group D	99.3±8.4	67.3±6.0[*]	96.3±1.7	42.6±2.2	94.7±5.1	4.1±0.4

Values are expressed as the mean±standard deviation. MAP =mean arterial pressure, HR = heart rate, SpO_2 = oxygen saturation, $P_{ET}CO_2$ = end-tidal carbon dioxide, RE = response entropy, OAA/S = observers assessment of alertness/sedation. [*]P<0.05 for intragroup compared with T1 time point in group D. [a]P<0.05 for groups P and E ompared with Group D in T_2 ~ T_6 time point.

significantly (P<0.05); compared with group E, the wake-up quality in group P was significantly reduced (P<0.05) (Table 3). Compared with group D, the incidences of hypertension, tachycardia, restlessness, coughing, and respiratory depression during the awakening period in group P and E were significantly increased (P<0.05), and the average incidence of adverse events was significantly increased (P<0.05). The incidence of hypotension and bradycardia was significantly decreased (P<0.05). Compared with group E, the average incidence rate in group D was significantly decreased (P<0.05). The incidence of memory about wake-up in surgery was not statistically significant in the three groups at follow-up visit (Table 4).

Table 3: Comparison of three group's arouse time and quality (n=20, x ±S)

Group	Arouse time (min)			Arouse quality			
	T3~TA	TA~T4	T3~T4	Grade I / case(%)	Grade II / case(%)	Grade III / case(%)	Grade IV / case(%)
P	12.7±3.1[a]	2.9±1.4[a]	15.6±4.4[a]	8(40%)[ab]	6(30%)	5(25%)[a]	1(10%)[ab]
E	13.0±3.6[a]	3.2±1.3[a]	16.2±4.7[a]	6(30%)[a]	6(30%)	6(30%)[a]	2(10%)[a]
D	9.5±2.8	1.8±0.7	11.3±3.5	12(60%)	7(35%)	1(5%)	0(0)

[a]P<0.05 for groups P and E compared with group D, [b]P<0.05 for group P compared with Group E.

Table 4: Comparison of three group's adverse event in awake period [n=20, case(%)]

Group	Hyper-tension	Hypo-tension	Tachy-cardia	Brady-cardia	Agitation	Cough	Respi-ratory depres-sion	Memories of awak-ening	Average incidence
P	3(15)[a]	2(10)[a]	2(10)[a]	3(15)[a]	2(10)[a]	1(5)[a]	2(10)[a]	1(5)	16 10.0)[a]
E	4(20)[ab]	1(5)[ab]	4(20)[ab]	1(5)[ab]	4(20)[ab]	3(15)[ab]	1(5)[ab]	1(5)	19 11.9)[ab]
D	1(5)	4(20)	0(0)	5(25)	0(0)	0(0)	0(0)	1(5)	11(6.9)

[a]P<0.05 for groups P and E compared with group D.
[b]P<0.05 for group D compare with Group E.

3. Discussion

Surgery on brain functional areas can easily lead to severe neurological impairment complications such as spasticity and aphasia (Hu et al. 2015). Accurate location and complete resection of the lesions while protecting normal nerve function is a challenge for functional neurosurgery. The most effective way to avoid complications is through intraoperative wake-up and intraoperative neuronavigation and electrophysiological techniques. To monitor the brain's functional area, current cortical micro-current stimulation (CES) is the most effective method (Tharin and Golby 2007). However, awakening anaesthesia in brain functional area surgery needs to meet the three requirements of surgery, electrophysiological monitoring and anesthesia itself. Rozet et al. (2008) believe that the ideal goals of the wake-up anaesthesia are: (1) adequate oxygenation and ventilation; (2) hemodynamic stability; (3) good cooperative status; (4) best brain conditions; (5) electrophysiological monitoring during surgery.

The entropy index is an ideal indicator of the effects of anesthetics and sedatives on sleep and level of consciousness. Its numerical change can reflect the sedative and hypnotic effects of general anesthetic drugs, and help to adjust the depth of general anesthesia. Its numerical change also shows high sensitivity to the patient's consciousness changes (Peng 2012), and it can predict the time of anesthesia decreased and consciousness recovery. Therefore, the entropy index can be used as a reliable indicator of awakening anesthesia during surgery. The entropy index mainly consists of SE (state entropy) and RE (response entropy). RE is a fast response index with a time window range of 1.92 ~ 15s. The change of RE value is about 4 min earlier than SE and BIS. RE's frontal EMG signal is particularly sensitive to noxious stimuli and responds quickly. Its changes can promptly reflect the subcortical excitement caused by stimulation such as tracheal intubation, and can reflect the immediate change of anesthetic depth at a certain time (Cheng et al. 2015). In this study, the value of RE was used as an indicator of awakening during surgery. The range of RE is 0 to 100, indicating that the anesthetic range from deep to shallow, 0 represents the deepest level of anesthesia, 40 to 60 represents the appropriate anesthesia state, 100 represents the awake state,

this article sets RE = 90 as the expected wake time point T_A, and records the RE value when preparing to wake up and fully awake.

Remifentanil is a synthetic short-acting opioid analgesic and is a specific μ-opioid receptor agonist. Because of its esterase-based metoblism (Martorano et al. 2008), has short half-life, minimal accumulation and hemodynamic stability, low restlessness and seizure rate, and very rapid onset and offset of clinical action. Due to these advantages, remifentanil is currently considered to be the most suitable analgesic for wake-up anesthesia (Frost and Booij 2007). However, after the withdrawal of remifentanil, the analgesic effect quickly disappears, and the pain stimuli swell in the short term. This causes cerebral vasospasm of the patient to reduce intracranial perfusion pressure and even cerebral ischemia. Therefore, it is necessary to combine it with other anesthetic drugs. Propofol has a rapid effect, short action and neuroprotective function, was once considered to be the ideal drug for wake-up anesthesia in the brain functional area during surgery (Hans and Bonhomme 2006), but in practical applications, there are some side effects, such as deep anesthesia, or wake delay (Frost and Booij 2007), cough, restlessness, hypertension, and respiratory depression occur. The results of this study are consistent with that in group P, the averaged awake time (T_3-T_4) about 15.6 min, and the incidence of adverse events during arousal was 10%. Etomidate has a slight effect on the circulation function, a short duration of action, decrease in intracranial pressure and cerebral oxygen metabolism rate by contraction of cerebral blood vessels, and has a protective effect on brain damage caused by hypoxia (Yang et al. 2011). Many scholars are using etomidate for awakening anesthesia during brain function surgery, but it can lead to injection pain and myoclonus (Liso et al. 2010); impede the production of cortisone and other corticosteroids in the adrenal cortex, causing temporary adrenocortical insufficiency, water sodium imbalance, hypotension, and shock; leading to apnoea, nausea, vomiting, involuntary muscle activity, cough, hiccups, and chills. In group E, the arousal quality of class III plus class IV was up to 40%, and the arousal quality was not as good as that of group P. The average incidence of adverse events during arousal was 11.9%, which was higher than that of group P. Obviously, etomidate is not ideal for awakening anesthesia.

Dexmedetomidine (DEX) is a highly selective α_2-adrenoceptor agonist, with sedative, analgesic sparing effects, anxiolytic, sympatholytic and minimal despression of respiration function, and is easily aroused (Gao et al. 2015). Dexmedetomidine mainly acts on the subcortex, does not involve the γ-aminobutyric acid (GABA) system, does not damage cognitive function, and does not interfere with intraoperative neuroelectrophysiological monitoring such as CES, ECoG (Souter et al. 2007). DEX has a dose-dependent sedative and analgesic effect, and its unique "consciousness and sedation" is similar to the non-rapid eye phase of natural sleep. Patients are in a state of sleep without external stimuli, but are easily aroused by verbal stimuli and are able to communicate with medical staff. When stimulation disappears, patients soon return to sleep and have almost no inhibition of breathing. Because of these characteristics, dexmedetomidine has been used by most anesthesiologist for awakening anesthesia during brain surgery. This study is consistent with the results of Forest and Booij (2007). Thus, dexmedetomidine and Remifentanil are the ideal drug combinations for wake-up anesthesia.

The wake-up time in group D was significantly shorter than that in groups P and E, and the awakening quality is significantly better than in groups P and E, the average incidence of adverse events during awakening was significantly lower than that of groups P and E. Although dexmedetomidine does not inhibit breathing during wake-up anesthesia, it can decrease sympathetic tone and make the parasympathetic nerves relatively excited, resulting in bradycardia and hypotension. In this study the blood pressure in the three groups was not significantly different at all time points, but in group D, heart rate from the beginning of T_2 was significantly lower than in groups P and E and heart rate was significantly lower than T_1 in the same group. It should be closely observed during surgery, ephedrine and atropine can be given for symptomatic treatment.

The brain is a complex nonlinear dynamic system. The entropy index is an EEG signal monitoring indicator that reflects the complexity of the system with a nonlinear model. It can be seen from preparation for wake up (T_3) to expectant awakening (T_A), from the expected awakening (T_A) to complete awakening (T_4), that the wake time in the dexmedetomidine group was significantly shorter than in the propofol and etomidate groups, and the awakening quality was also the best. There was no significant difference in the arousal time between etomidate and propofol groups, but the awakening quality in the propofol group was better than in the etomidate group. At the same time, we can also see from our wake-up schedule that in the dexmedetomidine group, time from expected awakening to complete awakening time was very short, about 1.8 min. This suggests that dexmedetomidine leads to a faster wake-up time and is more suitable for wake-up brain surgery on brain functional areas.

In the wake-up anesthesia, the most taboo is patient's body movement and cough during the wake-up process. We used the long-acting ropivacaine for craniotomy scalp nerve block, and local infiltration anesthesia for incision full-thickness and skull-pin placement. This provides a basic guarantee for the successful implementation of wake-up anesthesia. Nevetheless, it can be seen from the adverse effects of this trial that the P and E group patients still presented agitation and coughing. During the wake-up process, however, there was no case in the group D which may be related todexmedetomidine special sedative effects (Hall et al. 2010), mild analgesic effects (Arain and Ebert 2002) and good anti-stress effects of dexmedetomidine.

In summary, with the help of local anesthesia, the anesthesia of dexmedetomidine, propofol, etomidate, and remifentanil anesthesia can be safely and effectively be used to the wake-up brain functional areas surgery under the guidance of entropy index but the wake-up quality under dexmedetomidine is highest, and the incidence of adverse events is the lowest during wake-up period.

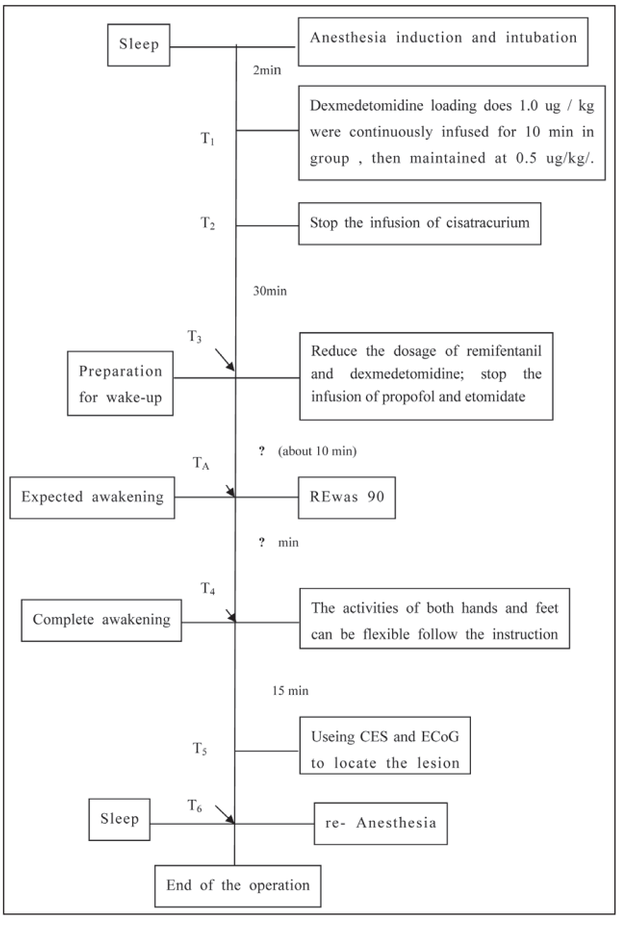

Fig: Timeline from induction of anesthesia to end of surgery

4. Experimental

4.1. Study design and participants

The study was discussed and approved by the Hospital Ethics Committee and informed consent was signed with the patient. Sixty patients (gender not limited, aged 18-60 years) with American Society of Anesthesiologists physical status I to II, and no history of mental illness. There were no communication disorders, motor dysfunction, high intracranial pressure, and morbid obesity (BMI>35 kg/m^2) before surgery; patients who met the above criteria were randomized to the dexmedetomidine group (group D), propofol group (group P) and etomidate group (group E), 20 patients in each group.

4.2. Anesthesia

The patients did not receive any medication before induction of anesthesia. The purpose and the program of anesthesia (Fig.) was to fully communicate with patients. At the start of anesthesia, peripheral venous access was established and compound sodium chloride was infused at 4 to 6 ml/kg/h. The central venous pressure (CVP) and mean arterial pressure (MAP) were monitored by local anesthesia with the right internal jugular vein and left radial artery puncture. Anesthesia was induced by an intravenous infusion of propofol 1.5 mg/kg, sufentanil 0.4 μg/kg, and cisatracurium besilate 0.2 mg/kg in groups D and P; etomidate 0.1 mg/kg , sufentanil 0.4 ug/kg, cisatracurium besilate 0.2 mg/kg in Group E. After tracheal intubation, mechanical ventilation was controlled to maintain a tidal volume 7 to 10 ml/kg, respiratory rate of 12 breath/min, and end-tidal carbon dioxide ($P_{ET}CO_2$) at 35 to 40 mmHg. Anesthesia was maintained by an intravenous infusion of remifentanil 0.1 μg/kg/min, cisatracurium besilate 0.1 mg/kg/h. Two min after tracheal intubation (T_1), group D received an infusion of propofol 4 mg/kg/h. Intravenous dexmedetomidine loading dose 1.0 ug / kg was continuously infused for 10 min, then maintained at 0.5 μg/kg/h/. At the end of the loading dose infusion, propofol was stopped. At the time of T_1, propofol in group P was infused with 4 mg/kg/h, and the etomidate group E received 10 μg/kg/min. Remifentanil 0.1 μg/kg/min was pumped at all three groups to maintain analgesia and cisatracurium besilate 0.1 mg/kg/h to maintain muscle relaxation. The pump maintenance dose of dexmedetomidine, propofol, or etomidate was adjusted intraoperative maintained RE 40 to 60. The blood pressure fluctuation was controlled intraoperative less than 30% of the baseline value, heart rate at 50 to 100 beats/min, if necessary, using dopamine or urapidil to control blood pressure, atropine or esmolol to control heart rate.

4.3. Intraoperative wake-up

All the operations were performed by the same group of doctors. After tracheal intubation, 0.25% ropivacaine hydrochloride was used to perform craniotomy scalp nerve block and local head infiltration anesthesia for skull-pin placement. 0.25% ropivacaine was used for local incision infiltration anesthesia before skin incision, the total amount of ropivacaine did not exceed 250 mg. After sawing the skull, the brains soaked with 2% lidocaine were applied to the dura mater for topical anesthesia for 10 min, intravenously dexamethasone 10 mg, 20% mannitol 250 ml, and tropisetron 5 mg. After the beginning of surgery, when the entropy index RE was 90, which is the time for awakening (T_A). About 40 min before T_A (T_2) stop the infusion of cisatracurium besilate and undergoing wake-up after 30 min (T_3). Remifentanil was reduced to 0.03 μg/kg/min in the three groups. In group D, dexmedetomidine was decreased to 0.2 μg/kg/h. Propofol was discontinued in group P, and infusion of etomidate in group E was stopped. Manually controlled breathing instead of mechanical ventilation after T_3 until spontaneous breathing is resumed and RE>80, call out the name of the patient every 30 s and ask the patient to make fist movements. After reaching the wake-up time point (T_A), and if the activities of both hands and feet can be flexible follow the instruction regarded as awake (T_4). When the T_A has arrived and the T_4 is not, ask the surgeon to wait. Fifteen minutes after T_4 (T_5), when the patient is awake with the use of CES and ECoG to locate the lesion and re-anesthesia (T_6) precise remove the lesion. During the period from T_3 to T_6, if the patient have coughing or body movement give propofol 0.5 mg/kg intravenously. After the test of the cerebral cortex functional area was completed, the dexmedetomidine infusion was discontinued and continuously infused with propofol, etomidate, remifentanil and muscle relaxants until the end of surgery. At the end of the surgery when the patient was completely awake, remove the endotracheal tube and sent the patient back to the ward. After 24 hours, ask the patient about memory of the awakening procedure and satisfaction with the awakening procedure. If the patient had a memory of the arousal process, make a detail inquiry if there was any pain in the memory.

4.4. Observation indices

Age, sex, body mass index (BMI), time from beginning of surgery to T_3, awakening time (T_3 to T_4), duration of awakening (T_4 to T_6), anesthesia time, surgery time, postoperative awake time, MAP, HR, RE, SpO_2, $P_{ET}CO_2$ at T_1 to T_6, and Observer's Assessment of Alertness/Sedation (OAA/S) scores (Table 5), arousal quality scores (Table 6) were recorded. Side effects in duration of awakening and satisfaction scores were evaluated after surgery.

4.5. Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences version 17.0 software (SPSS Inc.,Chicago IL). Normally distributed data were expressed as mean±standard deviation (x±s).Between groups comparisons were performed using Student's t test and intra-group comparison were performed using repeated-meassures analysis of variance. Count data is expressed as a percentage and using the χ^2 test. Rank data uses a non-parametric rank sum test. P<0.05 were considered to be statistically significant.

Table 5: Observers assessment of alertness/sedation (OAA/S) scores

Value	Description
5	Responds readily to name spoken in normal tone
4	Lethargic respond to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly for the individual to open their eyes
2	Responds only after moderate prodding or shaking
1	Does not respond to moderate prodding or shaking
0	Does not repond to deep stimulus

Table 6: Arousal quality scores

Class	Description
I	When have instructions, can move limbs quickly and accurately without any movement.
II	When have instructions, can move limbs, but slower with less accuracy.
III	When have instructions, can be slower and inaccurate move limbs and there is slight movement without affecting the operation.
IV	Unable to move limbs according to instructions, serious agitation affects operation.

Funding: This study was funded by the Science and Technology Program of Health and Family Planning Commision of Jiangxi province, China (20161035).

Conflicts of interest: None declared.

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