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Research Article

Preliminary evaluation of ketofol-based sedation for awake craniotomy procedures

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KEYWORDS

Ketofol;
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Abstract *Background:* The study aimed at evaluating the clinical efficiency of a ketofol-based sedation procedure during awake craniotomy for varied surgical indications.
Methods: The study included 28 patients; 19 males and 9 females with mean age of 33.4 ± 9.3 years. All patients received propofol (0.5 mg/kg/h) and ketamine (0.5 mg/kg/h) infusion mixture in 1:1 ratio. Conscious level was evaluated using the Modified Observer's Assessment of Alertness/Sedation scale and patients were maintained at level 3, at which the patients will respond after their name is called loudly or repeatedly; otherwise patient was considered over-sedated. Intra-operative (IO) monitoring included intracranial pressure (ICP), hemodynamic and respiratory changes, brain status, whether slack or tense, the frequency of over-sedations and adverse events. Duration of surgery, time till PACU transfer, total anesthesia time, postoperative (PO) complications and duration of hospital stay were reported. Patients' satisfaction, on 0–10 score, about the procedure used for awake sedation was inquired.
Results: Mean duration of surgery was 168.8 ± 19.4 min; mean time till PACU transfer after stoppage of infusion was 11.1 ± 1.7 min for a mean anesthesia time of 179.9 ± 19.2 min. Three patients had blood pressure changes, 4 had heart rate variability, 2 had respiratory depression and one had SpO_2 <90%. Two patients developed focal seizures, one had nausea and 2 patients were over-sedated. Brain was tense in only 3 patients (10.7%). Four patients had PO transient neurological

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deficits, 3 patients had PO seizures and only 2 patients had recurrent attacks of nausea and vomiting; however, these complications responded to treatment. Mean hospital stay was 3.1 ± 1.1 days. Mean satisfaction score was 9.1 ± 1.2; range: 6–10 with a satisfaction rate of 78.6%.

Conclusion: Conscious sedation during awake craniotomy using ketofol infusion mixture in 1:1 ratio was safe and efficient with minor hemodynamic and respiratory events and rapid smooth recovery profile.

1. Introduction

The progressive advances in the field of neurodiagnosis and neurosurgery opened the way for management of cases that were previously considered unmanageable. However, these advances and multiplicity of techniques imposed a challenge on the field of neuroanesthesia that must accommodate the race of advances in neurosurgery.

Awake anesthesia for neurosurgical procedures concerned with surgical management of epilepsy proved successful and became a routine for such surgeries [1,2]. A variety of anesthetic modalities became available to facilitate awake intraoperative examinations and cortical stimulation, which allow more aggressive resection of tumors in functionally important brain regions. Improving pharmacological agents especially that maintained the patient conscious and allowed early comfortable recovery and the availability of multiple combinations and variety of techniques freed the anesthetist's hand for anesthetic manipulations for awake craniotomy procedures.

Multiple studies evaluated the safety of intravenous ketamine/propofol combination ("ketofol") in the same syringe for procedural sedation and analgesia; Santiveri et al. [3] found low doses of ketamine associated with propofol improve puncture conditions for performing a retrobulbar block without increasing unwanted side effects. Willman and Andolfatto [4] found ketofol procedural sedation and analgesia is effective and appears to be safe for painful procedures in the emergency department and reported few adverse events that were either self-limited or responded to minimal interventions with rapid recovery and staff and patients were highly satisfied.

Mustafaeva et al. [5] found the mixture of ketamine and propofol has proved to be a safe and effective sedative; its use provides not only a good position comfort, possible avoidance of opioids, and no effect of ketamine on psychomotor recovery, but also a more controlled sedation than when these agents are used in the same doses alone during endoscopic interventions into the digestive tract. Thus, the present study aimed at evaluating the clinical efficiency of a ketofol-based sedation procedure during awake craniotomy for varied surgical indications.

2. Patients and methods

After obtaining Local Ethical Committee approval of the study protocol and fully informed written patients' consent; 28 cooperative patients assigned for craniotomies for tumor resection and are physically able to tolerate awake surgery were enrolled in the study.

Patients with morbid obesity, chronic obstructive pulmonary disease, complicated airway, history of allergy to local anesthetics or drugs used in the study, confusion, communication difficulties, or extreme anxiety were excluded of the study. Patients had tumors involving significant dural invasion which cause significant pain on resection or requires positioning other than supine or needs prolonged operative time for more than 4 h were not enrolled in the study.

The study included 28 patients; 19 males and 9 females with mean age of 33.4 ± 9.3; range: 21–56 years. There were 15 ASA I, 13 ASA II patients. There were a total of 16 left hemispheric tumors and 12 right hemispheric tumors. The patients presented most frequently with headache followed by symptoms of hemiparesis and/or seizures in varied combinations (Table 1).

No preoperative sedation was administered. On arrival to the operating room intravenous access was established for administration of intravenous ondanesetrone (8 mg), dexamethazone (8 mg) and slow intravenous injection of phenytoin 250 mg. Routine monitoring included an electrocardiogram, noninvasive arterial blood pressure, pulse oximetry, and end-tidal carbon dioxide and respiratory rate measured via an oxygen delivery nasal prongs. Supplemental oxygen was delivered at 4 l/min.

All patients received IV midazolam 15 μg/kg after they were placed on the operating table in the correct position for surgery using extra cushions and padding to ensure maximum patient comfort. Then, all patients received the same sedation solution using propofol (0.5 mg/kg/h) and ketamine (0.5 mg/kg/h) infusion mixture in 1:1 ratio.

The sites of pin insertion for rigid head fixation were infiltrated with local anesthesia (lidocaine 2% with 1:200,000 epinephrine), after fixation the infusion was briefly stopped to ensure patient comfort with head positioning and then restarted. Conscious level was evaluated using the Modified Observer's Assessment of Alertness/Sedation scale [6], patients were maintained at level 3, at which the patients will

Table 1 Patients' characteristics.

	Total
Age (year)	33.4 ± 9.3 (21–56)
Gender; M:F	19:9
Body weight (kg)	76.3 ± 10.5 (59–92)
ASA grade	
I	15 (53.6%)
II	13 (46.4%)
Lesion laterality	
Left hemisphere	16 (57.1%)
Right hemisphere	12 (42.9%)
Presenting symptoms	
Headache	22 (78.6%)
Motor deficit	9 (32.1%)
Seizure	8 (64.3%)

Data are presented as mean ± SD, ratio and numbers; ranges and percentages are in parenthesis.

respond after their name is called loudly or repeatedly; otherwise patient was considered over-sedated. At any time during the procedure when excessive pain was expected, such as the infiltration of the local anesthetic into the pin sites and scalp, additional anesthesia was given by increasing the infusion rate. Maintenance IV fluids consisted of normal saline at the rate of 50–100 ml/h. Approximately 5 min before brain mapping, infusion was discontinued, then infusion was resumed for tumor resection and closure. All patients received fentanyl 1–2 μg/kg for postoperative analgesia at the time of skin closure. Patients were transferred to the post-anesthetic care unit (PACU) for a 4-h stay before discharge to the ward.

Intracranial pressure was recorded using Codman Micro Sensor, Johnson & Johnson Medical Ltd. The Codman micro sensor was calibrated to zero according to the manufacturer's instructions prior to placement, it is then inserted into deep white matter, at a depth of 20–35 mm from the cortical surface and a baseline reading is taken through a mini-burr hole done under local anesthesia before starting of infusion. Intravenous mannitol 0.5 g/kg was administered prior to skin incision. ICP readings were recorded prior to initiation of infusion (baseline), at time pin insertion, before opening of dura, after dural closure and at end of surgery.

Intraoperative arterial blood pressure, heart rate, oxygen saturation, and respiratory rate were monitored and managed accordingly by manipulation of the infusion rate or administration of supplemental intravenous fluids. Also, the frequency of over-sedated patients and intraoperative adverse events as nausea, occurrence of focal seizures and respiratory depression was reported. Intraoperative brain status; whether tense or slack was documented and was arbitrarily abbreviated as yes or no for slack brain status and was scored as yes = 1 and no = 0.

Duration of surgery, time till PACU transfer and total anesthesia time were recorded. Postoperative pain was treated with IM non-steroidal anti-inflammatory drugs. Postoperative complications and duration of hospital stay were also reported. Patients' satisfaction, on 0–10 score, about the procedure used for awake sedation was inquired.

2.1. Statistical analysis

Obtained data were presented as mean ± SD, ranges, numbers and ratios. Inter-group variability of hemodynamics and ICP were analyzed using ANOVA test using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

3. Results

Mean duration of surgery was 168.8 ± 19.4; range: 150–215 min, mean time till PACU transfer after stoppage of infusion was 11.1 ± 1.7; range: 8–14 min for a mean anesthesia time of 179.9 ± 19.2; range: 158–226 min.

Intraoperative events occurred in 15 patients (53.6%) and included blood pressure changes in 3 patients (10.7%) and heart rate variability in 4 patients (14.2%). Respiratory depression was encountered in 2 patients (7.1%) and intraoperative peripheral blood desaturation with SpO_2 <90% occurred in one patient (3.6%). Focal seizures occurred in 2 patients (7.1%) and nausea occurred in only one patient (3.6%). Throughout intraoperative course, 2 patients (7.1%) were over-sedated due to increased dose of ketofol to combat the recorded episode of hypertension and these two patients were ready for discharge of theater at 12 and 14 min after infusion stoppage. Tense brain status was encountered in 3 patients (10.7%), while in the other 25 patients brain was slack (Table 2).

Table 2 Patients' distribution according to intraoperative events.

	Total
Hemodynamic changes	
Blood pressure	
Hypertensive episodes (SBP >150 mmHg)	2 (7.1%)
Hypotensive episodes (SBP <90 mmHg)	1 (3.6%)
Within acceptable range	25 (89.3%)
Heart rate	
Tachycardia (HR >110 beats/min)	3 (10.7%)
Bradycardia (HR <50 beats/min)	1 (3.6%)
Within acceptable range	24 (85.7%)
Respiratory events	
Respiratory depression	
No	26 (92.9%)
Occurred	2 (7.1%)
Desaturation (SpO_2 <90%)	
Occurred	1 (3.6%)
No	27 (96.4%)
Focal seizures	
Occurred	2 (7.1%)
No	26 (92.9%)
Nausea and vomiting	
Occurred	1 (3.6%)
No	27 (96.4%)
Over sedation	
Occurred	2 (7.1%)
No	26 (92.9%)
Brain status	
Slack	25 (89.3%)
Tense	3 (10.7%)

Data are presented as numbers and percentages are in parenthesis.

Mean ICP measures were significantly lowered prior to dural opening compared to both baseline and pin-insertion measures. Mean ICP measures after dural closure and skin closure showed non-significant difference and patients were discharged to PACU with ICP measures within normal range (Table 3).

Postoperative transient neurological deficits were recorded in 4 patients, 3 patients had postoperative seizures and only two patients had recurrent attacks of nausea and vomiting; however, these complications responded to treatment and did not recur. Mean hospital stay was 3.1 ± 1.1; range: 1–5 days.

Mean satisfaction score was 9.1 ± 1.2; range: 6–10; 4 patients found the sedation procedure unsatisfactory because of prolonged time till transfer to PACU; 2 patients (7.1%) scored their satisfaction by 6 and the other 2 patients (7.1%) by 7. Another 2 patients (7.1%) scored their satisfaction by

Table 3 ICP measures (mmHg) recorded throughout observation period.

	Mean ± SD	Range
Baseline	25.2 ± 1.8	20.5–28.4
At time of pin insertion	25.9 ± 1.7	20.6–27.8
Prior to dural incision	17.3 ± 0.9	15.8–18.8
After dural closure	12.2 ± 1.6	9.8–14.8
At time of skin closure	11 ± 2.7	7.2–14.8

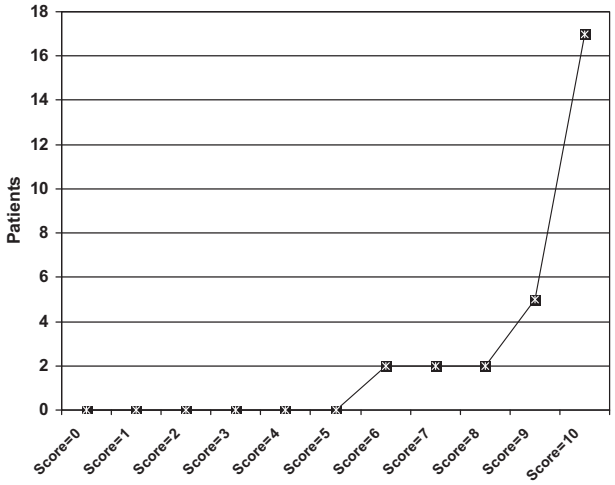

Figure 1 Patient's distribution according to satisfaction score about the applied sedation procedure.

8 and 5 patients (17.9%) scored it as 9, while 17 patients (60.8%) scored it by 10 (Fig. 1) for a satisfaction rate of 78.6%.

4. Discussion

Considering the present study as a preliminary trial for evaluation of the outcome of ketofol-based sedation for awake craniotomy, the reported outcome as regards the total frequency of intraoperative events (15 patients; 53.6%) was similar or superior to that reported in the literature concerning various modalities of conscious sedation for awake craniotomy; Manninen et al. [7] reported a total incidence of intraoperative complications/complaints of 56% with fentanyl/propofol and 64% with remifentanil/propofol with non-significant difference; however, respiratory complications occurred in total of 9 (18%) patients; 5 with fentanyl and 4 with remifentanil compared versus only 3 (10.7%) with ketofol in the current study. Sinha et al. [8] reported intraoperative complications namely; hypertension (19%), tight brain (14.2%), focal seizure (9.5%), respiratory depression (7.1%), deep sedation (7.1%), tachycardia (7.1%) and desaturation to $<95\%$ (4.8%) in a total of 42 patients underwent awake craniotomy under conscious sedation using fentanyl/propofol infusion.

Ketofol provided hemodynamic stability or minor changes that were manifested as minimal number of patients showed deviations from their baseline measures and maintenance of ICP after closure of dura and skin closure within the normal range without intraoperative episodes of increased ICP. These data coincided with Akin et al. [9] who found a significant decrease in mean arterial blood pressure in 11 patients (36.6%) with propofol compared to 3 patients (10%) with ketofol during cardiac catheterization in pediatric patients and concluded that the addition of low-dose ketamine to propofol preserved blood pressure without prolonging recovery or increasing the incidence of adverse events. These results could be attributed to the contradictory effect of both ketamine and propofol on autonomic nervous system, ketamine being sympathomimetic while propofol lessens this effect. A similar attribution was provided by Timm et al. [10] who reported that even low-dose S(+)-ketamine has a stimulatory effect on the cardiovascular system, but this stimulatory effect is nullified in the presence of a continuous propofol infusion at a dosage of more than 3 mg/kg BW/h, however, such high propofol dose used was not the applied in the current study and this could explain the occurrence of blood pressure changes occurred in 3 patients (10.7%) and heart rate variability in 4 patients (14.2%).

The reported mean time till PACU transfer after infusion stoppage was 11.1 ± 1.7; range: 8–14 min which is coincident with and superior to that previously reported in the literature; 15 min [4], 23.16 min [11], 10 min to first purposeful response [12], 14 minutes [13]. The shorter time till PACU transfer reported in the current study could be attributed to the used dosage ratio and goes in hand with Erden et al. [14] who reported 12.1 ± 1 min with propofol 0.5 mg/kg and ketamine 0.5 mg/kg and 13.8 ± 0.8 with propofol 0.5 mg/kg and ketamine 0.25 mg/kg.

The dosage ratio of propofol to ketamine in preparing ketofol infusion represents a challenge; Akin et al. [15] compared propofol (1.5 mg/kg) to propofol (1.5 mg/kg) plus ketamine (0.5 mg/kg) in a ratio of 3:1 and reported no cases of desaturation with ketofol, but with propofol 4/30 experienced desaturation and 6/30 had apnea, blood pressure and heart rate were significantly lower with propofol than ketofol and concluded that the addition of low dose ketamine to propofol reduced the risk of respiratory depression and the need for repeat medication administration. Sharieff et al. [12] used propofol 1 mg/kg and ketamine 0.5 mg/kg in a ratio of 2:1 for sedation for closed reduction of forearm fractures in pediatrics and found the combination provided effective sedation with rapid recovery and no clinically significant complications. Tosun et al. [16] compared propofol 1.2 mg/kg and ketamine 1 mg/kg in a ratio of 1.2:1 versus propofol/fentanyl in the same ratio and both combinations provided effective sedation and analgesia during dressing changes in pediatric burn patients, but propofol/ketamine combination was superior because of more restlessness in patients given propofol/fentanyl.

These previously stated data spotlight on an ongoing trend towards equalization of the ratio so as to minimize propofol-related adverse events especially cardiovascular and respiratory events, thus the current study was based on the application of ketofol infusion of propofol 0.5 mg/kg and ketamine 0.5 mg/kg in a ratio of 1:1. In support of the utility of such ratio; Andolfatto and Willman [13] used intravenous ketofol (mixed 1:1 ketamine/propofol) for emergency department procedural sedation and analgesia for primarily orthopedic procedures and found sedation was effective in all patients, 3 patients (1.4%) had airway events requiring intervention, 2 patients (0.9%) had unpleasant emergence requiring treatment, while all other adverse events were minor. Also, Erden et al.

[14] compared propofol 0.5 mg/kg and ketamine 0.5 mg/kg versus propofol 0.5 mg/kg and ketamine 0.25 mg/kg and reported no significant differences between the two groups with respect to hemodynamic data, oxygen saturation, or side-effects, however, the mean propofol dosage and the number of over-sedated patients (sedation score >4) was higher in group 2 and recommend propofol 0.5 mg/kg and ketamine 0.5 mg/kg which is associated with reduced rescue propofol requirements and therefore less over-sedation. In support of the validity of 1:1 ketamine/propofol ratio, Rapeport et al. [17] used ''ketofol'' (ketamine 200 mg and propofol 200 mg) infusion in conjunction with regional anesthesia for four high risk patients and found ketofol safe and effective with the advantages included analgesia, airway preservation, maintenance of spontaneous respiration, haemodynamic stability and rapid recovery.

In conclusion, ketofol (propofol 0.5 mg/kg and ketamine 0.5 mg/kg) provided safe and efficient conscious sedation during awake craniotomy with minor hemodynamic and respiratory events and rapid smooth recovery profile. However, wider scale studies are mandatory for establishment of these results and dosage regimen.

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