doi.org/10.36721/PJPS.2026.39.1.REG.14416.1

Effect of ketamine combined with remifentanil on analgesic sedation and inflammatory factors in severe brain injury

Wenting He[1] and Yixue Lu[2]*
[1]Department of GCP Office, Wuxi No.2 People's Hospital (Jiangnan University Medical Center), Wuxi, Jiangsu, China
[2]Department of Pharmacy, Wuxi No.2 People's Hospital (Jiangnan University Medical Center), Wuxi, Jiangsu, China

Abstract: **Background**: Severe brain injury patients often require effective analgesia and sedation to manage pain, agitation, and inflammatory responses, which can impact clinical outcomes. **Objectives**: This study aimed to analyze the effects of ketamine combined with remifentanil on analgesic sedation and inflammatory factors in patients with severe brain injury. **Methods**: Sixty patients were randomly divided into a remifentanil-only control group and a ketamine combined with remifentanil group. VAS, SAS, BCS, Ramsay scores, inflammatory factors (TNF-α, IL-2), and adverse reactions were compared. **Results**: Compared with pre-operative levels, both groups showed significant reductions in VAS, SAS scores, TNF-α, and IL-2 ($P < 0.05$). Compared with the control group, the combined group exhibited significantly lower VAS and SAS scores, higher Ramsay sedation and BCS scores, and lower TNF-α and IL-2 levels ($P < 0.05$). There was no statistically significant difference in adverse reactions between groups ($P > 0.05$). **Conclusion**: Ketamine combined with remifentanil provides better analgesic and sedative effects in severe brain injury patients, effectively reducing pain and agitation, improving comfort, and suppressing inflammatory responses, demonstrating good clinical application value.

Keywords: Analgesia; Ketamine; Remifentanil; Sedation; Severe brain injury

Submitted on 02-04-2025 – Revised on 26-08-2025 – Accepted on 28-08-2025

INTRODUCTION

Following the rapid development of society, advances in industry, construction and transportation, the number of patients with brain injury significantly increased due to work or traffic accidents, most of whom are middle-aged and young males (Einarsen *et al*., 2018, Lin *et al*., 2018). In addition to traumatic brain injury, other pathogenic factors include intracranial infections, medical procedures and acute cerebrovascular diseases (Tollefsen *et al*., 2018). Severe brain injury can easily cause disability or even death in young adults. There are as many as millions of patients who die or become disabled due to brain injury every year around the world (Swanson *et al*., 2018). Severe brain injury causes a strong injury, characterized as critical condition, complicated and changeable. It needs timely diagnosis and treatment, whereas current treatment still cannot effectively prevent the aggravation of brain cell damage, resulting in low survival rate, impaired quality of life and heavy burden on the family (Jang *et al*., 2017, Moe *et al*., 2018).

Due to nervous system damage, increased intracranial pressure, hypoxemia and other factors, severe brain injury is often accompanied by disturbance of consciousness, restlessness and other symptoms. It is unable to cooperate with mechanical ventilation and monitoring, which will further increase the blood pressure, aggravate the condition, or even induce complications (Ayubi *et al*., 2018, Vavilala *et al*., 2017). Thus, choice of effective analgesia and sedation is an important means for the treatment of severe brain injury. Remifentanil, a commonly used analgesic drug, belongs to ultrashort-acting opioids. It has the characteristics of rapid onset, fast elimination and a dose-dependent effect on the respiratory system (Salama and Amer, 2018, Wan Hassan *et al*., 2018). Remifentanil has a faster spontaneous breathing recovery than morphine for sedation in mechanically ventilated patients (Lu *et al*., 2018). Therefore, remifentanil is one of the commonly used analgesic and sedative drugs for severe craniocerebral injury. Ketamine is one of the N-methyl-D-aspartate receptor antagonists. It exerts hypnotic and sedative effects by regulating neuronal apoptosis and inhibiting inflammatory factors and has a relatively small impact on hemodynamics and respiration (Abass *et al*., 2018, Gilbert *et al*., 2018, Jonkman *et al*., 2018). However, the effect of ketamine combined with remifentanil on analgesic sedation and inflammatory factors in severe brain injury has not been reported. However, at present, there is still a lack of sufficient evidence regarding the analgesic and sedative effects of ketamine combined with remifentanil in severe brain injury and its influence on inflammatory factors. This study aims to explore the analgesic and sedative effects of ketamine combined with remifentanil on patients with severe brain injury and the influence of inflammatory factors, with the expectation of providing a more optimized treatment plan for clinical practice.

MATERIALS AND METHODS

General information

A total of 60 patients with severe brain injury were enrolled in this study. The diagnosis was confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) combined with clinical symptoms. All patients underwent surgical intervention. The cohort consisted of 42 males and 18 females with a mean age of 46.3 ± 3.5 (range: 22-62)

**Corresponding author:* e-mail: xunanxing2311@163.com

years and a mean body weight of 54.7 ± 6.8 (range: 42-83) kg. Routine B-ultrasound, electrocardiogram (ECG) and blood routine examinations were performed on all subjects before surgery. The postoperative 6h Glasgow Coma Scale (GCS) score was recorded as 8.4 ± 1.7 (range: 7-13) points. Mean systolic blood pressure was maintained above 90 mmHg and central venous pressure was above 8 mmHg. The average coma time was 126.1 ± 22.6 (range: 57-287) min. Types of craniocerebral injury included cerebral contusion, skull fracture, intracranial hematoma, intracerebral hemorrhage, aneurysm rupture and hemorrhage, subdural or epidural hematoma, subarachnoid hemorrhage and diffuse brain swelling. Exclusion criteria included the presence of other serious complications, significant impairment of vital organs such as the liver and kidney, cardiovascular diseases such as sinus bradycardia or ischemic heart disease, hypertensive crisis, a history of abnormal coagulation function, a history of allergy or resistance to anesthetic drugs, long-term use of sedatives and analgesics, long-term use of ventilators after surgery, mental disorders, inability to cooperate with researchers, or the occurrence of severe complications during treatment (such as acute respiratory failure requiring vasoactive drugs to maintain blood pressure) (Huang *et al*., 2017).

The sample size for this study was determined through a pre-statistical power analysis. Assuming a clinically significant difference of a 1.5-point decrease in the VAS score in the combination medication group, α was set at 0.05 (two-sided test) and β at 0.20 (power = 80%). As calculated by G*Power 3.1 software, a minimum of 27 patients were required in each group. Considering potential dropouts or data loss, 30 patients were ultimately included in each group, resulting in a total sample size of 60 cases.

Main reagents and instruments

Remifentanil injection was purchased from China Fortune Pharmaceutical Company. Ketamine injection was purchased from China Hengrui Pharmaceutical Company. Human TNF-α and IL-2 ELISA assay kits were purchased from eBioscience (USA). Other commonly used reagents were purchased from Sangon (Shanghai). Model 5424r Eppendorf centrifuge was purchased from Eppendorf (Germany). Labsystem Version 1.3.1 microplate reader was purchased from Bio-Rad (USA).

Grouping

The selected subjects were divided into two groups according to a double-blind design by using a computer-generated random number table. There was no statistically significant difference in age, gender, GCS score, injury time, etc. between the two groups of patients (Table 1). After craniocerebral surgery, all patients received a uniform baseline treatment, including: Reducing intracranial pressure (intravenous infusion of mannitol at 0.5-1.0 g/kg or 100-250 mL of hypertonic saline with a concentration of 3% every 6 hours), anti-inflammation/antipyretic (administration of acetaminophen at 500 mg when body temperature >38. 5ºC), neuroprotective agents (intravenous infusion of 30 mg) Edaravone and prophylactic antibiotics (ceftriaxone, 1g, taken once every 12 hours within 24 hours after the operation). The control group was treated with 50 μg remifentanil intravenous injection for 30 s, followed by micro-pump at 1.0 μg/kg/h. The combined group was simultaneously administered 0.5mg/kg ketamine on the basis of remifentanil, also by intravenous injection, with the time controlled within 30 seconds. After administration, continuous intravenous micro-pump infusion was given at a dose of 0.5mg/kg /h.

VAS, SAS, BCS and Ramsay scoring

All evaluations were conducted by professionals who were unaware of the groupings at 48 hours after the operation. Pain scores were recorded using VAS (1-10 points, 0 = no pain, 10 = highest possible pain). Self-rating anxiety score (SAS) was assessed by anthropometric scoring criteria (1-7 points, 1 point = no arousal, 7 points = dangerous agitation). Bruggrmann comfort score (BCS) was performed based on the Comfort Rating Scale (0-4 points, 0 points = persistent pain, 4 points = no pain when coughing). Ramsay sedation score was assessed (1-6 points, 1 point = anxiety, agitation, or unease, 6 points = no response to a noxious stimulus during sleep) (Dunstan and Scott, 2018, Sung and Wu, 2018, Xu *et al*., 2015).

Postoperative adverse reaction analysis

48 hours after the operation, the occurrence of adverse reactions in the patient's respiratory system (respiratory depression: respiratory rate <8 times /min, hypoxemia: spo2 <90% for 1 minute), circulatory system (bradycardia: HR <50 times /min, hypotension: MAP <65 mmHg) and other adverse reactions (nausea/vomiting, pruritus, restlessness) was recorded. Analyze the incidence of various adverse reactions and total adverse events.

Blood collection and storage

Blood samples were collected one day before the operation and 48 hours after the operation. Two milliliters of blood were collected from a peripheral vein and centrifuged at 3000 rpm for 15 minutes. The serum was collected and stored in a -20°C freezer.

ELISA

Serum levels of TNF-α and IL-2 were detected using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits strictly according to the manufacturer's instructions.

Statistical analysis

All data analyses were performed using SPSS 22.0 software. Measurement data were described as mean ± standard deviation (Mean ± SD). Comparisons within and between groups were made using repeated measures analysis of variance or independent samples t-tests, as appropriate. A P-value of less than 0.05 ($P < 0.05$) was considered statistically significant.

RESULTS

VAS score comparison

Both groups significantly reduced VAS scores compared with preoperative groups ($P < 0.05$). VAS scores were significantly lower in the combined group ($P < 0.05$). (Fig. 1).

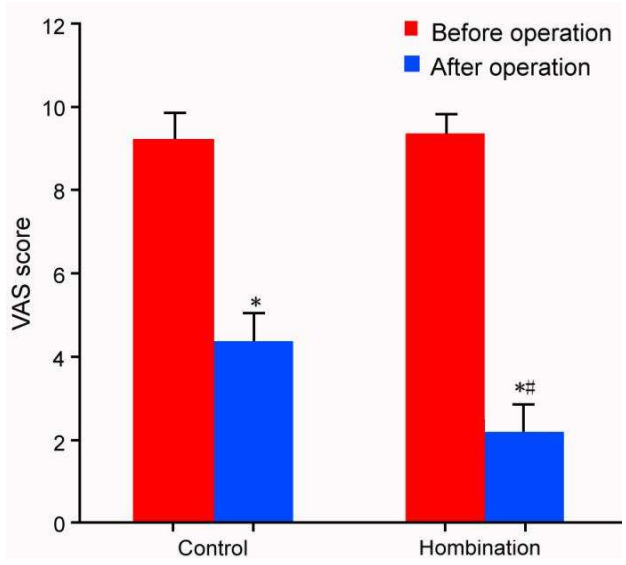

Fig. 1: VAS score comparison. * $P < 0.05$, compared with before operation; # $P < 0.05$, compared with control.

SAS score comparison

Both groups markedly reduced SAS scores compared with preoperative groups ($P < 0.05$). SAS in combined group was apparently declined ($P<0.05$) (Fig. 2).

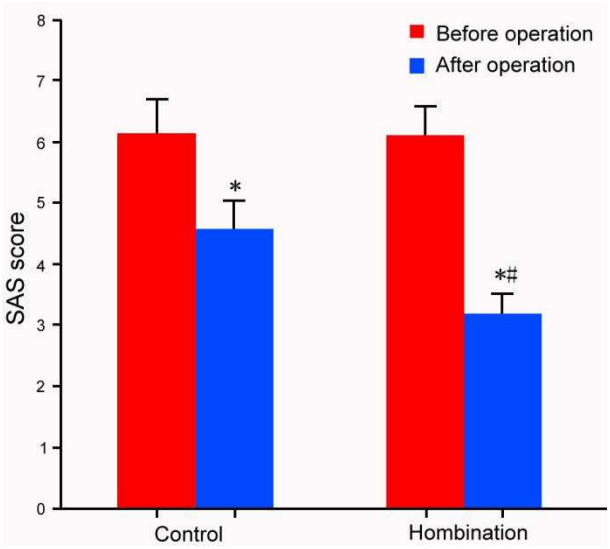

Fig. 2: SAS score comparison. * $P < 0.05$, compared with before operation; # $P < 0.05$, compared with control.

Ramsay score comparison

After treatment, Ramsay score was significantly increased in combination group ($P<0.05$) (Fig. 3).

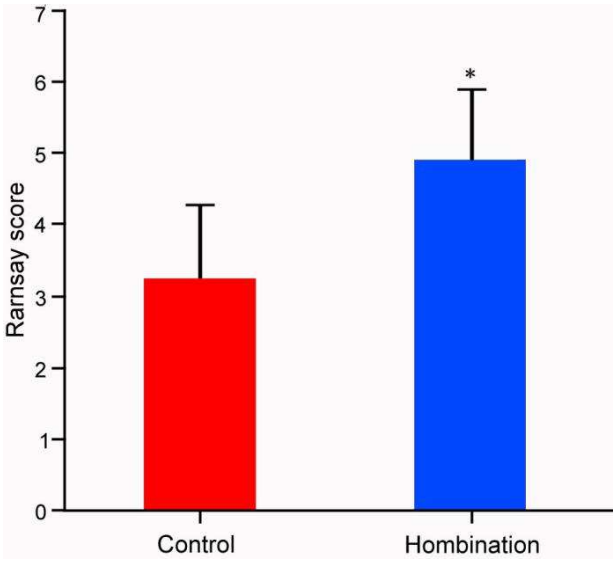

Fig. 3: Ramsay score comparison. * $P < 0.05$, compared with control.

BCS score comparison

After treatment, BCS score was obviously elevated in combination group ($P<0.05$) (Fig. 4).

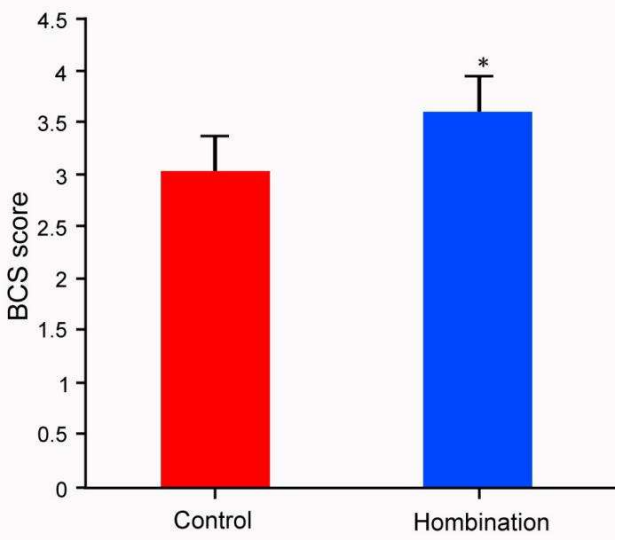

Fig. 4: BCS score comparison. * $P < 0.05$, compared with control.

Adverse reaction comparison

The results showed that although ketamine combined with remifentanil can reduce adverse reactions in patients with severe brain injury, it failed to exhibit statistical difference with the control group ($P > 0.05$) (Table 2).

The impact of ketamine combined with remifentanil on inflammatory factors in severe brain injury

Compared with before operation, both groups were able to reduce TNF-α and IL-2 ($P < 0.05$). Compared with control group, TNF-α and IL-2 levels in combined group were obviously decreased ($P < 0.05$) (Fig. 5).

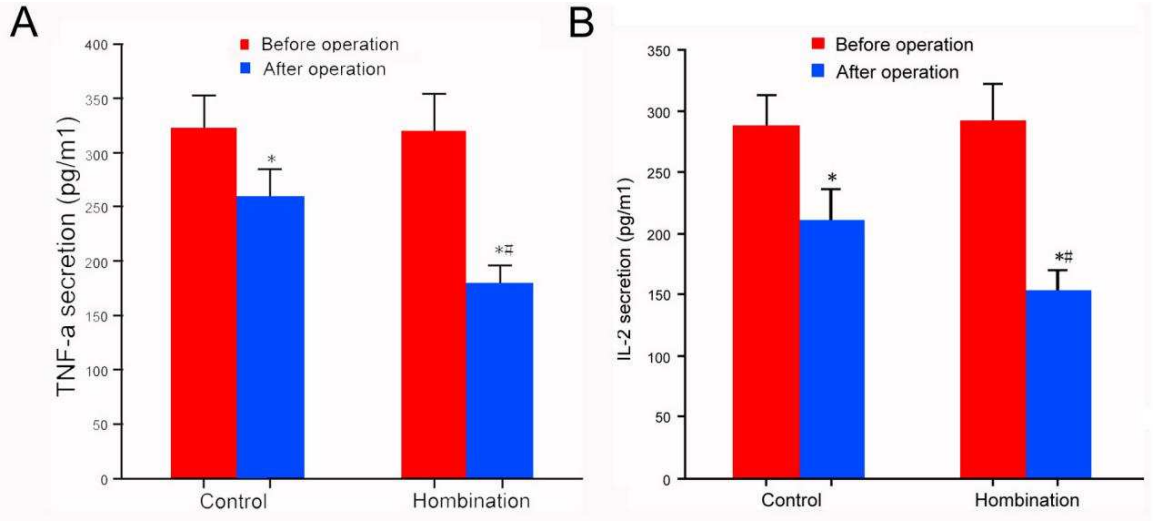

Fig. 5: The impact of ketamine combined with remifentanil on inflammatory factors in severe brain injury. * $P < 0.05$, compared with before operation; # $P < 0.05$, compared with control.

Table 1: Comparison of baseline data between the two groups

Groups	Age (Mean±SD, years)	Gender [n (%)] Male	Female	Injury time (Mean±SD, h)	Weight (Mean±SD, kg)	Groups
Control(n=30)	46.35±3.47	19(63.33)	11(36.67)	6.85±2.14	54.67±6.69	
Combination(n=30)	46.28±3.52	23(36.67)	7(63.33)	6.92±2.09	54.75±6.59	
T/χ^2	0.078	1.270	0.128	0.047		
P	0.938	0.260	0.899	0.963		

Table 2: Adverse reaction comparison (n%).

Group	Bradycardia	Itching	Hypotension	Nausea/Vomiting	Incidence
Control (n=30)	2 (6.6%)	5 (16.6%)	4 (13.3%)	6 (20.0%)	17 (56.6%)
Combination (n=30)	1 (3.3%)	4 (13.3%)	6 (20.0%)	5 (16.6%)	16 (53.3%)

DISCUSSION

Severe brain injury patients often exhibit agitation or restlessness after surgery, which can exacerbate the stress response, promote hypoxic-ischemic brain reactions, alter brain metabolism, increase intracranial pressure and lead to further damage to brain and nerve cells. Moreover, agitation may render patients unable to cooperate with essential mechanical ventilation and monitoring therapy. Thus, effective analgesic sedation constitutes a critical component in the management of severe brain injury after surgery (Haar *et al*., 2016, Humble *et al*., 2016). Appropriate analgesic and sedative medications help control cerebral perfusion pressure while simultaneously reducing systemic inflammation, suppressing endogenous catecholamine release, decreasing cerebral capillary hydrostatic pressure and alleviating cerebral edema (Launcelott *et al*., 2016, Pajoumand *et al*., 2016). Therefore, optimizing analgesia and sedation therapy can potentially improve the prognosis of patients with severe brain injury by reducing the body's metabolic rate and oxygen consumption.

The selection of analgesic and sedative drugs for traumatic brain injury should meet the criteria of causing no damage to the central nervous system and having rapid elimination properties (Welch *et al*., 2016). Remifentanil, an ultrashort-acting μ-opioid receptor agonist, exerts rapid and potent analgesic effects but demonstrates limited independent anti-inflammatory properties (Salama and Amer, 2018, Wan Hassan *et al*., 2018). Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has proven safe and effective for sedation in patients with neurological impairment. By blocking NMDA receptors, ketamine inhibits glutamate-induced excitotoxicity, reduces calcium influx and subsequent neuronal apoptosis and importantly, downregulates the expression of pro-inflammatory factors such as TNF-α and IL-6 (Abass *et al*., 2018, Gilbert *et al*., 2018). The distinct yet complementary mechanisms of these two drugs form the theoretical basis for their combination.

This study demonstrated that both remifentanil alone and the combination with ketamine effectively reduced VAS and SAS scores and decreased serum levels of TNF-α and IL-2 compared to preoperative values. However, the

combination therapy yielded significantly superior outcomes. Compared to remifentanil alone, the ketamine-remifentanil combination resulted in significantly lower VAS and SAS scores, higher Ramsay sedation and BCS comfort scores and greater reductions in TNF-α and IL-2 levels, without increasing the incidence of adverse reactions. The observed enhanced efficacy of the combination regimen can be attributed to mechanistic synergy. Remifentanil primarily provides rapid and controllable analgesia through activation of μ-opioid receptors, effectively addressing nociceptive stimuli. Ketamine, on the other hand, offers supplemental analgesia by antagonizing NMDA receptors to address central sensitization and hyperalgesia, thereby compensating for the limitations of opioids. Furthermore, its sympathomimetic activity counteracts opioid-induced hemodynamic instability, while simultaneously reducing levels of pro-inflammatory cytokines such as TNF-α and IL-2. This reduction thereby decreases the incidence of secondary brain injury, alleviates neuronal damage and edema, and improves prognostic outcomes (Haar *et al*., 2016). At the same time, by mitigating this inflammatory response, the combination therapy helps preserve neuronal integrity and potentially enhances long-term recovery. This synergistic action on both pain pathways and neuroinflammation further underscores the clinical value of the combination therapy beyond merely additive effects.

This study demonstrated that ketamine plus remifentanil was better than remifentanil alone in the management of analgesia and sedation in patients with severe brain injury. This is also consistent with the growing recognition of ketamine's multimodal benefits in intensive care sedation (Abass *et al*., 2018, Jonkman *et al*., 2018). However, previous research specifically focusing on the combination of remifentanil and ketamine for severe brain injury has been limited, which highlights the novelty of our study. While some studies support the safety and neuroprotective potential of ketamine in brain injury (Jonkman *et al*., 2018). Others have explored remifentanil-based regimens (Lu *et al*., 2018). Our results extend this understanding by demonstrating the tangible benefits of the combination therapy on both analgesic-sedative outcomes and inflammatory modulation in this specific patient population.

Despite the encouraging results, several limitations of this study should be considered. First, although the sample size was sufficient based on a priori calculation, it was relatively small, which may limit the generalizability of the findings and the ability to detect rare adverse events. Second, outcome assessments were conducted only within 48 hours after surgery. This short observation period is insufficient to evaluate long-term analgesic-sedative effects, sustained anti-inflammatory impact, or ultimate influence on neurological functional recovery and survival rates. Third, potential confounding factors-such as variations in the nature and severity of brain injury, the complexity of the surgical procedures performed and patients' pre-existing medical conditions—may have influenced the outcomes. Future studies with larger sample sizes, longer follow-up durations, inclusion of functional outcome measures and more detailed hemodynamic monitoring are warranted to confirm these findings and fully elucidate the long-term clinical significance of this combination therapy.

CONCLUSION

Ketamine combined with remifentanil showed better analgesic and sedative effects on severe brain injury. It can inhibit the pain and restlessness, improve comfort and suppress inflammation, thus has good clinical application value.

Acknowledgment
We gratefully acknowledge the Wuxi No. 2 People's Hospital for providing the necessary equipment for this study.

Authors' contributions
Wenting He: Conceptualization, Methodology, Investigation, Data Curation, Writing - Original Draft.
Yixue Lu: Formal analysis, Resources, Writing - Review & Editing, Supervision, Project administration.
All authors have read and approved the final manuscript.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability statement
All data generated or analyzed during this study are included in this published article**.**

Ethical approval
This study was approved by the Ethics Committee of Wuxi No.2 People's Hospital and informed consent was obtained (approval number: GSL20240502).

Conflict of interest
The authors declare that the study was conducted without any commercial or financial relationships that could be construed as potential conflicts of interest.

REFERENCES

Abass M, Picek S, Garzon JFG, Kuhnle C, Zaghlou A and Bettschart-Wolfensberger R (2018). Local mepivacaine before castration of horses under medetomidine isoflurane balanced anaesthesia is effective to reduce perioperative nociception and cytokine release. *Equine Vet J,* **50**(6): 733-738.

Ayubi E, Salimi Y and Safiri S (2018). Body mass index >35 as independent predictor of mortality in severe traumatic brain injury: Statistical and methodologic issues. *World Neurosurg,* **109**: 508.

Dunstan DA and Scott N (2018). Assigning clinical significance and symptom severity using the zung scales: Levels of misclassification arising from confusion between index and raw scores. *Depress Res. Treat,* **2018**: 9250972.

Einarsen CE, van der Naalt J, Jacobs B, Follestad T, Moen KG, Vik A, Haberg AK and Skandsen T (2018). Moderate traumatic brain injury: Clinical characteristics and a prognostic model of 12-month outcome. *World Neurosurg,* **114**: e1199-e1210.

Gilbert JR, Yarrington JS, Wills KE, Nugent AC and Zarate CA (2018). Glutamatergic signaling drives ketamine-mediated response in depression: Evidence from dynamic causal modeling. *Int. J. Neuropsychopharmacol.,* **21**(8): 740-747.

Haar CV, Lam FCW, Adams WK, Riparip LK, Kaur S, Muthukrishna M, Rosi S and Winstanley CA (2016). Frontal traumatic brain injury in rats causes long-lasting impairments in impulse control that are differentially sensitive to pharmacotherapeutics and associated with chronic neuroinflammation. *ACS Chem Neurosci,* **7**(11): 1531-1542.

Huang Q, Xu H and Xiao QS (2017). Clinical research of different analgesia methods on perianesthetic pain of patients with moderate and severe craniocerebral injury who have emergency operation. *Eur Rev Med Pharmacol Sci,* **21**(3): 88-92.

Humble SS, Wilson LD, Leath TC, Marshall MD, Sun DZ, Pandharipande PP and Patel MB (2016). ICU sedation with dexmedetomidine after severe traumatic brain injury. *Brain Inj,* **30**(10): 1266-1270.

Jang SH, Ha JW, Kim HY and Seo YS (2017). Recovery of injured Broca's portion of arcuate fasciculus in the dominant hemisphere in a patient with traumatic brain injury. *Medicine,* **96**(51): e9183.

Jonkman K, van der Schrier R, van Velzen M, Aarts L, Olofsen E, Sarton E, Niesters M and Dahan A (2018). Differential role of nitric oxide in the psychedelic symptoms induced by racemic ketamine and esketamine in human volunteers. *Br J Anaesth,* **120**(5): 1009-1018.

Launcelott ZA, Palmisano MP, Stefanacci JD and Whitney BL (2016). Ventricular pneumocephalus, cervical subarachnoid pneumorrhachis, and meningoencephalitis in a dog following rhinotomy for chronic fungal rhinitis. *J Am Vet Med Assoc,* **248**(4): 430-435.

Lin CR, Tsai JH, Wu SS, Chang YP, Wen YH, Liu JS and Lung FW (2018). Quantitative comorbidity risk assessment of dementia in Taiwan: A population-based cohort study. *Medicine (Baltimore),* **97**(15): e0298.

Lu Z, Li W, Chen H and Qian Y (2018). Efficacy of a dexmedetomidine-remifentanil combination compared with a midazolam-remifentanil combination for conscious sedation during therapeutic endoscopic retrograde cholangio-pancreatography: A prospective, randomized, single-blinded preliminary trial. *Dig Dis Sci,* **63**(6): 1633-1640

Moe HK, Moen KG, Skandsen T, Kvistad KA, Laureys S, Haberg A and Vik A (2018). The influence of traumatic axonal injury in thalamus and brainstem on level of consciousness at scene or admission: A clinical magnetic resonance imaging study. *J Neurotrauma,* **35**(7): 975-984.

Pajoumand M, Kufera JA, Bonds BW, Devabhakthuni S, Boswell S, Hesselton K, Scalea TM and Stein DM (2016). Dexmedetomidine as an adjunct for sedation in patients with traumatic brain injury. *J Trauma Acute Care Surg,* **81**(2): 345-351.

Salama ER and Amer AF (2018). The effect of pre-emptive gabapentin on anaesthetic and analgesic requirements in patients undergoing rhinoplasty: A prospective randomised study. *Indian J Anaesth,* **62**(3): 197-201.

Sung YT and Wu JS (2018). The visual analogue scale for rating, ranking and paired-comparison (VAS-RRP): A new technique for psychological measurement. *Behav Res Methods,* **50**(4): 1694-1715.

Swanson RL, Hampton S, Green-McKenzie J, Diaz-Arrastia R, Grady MS, Verma R, Biester R, Duda D, Wolf RL and Smith DH (2018). Neurological manifestations among US Government personnel reporting directional audible and sensory phenomena in Havana, Cuba. *JAMA,* **319**(11): 1125-1133.

Tollefsen MH, Vik A, Skandsen T, Sandrod O, Deane SF, Rao V and Moen KG (2018). Patients with moderate and severe traumatic brain injury: Impact of preinjury platelet inhibitor or warfarin treatment. *World Neurosurg,* **114**: e209-e217.

Vavilala MS, Lujan SB, Qiu Q, Bell MJ, Ballarini NM, Guadagnoli N, Depetris MA, Faguaga GA, Baggio GM, Busso LO, Garcia ME, Gonzalez Carrillo OR, Medici PL, Saenz SS, Vanella EE, Farr CK and Petroni GJ (2017). Intensive care treatments associated with favorable discharge outcomes in Argentine children with severe traumatic brain injury: For the South American Guideline Adherence Group. *PLoS One,* **12**(12): e0189296.

Wan Hassan WMN, Tan HS and Mohamed Zaini RH (2018). Comparison of the effects of dexmedetomidine on the induction of anaesthesia using marsh and schnider pharmacokinetic models of propofol target-controlled infusion. *Malays J Med Sci,* **25**(1): 24-31.

Welch TP, Wallendorf MJ, Kharasch ED, Leonard JR, Doctor A and Pineda JA (2016). Fentanyl and midazolam are ineffective in reducing episodic intracranial hypertension in severe pediatric traumatic brain injury. *Crit Care Med,* **44**(4): 809-818.

Xu J, Jin C, Cui X and Jin Z (2015). Comparison of Dexmedetomidine versus propofol for sedation after uvulopalatopharyngoplasty. *Med Sci Monit,* **21**: 2125-2133.