Turk Neurosurg, 2022

Original Investigation

DOI: 10.5137/1019-5149.JTN.36585-21.2

Received: 25.09.2021
Accepted: 07.02.2022

Published Online: 02.08.2022

Clinical Study of Dexmedetomidine in Combination with Butorphanol for the Treatment of Postoperative Traumatic Brain Injury (TBI)

Xuejian WANG, Zhifeng WANG, Chen SUN, Zhiming CUI

Affiliated Hospital 2 of Nantong University, Department of Neurosurgery, Nantong University, Nantong, Jiangsu, PR China

Corresponding author: Xuejian WANG ✉ 6841441@163.com

ABSTRACT

AIM: To explore whether the combination of dexmedetomidine (Dex) and butorphanol (But) could benefit patients with traumatic brain injury (TBI).

MATERIAL and METHODS: A total of 208 TBI patients admitted from February 2018 to January 2020 were randomly divided into four groups as follows: control group (A), Dex group (B), But group (C), and combination of dexmedetomidine and butorphanol group (D). Four groups of patients were treated and studied clinically. Statistical analysis was performed to assess the changes in signs of life, oxygen saturation, serum neuroendocrine data, pain, and agitation scores.

RESULTS: The statistical data of signs of life and blood oxygen saturation of the four groups were compared, and the differences between group A and group D were statistically significant ($p<0.05$), indicating that a combination of sedative and analgesic agents at low doses could improve the signs of life of TBI patients, and the safety was relatively good. The Glasgow Coma Scale (GCS) score of the group D on the 5th day post-surgery was improved compared with the control group (A group), suggesting that the combination of sedative and analgesic agents could improve patients' consciousness. The neuroendocrine data of the combination group showed little fluctuation, indicating that a combination of sedative and analgesic agents could significantly reduce the stress response. The scores of pain and agitation in the combination group were significantly improved on the 3rd and 5th days, suggesting that the combination group was better compared with the control group.

CONCLUSION: The combination of Dex and But was more stable for the treatment of vital signs. Compared with the individual treatment groups, the patients in the combination group had a rapid improvement. The time from treatment to stabilization was shortened, and the prognosis was significantly better compared with the control group. A combination of Dex and But at low doses could significantly maintain neuroendocrine stability. Meanwhile, a combination of sedative and analgesic agents had obvious synergistic effects on enhancing sedation and analgesia as well as anti-muscle tension. Collectively, the combination of Dex and But could significantly benefit the prognosis of TBI.

KEYWORDS: Drug combination, Sedation and analgesia, Traumatic brain injury (TBI), Postoperative, Brain protection

INTRODUCTION

As one of the most important diseases in neurosurgery, traumatic brain injury (TBI) is characterized by its critical condition, high fatality rate, and poor prognosis. Therefore, more attention should be paid to clinical treatment to reduce the mortality rate, improve the cure rate of patients, and decrease the social burden (14,20). TBI patients are often accompanied by strong stress reactions after surgery, as well as fierce adverse reactions, such as increased blood pressure, rapid heart rate, dyspnea, and agitation. Excessive stress reaction often leads to poor prognosis in patients. It is necessary to stabilize postoperative vital signs and reduce stress state in patients with severe craniocerebral injury. In

Xuejian WANG : 0000-0003-0389-5674
Zhifeng WANG : 0000-0001-8154-0356
Chen SUN : 0000-0002-0939-5550
Zhiming CUI : 0000-0002-0939-5550

the past several decades, no attention has been paid to the use of analgesic and sedative agents, leading to failure in solving the pain, fear, and agitation problems. The widespread use of narcotic analgesics, such as morphine/fentanyl, in clinical practice can result in different degrees of respiratory depression while inhibiting the stress response. However, only very few clinical reports have investigated the use of the sedative agent dexmedetomidine (Dex) in combination with the opioid receptor agonist-antagonist butorphanol (But) after the operation. In the present study, we aimed to evaluate the efficacy and feasibility of the combination of Dex and But for the treatment of TBI.

MATERIAL and METHODS

This study was approved by the Ethics Committee of our hospital, and written informed consent was obtained from all patient guardians.

General Information

A total of 584 TBI patients who underwent surgery and head CT (or MRI) were admitted to our department from February 2018 to January 2020. This study was approved by the Ethics Committee of our hospital, and written informed consent was obtained from all patient guardians.

Inclusion criteria

Inclusion criteria were set as follows: [1] patients meeting the diagnostic criteria of acute craniocerebral trauma; [2] patients with timely admission to hospital for treatment after trauma (<24 h); [3] patients with imaging examination confirming the existence of cerebral contusion and laceration with intracerebral hematoma; [4] patients with Glasgow Coma Scale (GCS) of 5-12 points, and systolic blood pressure >90 mmHg; [5] patients aged between 20 and 80 years old; [6] patients in line with surgical indications; [7] craniocerebral injury was not combined with other injuries; [8] patients without existing basic diseases, such as cardiopulmonary diseases; and [9] patient guardians agreed to participate in the study, and their family members signed the "Informed consent to treatment".

Exclusion criteria

Exclusion criteria were set as follows: [1] patients with other severe system injuries; [2] patients with other neurological diseases before the trauma, such as ischemic cerebrovascular disease, cerebral infarction, brain tissue, cognitive dysfunction, and so on; [3] patients with chronic diseases of liver and kidney; [4] patients with malignant tumors; [5] patients with surgical contraindications; [6] patients allergic to the relevant drugs and ingredients used in this study; and [7] family members of patients refused to participate in the study. There were 126 patients with complex injuries, 103 patients whose patient guardians refused to participate in this study, and 147 patients with basic diseases, such as heart and lung diseases. Finally, 208 patients aged 21-78 years were included in the study, including 137 males and 71 females.

Eligible patients were randomly divided into the Dex+But group (N=52), Dex group (N=52), But group (N=52), and control group (N=52) using the random number method.

Treatment Strategy

The control group was given routine symptomatic treatment. During the treatment, agitated patients were temporarily subjected to hibernation treatment for relief. In addition to conventional symptomatic treatment, the patients in the Dex group were slowly injected with Dex at a dose of 1 μg/kg, followed by an intravenous infusion of the maintenance dose at 0.2-0.7 μg/kg per hour. The dose was adjusted according to the patient's condition. In the But group, the patients were given 48 mL normal saline containing 4 mg But in 12 hours. In the combination group, the patients were given both Dex and But at the above-mentioned doses.

The vital signs of the patients were closely monitored during the treatment. Patients with dyspnea or low oxygen saturation were given assisted ventilation. The objectives of sedation and analgesia were as follows: the patient's Ramsay score (3-4 points), or Sedation-Agitation Scale (SAS) (26) score (3-4 points in the daytime and 2-3 points in the night). The data were recorded by specially-assigned personnel, the patient's vital signs were maintained stable, and the patient's drug usage was adjusted accordingly.

Contents of Collection Records

Vital signs (T, P, R, BP, and SPO_2), stress- and inflammation-related indicators (cortisol, endorphin, IL-6, and so on), as well as Ramsay and SAS scores of the above-mentioned four groups, were collected and recorded preoperative and postoperative at 1, 3, and 5 days. In the experimental groups, sedative and analgesic agents were terminated every 6 hours. Patients were awakened as soon as possible, and GCS, Wong-Baker Scale (WBS), and SAS (26) scores were recorded. The average blood pressure, heart rate, respiration, and other indexes of all groups were compared.

Statistical Analysis

Statistical analysis was conducted using the SPSS 20.0 statistical software. Data were expressed as means±standard deviation, and differences between two groups were analyzed by the Student's t-test. Comparison between count datasets was performed by $\chi 2$ test. $p<0.05$ was considered statistically significant.

RESULTS

There was a statistical difference in vital signs between the combination group and control group ($p<0.05$), indicating that a combination of sedative and analgesic agents at low doses could improve the vital signs of TBI patients, and the safety was good (Table I). The GCS score of the combination group on day 5 post-surgery was improved compared with the control group, suggesting that the combination regimen was beneficial for improving patients' consciousness (Table II). The neuroendocrine data of the combination group fluctuated less significantly, indicating that the combination regimen could significantly reduce the stress response (Table III). The score of pain and agitation was significantly improved on days 3 and 5 post-surgery, suggesting that the combination group was remarkably improved compared with the control

group. The patients in the combination group showed a rapid improvement, a shorter time from treatment to stability, and a significantly better prognosis compared with the control group (Table IV-V).

DISCUSSION

Procedural sedation and analgesia (PSA) therapy after craniocerebral surgery can stabilize vital signs, avoid the secondary injury of brain tissue, and improve the basic metabo-

Table I: Comparison of Vital Signs Parameters of Four Groups

Evaluation item	A group	B group	C group	D group
Blood pressure (MAP)	112.6 ± 7.8	96.4 ± 7.2	99.3 ± 6.6	88.2 ± 6.8
Heart rate	94.2 ± 9.2	84.3 ± 7.3	83.2 ± 7.9	75.2 ± 7.6
Respiration	20.2 ± 2.9	18.1 ± 1.6	18.7 ± 1.2	17.2 ± 1.4
SpO2	92.4 ± 8.8	93.3 ± 4.7	94.2 ± 3.7	95.6 ± 4.2
Body temperature	37.6 ± 3.7	37.1 ± 3.6	36.8 ± 3.9	36.3 ± 3.4

The combination group (D) is significantly improved compared with the control group (A), p<0.05. mean arterial pressure: MAP; Dex in combination with But group (D), Dex group (C), But group (B), and control group (A).

Table II: Comparison of Glasgow Scores

DAY	A group	B group	C group	D group
Return to the Ward	6.8 ± 2.64	6.7 ± 2.45	6.3 ± 2.23	6.5 ± 2.74
POD 1	7.11 ± 2.91	7.02 ± 2.73	7.08 ± 2.56	7.03 ± 2.57
POD 3	7.41 ± 2.18	7.57 ± 2.34	7.62 ± 2.13	7.82 ± 2.37
POD 5	8.16 ± 1.93	8.66 ± 2.25	8.83 ± 2.36	9.67 ± 2.43

The state of consciousness is improved after the operation. On day 5 after the operation (POD 5), the P value of the combination group (D) was significantly improved compared with the control group (A) (t=3.5089, p<0.05). Postoperative day (POD), combination group (D), Dex group (C), But group (B), and control group (A).

Table III: Comparison of Neuroendocrine Numerical Indexes

Evaluation Item	A group	B group	C group	D group
Endorphin (ng/ml)	426.3 ± 95.7	374.3 ± 84.8	356.6 ± 87.9	273.2 ± 67.3
IL-6 (ng/ml)	221.13 ± 36.3	191.16 ± 37.7	181.12 ± 31.2	162.14 ± 18.1
Cortisol (ng/ml)	384 ± 28.1	281 ± 24.3	312 ± 22.8	231 ± 25.7

Comparison of neuroendocrine numerical indexes. The p value of the combination group (D) was significantly improved compared with the control group (A) (P<0.05). IL: interleukin; combination group (D), Dex group (C), But group (B), and control group (A).

Table IV: Comparison of Pain Between the Four Groups

The ache grades (Wong-Baker)				
Time	A group	B group	C group	D group
Return to the Ward	7.3 ± 1.62	7.3 ± 1.63	7.2 ± 1.64	7.3 ± 1.54
POD 1	6.8 ± 1.43	6.5 ± 1.73	6.6 ± 1.74	6.1 ± 1.89
POD 3	6.5 ± 1.66	6.1 ± 1.67	5.8 ± 1.68	4.8 ± 1.45
POD 5	5.4 ± 1.44	4.7 ± 1.56	5.2 ± 1.43	3.6 ± 1.13

Comparison of pain among the four groups. The p value on the 1st/3rd/5th day after the operation in the combination group was significantly improved compared with the control group (A group) (p<0.05).

Table V: Comparison of Agitation Between the Four Groups

Sedation-Agitation Scale(SAS)				
Time	**A group**	**B group**	**C group**	**D group**
Return to the Ward	6.4 ± 1.53	6.3 ± 1.64	6.4 ± 1.25	6.3 ± 1.61
POD 1	5.8 ± 1.72	5.6 ± 1.61	5.7 ± 1.58	5.5 ± 1.79
POD 3	5.5 ± 1.68	5.1 ± 1.32	4.9 ± 1.43	4.2 ± 1.59
POD 5	5.1 ± 1.54	4.5 ± 1.47	4.3 ± 1.36	3.1 ± 1.56

Comparison of agitation among the four groups. The p value on the 3rd/5th day after the operation in the combination group was significantly improved compared with the control group (A group) ($p<0.05$).

lism of brain cells. PSA is one of the main treatment regimens after craniocerebral trauma, which has been gradually recognized by all patients and physicians. Therefore, research on PSA for craniocerebral injury has been gradually carried out in recent years (4,13,15,32). Several previous clinical or animal studies have suggested that sedation or analgesia has beneficial effects on craniocerebral injury (3,6,17,21,32).

TBI patients often suffer from postoperative confusion and irritability. PSA can relieve the fluctuation of intracranial pressure and maintain the stability of postoperative vital signs (5,29). Pethidine and other drugs traditionally used have many complications, such as postural hypotension, respiratory depression, reduced cough reflex, obstructed respiratory tract, deeper consciousness disorder, delayed wakefulness, and prolonged course of the disease. In clinical practice, muscle injection is mainly used, which is inconvenient for dose adjustment (8,29,31). The causative sites of TBI are relatively special, often accompanied by disorders of direct consciousness. Therefore, it is significantly important to maintain the stability of patients' vital signs during and after surgery by reducing the intracranial pressure and promoting the recovery of neurological function (19).

Studies have shown that 60-84% of neurosurgical patients have varying degrees of pain after craniotomy, and relatively severe pain exists in the short term (within 12 hours) (10,24,25). After TBI, there is an inflammatory reaction following tissue injury, leading to peripheral sensitization of pain. The conduction of the noxious stimulus is increased, which enhances the response of neurons to pain and results in central sensitization. Therefore, TBI patients exhibit irritability and other uncomfortable manifestations. Restraint bands are usually used to restrict TBI patients with postoperative agitation. However, restraint bands often cause the escalation of resistance and trigger agitation in patients, resulting in increased intracranial pressure and affecting the treatment of postoperative patients. Pipertitin and other drugs are also used postoperatively, mainly for intramuscular injection, with certain timeliness, interval administration, and inconvenience in drug control and regulation. At present, some studies have suggested that continuous postoperative analgesics can control pain. Moreover, many reports have revealed that tramadol and other drugs are used in patients with postoperative analgesia of the chest, abdomen, or limbs (analgesia pump). However, only very few reports have investigated analgesia and sedation in TBI patients. The researchers have concluded that the reasons may be as follows. [1] Patients with TBI, especially severe craniocerebral injury, are often accompanied by unstable vital signs. For example, the use of sedative and analgesic drugs may affect circulation and respiratory function and cause life risks [2]. The conditions of consciousness and pupils of TBI patients should be observed regularly. The use of sedative and analgesic agents may affect the observation of consciousness [3]. At present, the PSA treatment is not often used after the operation, and most doctors have not been used to it [4] since it is difficult to control the depth of sedation and analgesia. To achieve the effects of sedative and analgesic agents alone, continuous administration at high doses should be applied, leading to significant adverse reactions [5]. Many hospitals do not have independent neurosurgical care units or corresponding monitoring equipment.

Propofol and other single drugs have been reported in the past for controlling sedation in TBI patients. However, single drugs have disadvantages, such as short duration of action, large dosage, many adverse reactions, and incomplete control of agitation (31). Dex is a highly selective α2 adrenoceptor-activating drug with quick onset, short duration of action, both sedative and analgesic effects, and has no respiratory depression. Recently, Dex has attracted more and more attention in clinical practice (1,27). The combined application of Dex and opioids can not only enhance the analgesic effect of opioids but also reduce the dosage of opioids and effectively prevent the adverse reactions caused by opioid overdose. But is part of the agonist of opioid receptor, the main agonist κ1 receptor, and its analgesic effect is 3.5 ~ 7 times higher compared with morphine, with some sedative effects (9,11). It can relieve moderate and severe pain and has the advantages of fewer adverse reactions, low addiction, and low toxicity (11,24,28,30). Previously, Dex and But have been used in cat/dog studies (2,16,18,22), as well as PSA treatment for gastrointestinal or abdominal surgery (12,31,33). However, Dex and But have not been used after TBI (23,31). In the present study, Dex and But were selected as sedative and analgesic agents, respectively. The results suggested that the combination of Dex and But was beneficial to TBI patients, ensuring the stability of vital signs and reducing pain stress.

Bruder and Ravussin (7) have found that after craniocerebral surgery, 13%-27% of patients have increased blood pressure,

elevated cerebral blood flow, and increased cerebral oxygen consumption, leading to elevated intracranial pressure and incidence of postoperative intracranial hemorrhage and cerebral edema, and resulting in further secondary brain damage (7). In the present study, compared with the control group, the vital signs of the combination group, Dex group, and But group were more stable, and the vital signs of the combination group were significantly improved (Table I). Moreover, the GCS scores of the combination group, Dex group, and But group were all improved compared with the control group, and the GCS scores of the combination group were significantly improved on day 5 post-surgery ($p<0.05$) (Table II). In terms of neuroendocrine indicators, the combination group showed more stable neuroendocrine tests compared with the control group ($p<0.05$) (Table III). In terms of WBS and SAS scores, the combination group had a significantly better pain score and agitation score compared with the control group ($p<0.05$) (Table IV, V). Taken together, we found that the TBI patients in the combination group had better pain control and patient comfort.

CONCLUSION

The combination of sedative and analgesic drugs is a new trend in the application of narcotic drugs. The combined use of Dex and But has obvious synergistic effects, such as enhanced analgesia, sedation, and anti-muscle tension, and can reduce adverse reactions of each drug, leading to significantly reduced impact on the respiratory and circulatory system. Moreover, such a combination regimen can decrease the dosage of single drugs and also reduce the cost. Therefore, the combination of Dex and But was a feasible PSA therapy for TBI patients, which could reduce pain-induced stress and improve patients' conditions.

ACKNOWLEDGEMENTS

This work was supported by the Science and Technology Program of Nantong Health Committee (MB2021026; MA2021017; MB2021027); and the Science and Technology Program of Nantong City (Key 003); Kangda College of Nanjing Medical University (KD2021JYYJYB025)

AUTHORSHIP CONTRIBUTION

Study conception and design: XW, ZC

Data collection: XW, ZC

Analysis and interpretation of results: XW

Draft manuscript preparation: XW, ZW

All authors (XW, ZW, CS, ZC) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Afonso J, Reis F: Dexmedetomidine: Current role in anesthesia and intensive care. Rev Bras Anestesiol 62(1):118-133, 2012
2. Ahsan MZ, Khan FU, Zhao MJ, Wang YX: Synergistic interaction between butorphanol and dexmedetomidine in antinociception. Eur J Pharm Sci 149:105322, 2020
3. Arbabi S, Ahrns KS, Wahl WL, Hemmila MR, Wang SC, Brandt MM, Taheri PA: Beta-blocker use is associated with improved outcomes in adult burn patients. J Trauma 56(2):265-269; discussion 269-2671, 2004
4. Ayer RE, Zhang JH: Oxidative stress in subarachnoid haemorrhage: Significance in acute brain injury and vasospasm. Acta Neurochir Suppl 104:33-41, 2008
5. Basali A, Mascha EJ, Kalfas I, Schubert A: Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. Anesthesiology 93(1):48-54, 2000
6. Bedford RF, Persing JA, Pobereskin L, Butler A: Lidocaine or thiopental for rapid control of intracranial hypertension? Anesth Analg 59(6):435-437, 1980
7. Bruder N, Ravussin P: Cerebral and systemic haemodynamic changes during neurosurgical recovery. Ann Fr Anesth Reanim 23(4):410-416, 2004
8. Colvin LA, Bull F, Hales TG: Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet 393(10180):1558-1568, 2019
9. Commiskey S, Fan LW, Ho IK, Rockhold RW: Butorphanol: Effects of a prototypical agonist-antagonist analgesic on kappa-opioid receptors. J Pharmacol Sci 98(2):109-116, 2005
10. De Benedittis G, Lorenzetti A, Migliore M, Spagnoli D, Tiberio F, Villani RM: Postoperative pain in neurosurgery: A pilot study in brain surgery. Neurosurgery 38(3):466-469; discussion 469-470, 1996
11. Du BX, Song ZM, Wang K, Zhang H, Xu FY, Zou Z, Shi XY: Butorphanol prevents morphine-induced pruritus without increasing pain and other side effects: A systematic review of randomized controlled trials. Can J Anaesth 60(9):907-917, 2013
12. Du J, Li JW, Jin J, Shi CX, Ma JH: Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy. Exp Ther Med 16(5):4063-4069, 2018
13. Fujitani T, Adachi N, Miyazaki H, Liu K, Nakamura Y, Kataoka K, Arai T: Lidocaine protects hippocampal neurons against ischemic damage by preventing increase of extracellular excitatory amino acids: A microdialysis study in Mongolian gerbils. Neurosci Lett 179(1-2):91-94, 1994
1. Hiquet J, Gromb-Monnoyeur S: Severe craniocerebral trauma with sequelae caused by Flash-Ball® shot, a less-lethal weapon: Report of one case and review of the literature. Med Sci Law 56(3):237-240, 2016
15. Ker K, Perel P, Blackhall K: Beta-2 receptor antagonists for traumatic brain injury: A systematic review of controlled trials in animal models. CNS Neurosci Ther 15(1):52-64, 2009
16. Khenissi L, Nikolayenkova-Topie O, Broussaud S, Touzot-Jourde G: Comparison of intramuscular alfaxalone and ketamine combined with dexmedetomidine and butorphanol for castration in cats. J Feline Med Surg 19(8):791-797, 2017
17. Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J, Schmelz M, Hering W: Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg 98(4):1050-1055, 2004

18. Krimins RA, Ko JC, Weil AB, Payton ME, Constable PD: Hemodynamic effects in dogs after intramuscular administration of a combination of dexmedetomidine-butorphanol-tiletamine-zolazepam or dexmedetomidine-butorphanol-ketamine. Am J Vet Res 73(9):1363-1370, 2012
19. Li W, Bai YA, Li YJ, Liu KG, Wang MD, Xu GZ, Shang HL, Li YF: Magnesium sulfate for acute traumatic brain injury. J Craniofac Surg 26(2):393-398, 2015
20. Liu Y, Liu W, Chen K: Unanticipated bleeding from the tongue during intubation of a craniocerebral trauma patient. J Neurosurg Anesthesiol 29(2):183-184, 2017
21. LoPachin RM, Gaughan CL, Lehning EJ, Weber ML, Taylor CP: Effects of ion channel blockade on the distribution of Na, K, Ca and other elements in oxygen-glucose deprived CA1 hippocampal neurons. Neuroscience 103(4):971-983, 2001
22. Medeiros LQ, Gozalo-Marcilla M, Taylor PM, Campagnol D, de Oliveira FA, Watanabe MJ, de Araujo Aguiar AJ: Sedative and cardiopulmonary effects of dexmedetomidine infusions randomly receiving, or not, butorphanol in standing horses. Vet Rec 181(15):402, 2017
23. Mishra L, Rajkumar N, Singh S, Dubey R, Yadav G: A comparative study of propofol and isoflurane anaesthesia using butorphanol in neurosurgery. Indian J Anaesth 53(3):324-329, 2009
24. Nelson KE, Eisenach JC: Intravenous butorphanol, meperidine, and their combination relieve pain and distress in women in labor. Anesthesiology 102(5):1008-1013, 2005
25. Quiney N, Cooper R, Stoneham M, Walters F: Pain after craniotomy. A time for reappraisal? Br J Neurosurg 10(3):295-299, 1996
26. Riker RR, Picard JT, Fraser GL: Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 27(7):1325-1329, 1999
27. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, Bin Kadiman S, McArthur CJ, Murray L, Reade MC, Seppelt IM, Takala J, Wise MP, Webb SA; ANZICS clinical trials group and the SPICE III investigators. Early sedation with dexmedetomidine in critically Ill patients. N Engl J Med 380(26):2506-2517, 2019
28. Wang F, Shen X, Liu Y, Xu S, Guo X: Continuous infusion of butorphanol combined with intravenous morphine patient-controlled analgesia after total abdominal hysterectomy: A randomized, double-blind controlled trial. Eur J Anaesthesiol 26(1):28-34, 2009
29. Wang X, Deng Q, Liu B, Yu X: Preventing emergence agitation using ancillary drugs with sevoflurane for pediatric anesthesia: A network meta-analysis. Mol Neurobiol 54(9):7312-7326, 2017
30. Wu Z, Kong M, Wang N, Finlayson RJ, Tran QH: Intravenous butorphanol administration reduces intrathecal morphine-induced pruritus after cesarean delivery: A randomized, double-blind, placebo-controlled study. J Anesth 26(5):752-757, 2012
31. Xu G, Zhao J, Liu Z, Liu G, Liu L, Ren C, Liu Y: Dexmedetomidine combined with butorphanol or sufentanil for the prevention of post-operative nausea and vomiting in patients undergoing microvascular decompression: A randomized controlled trial. Front Med (Lausanne) 7:583031, 2020
32. Xu JY, Chen C: Endocannabinoids in synaptic plasticity and neuroprotection. Neuroscientist 21(2):152-168, 2015
33. Zhang XK, Chen QH, Wang WX, Hu Q: Evaluation of dexmedetomidine in combination with sufentanil or butorphanol for postoperative analgesia in patients undergoing laparoscopic resection of gastrointestinal tumors: A quasi-experimental trial. Medicine (Baltimore) 95(50):e5604, 2016