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Original Research Article

Effect of Dexmedetomidine with Adjuvants (Fentanyl and Butorphanol) on Postoperative Analgesia and Cognitive Dysfunction Following Cardiac Surgery: A Prospective, Double-Blinded Randomized Controlled Trial

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Abstract

Background: Painafter cardiac surgery has various sites of origin and is caused by several factors. Postoperative analgesia improves patient satisfaction, reduces the incidence of postoperative complications and shortens the duration of hospital stay.

Objectives: To evaluate and compare the effect of intravenous infusion of dexmedetomidine and fentanyl versus intravenous infusion of dexmedetomidine and butorphanol on postoperative analgesia and postoperative cognitive dysfunction in patients undergoing cardiac surgery.

Materials and Methods: This study was conducted at tertiary care teaching hospital of Rajasthan from February 2019 to June 2020. Patients in the two groups received intravenous infusion of Dexmedetomidine 0.15µg/kg/h and Fentanyl 0.5µg/kg/h immediately postoperatively (Group DF) and intravenous infusion of Dexmedetomidine 0.15µg/kg/h and Butorphanol 2 µg/kg/h immediately postoperatively (Group DB) respectively. Both groups were compared for demographic data, postoperative hemodynamic data, Ramsay sedation scale, visual analogue scale (VAS) for pain and Montreal Cognitive assessment (MoCA) for cognitive function.

Results: There was no statistical difference in the VAS score of the patients between the group DB and DF at post extubation intervals of 12, 18, 24 and 48 Hours ($p>0.05$) except at 4 hours and 8 hours post extubation ($p<0.05$). Time to first rescue analgesic was significantly earlier for DF as compared to DB group ($p<0.05$). There was no statistical significant difference found in the mean of MoCA score between both the groups for both 1 day prior to surgery and 24hrs Post extubation ($p>0.05$). Drowsiness had the highest incidence in both the groups among all the adverse effects. There was no significant difference in terms of adverse effects ($p>0.05$) except drowsiness which was significantly higher in group DB ($p<0.05$).

Conclusion: The present study concluded that Dexmedetomidine in combination with Butorphanol is more effective as an analgesic than Dexmedetomidine with Fentanyl but no significant cognitive dysfunction was found among the patients in both groups.

Keywords: dexmedetomidine, Fentanyl, Butorphanol, cognitive dysfunction, postoperative analgesia

Introduction

Postoperative pain is the one of the important consequences of surgeries. Pain after cardiac surgery has various sites of origin and is caused by several factors. Sternotomy, retraction of sternum/ribs, pericardiotomy, harvesting of saphenous vein and internal mammarian artery, insertion of chest tube and other musculoskeletal trauma during surgery are the factors causing pain after cardiac surgery. Additionally, anxiety associated with major surgery also aggravates pain [1,2]. It is essential to manage pain effectively to prevent poor outcome after cardiac surgery.

Postoperative analgesia improves patient satisfaction, reduces the incidence of postoperative complications and shortens the duration of hospital stay [3,4]. Various methods have been used to control pain after cardiac surgery and these include use of narcotic and nonnarcotic analgesic drugs in infusion form or in bolus doses. According to the available protocols the ideal method to manage postoperative pain is to use combination of drugs.

Fentanyl is the most commonly used intraoperative opioid agent for bolus dosing during general anaesthesia or monitored anaesthesia care (MAC). It is a synthetic derivative of morphine, in the phenylpiperidine family of opioid agents. It is a μ-opioid receptor agonist and is hundred times more potent than morphine. Dexmedetomidine is a short-acting alpha2-agonist that possesses anxiolytic, sedative, hypnotic, and analgesic properties. At therapeutic dose it does not cause respiratory depression and retains the response to verbal commands. It acts on the central nervous system receptors, particularly in the locus ceruleus, regulating memory, affect, awareness, and nociception. Studies on the combination of dexmedetomidine with various opioid-based IV-PCA techniques have shown to provide better analgesia and opioid-sparing effects [5,6]. Butorphanol, a synthetic opioid, is a μ-opioid antagonist and a k-receptor agonist. Continuous intravenous patient-controlled analgesia (PCA) of butorphanol has been demonstrated since the 1980s [7]. Although it relieves severe pain, the drug does not usually elevate mood, and it may occasionally cause dysphoria. Counterbalancing its disadvantages there is a wealth of clinical experience that shows Butorphanol has an impressive record of safety and has also been shown to have a better maintenance phase than fentanyl [8].

Elderly patients frequently undergo cognitive dysfunction after surgery which is characterized by mental derangement, personality changes, anxiety and memory impair. These changes in mental, personality, social and cognitive ability following surgery are described as post-operative cognitive dysfunction (POCD) [9]. POCD is a complicated entity with subjective variability and numerous contributory factors. The causes and current preventive strategies are grouped into patient, surgical, and anaesthesia related factors. Age, mental health, educational level and co morbidities are contributory patient factors [10]. The syndrome may be detected days to weeks after surgery and may also remain as a permanent disorder resulting in significant functional impairment. Low cerebral oxygenation, neuroinflammation and use of potentially neurotoxic drugs are possible aetiological factors. As the duration and complexity of surgery increase so do the incidence and severity of POCD [11]. Dexmedetomidine, a potent and highly selective transmembrane G protein coupled central a2-receptor agonist has been revealed to improve POCD [12].

There is no sufficient data that shows effect of dexmedetomidine in combination

with fentanyl and butorphanol on postoperative analgesia and cognitive dysfunction in post cardiac surgery patients. This study was planned to evaluate and compare the effect of intravenous infusion of dexmedetomidine and fentanyl versus intravenous infusion of dexmedetomidine and butorphanol on postoperative analgesia and postoperative cognitive dysfunction in patients undergoing cardiac surgery.

Materials &Methods

This study was conducted at tertiary care teaching hospital of Rajasthan from February 2019 to June 2020 only after obtaining approval from the Institutional Ethics Committee. A total of 70 patients of American Society of Anaesthesiologists (ASA) class I and II between the age group of 18-70 years with BMI≤28kg/m^2 posted for coronary artery bypass grafting (CABG) and valve replacement surgeries under general anaesthesia were included in this study only after written informed patient consent. Patients with neurological or psychiatric disease, hepatic disease, severe renal insufficiency, respiratory disease, pregnant women, patients with allergy to study drugs, patients on chronic analgesic medications, opioids or substance abuse, drug addicts, patients having bradycardia were excluded from the study.

Sample size: N=21 in each group using formula $N = (Z_{1-\alpha/2} + Z_{1-\beta})^2 (\sigma1^2+\sigma2^2 /r)/(\mu1-\mu2)^2$

Where $Z_{1-\alpha/2}$ = Z statistics for level of significance (0.05), $Z_{1-\beta}$ = Z statistic for 80% power of study, σ1=1.94 standard deviation in group I based on past literature, σ2=0.92 standard deviation in group II based on past literature. μ1=1.45 mean VAS score in group I, μ2=2.30 mean VAS score in group II, r = group size. Due to paucity of literature of similar studies, a comparison effect size was based on bolus dosing as compared to IV infusion. Considering rate of procedure in our institute and considering dropouts, 70 patients were randomly allocated in two groups of 35 each.

Study design and group allocation: This study was a prospective, randomized, double blinded controlled trial. Randomization was performed using computerized randomization schedule. Patients were randomly assigned into two groups containing 35 patients each. Group assignments were sealed within opaque envelopes. The envelope was opened by a principle administrator just before the administration of study drug. Anaesthesiologist (who was not one of the observers of the study) prepared the study drug. The anaesthesiologist (who monitored and recorded the haemodynamic parameters), nurses, surgeon, research assistant and the patient were blinded to the randomization.

Patients in the two groups received study drug postoperatively as per the following protocol:

Group DF: This group of patients were started on intravenous infusion of Dexmedetomidine 0.15μg/kg/h and Fentanyl 0.5μg/kg/h immediately postoperatively.

Group DB: This group of patients were started on intravenous infusion of Dexmedetomidine 0.15μg/kg/h and Butorphanol 2 μg/kg/h immediately postoperatively.

Procedure and conduct of study: A routine pre anaesthetic evaluation of each case was done one day prior to surgery and an informed consent of patient was obtained after complete explanation of the study to be conducted. Patients were kept nil per orally 8 hours prior to surgery. Montreal Cognitive assessment (MoCA) was done one day prior to surgery (baseline). A score greater or equal to 26 out of 30 was considered normal. On arrival in operation theatre, baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR) and oxygen saturation were

monitored. Arterial line in radial artery for invasive BP monitoring and central line for central venous pressure monitoring were inserted under local anaesthesia. Baseline ABG was recorded. All patients were given general anaesthesia and were induced with midazolam 1-2 mg, fentanyl 5µg/kg, etomidate 0.3mg/kg, vecuronium 0.1mg/kg and lignocaine 1.5mg/kg. After induction and intubation patients were maintained with oxygen, air and inhaled sevoflurane. After surgery the patients were shifted to CTVS ICU with ETT in-situ.

Data recording: Data were recorded in a structured proforma. Demographic data, postoperative hemodynamic data recording, respiratory rate (RR), oxygen saturation (SpO_2), visual analogue scale (VAS) scores, ramsay sedation score (RSS) at time of extubation and at 4 hrs, 8 hrs, 12 hrs, 18 hrs, 24 hrs and 48 hrs from the time of extubation. Sedation was measured through Ramsay sedation scale and pain by visual analogue scale (VAS).

Montreal Cognitive assessment (MoCA) was repeated again at 24 hours post extubation and score was noted [13]. Patient satisfaction score was recorded as score 1, 2, 3 and 4 corresponding to poor, moderate, good and excellent satisfaction grade respectively.

Time to first rescue analgesia in hours, total number of times rescue analgesics given on first and second postoperative day were noted. Either Inj. Paracetamol 1 gm or Inj. Tramadol 75mg were given when visual analogue score was either 4/5. Combination of Inj. Paracetamol 1 gm and Inj. Tramadol 75 mg were given with VAS score>5.

Any incidence of bradycardia and tachyarrhythmia was noted postoperatively in terms of total number of episodes at or after extubation. Glycopyrrolate 0.2mg was given if there was an episode of Bradycardia and either Amiodarone/Ibutilide was given if there was any episode of tachyarrhythmia.

Incidence of adverse effects like nausea, vomiting, drowsiness, hypotension, bradycardia, respiratory distress, mental confusion, and pruritis were also recorded.

Statistical analysis: A total of 70 patients were considered. Study data was entered into the SPSS software (version 17, SPSS, Chicago, IL) and was analysed with the chi- square test for qualitative and paired-t for quantitative variables. Data was presented as mean, standard deviation, median (range), or percentage, as appropriate. The value $p<0.05$ was considered statistically significant.

Results

Demographic parameters like age, gender, weight, height, body mass index were comparable among the two groups. There was no statistically significant difference for any of the parameter ($p>0.05$). (Table 1) There was no statistical difference in heart rates, SBP, DBP, MAP, RR, SpO_2 at the time of extubation and post operative period at different time intervals (4^{th}, 8^{th},12^{th},18^{th}, 24^{th}, 48^{th} hour after extubation) between the groups ($p>0.05$).

Table 1: Comparison of Demographic Parameters between Groups

Parameters	Group		P value
	DB (n = 35)	DF (n = 35)	
Age (Years)	51.26±15.71	52.11±15.66	0.82
Male/female ratio	28/7	25/10	0.578
Weight (Kgs)	58.36±7.26	59.68±7.40	0.452
Height (mtrs)	1.60±0.12	1.59±0.11	0.607
BMI (kg/m2)	22.72±3.20	23.57±2.67	0.229

There was no statistical difference in the VAS score of the patients between the group DB and DF at post extubation intervals of 12, 18, 24 and 48 Hours ($p>0.05$). However, there was a statistically significant difference at extubation and at 4 hours and 8 hours post extubation ($p<0.05$). (Table 2)

Table 2: Comparison of VAS score between the groups at different time intervals

VAS	Drug Group	Mean	Std. Deviation	P value
At extubation	DB	2.97	1.403	0.026*
	DF	5.42	0.502	
4Hrs	DB	2.17	0.71	0.021*
	DF	5.60	0.500	
8Hrs	DB	1.80	0.800	0.019*
	DF	4.66	0.540	
12Hrs	DB	1.57	.558	0.304
	DF	1.69	.900	
18Hrs	DB	1.54	.741	0.622
	DF	1.54	1.067	
24Hrs	DB	1.57	.741	0.655
	DF	1.57	1.243	
48Hrs	DB	1.28	.710	0.685
	DF	1.29	.957	

*Significant

Mean time to first rescue analgesic for the patients in DB and DF group was 10.6±2.48 hr and 4.45±2.46 hr respectively. Time to first rescue analgesic was significantly earlier for DF as compared to DB group ($p<0.05$). Rescue analgesic required within 24 hours was significantly more for DF as compared to DB ($p<0.05$). 3 patients in group DB and 6 patients in group DF required 1 time rescue analgesic; 2 patients in group DB required 2 times rescue analgesic and only 2 patients in group DF required 3 times rescue analgesic. There was no statistical significant difference between the number of times rescue analgesic was given in 24-48hours and the two study groups ($p>0.05$). (Table 3)

Table 3: Comparison of Time to First Rescue Analgesic (Hrs) and rescue analgesic between Groups

	Mean		Std. Deviation	P value
Time to First Rescue Analgesic (Hrs)				
DB	10.6		2.48	0.004*
DF	4.45		2.46	
Rescue analgesic-Total No of times given in 24hrs	**1**	**2**	**3**	
DB	3 (8.57%)	2(5.71%)	0 (0.0%)	0.047*
DF	6(17.14%)	0(0.0%)	2 (5.71%)	
Rescue analgesic-Total No of times given in 24- 48hrs	**1**	**2**	**3**	
DB	2 (5.71%)	1(2.85%)	0	0.862
DF	3 (8.57%)	2(5.71%)	0	

*Significant

There was no statistical significant difference found in the mean of MoCA score between the patients in group DB and group DF for both 1 day prior to surgery and 24hrs Post extubation (p>0.05). (Table 4)

Table 4:Comparisonof MoCAScorebetweenGroups

MoCA Score	DrugGroup	Mean	Std. Deviation	P value
1 day prior to surgery	DB	28.00	1.085	
	DF	27.86	1.089	0.584
24 hrs Post extubation	DB	26.74	1.421	
	DF	26.46	1.358	0.393

In the DB group, 17 patients rated treatment to be excellent, 17 good and 1 moderate. Similarly, in the DF group, 18 rated excellent, 15 good and 2 moderates. No patient in both groups had poor satisfaction. There is no statistically significant interaction found between the satisfaction score grade and the two study groups (p>0.05). (Table 5)

Table 5: Comparison of Satisfaction Score Grade between Groups

Drug Group	Satisfaction Score Grade				P value
	(Excellent)	(Good)	(Moderate)	(Poor)	
DB	17 (48.57%)	17 (48.57%)	1 (2.85%)	0 (0.0%)	0.784
DF	18 (51.42%)	15 (42.85%)	2 (5.71%)	0 (0.0%)	

Drowsiness had the highest incidence in both the groups among all the adverse effects. Furthermore, incidence of drowsiness was significantly higher in group DB as compared to group DF (p<0.05). There was no significant difference between the groups DB and DF in terms of other adverse effects (p>0.05). (Table 6)

Table 6: Comparison of Adverse Effects between Groups

Adverse Effects	Drug Group		P value
	DB (n=35)	DF (n=35)	
Nausea	7 (20.0%)	12 (34.28%)	0.190
Vomiting	2 (5.71%)	5 (14.28%)	0.293
Drowsiness	27 (77.14%)	16 (45.71%)	0.032*
Hypotension	3 (8.57%)	0 (0.0%)	0.120
Bradycardia	3 (8.57%)	3 (8.57%)	0.663
Respiratory Depression	2 (5.71%)	1 (2.85%)	0.500
Mental Confusion	4 (11.42%)	1 (2.85%)	0.178
Pruritis	2 (5.71%)	1 (2.85%)	0.500

*Significant

Discussion

Demographically both the groups were similar which was similar to other studies [14-16]. Hemodynamically also both the groups were stable and did not show any significant change at extubation and post operative period at different time intervals. Similar results were shown in the study of Arora *et al* [15] Kaur *et al* [16] study also found no significant difference in values of heart rate. Pandit *et al* [14] and Thakore *et al* [17] studies found significant difference for few parameters. The variations in haemodynamics at different time intervals between studies could also be explained in terms of specific population, sample size, study design, higher drug dose, mechanism of action of the drugs and also the allocation of the groups.

VAS score was found significant higher for the group DF vs group DB at extubation [5.42±0.50 vs 2.97±1.40], at 4hrs [5.60±0.50 vs 2.17±0.71] and at 8hrs [4.66±0.50 vs 1.80±0.80] but at the 12 hrs,

18 hrs, 24 hrs, 48 hrs there was no significant difference. In Pandit *et al* study [14] there was a significantly higher VAS score for Fentanyl group. Rapid redistribution of fentanyl might explain this difference. A larger dose of fentanyl might help provide better analgesia. Another reason could be of a possible synergistic action of dexmedetomidine and butorphanol in terms of analgesia by suppression of ascending pain pathways. Thakore *et al* [17] found no significant difference in the VAS score for both the groups except at the 8th hour [group F 1.16±1.03; group B 0.78±0.58] after extubation where it was significantly higher for patients receiving fentanyl as compared to butorphanol. This could be because of larger dose of drugs in their study and a lack of possible synergistic action with dexmedetomidine. They also found that higher number of patients in the fentanyl group required rescue analgesics than in the butorphanol group which was similar to present study. This additional analgesia given in the fentanyl group have resulted in comparable and acceptable pain scores in both of their groups as well as in present study. Similar result was also noted in a study by Atkinson *et al* [18]. Philip *et al* [19] had also found similar trend but without significant difference. That study compared fentanyl and butorphanol in ambulatory surgeries and for labour analgesia respectively and concluded that butorphanol provided better initial analgesia.

In the present study, time to first rescue analgesic was significantly higher for the DF group. The total number of rescue analgesic doses required in first 24 hrs was also significantly higher for the DF group. Similar results were also obtained in the study of Pandit *et al* study [14]. Moreover, in the study conducted by Thakore *et al* [17], it was found that the requirement of rescue analgesic in first 24 hrs was significantly higher for the fentanyl group till 12 hrs time interval. Smaller dosage and shorter duration of action of fentanyl as compared to butorphanol may be the reason for the increased demands of rescue analgesic. Decreasing trend in the number of demands after the first 12 hrs could be as a result of steady plasma levels of the drug being reached.

In the present study no significant difference was found in mean of MoCA score between both the groups at one day prior to surgery also at 24hrs post extubation. This finding was similar to a study conducted by Park *et al* [20] where incidence of delirium was significantly less in the group that received dexmedetomidine. A meta-analysis conducted by Yang *et al* [21] also found that perioperative dexmedetomidine treatment is associated with significantly reduced incidence of POCD. Li *et al* [13] study in contrast showed that dexmedetomidine administered during anaesthesia and early postoperative period did not decrease the incidence of postoperative delirium in elderly patients undergoing elective cardiac surgery. Administration of less dose of postoperative dexmedetomidine and more doses of benzodiazepines in dexmedetomidine group could be the reason of increased the occurrence of delirium. This might have counteracted the effect of dexmedetomidine on POCD.

In present study 48.57% patients in group DB and 51.42% in group DF reported excellent satisfaction with analgesia. None of the patient was poorly satisfied. There is a trend for better satisfaction score in studies using dexmedetomidine in combination with opioids such as sufentanil and butorphanol [22,23].

In present study drowsiness was significantly higher in the DB group as compared to group DF. Except drowsiness there was no significant difference for other adverse effects. Study conducted by Pandit *et al* [14] showed more incidence of drowsiness in butorphanol group compared to fentanyl group. Thakore *et al* [17] also found drowsiness to be more common in butorphanol group. Kappa opioid agonists are known to be sedating.

The incidence of increased sedation with butorphanol could be due its effect on kappa receptors. This effect may be a consequence of the anatomic localization of kappa receptors in deep layers of cerebral cortex. The increased sedation in group DB in the present study could be due to effect of dexmedetomidine on α2A and α2C receptors at locus ceruleus of the brain stem and k-receptor agonist action of butorphanol.

Conclusion

The present study concluded that Dexmedetomidine in combination with Butorphanol is more effective as an analgesic than Dexmedetomidine with Fentanyl in the initial hours after extubation as being evident by reduced VAS scores and less requirement of rescue analgesics however this combination was associated with increased incidence of drowsiness. No significant cognitive dysfunction was found among the patients in both groups however this might change if robust follow up of the patients could be done at a later time period.

References

1. Hamid M, Gangwani AL, Akhtar MI. A quality improvement survey to assess pain management in cardiac surgery patients. Open Journal of Anesthesiology. 2015; 5:105-112.
2. Rafiq S, Steinbruchel DA, Wanscher JM, Andersen LA, Navne A, Lilleover BN, Olsen PS. Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial. Journal of Cardiothoracic Surgery. 2014; 9:52.
3. Mazzeffi M, Khelemsky Y. Post sternotomy pain: a clinical review. J Cardiothorac Vasc Anesth. 2011; 25(6):1163-78.
4. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006; 367(9522):1618-25.
5. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother. 2007; 41(2):245-52.
6. Kim NY, Kwon TD, Bai SJ, Noh SH, Hong JH, Lee H, et al. Effects of dexmedetomidine in combination with fentanyl-based intravenous patient-controlled analgesia on pain attenuation after open gastrectomy in comparison with conventional thoracic epidural and fentanyl-based intravenous patient- controlled analgesia. Int J Med Sci. 2017; 14(10): 951-60.
7. Wermeling DP, Foster TS, Farrington EA, Witt WO, Gallion HH, Donaldson E, et al. Patient-controlled analgesia using butorphanol for postoperative pain relief: an open-label study. Acute Care. 1988; 12:31-9.
8. Rosow CE. Butorphanol in perspective. Acute Care. 1988; 12(1):2-7
9. Van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuro inflammation associated with cardiac surgery and anaesthesia. Anaesthesia. 2012;67(3):280-93.
10. Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction - current preventive strategies. Clin Interv Aging. 2018; 13:2267-73.
11. Kotekar N, Kuruvilla CS, Murthy V. Post-operative cognitive dysfunction in the elderly: A prospective clinical study. Indian J Anaesth. 2014; 58(3): 263-8.
12. Arpaci AH, Bozkırlı F. Comparison of sedation effectiveness of remifentanil-dexmedetomidine and remifentanil-midazolam combinations and their effects on postoperative cognitive functions in cystoscopies: a randomized clinical trial. J Res Med Sci. 2013;18(2):107-14.
13. Li X, Yang J, Nie X, Zhang Y, Li X, Li L et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. PLOS ONE. 2017;12(2): e0170757.

14. Pandit SK, Kothary SP, Pandit UA, Mathai MK. Comparison of fentanyl and butorphanol for outpatient anaesthesia. Can J Anaesth. 1987; 34(2):130-4.
15. Arora V, Bajwa S, Kaur S. Comparative evaluation of recovery characteristics of fentanyl and butorphanol when used as supplement to propofol anaesthesia. International Journal of Applied and Basic Medical Research. 2012;2(2):97.
16. Kaur J, Bajwa SS. Comparison of epidural butorphanol and fentanyl as adjuvants in the lower abdominal surgery: A randomized clinical study. Saudi J Anaesth. 2014; 8:167-71.
17. Thakore B, D'Mello J, Saksena S, Butani M. Comparison of fentanyl and butorphanol for postoperative pain relief with intravenous patient-controlled analgesia. Acute Pain. 2009; 11(3-4):93-9.
18. Atkinson BD, Truitt LJ, Rayburn WF, Turnbull GL, Christensen HD, Wlodaver A. Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. Am J Obstet Gynecol. 1994;171(4):993-8.
19. Philip BK, Scott DA, Freiberger D, Gibbs RR, Hunt C, Murray E. Butorphanol compared with fentanyl in general anaesthesia for ambulatory laparoscopy. Can J Anaesth. 1991; 38(2):183-6.
20. Park J, Bang S, Chee H, Kim J, Lee S, Shin J. Efficacy and Safety of Dexmedetomidine for Postoperative Delirium in Adult Cardiac Surgery on Cardiopulmonary Bypass. The Korean Journal of Thoracic and Cardiovascular Surgery. 2014;47(3):249-54.
21. Yang W, Kong L, Zhu X, Wang R, Liu Y, Chen L. Effect of dexmedetomidine on postoperative cognitive dysfunction and inflammation in patients after general anaesthesia. Medicine. 2019; 98(18):e15383.
22. Gao Y, Deng X, Yuan H, Leng Y, Zhang T, Xu X et al. Patient-controlled Intravenous Analgesia with Combination of Dexmedetomidine and Sufentanil on Patients After Abdominal Operation. The Clinical Journal of Pain. 2018;34(2):155-61.
23. Du J, Li J, Jin J, Shi C, Ma J. Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy. Experimental and Therapeutic Medicine. 2018; 16(5): 4063-9.