KJCCM
Korean J Crit Care Med
2015 November 30(4):272-279 / http://dx.doi.org/10.4266/kjccm.2015.30.4.272
ISSN 2383-4870 (Print) · ISSN 2383-4889 (Online)

■ Original Article ■

Dexmedetomidine Use in Patients with 33°C Targeted Temperature Management: Focus on Bradycardia as an Adverse Effect

Hyo-yeon Seo, M.D., Byoung-joon Oh, M.D., Eun-jung Park, M.D., Young-gi Min, M.D., and Sang-cheon Choi, M.D.

Department of Emergency Medicine, Ajou University School of Medicine, Suwon, Korea

Background: This study aimed to investigate bradycardia as an adverse effect after administration of dexmedetomidine during 33°C target temperature management.
Methods: A retrospective study was conducted on patients who underwent 33°C target temperature management in the emergency department during a 49-month study period. We collected data including age, sex, weight, diagnosis, bradycardia occurrence, target temperature management duration, sedative drug, and several clinical and laboratory results. We conducted logistic regression for an analysis of factors associated with bradycardia.
Results: A total of 68 patients were selected. Among them, 39 (57.4%) showed bradycardia, and 56 (82.4%) were treated with dexmedetomidine. The odds ratio for bradycardia in the carbon monoxide poisoning group compared to the cardiac arrest group and in patients with higher body weight were 7.448 (95% confidence interval [CI] 1.834-30.244, p = 0.005) and 1.058 (95% CI 1.002-1.123, p = 0.044), respectively. In the bradycardia with dexmedetomidine group, the infusion rate of dexmedetomidine was 0.41 ± 0.15 μg/kg/h. Decisions of charged doctor's were 1) slowing infusion rate and 2) stopping infusion or administering atropine for bradycardia. No cases required cardiac pacing or worsened to asystole.
Conclusions: Despite the frequent occurrence of bradycardia after administration of dexmedetomidine during 33°C target temperature management, bradycardia was completely recovered after reducing infusion rate or stopping infusion. However, reducing the infusion rate of dexmedetomidine lower than the standard maintenance dose could be necessary to prevent bradycardia from developing in patients with higher body weight or carbon monoxide poisoning during 33°C targeted temperature management.

Key Words: adverse effects; bradycardia; dexmedetomidine; hypothermia, induced.

Introduction

Dexmedetomidine, the highly selective alpha 2-adrenergic agonist, produces sedative and pain-relieving effects through its action in the locus ceruleus-spinal cord and causes much less respiratory suppression than other sedatives.[1-3] Dexmedetomidine is known to have better clinical benefits than benzodiazepines because it improves patient's ability to communicate pain, shortens the duration of intensive care unit (ICU) stay and mechanical ventilation and reduces the risk of delirium, making it the drug of choice for sedative in critically ill patients.[1-6]

Based on these findings, the Society of Critical Care Medicine guidelines describe non-benzodiazepines such as dexmedetomidine and propofol as better sedative agents than benzodiazepines for the treatment of adult critically ill patients.[1] The use of dexmedetomidine along with propofol is expected to rise in intensive care setting. Beside, Ma et al.[7] reported

Received on June 5, 2015 Revised on October 7, 2015
Accepted on October 21, 2015
Correspondence to: Sang-cheon Choi, Department of Emergency Medicine, Ajou University School of Medicine, 206 World cup-ro, Yeongtong-gu, Suwon 16499, Korea
Tel: +82-31-219-7754, Fax: +82-31-216-7760
E-mail: avenue59@ajou.ac.kr

*No potential conflict of interest relevant to this article was reported.

that dexmedetomidine provided the protection of the central nerve against neural cell death or damage resulting from hypoxia and ischemia, signaling further beneficial benefits of this sedative drug in the treatment of critically ill patients with brain damage, if their claim is supported by more evidence.

However, dexmedetomidine was found to cause adverse reactions such as bradycardia in previous studies involving cardiovascular patients, although the incidence of bradycardia was controlled by low intravenous maintenance dose of 0.7 μg/kg/h in another study.[5,8] Thus, they could treat bradycardia by lowering dose of dexmedetomidine without causing systemic hypotension.[5,8] However, when authors were using intravenous dexmedetomidine maintenance dose of 0.2-0.7 μg/kg/h for patients undergoing target temperature management (TTM) at 33℃, bradycardia occurred in 66.0% of the patients, which was much higher than the range of 0-13.8% reported in previous studies. We considered this high incidence of bradycardia is associated with TTM.[8] While the incidence of bradycardia caused by dexmedetomidine during TTM has been rarely studied, we explored the cause of bradycardia during TTM and estimated that common decline in drug metabolism and subsequent sudden increase in serum dexmedetomidine concentration together result in the condition.[9-16]

Clinical application of TTM are likely to expand to encompass a broader range of conditions, including cerebral edema accompanying severe ischemic cerebral artery infarct, sepsis, carbon monoxide poisoning, beyond cardiac arrest accompanying sepsis, promoting increasing use of dexmedetomidine in critically ill patients.[17-19] We therefore aimed to investigate the frequency of bradycardia and associated clinical characteristics in patients given dexmedetomidine during TTM at 33°C.

Materials and Methods

1) Study subjects

The present study was approved by a clinical research ethics committee. This study was conducted with patients admitted to our emergency care and treated with TTM from January 2011 to January 2015. The inclusion criteria were patients prescribed "ARTICGEL PAD" "therapeutic hypothermia" and subsequently "midazolam", "Dormicum" "Precedex", because they are prescription names used in relation to dexmedetomidine. Selected patients were divided into two groups based on which sedative drug was administered during TTM on the condition that the administration continued for more than 75% of total days of hypothermia treatment: the dexmedetomidine (DEX) group and the midazolam (MID) group. Patients were excluded if they developed bradycardia less than 60 times before TTM was implemented, if they did not sedate although dexmedetomidine or midazolam was mainly administrated, if they died within one hour after TTM and if their family did not want to have hypothermia treatment. The patients treated with TTM were divided into the resuscitated group from cardiopulmonary resuscitation (CPR; CPR group) and the carbon monoxide poisoning group (CO group). The contraindications of TTM included bleeding in the digestive tract, cerebral hemorrhage, international normalized ratio > 1.7 or higher, prothrombin time > 15 seconds or longer, acute bleeding tendency and pregnant women.

2) Study methods

In analysis of medical records, we identified sex, age, weight (kg), average heart rate (beat/min) measured at every 1-hour interval during TTM, medical history, liver failure, renal failure, model for end-stage liver diseases (MELD) score within 24 hours after admission and hypoalbuminemia. The albumin level of less than 3.5 g/dL was defined as hypoalbuminemia as the level cap is applied in clinical practice. The presence of cardiac arrest was confirmed by identification of the cause and cerebral performance category (CPC) score. Therapeutic approaches provided at the incidence of bradycardia were identified from medical records and classified into three categories: use of atropine, infusion rate decrease/stoppage and wait-and-see approach. When infusion rate was reduced or infusion stopped, outcome of bradycardia within 4 hours was assessed, and when atropine was given, outcome of bradycardia within 30 minutes was assessed. We also addressed the duration from the initiation of TTM and the onset of bradycardia (min), the onset timing of bradycardia and the infusion rate (μg/kg/h) at the onset of bradycardia.

Therapeutic hypothermia was induced to the target temperature of 33℃ using external cooling device that uses

hydrogel pasts (Arctic Sun®; Arctic Sun 2000, Medivance, Louisville, CO, USA), and core body temperature was monitored via the indwelling urinary catheter (Arctic Sun 2000, Medivance, Louisville, CO, USA). The duration of TTM ranged from 12 to 24 hours in the CPR group, but the duration in the CO group was decided by attending physician in light with the needs of individual patients while total time period of 36-96 hour was basically encouraged.

In this study, data were compiled from medical records by two emergency medicine residents who were not aware of the objectives of this study. Disagreement in data analysis between the reviewers was resolved with discussion with an experienced physician.

Compiled data were coded and analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Normal variables were expressed as frequencies and percentages, and continuous variables as means and ± standard deviations or medians (inter-quartile ranges). The paired t-test was performed to compare continuous and normally distributed variables, and Mann-Whitney U test was used to compare 3 continuous, but not normally distributed variables. Chi-square test and Fisher's exact test to compare normal variables. Multiple logistics regression was used to determine which factors were significantly related to bradycardia. Generally, p value of less than 0.05 was considered statistically significant.

Results

1) Characteristics of subjects

The study population included 85 patients, and data from 68 patients were used for the study. Of 17 patients excluded, 15 were not sedated to meet subject requirements, one died after TTM, one did not undergo TTM because his family did not want TTM. There was no case in which dexmedetomidine was subsequently discontinued due to side effects.

Of 68 selected subjects, 56 were mainly given dexmedetomidine during TTM and 12 mainly received midazolam. They were further divided into the bradycardia group (39) and the nonbradycardia group (29). The general characteristics of subjects are presented in Table 1. The causes of cardiac arrest in the CPR group wee divided into cardiac origin (22 cases) and non-cardiac origin (14 cases), which included 11 suffocations, 1 hyperkalemia, 1 amniotic fluid embolism and 1 drug abuse.

2) Comparisons between bradycardia and nonbradycardia groups

In univariate analysis, there were significant differences in weight, average heart rate, MELD score, diagnosis name, sedative agent, hypoalbuminemia between the two groups. In multivariate analysis of these factors, the odds ratio for the DEX group vs. the MID group was 4.506 (95% confidence interval [CI] 0.717-28.334, p = 0.109), the odds ratio for the CPR group vs. the CO group was 7.448 (95% CI

Table 1. Characteristics of selected patients

Characteristics	Total (n = 68)	DEX (n = 56)	MID (n = 12)
Age (yr)	45.2 ± 14.5	44.7 ± 14.8	47.8 ± 13.3
Weight (kg)	65.0 ± 11.4	65.0 ± 11.5	64.3 ± 11.0
AVR HR (beat/min)	70.4 ± 15.5	68.8 ± 15.3	77.6 ± 15.0
MELD score	9.2 (6.5-12.2)	8.8 (6.4-11.8)	11.5 (10.3-21.6)
Sex, male	54 (79.4)	43 (76.8)	11 (91.7)
Diagnosis			
CPR	36 (52.9),	24 (42.9)	12 (100)
CO	32 (47.1)	32 (57.1)	0
HypoAlb	12 (17.6)	10 (17.9)	2 (13.3)
Past Hx	None	None	None

Values are presented as mean ± standard deviation, median (interquartile range) or number (percentage).
DEX : dexmedetomidine group; MID: midazolam group; AVR HR: hourly mean heart rate during target temperature management; MELD: model for end-stage liver disease; CPR: cardic arrest with successful resuscitation; CO: toxic effect of carbonmonoxide; HypoAlb: hypoalbuminemia (serum albumin < 3.5 g/dL); Past Hx: past history of active liver diseases or renal failure.

Table 2. Comparison of the bradycardia group and non-bradycardia group (characteristics)

	Bradycardia group (n = 39)	Non-brady (n = 29)	p-value
Age (yr)	44.1 ± 14.5	46.8 ± 14.6	0.439
Weight (kg)	67.3 ± 11.6	61.6 ± 10.3	0.042
AVR HR (beat/min)	61.6 ± 9.3,	82.2 ± 14.4	< 0.001
MELD score	8.0 (0-10.9)	10.4 (8.6-14.5)	0.002
Sex, male	31 (79.5)	23 (79.3)	0.986
Diagnosis CO	27 (69.2)	5 (17.2),	< 0.001
Sedative drug, DEX	37 (94.9)	19 (65.5)	0.006
HypoAlb	3 (10.3)	9 (31.0)	0.020

Values are presented as mean ± standard deviation, median(interquartile range) or number (percentage).
Non-brady: non-bradycardia group; AVR HR: hourly mean heart rate during target temperature management; MELD: model for end-stage liver diseases; CO: toxic effect of carbonmonoxide; DEX: dexmedetomidine; HypoAlb: hypoalbuminemia (serum albumin < 3.5 g/dL).

Table 3. Logistic regression analysis for variables predicting bradycardia occurrence

Variables	Univariate		Multivariate	
	OR	95% CI p-value	OR	95% CI p-value
Diagnosis, CO	10.800	3.321-35.123, < 0.001	7.448	1.834-30.244, 0.005
Sedative drug, DEX	9.737	1.935-48.996, 0.006	4.506	0.717-28.334, 0.109
HypoAl	0.185	0.045-0.763, 0.020	0.380	0.071-2.020, 0.256
Weight (kg)*	1.050	1.000-1.101, 0.048	1.058	1.002-1.123, 0.044

OR: odds ratio; CI: confidence interval; CO: toxic effect of carbonmonoxide; DEX: dexmedetomidine; HypoAlb: hypoalbuminemia (serum albumin < 3.5 g/dL)
*The odds ratio is increased in patient with higher weight.

1.834-30.244, p = 0.005), The odds ratio for weight was 1.058 (95% CI 1.002-1.123, p = 0.044), The odds ratio for hypoalbuminemia (presence or absence) was 0.380 (95% CI 0.071-2.020, p = 0.256). There were signficant differences in weight and diagnosis name, and a higher odds of being overweight was found in the CO group, compared with the CPR group. Detailed results are presented in Table 2 and Table 3.

In the bradycardia group (39), 24 (61.5%) had CPC score of 1-2, 13 (33.3%) had 3-4 and 2 (5.1%) had 5. In the non-bradycardia group (29), 15 (51.7%) had CPC score of 1-2, 10 (34.5%) had 3-4 and 4 (13.8%) had 5.

3) The management of bradycardia developed during concomitant use of dexmedetomidine and TTM

The incidence of bradycardia 66.0% in the DEX group (37/56). Treatment on the onset of bradycardia included a reduction in dosage of dexmedetomidine in 62% (23/37) of the bradycardia group, followed by a wait-and see approach without adjustment of therapy (35.1%, 13/37), atropine administration (2.7%, 1/37). In 36 patients receiving lower doses of dexmedetomidine or being monitored without therapy adjustment, no worse outcomes that required additional cardiac rhythm management were found. Instead, the heart rate (beat/min) rose to more than 50 within 4 hours after dose adjustment in 16 (69.6%) of 23 patients given

Table 4. Characteristics of bradycardia group with dexmedetomidine

Characteristics (n = 37)	
Management of bradycardia	
Decrease infusion rate	23 (62.2)
Observation	13 (35.1)
Administration of atropine	1 (2.7)
Asystole or need for pacing	None
Time of bradycardia occurrence	
Induction period	12 (32.4)
Maintenance period	25 (67.6)
Time interval from maintenance period to bradycardia (min) (n = 25)	475 (268-778)
Dexmedetomidine infusion rate when bradycardia occurs (μg/kg/h)	0.41 ± 0.15

Values are presented as mean ± standard deviation, median (interquartile range) or number (percentage).

lower doses of dexmedetomidine. The patient given 0.5 mg of atropine once showed no rise in heart rate within 30 min after administration.

Patients were classified into two groups according to the onset timing of bradycardia: 34% (12/37) developed bradycardia during initiation of TTM or within 30 min after induction, the remaining 67.6% (25/37) during the maintenance period of TTM. In the latter group, the time interval from induction of TTM at 33℃ to the onset of bradycardia was 475 (268-778)(min), and the mean infusion rate of dexmedetomidine was 0.41 ± 0.1 μg/kg/h (Table 4).

Discussion

In this study, the bradycardia incidence rate of 66.0% (37/56) in the DEX group was much higher, when compared with the range of 0-13.8% calculated for critically ill patients who did not undergo TTM.[8] However, there was no statistically significant relationship between dexmedetomidine and the incidence of bradycardia in multivariate analysis. Nonetheless, the incidence rate of 66% in the DEX group, backed by the high odds (9.737) of having bradycardia, provide meaningful insight into the impact of dexmedetomidine, when compared with a much lower incidence of 16% (2/12) in the MID group. In analysis of factors related to the high incidence of bradycardia, we also estimated the typical decline in drug metabolism during TTM. Dexmedetomidine has a volume of distribution at steady state of 1.33 L/kg or 118 L, distribution half-life of 6 minutes and a short half-life of 2-2.5 hours and high protein binding so that it is quickly eliminated from the body.[9] Because most dexmedetomidine is metabolized in the liver by cytochrom P450, enzyme 2A6 and uridine diphosphate glucuronosyltransferase (UGT), the elimination of the drug can fall by up to 50% in the presence of severe liver failure, calling for low doses for the elderly patients and those with renal failure, low plasma albumin concentration, decreased cardiac output. As the relationship between lower doses and TTM has not been discussed in previous studies, further study is needed to validate the presumed impact of hypothermia conditions.[9-11] Based on literature analysis of the relationship between drug metabolism and TTM, the decline in UGT, cytochrom P450, enzyme decreases drug metabolism and thereby increases concentration, which will eventually cause adverse effects.[12-14] As part of strategic approach to anticipated increases of concentration, reduced doses of sedative drug is recommended during the maintenance period of TTM after bolus injection of the first dose.[12-16] Given the pharmacokinetic features of dexmedetomidine, its concentration appears to increase in hypothermia conditions and subsequently causes bradycardia. Ezzati et al.[20] reported that increased concentration of dexmedetomidine led to cardiocvascular-related adverse effects during TTM in an animal model of hypoxic and ischemic brain damage.

As indicated in Table 3, diagnosis and weight were significantly related to the incidence of bradycardia. In comparison of pathophysiologic conditions used for diagnosis, both groups (CPR and CO) developed myocardia stunning and local sympathomimetic brain damage as a consequence of over secretion of catecholamine from the heart muscle and the edge of the synapse.[21-23] Rivers et al.[24] also claimed the level of catecholamine increased more than 32 times normal in the event of cardiac arrest and more than 90 times normal during CPR after injection of epinephrine. Thus, exogenous and endogenous toxicity of plasma catecholamine can occur in addition to a high concentration in synaptic vesicles, leading to systemic toxicity of catecholamine in patients during and after CPR. Such toxicity of catecholamine appears to occur in the CRP group in this study. Given the fact that TTM is implemented immediately after CPR, the toxicity of catecholamine may have largely contributed to a lower incidence of dexmedetomidine-induced bradycardia, compared with the CO group. The differences between the two groups are also explained by the nature of implications in patients: CO poisoning is tissue toxicity triggered by a combination of lack of oxygen during COHb formation and inactive components in cytochrom oxidase whereas patients resuscitated from CPR have more serious and extensive hypoxic ischemia-reperfusion injury inflicted on the internal organs.[21,22,25] In addition, the primary causes of cardiac arrest are heterogeneous, implying continuous effects on patient conditions even after resuscitation, which is one of the

http://dx.doi.org/10.4266/kjccm.2015.30.4.272

characteristics specific to the CPR group.[23] When combined, these factors may have affected the effects of dexmedetomidine on cardiovascular function, leading to low incidence of bradycardia. Thus, this study suggests the possibility that the incidence of bradycardia may be affected by heterogeneity between groups, meaning that precaution should be taken when designing further study with a greater number of patients undergoing TTM. This study also suggests the need for adjusting the infusion rate of dexmedetomidine in consideration of high incidence of bradycardia in 66% (37/56) patients undergoing TTM and anticipated increases in concentration along with the duration of TTM extends.

As far as weight is concerned, we conclude as follows: the plasma concentration of drug at steady state can be calculated by multiplying infusion rate by clearance (inversely proportional).[11] Therefore, if there are no factors that can increase clearance of an infused drug, the plasma concentration will increase with the rate of infusion. In this study, as the infusion rate of dexmedetomidine was decided in proportion to weight, the plasma concentration of drug is positively correlated with weight when clearance is declined in hypothermia conditions, increasing the risk of bradycardia in overweight patients. In descriptive analysis of 37 patients in the bradycardia group, the infusion rate of dexmedetomidine at the onset of bradycardia was 0.41 ± 0.15 μg/kg/h. Despite the steady infusion of dexmedetomidine at the known safe range of 0.2-0.7 μg/kg/h in the absence of loading dose, the incidence of bradycardia was high. This finding underscores the importance of dose reduction in hypothermia condition to prevent bradycardia.

As presented in Table 4, among the 37 patients who showed bradycardia, 29 patients recovered heart rate by more than 50 beats per min after therapeutic interventions such as dose adjustment and atropine administration. The rest 8 patients failed to recover heart rate by more than 50 beats per min irrespective of therapeutic interventions. However, a total of the 37 patients developed no worse outcomes such as asystole and unstable or lethal bradycardia that required additional cardiac rhythm management. Previous studies have found that declined cellular metabolism in hypothermia conditions decreased demand for cardiac output while cardiac contraction remained intact. This means that increasing heart rate using medication as part of the management of bradycardia, not accompanied by hypoperfusion may result in decreases in cardiac contraction or cardiac output. In less severe forms of bradycardia, cardiac rhythm management is also considered dangerous due to the risk of arrhythmia such as ventricular fibrillation.[15,16] Studies of adverse effects of dexmedetomidine on patients in hypothermia conditions are scarce. Tobias[26] reported a case in which child patients developed bradycardia during TTM at 35-36℃. In the case report, two children with severe traumatic brain damage were given dexmedetomidine but developed bradycardia during TTM when therapeutic hypothermia was additionally added. In these cases, bradycardia characterized by heart rate of 40 beat per min within 24 hours after TTM. However, there were no reduction in blood pressure and cerebral perfusion pressure, and the patients recovered normal heart rate 2 hours only after administration of dexmedetomidine discontinued. Although these cases are not comparable with this study due to the differences in study population and type of study, the results are consistent because the case reports also implies the importance of infusion control when bradycardia occurs when dexmedetomidine and TTM are combined.

This study however has limitations as follows: First, this study was conducted retrospectively by reviewing medical records and is susceptible to selection bias because variables not listed in medical records were excluded. Secondly, in this study, dexmedetomidine was administered by intravenous instillation, and loading dose was not used. Intravenous instillation is less effective than loading dose or cumulative dose, which can be calculated by referring to medical records, to identify the relationship between dexmedetomidine administration and the onset timing of bradycardia. Also, if desired sedation is not achieved by intravenous instillation of dexmedetomidine, a benzodiazepine could be added, but the effects of this addition were not investigated. Thirdly, patients become hemodynamically unstable during the induction period of TTM, regardless of the use of dexmedetomidine. However, it was impossible to identify the causes of unstability based on medical records. In cases of hypotension or increased vasopressor,

the effects of dexmedetomidine could not be identified although the sedative agent is deemed to have mpacts on these symptoms and eventually the results of study. Fourthly, sedation of patients admitted to the ICU is initially evaluated with Ramsay and glasgow coma scale at the critical care unit of emergency department in our institution. However, there are usually crowded patients and relative deficits of human resources including doctors and nureses in the emergency department. Therefore, assessment of the symptoms and recordings regarding sedation were insufficiently achieved, which might make the analysis of this study incomplete. A sedation protocol needs to be implemented in emergency department as a requirement for the care of critically ill patients to prevent bradycardia in patients requiring TTM by adjusting doses of dexmedetomidine accurately and objectively. [27] Lastly, this study found a high incidence of bradycardia induced by dexmedetomidine in hypothermia conditions. However, data provided to support for this claim is limited because plasma dexmedetomidine concentration was not measured and the sample size of 12 in the MID group was too small.

In conclusion, this study proposes the following approaches for using dexmedetomidine safely in hypothermia conditions and ensuring sedative and clinical efficacy: First, consistent attention to the risk of bradycardia is required during the period of TTM because the frequency of dexmedetomidine-induced bradycardia is closely affected by diagnosis and weight in patients undergoing TTM. Secondly, for the doses of dexmedetomidine aimed to prevent bradycardia in hypothermia conditions, intravenous instillation of 0.2-0.7 μg/kg/h is recommended as the starting dose, and further reduction in dosage is necessary during the induction and maintenance period of TTM. Thirdly, if bradycardia occurs during the period when the starting dose was used, the rate of infusion can be decreased instead of stopping the infusion. Fourthly, in light of increasing plasma concentration of drug in hypothermia conditions and subsequent risk of developing bradycardia, high doses/high infusion rate of sedatives and the use of loading dose are discouraged. Lastly, it is important to identify pathophysiologic conditions between groups in a large scale study and to decrease infusion rate in accordance with the duration of TTM. Also, protocol-directed sedation is ultimately necessary to improve sedation practices.

ORCID

Hyo-yeon Seo http://orcid.org/0000-0002-6636-3141
Byoung-joon Oh http://orcid.org/0000-0001-9310-8405
Eun-jung Park http://orcid.org/0000-0001-7854-0961
Young-gi Min http://orcid.org/0000-0003-0930-5997
Sang-cheon Choi http://orcid.org/0000-0003-2271-3434

References

1) Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41: 263-306.
2) Reade MC, Finfer S: Sedation and delirium in the intensive care unit. N Engl J Med 2014; 370: 444-54.
3) Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al: Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med 2013; 41(9 Suppl 1): S30-8.
4) Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al: Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JANA 2009; 301: 489-99.
5) Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M: Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. Intensive Care Med 2004; 30: 2188-96.
6) Patel SB, Kress JP: Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med 2012; 185: 486-97.
7) Ma D, Rajakumaraswamy N, Maze M: alpha2-Adrenoceptor agonists: shedding light on neuroprotection? Br Med Bull 2005; 71: 77-92.
8) Tan JA, Ho KM: Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a

meta-analysis. Intensive Care Med 2010; 36: 926-39.
9) Holliday SF, Kane-Gill SL, Empey PE, Buckley MS, Smithburger PL: Interpatient variability in dexmedetomidine response: a survey of the literature. ScientificWorldJournal 2014; 2014: 805013.
10) Yu SB: Dexmedetomidine sedation in ICU. Korean J Anesthesiol 2012; 62: 405-11.
11) Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, Kurvinen JP, et al: Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. Br J Anaesth 2012; 108: 460-8.
12) Zhou J, Poloyac SM: The effect of therapeutic hypothermia on drug metabolism and response: cellular mechanisms to organ function. Expert Opin Drug Metab Toxicol 2011; 7: 803-16.
13) Zhou J, Empey PE, Bies RR, Kochanek PM, Poloyac SM: Cardiac arrest and therapeutic hypothermia decrease isoform-specific cytochrome P450 drug metabolism. Drug Metab Dispos 2011; 39: 2209-18.
14) Tortorici MA, Kochanek PM, Poloyac SM: Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007; 35: 2196-204.
15) Polderman KH, Herold I: Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med 2009; 37: 1101-20.
16) Polderman KH: Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009; 37(7 Suppl): S186-202.
17) Hong JH, Jeong JH, Chang JY, Yeo MJ, Jeong HY, Bae HJ, et al: Repeated hypothermia for rebound cerebral edema after therapeutic hypothermia in malignant cerebral infarction. Korean J Crit Care Med 2013; 28: 221-4.
18) Chang JY, Hong JH, Jeong JH, Nam S-J, Jang JH, Bang JS, et al: Therapeutic hypothermia after decompressive craniectomy in malignant cerebral infarction. Korean J Crit Care Med 2014; 29: 93-8.
19) Lee YH, Sohn YD, Park SM, Lee WW, Ahn JY, Ahn HC: Treatment of carbon monoxide poisoning with therapeutic hypothermia. Korean J Crit Care Med 2013; 28: 218-20.
20) Ezzati M, Broad K, Kawano G, Faulkner S, Hassell J, Fleiss B, et al: Pharmacokinetics of dexmedetomidine combined with therapeutic hypothermia in a piglet asphyxia model. Acta Anaesthesiol Scand2014; 58: 733-42.
21) Park EJ, Min YG, Kim GW, Cho JP, Maeng WJ, Choi SC: Pathophysiology of brain injuries in acute carbon monoxide poisoning: a novel hypothesis. Med Hypotheses 2014; 83: 186-9.
22) Jung YS, Lee JS, Min YG, Park JS, Jeon WC, Park EJ, et al: Carbon monoxide-induced cardiomyopathy. Circ J 2014; 78: 1437-44.
23) Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al: Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008; 118: 2452-83.
24) Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM: The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. Chest 1994; 106: 1499-507.
25) Alonso JR, Cardellach F, López S, Casademont J, Miró O: Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. Pharmacol Toxicol 2003; 93: 142-6.
26) Tobias JD: Bradycardia during dexmedetomidine and therapeutic hypothermia. J Intensive Care Med 2008; 23: 403-8.
27) Gerlach AT, Dasta JF, Steinberg S, Martin LC, Cook CH: A new dosing protocol reduces dexmedetomidine-associated hypotension in critically ill surgical patients. J Crit Care 2009; 24: 568-74.