(Acta Anaesth. Belg., 2020, 71, 183-188)

Feasibility of sedation with sevoflurane inhalation via AnaConDa for Covid-19 patients under venovenous extracorporeal membrane oxygenation

P. Paccaud, M. Dechamps, L.M. Jacquet

Abstract : Critical care centers around the world have faced a shortage of intravenous sedatives caused by the coronavirus pandemic. Many patients infected with SARS-CoV-2 virus develop severe Acute Respiratory Distress syndrome (ARDS) for which some of them are supported by extra corporeal membrane oxygenation. Under these circumstances, the pharmacokinetics of the sedatives is modified. We observed that many of our COVID-19 infected patients receiving Extracorporeal Membrane Oxygenator (ECMO) require high doses of intravenous drugs. Continuous sedation with halogenated gases in the intensive care unit has shown many benefits on systemic inflammation and offers the possibility of a rapid recovery of consciousness. In this article we describe 3 cases that show the feasibility of sedation with sevoflurane via AnaConDa (Sedana Medical AB, Danderyd, Sweden) for Covid-19 patients under ECMO. Halogenated drugs could be considered as an interesting alternative to intravenous sedatives especially in the context of drug shortage.

Keywords : Covid-19 ; SARS-CoV2 ; venovenous ECMO ; extra corporeal membrane oxygenation ; sedation ; AnaConda ; Sevoflurane inhalation ; poly-methyl-pentene membrane.

Introduction

SARS-CoV-2 infection may cause severe ARDS (1). The role of venovenous extracorporeal membrane oxygenation for this condition has shown similar survival rates at 60 days in comparison with previous studies (2). According to the European Life Support Organization registry more than 3200 confirmed or suspected cases have been, or are currently ECMO supported around the world at the moment of this writing (3). The shortage of sedatives and ventilator-associated drugs caused by the pandemic (4) has been a major issue for critical care practitioners, therefore the use of other agents such as inhaled anesthetics is of interest. Our current practice has shown the feasibility of sevoflurane sedation via AnaConDa (Sedana Medical AB, Danderyd, Sweden) for patients under venovenous extracorporeal membrane oxygenation.

Volatile anesthetics

Sevoflurane is the most commonly used volatile inhaled agent in developed countries. Its low blood-gas partition coefficient allows fast recovery of consciousness. It has bronchodilation properties and offers possible advantages of cardiac and lung protection(5, 6). The role of sedation with sevoflurane in the intensive care unit has been investigated many times, and is an alternative solution to intravenous drugs according to the 2015 German guidelines on sedation and delirium management (7).

In patients suffering from ARDS, sedation with sevoflurane compared to midazolam led to better oxygenation and decreased levels of inflammatory markers including a marker of epithelial injury (8). Ferrando et al. demonstrated that sevoflurane reduces the lung inflammatory response and improves oxygenation in acute respiratory distress syndrome to a greater extent than propofol (9). The feasibility of sedation with isoflurane in critically ill patients on ECMO was demonstrated and showed beneficial effects such as fewer opioid requirements and the possibility of spontaneous breathing (10).

Paul Paccaud, MD ; Mélanie Dechamps, MD ; Luc-Marie Jacquet, MD, PhD
Department of Cardiovascular Intensive Care, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium.
Corresponding author: Paul Paccaud, Department of Cardiovascular Intensive Care, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium.
E-mail: paul.paccaud@gmail.com

Paper submitted on July 10, 2020 and accepted on November 26, 2020
Conflict of interest: None

These effects led some authors to conclude that the use of volatile anesthetics in the intensive care unit could increase in the future because of their potential benefits (11).

Halogenated drugs are often used in operating theaters via vaporizers mounted on anesthesia machines with circular circuits. They are eliminated by a scavenging system that vents out the exhaled anesthetic gases in order to maintain a vapor-free environment. Intensive care ventilators use high-flow, non-rebreathing, non-circular circuits. The anesthetic conserving device (AnaConDa) is a system placed between the Y piece and the patient, which allows the administration of volatile anesthetics for these ventilators. It requires a minimum tidal volume, which can be a drawback for non-compliant lungs**.** The device contains a medium that adsorbs exhaled halogenated drugs and releases them during inspiration. This phenomenon is also observed with CO_2 that causes a dead space effect larger than the internal volume of the AnaConDa. For some authors, the impossibility to achieve normocapnia with tidal volumes < 6 ml/kg limit its use with low tidal ventilation strategies (12).

Most of the critical care units are not equipped with a scavenging system for waste gases and the possibility of removing them is achieved by a charcoal filter connected to the ventilator outflow.

ECMO and pharmacokinetics

ECMO affects drug pharmacokinetics (PK) through circuit sequestration, circuit priming, and circuit age (13-15). Some authors described an altered PK profile of intensive care unit drugs under ECMO (16). The distribution of inhaled sevoflurane via AnaConDa for patients under venovenous ECMO is uncertain. A transient loss of volatile anesthetics in PVC tubing has been demonstrated in vitro (17) but should only play a minor role in clinical settings.

Case description 1

The first case is a 55-year-old overweight male patient known for high blood pressure treated by a beta-blocker and a diuretic (bisoprolol and hydrochlorothiazide). He was rapidly transferred from the emergency room to the intensive care unit for acute respiratory failure. Orotracheal intubation and invasive ventilation were initiated in the first hours based on deteriorating gas exchange and altered mental status. In order to prevent droplet transmission, closed circuit endotracheal suctioning was used.

A continuous neuromuscular blockade administration was initiated for 48 hours while the patient was ventilated according to a lung-protective strategy (volume control mode with tidal volumes around 6 ml/kg of predicted body weight with plateau pressures < 30 cm H_2O, a PEEP of 12 cm H_2O, a mean driving pressure of 18 cm H_2O and a fraction of inspired oxygen of 100%. These parameters resulted in an average compliance of 12,2 ml/cm H2O. He received inhaled nitric oxide (10ppm), underwent 16 hours of prone position and was also treated with hydroxychloroquine according to current expert recommendations.

Despite the aforementioned measures, no oxygenation improvements were noticed. A persistent PaO_2/FiO_2 ratio < 80 (on average 68,5 mmHg) during more than 6 hours led to the decision of initiating venovenous ECMO therapy. The implementation was successfully done under stable hemodynamics by femoral and jugular vein cannulation. We used EUROSETS A.L.ONE ECMO oxygenator (Eurosets, Medolla, MO, Italy) at a circuit flow between 4,5 and 5 l/min with an initial fraction of delivered oxygen of 100% and a sweep gas flow adjusted to obtain CO_2 values between 35-45 mmHg.

After ECMO initiation, deep sedation assessed by the Richmond Agitation-Sedation Scale (RASS) of -4 to -5 was hardly achieved by multimodal anesthesia. High doses of sedative drugs were required : propofol 3-3,6 mg/kg/h of total body weight (TBW), clonidine 0,875 µg/kg/h (TBW), ketamine 0,5 mg/kg/h (TBW), dehydrobenzoperidol 2 µg/kg/h (TBW) and midazolam 0,14 mg/kg/h (TBW). Given the potential harmful effect of these high doses and the risk of a delayed recovery we decided to pursue maintenance of sedation with inhaled anesthetics.

Sevoflurane sedation via AnaConDa was started at the rate of 5 ml/h and adjusted in order to obtain end-expiratory concentration (Fet value) around 1 -1,5%. The clinician assessed its administration regularly in order to achieve similar RASS scores. In order to avoid room air pollution with vapors, the charcoal filter FlurAbsorb (Sedana Medical AB, Danderyd, Sweden) was connected to the gas outlet of the ventilator. The introduction of anesthetic vapors allowed to stop the infusion of all the aforementioned drugs in the first hours except clonidine which was reduced to an infusion rate of 0,5 µg/kg/h (TBW).

The sedation with volatile anesthetics lasted 4 days and resulted in spontaneous breathing assisted ventilation. We noted a slight improvement of lung compliance whose average value was 16 ml/cm H_2O during the first 24 hours after the initiation of halogenated gases. This intervention helped maintaining a lung-protective ventilation strategy and the recovery of a diaphragmatic activity without patient-ventilator asynchrony. Finally, the subject was weaned from ECMO 27 days after its initiation. He unfortunately died the day after of a sudden refractory septic shock despite broad-spectrum antibiotics and resuscitation maneuvers including the implementation of a venoarterial ECMO.

Case description 2

The second case is a healthy 54-year-old male without any comorbidity, who was transferred from the Covid-19 ward to the intensive care unit for respiratory failure. He received hydroxychloroquine for five days and was initially treated by non-invasive ventilation. Orotracheal intubation was performed the day after his arrival. He was ventilated in pressure control mode with a maximum plateau of 30 cm H_2O resulting in tidal volumes of 6 ml/kg of predicted body weight, a PEEP of 12 cm H_2O and a fraction of inspired oxygen of 100%. We measured an average lung compliance of 25,7 ml/cm H_2O and a mean driving pressure of 13 cm H_2O during the 24 hours before ECMO therapy. The worsening of gas exchange (PaO_2/FiO_2 ratio of 63,3 before cannulation) despite one session of prone position, inhaled nitric oxide (10ppm) and a continuous neuromuscular blocking agent administration for 24 hours led the clinician to decide for the implementation of venovenous ECMO 5 days after his admission. The ECMO machine delivered a circuit flow of 4,5-5 l/min, a delivered fraction of oxygen of 100% and sweep gas flow adjusted to obtain normal CO_2 values.

Later, because of a moderate pulmonary hypertension, he developed right heart failure for which dobutamine and then milrinone were given. Concomitantly he was treated by ceftazidime during nine days for a ventilator-associated pneumonia (VAP) due to pseudomonas aeruginosa.

In order to achieve a RASS of -4 to -5 the patient needed high doses of sedatives : ketamine 0,75-1 mg/kg/h (TBW), fentanyl 0,625-1,875 mg/kg/h (TBW) 3,75-4,25 mg/kg/h (TBW), clonidine 0,47 µg/kg/h (TBW). The initiation of sevoflurane to reach a Fet value between 1-1.5 % at an average rate of 7 ml/h allowed to stop the infusion of all intravenous sedatives except ketamine which was diminished by half. We also noticed with the same ventilatory settings an improvement of lung compliance whose mean value during the first 24 hours after sevoflurane initiation was 35,3 ml/cm H2O. The patient was kept under inhalational anesthetics for 8 days and experienced no adverse effects from these drugs. Finally, he died of a sudden vasoplegic shock. The autopsy revealed a bilateral organized pneumonia and the infarction of the right middle lobe.

Case description 3

The third patient is a 49-year-old male, known for untreated hypercholesterolemia. After the confirmation of SARS-CoV-2 infection, he received steroids (32mg of methylprednisolone per day) and hydroxychloroquine during five days before his admission in the intensive care unit. At this moment, a deep venous thrombosis of the right leg was treated by therapeutic low molecular weight heparin. Orotracheal intubation and protective lung strategy were initiated five days after his admission.

His gas exchanges continued to deteriorate in spite of one prone position session, protective lung strategy and a continuous infusion of neuromuscular blocking agents for 24 hours. Before the implementation of a venovenous ECMO the patient was ventilated in pressure control mode with a maximum plateau of 30 cm H_2O, a PEEP of 12 cm H_20, a FiO2 of 80% resulting in tidal volumes of 6 ml/kg of predicted body weight and a lung compliance of 26 ml/cm H_2O. The PaO_2/FiO_2 ratio before cannulation was 58. Femoro-jugular venovenous ECMO was successfully implemented at a circuit flow of 4.8 l/min, a delivered fraction of oxygen of 100% and a sweep flow gas of 4.0 l/min. In order to maintain a RASS between -4 and -5, high doses of intravenous sedatives were required : ketamine 0,5 mg/kg/h (TBW), propofol 2,5 mg/kg/h (TBW), clonidine 0,3125 µg/kg/h (TBW) and sufentanil 0,125 µg/kg/h (TBW). A bolus of 5mg of midazolam was required a few minutes before the initiation of the halogenated gases. Sevoflurane was initiated at a rate of 5 ml/h in order to obtain Fet values of 1-1.5% resulting in similar RASS scores. This maneuver allowed stopping all the sedatives except sufentanil. For this case we didn't notice any lung compliance

improvement in the first days following ECMO treatment. However, spontaneous breathing assisted ventilation without patient ventilatory asynchrony was established. The patient was weaned from ECMO after 63 days and resumed his activities 4 months after his admission to the intensive care unit. He suffered from a ventilator-associated pneumonia by staphylococcus aureus treated by oxacilline and later developed a DRESS syndrome supposedly due to hydroxychloroquine.

Discussion

The implementation and management of inhalational anesthetics via AnaConDa was done without any identified issues. The potential aerosolization risk of the virus was considered and we complied with the same airborne and droplet precautions used for SARS-CoV-2 infected patients requiring mechanical ventilation**.** In order to minimize the risk, closed circuit endotracheal suctioning was used. Endo-tracheal tube clamping was realized with ECMO clamps (18) during the installation of the device, which requires disconnection and reconnection from the ventilatory circuit**.** According to Sedana Medical, the virus filtration capacity of AnaConDa is superior to 99.9% for 27 nm particles, which corresponds to less than a quarter of the SARS-CoV-2 virus size (120-160mm) (19). This implies a very low risk of passage through the device to the respiratory circuit. The anesthetic gas analyzer used for all patients (Carescape 8650, GE healthcare, Finland) (20) contains a filter and a D-FEND water trap made from polytetrafluoroethylene with 99.9% virus and bacteria filtration efficiency. Regarding the ECMO membrane, Dres and al. didn't detect SARS-CoV-2 RNA in the membrane oxygenator gas outlet of 25 patients and concluded that the virus does not spread through extracorporeal membrane oxygenation (21).

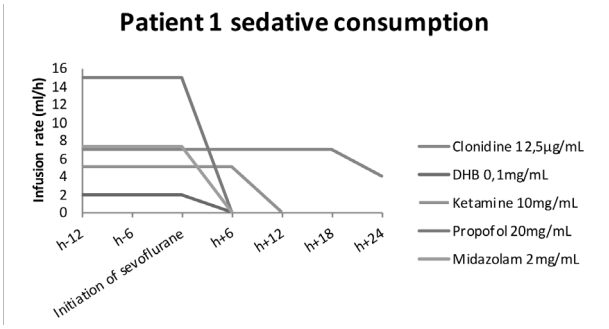
Another concern was the possible elimination of halogenated gas through the ECMO membrane. The A.L.ONE oxygenator is composed of polymethylpentene membranes coated with phosphorylcholine that are supposed to be poorly permeable to volatile anesthetics. Comparing polypropylene and polymethylpentene (PMP) membranes during cardiopulmonary bypass, Prasser showed that blood concentrations of previously applied sevoflurane were better maintained with PMP than with polypropylene membranes (22). Therefore, we first tested the administration of sevoflurane on the extracorporeal circuit by a vaporizer Drager Vapor 2000 (Drager Medical AG, Lubeck, Germany) connected to the gas supply line at a fresh gas flow of 5 l/min with increasing inhaled halogenated concentrations. No sevoflurane was detected in the patient's expired gases by the anesthesia gas monitor connected to the respiratory circuit. Attempts at decreasing sedatives were also unsuccessful. We used in our current practice a PMP membrane coated with acetylcholine and observed that it was not permeable to halogenated gas avoiding any risk of room air pollution. This trial demonstrated that the oxygenator membrane was poorly permeable to the halogenated anesthetic and that its use by inhalation would not result in vapors present in the exhaled gas of the oxygenator.

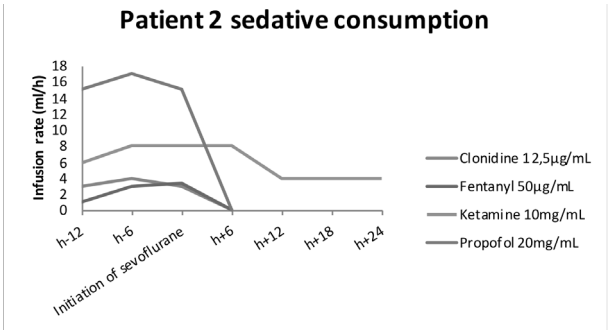
These 3 cases have shown a drastic diminution of intravenous sedatives requirements after the initiation of sevoflurane in order to achieve similar RASS scores (Figures 1, 2 and 3). No adverse effect related to the halogenated anesthetics, and no significant hemodynamic changes were observed during their administration. Several clinical advantages can be emphasized. The quick recovery after sevoflurane temporary withdrawal allowed easy neurological assessment. High doses of intravenous sedative agents increase the risk for delirium and ICU acquired weakness (23). The possibility to decrease their use thanks to halogenated gases might therefore be a beneficial effect. Weaning of intravenous sedatives also led to a reduction of administered fluids (on average 500 ml per day), which is fully in line with a conservative fluid strategy in the settings of ARDS.

Finally, the cost of the kit and vials could be a certain drawback for this practice. This is partly counterbalanced by the total costs of the intravenous sedatives and the ability to avoid paralytics in some cases, thanks to the relaxing properties of volatile anesthetics.

Conclusion

These three cases have demonstrated the feasibility of sedation with sevoflurane inhalation via AnaConDa for Covid-19 patients under venovenous extracorporeal membrane oxygenation. No evidence of implementation or security issues was noticed during the administration of the halogenated gases. In addition to the possibility of easy neurological assessment, inhalational anesthetics contributed to a conservative fluid strategy.





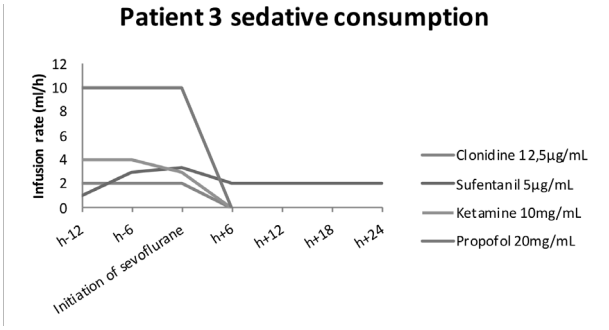


Figure 1, 2 and 3. — These 3 figures represent the sedative consumptions of the 3 patients for a RASS of -4 to -5. For simplicity reasons, the vertical axis of these graphs represents the flow rates (ml/h) of the infusion pumps. The drug concentrations are listed beside the graphs. The horizontal axis is a timeline ranging from 12 hours before the initiation of the halogenated drugs to 24 hours after. Each graduation corresponds to 6 hours. These 3 figures show the decrease of all intravenous sedatives after the initiation of sevoflurane.

Therefore, sevoflurane represents an alternative to intravenous sedatives, especially in case of intravenous drug shortage related to the covid-19 pandemic.

References

1. Li X and Ma X. 2020. Acute respiratory failure in COVID-19: is it "typical" ARDS? Crit Care;24(1):198. doi: 10.1186/s13054-020-02911-9 [published Online First: 2020/05/08]
2. Schmidt M, Hajage D and Lebreton G, et al. 2020. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med doi: 10.1016/s2213-2600(20)30328-3 [published Online First: 2020/08/18]
3. COVID-19 Cases on ECMO in the ELSO Registry 2020 [Available from : https://www.elso.org/Registry/FullCOVID19RegistryDashboard.aspx2020.
4. Badreldin HA and Atallah B. 2020. Global drug shortages due to COVID-19: Impact on patient care and mitigation strategies. Res Social Adm Pharm:S1551-7411(20)30569-6. doi : 10.1016/j.sapharm.2020.05.017
5. Ramirez-Aliaga M, Escalona-Belmonte JJ and Ramirez-Fernandez A, et al. 2018. Mechanisms of Cardioprotection of Halogenated Agents During Extracorporeal Circulation in Cardiac Surgery. Curr Vasc Pharmacol;16(4):319-28. doi : 10.2174/1570161115666171116170806 [published On-line First: 2017/11/19]
6. O'Gara B and Talmor D. 2016. Lung protective properties of the volatile anesthetics. Intensive Care Med;42(9):1487-9. doi : 10.1007/s00134-016-4429-x [published Online First: 2016/07/05]
7. Baron R, Binder A and Biniek R, et al. 2015. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision (DAS- Guideline 2015) - short version. Ger Med Sci 2015;13:Doc19. doi: 10.3205/000223 [published Online First: 2015/11/27]
8. Jabaudon M, Boucher P and Imhoff E, et al. 2017. Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. Am J Respir Crit Care Med;195(6):792-800. doi: 10.1164/rccm.201604-0686OC [published Online First: 2016/09/10]
9. Ferrando C, Aguilar G and Piqueras L, et al. 2013. Sevoflurane, but not propofol, reduces the lung inflammatory response and improves oxygenation in an acute respiratory distress syndrome model: a randomised laboratory study. Eur J Anaesthesiol;30(8):455-63. doi : 10.1097/EJA.0b013e32835f0aa5 [published Online First: 2013/04/03]
10. Meiser A, Bomberg H and Lepper PM, et al. 2017. Inhaled Sedation in Patients With Acute Respiratory Distress Syndrome Undergoing Extracorporeal Membrane Oxygenation. Anesth Analg;125(4):1235-39. doi : 10.1213/ane.0000000000001915 [published Online First : 2017/03/17]
11. Laferriere-Langlois P, d'Aragaon F and Manzanares W. 2017. Halogenated volatile anesthetics in the intensive care unit : current knowledge on an upcoming practice. Minerva Anestesiol;83(7):737-48. doi : 10.23736/s0375-9393.17.11735-9 [published Online First: 2017/03/10]
12. Sturesson LW, Bodelsson M and Jonson B, et al. 2014. Anaesthetic conserving device AnaConDa : dead space effect and significance for lung protective ventilation. Br J Anaesth;113(3):508-14. doi : 10.1093/bja/aeu102 [published Online First: 2014/05/30]
13. Hasni N, Lemaitre F and Fernandez C, et al. 2011. [Impact of ECMO on drugs pharmacokinetics]. Therapie; 66(5):405-12. doi : 10.2515/therapie/2011054 [published Online First : 2011/10/28]
14. Ha MA and Sieg AC. 2017. Evaluation of Altered Drug Pharmacokinetics in Critically Ill Adults Receiving Extracorporeal Membrane Oxygenation. Pharmacotherapy;37(2):221-35. doi : 10.1002/phar.1882 [published Online First: 2016/12/09]
15. Cheng V, Abdul-Aziz MH and Roberts JA, et al. 2018. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. J Thorac Dis;10 (Suppl 5): S629-s41. doi : 10.21037/jtd.2017.09.154 [published Online First: 2018/05/08]
16. Shekar K, Fraser JF and Smith MT, et al. 2012. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care;27(6):741.e9-18. doi : 10.1016/j.jcrc.2012.02.013 [published Online First: 2012/04/24]
17. Suzuki T, Uchida I and Mashimo T. 2005. Sorptive loss of volatile and gaseous anesthetics from in vitro drug application systems. Anesth Analg;100(2):427-30. doi :

10.1213/01.Ane.0000142112.30807.5c [published Online First: 2005/01/28]
18. Turbil E, Terzi N and Schwebel C, et al. 2020. Does endotracheal tube clamping prevent air leaks and maintain positive end-expiratory pressure during the switching of a ventilator in a patient in an intensive care unit? A bench study. PLoS One;15(3):e0230147. doi : 10.1371/journal.pone.0230147 [published Online First: 2020/03/12]
19. Medical S. COVID-19 and the use of AnaConDa 2020 [Available from : https://www.sedanamedical.com/?page_id=15766.
20. Medical S. Virus filtering capacity gas monitors 2017 [Available from : https://www.sedanamedical.com/wp-content/uploads/2017/_downloads/covid-19/Appendix%20B%20Virus%20filtering%20capacity%20gas%20monitors.pdf2017.
21. Dres M, Burrel S and Boutolleau D, et al. 2020. SARS-CoV-2 Does Not Spread Through Extracorporeal Membrane Oxygenation or Dialysis Membranes. Am J Respir Crit Care Med;202(3):458-60. doi: 10.1164/rccm.202004-1339LE [published Online First: 2020/06/12]
22. Prasser C, Zelenka M and Gruber M, et al. 2008. Elimination of sevoflurane is reduced in plasma-tight compared to conventional membrane oxygenators. Eur J Anaesthesiol;25(2):152-7. doi : 10.1017/s0265021507001330 [published Online First : 2007/07/28]
23. Reade MC and Finfer S. 2014. Sedation and delirium in the intensive care unit. N Engl J Med;370(5):444-54. doi : 10.1056/NEJMra1208705 [published Online First : 2014/01/31]