

AAGA during general anaesthesia in intensive care



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HEADLINE

- 17.1. There were seven case of AAGA reported during intended general anaesthesia in critically ill patients in the Intensive Care Unit or Emergency Department. Themes included underestimating anaesthetic requirements in sick, obtunded or hypotensive patients. Problems also arose when low-dose propofol infusions were used to maintain anaesthesia for procedures or transfers. All patients were paralysed during their AAGA and experienced distress or psychological harm. Most episodes were judged to be avoidable.

BACKGROUND

ICU and NAP5

- 17.2 Critically ill patients admitted to intensive care units (ICUs) are often deeply sedated for relatively prolonged periods (e.g. days or weeks) to reduce the discomfort caused by tracheal tubes or to increase patient compliance with mechanical ventilation (Samuelson et al., 2006; Rowe et al., 2008). This is in contrast to the predominantly healthy elective surgical population who undergo short episodes of general anaesthesia for definitive procedures.
- 17.3 Common practice is to use continuous sedation for prolonged ventilation and other invasive organ support (Payen et al., 2007; Jackson et al., 2010). This is not intended to be 'anaesthesia', since complete unconsciousness is not intended. During periods of critical illness and recovery the level of sedation is often intentionally varied. It would be expected for patients to have clear awareness of their surroundings and events during much of their recovery.
- 17.4 It is widely recognised that patients may have distressing recall of their time on ICU (Schelling et al., 1998; Jones et al., 1979; Jones et al., 2001). Notwithstanding the importance of this topic, NAP5 restricted itself to the examination of awareness *during general anaesthesia* and therefore this aspect is outwith its remit.
- 17.5 Many invasive procedures (e.g. tracheal intubation, tracheostomy, transfer of patients for procedures outside ICU, surgical procedures) are performed on ICU patients using general anaesthesia. NAP5 therefore did include reports of AAGA arising from ICU patients during procedures performed with intended general anaesthesia. We also included reports that arose during the initiation of intensive care management (which might have been in the emergency department (ED) or elsewhere outside ICU), and reports that related to the transfer of patients to and from the ICU. We classed all these as 'ICU reports' (Class D).
- 17.6 Critical illness is associated with rates of delirium as high as 83% (Ely et al., 2001). Delirium can lead

to the formation of delusional memories (Jones et al., 2000), which can persist beyond the duration of critical illness (Jones et al., 2001). This makes separating false or distorted memories from fact difficult, and means that investigating reports of AAGA in ICU is a significant challenge.

Therefore, the purpose of this chapter is to:

- (a) Present the reported cases of AAGA in the intensive care population.
- (b) Discuss any inferences that can be made from the data and highlight any areas in which improvements in management might be made.

AAGA and critical illness

- 17.7 Because of their critical illness and actual or potential organ failure, there are likely to be physiological and pharmacological factors that influence safe conduct of general anaesthesia and may predispose these patients to AAGA. Organisational and cultural aspects of ICU care might influence this risk too.
- 17.8 Induction of anaesthesia in critically ill patients poses several problems. First, during the early phase of their illness, patients can often present with a combination of hypovolaemia, vasodilatation, hypotension and organ failure. Use of standard doses of anaesthetic induction agents risks cardiovascular complications including further hypotension, myocardial depression, cardiovascular collapse, deterioration of organ function or cardiac arrest. Most induction and sedative agents have a dose-dependent effect on blood pressure in the healthy population (Sebel & Lowden, 1989; Grounds et al., 1985; Battershill et al., 2006; Win et al., 2005) and this is exaggerated in the critically ill (Aitkenhead et al., 1989).
- 17.9 Jaber et al. (2006) examined 253 ICU tracheal intubations with a variety of intravenous induction agents, and reported a 25% rate of cardiovascular collapse (systolic BP <65mmHg, or <90mmHg for >30 minutes despite fluid loading) and 2% rate of cardiac arrest. An observational study of 410 ED emergency tracheal intubations reported a cardiac arrest rate of 4.5% (Heffner, 2013). In contrast, the cardiac arrest rate in the elective anaesthetic population is reported to be 0.014% (1.4:10,000) (Newland et al., 2002).
- 17.10 Secondly, critically ill patients may be obtunded as a result of their illness, further complicating an assessment of required drug dosages. In several studies, tracheal intubation on the ICU occurred in between 7% and 9% without the use of an induction agent (Jaber et al., 2006, Koenig et al., 2014).
- 17.11 Airway difficulty or failure in critically ill patients is increased compared with the operating theatre setting (Cook et al 2011a and b; Nolan & Kelly, 2011). Contributory factors likely include the almost universal need for rapid sequence induction (RSI), lack of respiratory reserve, inexperienced personnel and environmental factors (Cook et al 2011a and b).
- 17.12 As a consequence of the above factors, it is a common and rational practice to reduce the dose of induction agent used for induction of anaesthesia in the critically ill (Reschreiter et al., 2008). In a recent study of 472 urgent tracheal intubations on a medical ICU (Koenig et al., 2014), propofol was used as a sole agent in 87% of cases with a mean dose of 99 mg (1.4 mg/ for a 70 kg adult). Rates of AAGA were not reported. In recent years ketamine has increased in prominence as an induction agent for the critically ill as it better maintains cardiovascular stability, but judging point of loss of consciousness can be difficult (Smischney et al., 2012).
- 17.13 The trend in management of critically ill patients is to minimise the depth and duration of sedation and, even in the most heavily sedated, to periodically interrupt sedation to assess cognitive function and minimise drug loads (Reschreiter et al., 2008; Jackson et al., 2010; Barr et al., 2013; Strøm et al., 2010; Kress et al., 2000). However, many critically ill patients require general anaesthesia for painful procedures, surgical interventions and for transfer outside the ICU for investigations or treatment. It is likely that practice varies between ICUs and the number of general anaesthetics administered on ICUs or for transfer is unknown.
- 17.14 AAGA may occur when general anaesthesia is administered to ICU patients for specific procedures. Many of the reasons described above regarding AAGA at tracheal intubation also apply here. Further factors potentially predisposing to AAGA might include: the necessity to use intravenous anaesthesia, the absence of anaesthetic machines, the absence of nitrous oxide, lack of an endpoint when inducing anaesthesia in an already obtunded or already sedated patient, the complexity of providing anaesthesia while 'in motion' for transfers, and on-going physiological instability and organ dysfunction which alter safe dosing, pharmacokinetics and pharmacodynamics.

NAP5 CASE REVIEW AND NUMERICAL ANALYSIS

- 17.15 The NAP5 Activity Survey provides an estimate of 29,000 general anaesthetics per year administered (by anaesthetists) in either the ICU or the ED (equivalent to ~1% of all UK anaesthetist-delivered general anaesthetics), and 54% involved RSI.
- 17.16 Of the 308 cases reviewed by the NAP5 panel, 7 (2.3%) cases involved intensive care patients either in ICU (three cases), ED (two cases) or during a transfer from ICU (two cases). Five reports involved female patients and five involved a morbidly obese patient (BMI 45–60 kg/ m²). All of these reports were considered to be based on high quality (grade A) evidence.
- 17.17 In four cases anaesthesia care was provided by a consultant intensivist or anaesthetist and in the remainder by anaesthetic/ICU trainees ranging from CT1 to ST6.

Reports at intubation

- 17.18 There were three cases where AAGA occurred around the time of induction and intubation; RSI was used in all cases.
- 17.19 AAGA was reported by two peri-arrest patients (one during CPR) and by several patients during documented profound hypotension.
- 17.20 In several cases the dose of induction agent (or even its complete omission) made the possibility of AAGA likely, and in several reports both the LC and the Panel judged the dose of induction agent was too low.
- 17.21 In only one of the seven reports of AAGA in ICU were vasopressors or inotropes used to support the cardiovascular system during induction of anaesthesia. Three reports described recall of induction of anaesthesia and tracheal intubation. All three patients received non-depolarising neuromuscular blockade after initial suxamethonium administration. In one case, in a peri-cardiac arrest situation, a neuromuscular blocking drug was administered as a sole agent to facilitate tracheal intubation. In the other two cases, propofol (+/- ketamine) was used for induction with doses of approximately 0.4 mg/kg and 1.2 mg/kg respectively.

An otherwise healthy middle-aged patient, was tracheally intubated in the ED for management of acute severe asthma. An RSI was conducted by an anaesthetic trainee with ketamine 20mg, propofol 30mg and suxamethonium followed by rocuronium. Significant hypertension was present immediately after intubation requiring further boluses of propofol before a propofol infusion was started. The following day after extubation the patient reported being aware throughout the entire intubating process lasting several minutes.

A middle-aged, obese patient collapsed due to arrhythmia after a procedure performed under local anaesthesia. Intubation was attempted, initially unsuccessfully without medication and then successfully after administering suxamethonium. Isoflurane anaesthesia was then commenced and a central line inserted. The patient was then transferred to radiology and anaesthesia was maintained with low dose boluses of propofol and continued neuromuscular blockade. Sedative infusions using a pump were started only after arrival in ICU. When extubated, the patient immediately reported the episode of awareness describing a period of AAGA throughout resuscitation, intubation, and transfer to and from radiology.

- 17.22 One of the three cases involved difficulty in intubation by a very junior anaesthetist, requiring a second more senior operator to take over. No recorded additional hypnotic agent was administered during intubation until patient 'distress' was noted.

Maintenance of anaesthesia and transfer in the critically ill

- 17.23 Two reports described events likely to have occurred soon after intubation (insertion of invasive monitoring lines, nasogastric tube insertion, patient transfer) and two during interventions performed later on during their stay.
- 17.24 In all these cases a neuromuscular blocking drug was administered before the episode of AAGA.

A middle-aged patient on chronic multiple opiate and benzodiazepine medications was anaesthetised in the ED for management of severe pneumonia. Modified RSI and tracheal intubation was followed by initiation of neuromuscular blockade and an infusion of propofol at 100mg/hr. The patient was transferred to radiology. After extubation the following day the patient reported awareness of events after intubation, including arterial line insertion, transfer and positioning in radiology (but not tracheal intubation).

A middle-aged, morbidly obese, patient required urgent endoscopy for bleeding. After tracheal intubation with a modified RSI and neuromuscular blockade, anaesthesia was continued by administration of a bolus dose and a propofol infusion at 100mg/hr. The patient subsequently reported AAGA throughout the procedure lasting at least 30 minutes. The patient reported inability to move and that they were “trying to move to tell them to stop”. Movements eventually alerted staff to the patients wakefulness. The patient suffered psychological distress as a result of the experience.

- 17.25 In all four cases, hypnotics were administered by infusion: propofol in three cases and midazolam/fentanyl in one. Depth of anaesthesia (DOA) monitoring was not used in any of the cases.
- 17.26 Perhaps notably, all patients reporting AAGA on ICU received only a short duration of sedation and mechanical ventilation, lasting approximately 24 hours. Most reports were made soon after extubation and all within four days of the event.
- 17.27 In addition to the seven reports from ICU and ED there were three further Certain/probable cases (Class A) that involved transfer of a post-operative patient to ICU. AAGA occurred during transfer in two of these cases and either during emergence or transfer in the third. All involved transfer with anaesthesia maintained with a low dose non-TCI propofol infusion. All were judged definite AAGA and were judged preventable. All involved neuromuscular blockade, all involved patient experience of paralysis, two involved patient distress and two led to prolonged psychological sequelae. The cases have very similar themes to the ICU cases.

Transfer of ventilated patients often requires paralysis. If adequate anaesthesia is not also provided the patient may experience AAGA. A low dose fixed rate propofol infusion may not guarantee anaesthesia



Patient experiences and psychological effects

- 17.28 Patient experiences of AAGA were assessed using the Michigan scoring system. All patients experienced distress during the episode of awareness, characterised by fear, anxiety and/or a feeling of suffocation. Two patients reported paralysis and distress without pain (Michigan score 4D) and five reported pain, paralysis and distress (Michigan score 5D) (Mashour et al., 2010).

A patient experienced AAGA during transfer and a procedure performed in radiology. The patient reported awareness throughout the procedure, including the painful insertion of a drain, which was described as “something exploding in my tummy”.

The patient recalled something being pushed down his throat and the sensation of being strangled, lasting several minutes.

After reporting an episode of AAGA the patient self-discharged from ICU. The patient described the episode which occurred during intubation as “one of the worst things I have ever been through” and as “really hurting”. The patient stated “I have never been so scared in my life and I was scared during my whole stay.”

- 17.29 The degree of longer-term harm as assessed by the modified NPSA scale was moderate or severe in five of seven cases.
- 17.30 The NAP5 panel judged four of these seven cases of AAGA to be preventable.
- 17.31 No reports of AAGA from ICU were judged to be a result of delirium, delusion or false memory.

DISCUSSION

- 17.32 Because of the structure and focus of NAP5 it is likely that reports of AAGA occurring in ICU were less likely to be captured than those in an anaesthetic environment. The complexity of ICU interventions inevitably means that the line between what is judged an ‘intervention’ and ‘maintenance treatment’ is a fine one.
- 17.33 NAP5 received seven reports of AAGA arising from general anaesthetics administered in the ICU or ED and, as the Activity Survey estimates 29,000 general anaesthetics are delivered in these departments per year in the UK, the apparent

incidence of reports of AAGA in this population is ~1 : 4,100. However there are major caveats to this estimate. First, the Activity Survey did not include tracheal intubation for initiation of critical care management as an anaesthetic procedure, and it is also likely that the activity survey may not have captured all general anaesthesia used for patient transfers. Second, on receiving a report of possible AAGA in an ICU patient, clinicians had to judge if the report related to a period of maintenance (not reportable to NAP5) or to an intervention (reportable to NAP5): this may have been difficult. Third, as with all incidences reported in NAP5, it should be noted that all estimates relate to reports reaching clinicians, rather than absolute incidences of AAGA. The fact that no reports were made after prolonged delays after the experience raises the possibility that delayed memories (discussed in Chapter 7, Patient Experience) may be responsible for under-reporting.

- 17.34 The small number of reports of AAGA from ICU makes inferences difficult. All cases were considered to be supported by high quality evidence, and all involved a clinical setting where general anaesthesia rather than sedation would have been expected/intended. We therefore simply comment on some apparent themes and identify learning points, but do not make recommendations for clinical practice.

Procedures such as percutaneous tracheostomy require general anaesthesia in a critically ill patient, usually performed on the ICU. Both patient and location present challenges for delivery of safe and effective general anaesthesia



Learning points

- 17.35 All cases where AAGA was reported from the ICU/ED involved critically ill patients. Concerns about the adverse effects of induction of anaesthesia would have been justified. The performed procedures were appropriate and RSI was used appropriately.
- 17.36 In common with the vast majority of anaesthetic reports, all cases of AAGA from ICU involved patients who had received a neuromuscular blocking drug, so when used, the risk of AAGA should reasonably be considered higher.
- 17.37 All ICU reports were associated with distress and the majority with subsequent psychological harm. This should guide a supportive approach to an ICU patient who reports AAGA (see Psychological Support Pathway, Chapter 7, Patient Experience).
- 17.38 AAGA in the critically ill may occur despite cardiovascular instability. Early support of the cardiovascular system that then enables increased doses of anaesthetic agents is likely to reduce distressing AAGA.
- Early use of fluids and vasopressors may enable effective doses of anaesthetic to be administered. However, in critically ill patients this may be a particular challenge*



- 17.39 Critical illness, leading to an obtunded mental state also does not guarantee absence of consciousness that retention of a memory for events. This implies the pathological brain state preventing spontaneous or reflex movement does not inevitably prevent perception. Even patients with lowered conscious levels should receive adequate anaesthesia for intubation and surgical procedures where this is safe.
- 17.40 Where critical illness demands a significant reduction in the doses of anaesthetic agents that can be safely administered, the possibility of wakefulness should be considered. Patient explanation and reassurance are likely to be of benefit to patients experiencing AAGA.
- 17.41 Notwithstanding these comments, the Panel noted that AAGA during anaesthesia in the critically ill may not be completely avoidable without putting patients at risk of major harm from the cardiovascular complications of anaesthetic agents.

- 17.42 In several cases AAGA arose soon after intubation and involved infusions of propofol (without opioids) in patients who had received neuromuscular blocking drugs. Delay in starting infusions and use of very low dose infusions contributed. Patients receiving low dose non-TCI infusions of propofol while paralysed are likely to be at increased risk of AAGA (see Chapter 18, TIVA). Use of TCI infusions might lead to more appropriate doses of anaesthetic agent being administered. Using a checklist prior to intubation (such as that described in NAP4, (Cook et al., 2011c), or a checklist as suggested in Chapter 8 (Induction), should reduce the risk of delays in initiating appropriate anaesthetic/sedative (and vasopressor/inotrope) infusions.
- 17.43 There is scope for research in validating the use of DOA monitoring in the critically ill (Nasraway et al., 2002; Vivien et al., 2003). In the Activity Survey, only three patients out of 29,000 undergoing general anaesthesia in ICU or ED received DOA monitoring (one BIS, one entropy and one other; ~1:10,000). It is not known how many UK or Irish ICUs have immediate access to DOA monitoring.
- 17.44 Delays in starting infusions of anaesthetic agents were on more than one occasion, attributed to distraction. In one case, difficult airway management and a failure to administer extra induction agent, likely contributed to AAGA. Management of critical illness is inevitably complex and is a rich potential source of human factors impacting on delivery of reliable safe care.
- 17.45 It is notable that all ICU AAGA reports were made by patients who had short ICU stays with a short period of intubation, and that the interval to reporting the episodes was also consistently short. This raises several questions, including the possibility that episodes of AAGA may occur but be forgotten when critical illness or sedation is prolonged.
- 17.46 Overall the data reported here raise concerns about a higher incidence of AAGA during anaesthesia in patients from ICU than in other settings. However our methodology, which focussed primarily on theatre practice, means we cannot confirm this. Relevant national organisations could usefully consider whether further research should be commissioned to study this important area and whether our learning points could drive recommendations for practice.

IMPLICATIONS FOR RESEARCH

Research Implication 17.1

There is scope for further research on the utility of specific depth of anaesthesia monitoring in the ICU setting. The current access of ICUs to specific depth of anaesthesia monitoring is unknown.

Research Implication 17.2

Research might better establish if anaesthesia induction of the critically ill using drugs such as ketamine (with or without opioid), with intrinsic sympathomimetic properties, can better maintain cardiovascular stability.

Research Implication 17.3

Further research might establish if there is a role for targeted controlled infusions of propofol in both anaesthesia for and transfer of ICU patients.

REFERENCES

- Aitkenhead AR, Willatts SM, Park GR, Collins CH. Comparison of propofol and midazolam for sedation in critically ill patients. *The Lancet* 1989;**334**:704–709.
- Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine* 2013;**41**:263–306.
- Battershill AJ, Keating GM. Remifentanyl: a review of its analgesic and sedative use in the intensive care unit. *Drugs* 2006;**66**:365–85.
- Cook TM, Woodall N, Frerk C. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: Anaesthesia. *British Journal of Anaesthesia* 2011;**106**:617–31.
- Cook TM, Woodall N, Harper J, Benger J. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: Intensive care and emergency departments. *British Journal of Anaesthesia* 2011;**106**:632–42.
- Cook TM, Woodall N, Frerk C. *Major Complications of Airway Management in the United Kingdom. Report and Findings. Fourth National Audit Project of the Royal College of Anaesthetists and Difficult Airway Society.* Editors Cook TM, Woodall N, Frerk C. London Royal College of Anaesthetists, 2011 (www.rcoa.ac.uk/nap4).
- Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *Journal of the American Medical Association* 2001;**286**:2703–10.
- Grounds RMR, Twigley AJA, Carli FF, Whitwam JGJ, Morgan MM. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985;**40**:735–40.
- Heffner AC, Swords DS, Neale MN, Jones AE. Incidence and factors associated with cardiac arrest complicating emergency airway management. *Resuscitation* 2013;**84**:1500–504.

- Jaber S, Amraoui J, Lefrant J-Y, Arich C, Cohendy R, Landreau L, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Critical Care Medicine* 2006;**34**:2355–61.
- Jackson JC, Girard TD, Gordon SM, Thompson JL, Shintani AK, Thomason JWW, et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. *American Journal of Respiratory Critical Care Medicine* 2010;**182**:183–91.
- Jones C, Griffiths RD, Humphris G. Disturbed memory and amnesia related to intensive care. *Memory* 2000;**8**:79–94.
- Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Critical Care Medicine* 2001;**29**:573–80.
- Jones J, Hoggart B, Withey J, Donaghue K, Ellis BW. What the patients say: A study of reactions to an intensive care unit. *Intensive Care Medicine* 1979;**5**:89–92.
- Koenig SJ, Lakticova V, Narasimhan M, Doelken P, Mayo PH. Safety of propofol as an induction agent for urgent endotracheal intubation in the medical intensive care unit. *Journal of Intensive Care Medicine* 2014 Feb 17. [Epub ahead of print].
- Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine* 2000;**342**:1471–77.
- Mashour GA, Esaki RK, Tremper KK, Glick DB, O'Connor M, Avidan MS. A novel classification instrument for intraoperative awareness events. *Anesthesia Analgesia* 2010;**110**:813–15.
- Nasraway SA, Wu EC, Kelleher RM, Yasuda CM, Donnelly AM. How reliable is the Bispectral Index in critically ill patients? A prospective, comparative, single-blinded observer study. *Critical Care Medicine* 2002;**30**:1483–87.
- Newland MC, Ellis SJ, Lydiatt CA, Peters KR. Anesthetic-related cardiac arrest and its mortality: a report covering 72,959 anesthetics over 10 years from a US Teaching Hospital. *Anesthesiology* 2002;**97**:108–15.
- Nolan JP, Kelly FE. Airway challenges in critical care. *Anaesthesia* 2011;**66**(Suppl 2):81–92.
- Payen J-F, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou J-L, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients - a prospective multicenter patient-based study. *Anesthesiology* 2007;**106**:687–95.
- Reschreiter H, Maiden M, Kapila A. Sedation practice in the intensive care unit: a UK national survey. *Critical Care* 2008;**12**:R152.
- Rowe K, Fletcher S. Sedation in the intensive care unit. *Continuing Education in Anaesthesia, Critical Care and Pain*. 2008;**8**:50–55.
- Samuelson K, Lundberg D, Fridlund B. Memory in relation to depth of sedation in adult mechanically ventilated intensive care patients. *Intensive Care Medicine* 2006;**32**:660–67.
- Schelling G, Stoll C, Haller M, Briegel J. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Critical Care* 1998;**28**:651–59.
- Sebel PS, Lowdon JD. Propofol - a new intravenous anesthetic. *Anesthesiology* 1989;**71**:260–77.
- Smischney NJ, Beach ML, Loftus RW, Dodds TM, Koff MD. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. *Journal of Trauma and Acute Care Surgery* 2012;**73**:94–101.
- Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *The Lancet* 2010;**375**:475–80.
- Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of bispectral index in sedated intensive care unit patients revealed by administration of muscle relaxant. *Anesthesiology* 2003;**99**:9–17.
- Win NN, Fukayama H, Kohase H, Umino M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesthesia & Analgesia* 2005;**101**:97–102.