Ketamine/propofol (ketofol) versus propofol/fentanyl for induction of general anesthesia in parturients with rheumatic valvular lesions undergoing elective cesarean section

Nashwa Samy ELZayyat[a], Amira Refae Hassan[a], Ahmed Ibrahim ELSakka[a], Ahmed Hussein Saad[b]

[a]Departments of Anesthesia and Intensive Care [b]Obstetrics and Gynecology, Cairo University, Cairo, Egypt

Correspondence to Nashwa Samy ELZayyat, 12 Ahmed Mokhtar Hegazy-Manial
Tel: +2012 22 39 4934;
e-mail: nanosami@yahoo.com

Received 17 October 2012
Accepted 29 December 2012

The Egyptian Journal of Cardiothoracic Anesthesia 2013, 7:79–84

In this study, we assumed that the addition of ketamine to propofol (ketofol) would maintain cardiac stability in parturients with valvular heart without any deleterious effect on the fetus, that is no respiratory depression for the baby and hence a better Apgar score. This open-label randomized study was carried out in the High-risk Obstetric Unit, Cairo University Hospitals, in collaboration with the Anesthesia Department. The study included full-term parturients, 36–38 weeks' gestational age, 25–40 years old with severe rheumatic valvular heart lesions (mitral stenosis, mitral regurge, aortic stenosis, aortic regurge) of functional class II or III according to the New York Heart Association Classification. At the time of induction, patients were allocated randomly to one of the two study groups: group K ($n = 25$) received intravenous ketamine 1 mg/kg combined with propofol 1 mg/kg. Group P ($n = 25$) received propofol 2 mg/kg and fentanyl 2 mg/kg. Mean arterial blood pressure (MAP), heart rate (HR), and central venous pressure were recorded at the following times:T1, T2, T3, T4, T5, and T6. Decrease in MAP was only significant in group P ($P < 0.001$ at T2 and T3). The magnitude decreases in MAP. The absolute value of MAP was significantly lower in group P after induction, intubation, and skin incision. The median decrease in MAP was significantly higher in group P after induction and intubation. HR increased significantly after induction of anesthesia and after endotracheal intubation in the two groups. It reverted to near baseline values thereafter. The magnitude decreases in HR. The absolute value of HR was significantly lower in group P after intubation and skin incision. Apgar scoring was significantly better (higher) in the ketofol group at 1 and 5 min. We can conclude that a combination of ketamine and propofol seems to be an appropriate choice for anesthesia of critically ill rheumatic cardiac parturients undergoing cesarean section. It proved to be effective and hemodynamically safe for such a critical situation.

Keywords:
apgar score, cardiac parturients, ketamine/propofol (ketofol),valvular lesions

Egypt J Cardiothorac Anesth 7:79–84

1687-9090

Introduction

Ketamine, which has been used as an induction agent during general anesthesia since the 1960s, has been shown to cause dissociative anesthesia and a potent analgesic effect. Although ketamine can maintain the muscle tones and airway reflexes, its use was limited because of its sympathomimetic effect, hallucination during emergence, nausea, and vomiting [1].

Propofol is another induction agent that has been discovered since the 1970s. It has a rapid onset of action with antiemetic and anticonvulsive effects; however, it may cause severe myocardial depression and hypotension [2].

Frizelle *et al.* [3] postulated that the use of both drugs as a combination in the same syringe was pharmaceutically accepted by the use of different concentrations of both drugs, and it was assumed that it exerts an additive effect with a decrease in the side effects of hypotension, and nausea and vomiting.

Mitral stenosis and aortic stenosis are considered the most common valvular heart lesions in parturients, especially in developing countries [4]. Valvular heart disease represents the leading etiology of cardiac disease during pregnancy in developing countries. A recent study from Egypt reported a frequency of 1.66/100 deliveries; two-thirds of cases were rheumatic in nature [5]. Patients with a tight valvular lesion have a fixed cardiac output and any decrease in the systemic vascular resistance caused by regional anesthesia is poorly tolerated in these patients, which makes general anesthesia a better alternative option [6].

Anesthesia used for these patients usually depended on fentanyl as a narcotic analgesic combined with propofol as an induction agent; these drugs have been proved to

maintain cardiac stability, but a decreased Apgar score for infants in the first and fifth minute with associated respiratory depression and hypnosis was observed [7].

We assumed that the addition of ketamine to propofol (ketofol) would maintain cardiac stability in parturients with a valvular heart without any deleterious effect on the fetus, that is no respiratory depression for the baby and hence a better Apgar score.

Patients and methods

This open-label randomized study was carried out in the High-risk Obstetric Unit, Cairo University Hospitals, in collaboration with the Anesthesia Department. The study was approved by the Departmental Ethical and Research Committee and an informed written consent was obtained from all patients. The study was carried out in accordance with the provision of the world medical association Declaration of Helsinki. The study extended over the period from March 2010 to September 2011 (18 months).

The primary outcome measure was mean arterial blood pressure (MAP). The secondary outcome measures included other haemodynamics [heart rate (HR) and central venous pressure (CVP)], postoperative nausea and vomiting (PONV), and fetal outcome in terms of the Apgar score.

Inclusion criteria

The study included full-term parturients, 36–38 weeks' gestational age, 25–40 years old with severe rheumatic valvular heart lesions (mitral stenosis, mitral regurge, aortic stenosis, aortic regurge) of functional class II or III according to the New York Heart Association Classification (NYHAC) (Table 1). Fifty parturients fulfilled the inclusion criteria and were enrolled in the study.

Exclusion criteria

Patients who had undergone valvular replacement, valvotomy, commissurotomy, had severe pulmonary hypertension (mean pulmonary artery pressure>55 mmHg), pregnancy-induced hypertension, or other associated comorbidities such as diabetes or heart failure, and any fetal abnormalities or fetal distress were excluded.

Table 1 New York Heart Association Functional Classification of heart disease [4]

Class	Functional description
I	Asymptomatic except during severe exertion
II	Symptomatic with moderate activity
III	Symptomatic with minimal activity
IV	Symptomatic at rest

Study procedure

The anesthesiologist interviewed, assessed, and examined patients preoperatively and explained the anesthetic intervention. The patients were allocated randomly to the two study groups using a computer-generated table. Prophylaxis against acid aspiration was provided in the form of 150 mg ranitidine intravenously on the night before and on the morning of the procedure.

Preoperative

On arrival to the operating room, all patients were monitored according to the basic American Society of Anesthesiologists standards. A peripheral intravenous line was secured. The radial artery and internal jugular vein were cannulated before induction of anesthesia using lidocaine infiltration. Fetal HR monitoring was performed by one of the surgeons from the time of entry to the theater till surgical site sterilization.

Intraoperative

All patients were preoxygenated by 100% oxygen using a face mask for 5 min. At the time of induction, patients were allocated randomly to one of the two study groups: group K (n = 25) received intravenous ketamine 1 mg/kg combined with propofol 1 mg/kg. Group P (n = 25) received propofol 2 mg/kg and fentanyl 1 μg/kg. Cricoid pressure was maintained after loss of eye lash reflex, endotracheal intubation was facilitated with the use of succinylcholine 1 mg/kg, and intubation was applied in rapid sequence induction. Sevoflurane at a mean alveolar concentration of 2% was used. Higher doses were avoided to prevent any uterine atony. Fractional inspired oxygen concentration (FiO2) of 1.0 was used throughout the operation. The lungs were ventilated using the volume-controlled mode of ventilation adjusted to maintain normocapnia. Normocapnia was monitored continuously to optimize the pulmonary vascular resistance and also to optimize the HR and avoid tachycardia. The patient's position was adjusted in the left uterine displacement by applying a wedge under the right flank. Oxytocin regimen: 5 mg diluted to 10 ml saline slowly intravenously as a bolus dose over 10 min then 10 U in 500 ml saline infusion over 30 min. Hypotension was treated using ephedrine boluses aiming to maintain the MAP within 10% of the preoperative values. At the end of the operation, the patients were extubated and monitored continuously for normocarbia and maintenance of blood pressure until they were transferred to the cardiac ICU unit.

MAP, HR, and CVP were recorded at the following times:

1. T1: just before induction of anesthesia (baseline).
2. T2: just after induction of anesthesia (injection of intravenous anesthetics and before intubation).
3. T3: after endotracheal intubation.
4. T4: at skin incision and before delivery of the baby.
5. T5: after delivery of the baby.
6. T6: after oxytocin bolus.
7. T7: in the recovery room.

Apgar scores at 1 and 5 min were recorded to assess the neonatal outcome. A follow-up interview was conducted by the in-charge anesthesiologist 24 h after cesarean section and patients were asked about recall, quality of sleep, dreams, PONV.

Sample size and estimation

On the basis of an estimated difference of MAP after induction of anesthesia of 4 mmHg between ketofol and propofol with a common SD of 4.2 mmHg, a sample size of 24 cases in each group will be satisfactory and convenient for an α level of 0.05 and a power of the test of 90% [8].

Statistical analysis

Categorical variables were assessed using the $\chi 2$ or the Fischer exact test when appropriate. Normally distributed data are presented as mean ± (SD) and were analyzed using Student's *t*-test and two-way analysis of variance with repeated measures and post-hoc Dunnett's test as appropriate. Data not normally distributed (tested by the Kolmogorov–Smornov test) are presented as median (range) and were analyzed using the Mann–Whitney *U*-test or the Kruskal–Wallis test as appropriate. The software SPSS v 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

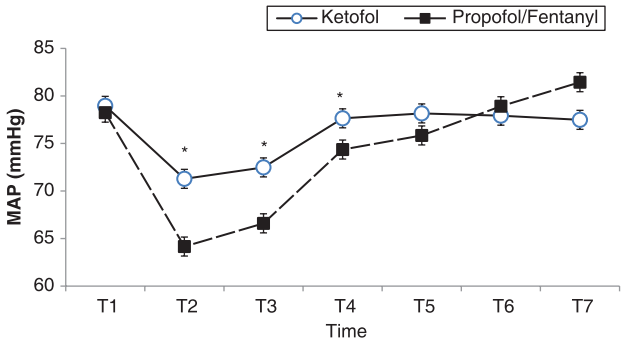
Results

Demographic data of both groups were comparable, with no statistically significant differences (Table 2).

Echocardiography performed before and after measurement of the ejection fraction values showed no statistically significant difference between groups and in the same group: (62 ± 9.5, 62 ± 9.7%) in group (K) compared with (61 ± 8.9, 63 ± 9.2%) in group P, respectively.

As shown in Figure 1, MAP decreased after induction of anesthesia with a slight increase after endotracheal intubation in the two groups. The decrease in MAP was only significant in group P ($P < 0.001$ at T2 and T3). The magnitude of decrease in MAP is shown in Table 2. The absolute value of MAP was significantly

Figure 1



Mean arterial pressure (MAP) in the two groups studied (mean ± SD). *Significant difference between the two groups.

Table 2 Demographic data and patients' characteristics

Data	Group K (ketofol)	Group P (propofol/fentanyl)
Age (years)	35 ± 4	33 ± 7
Valvular lesion		
Mitral stenosis (MS)	14	12
Double mitral	5	4
Aortic stenosis (AS)	6	7
Echocardiography (EF) (%)		
Preoperative	62 ± 9.5	61 ± 8.9
Postoperative	62 ± 9.7	63 ± 9.2
Recall and hallucination	0	0
Postoperative nausea and vomiting	0	1 (only one patient)

Table 3 Percentage change in mean arterial pressure and heart rate during surgery in the two groups studied

	Group K (n = 25)	Group P (n = 25)	*P* value
Percent change of MAP			
After induction	−10 (−17 to −1)	−17 (−34 to 12)	<0.001
After intubation	−9 (−21 to 5)	−14 (−29 to 8)	0.006
At skin incision	0 (−13 to 6)	−4 (−24 to 13)	0.200
Percent change of HR			
After induction	11 (−11 to 29)	12 (3 to 30)	0.749
After intubation	−3 (−25 to 11)	0 (−20 to 25)	0.020
At skin incision	1 (−22 to 13)	4 (−13 to 34)	0.019

Data as median (range); HR, heart rate; MAP, mean arterial pressure.

Table 4 Apgar score

Variable	Apgar score in group K (ketamine/propofol)	Apgar score in group P (propofol/fentanyl)	*P* value
At 1 min	8.5 ± 1.2	6.1 ± 1.3	0.002*
At 5 min	9.8 ± 0.7	8 ± 1.15	0.023*

*$P \leq 0.05$ is considered statistically significant.

lower in group P after induction, intubation, and skin incision (Figure 1). The median decrease in MAP was significantly higher in group P after induction and intubation (Table 3).

HR increased significantly after induction of anesthesia and after endotracheal intubation in the two groups. It reverted to near baseline values thereafter. The magnitude of decrease in HR change is shown in Table 2. The absolute value of HR was significantly lower in group P after intubation and skin incision (Fig. 2). The median change in HR was significantly different between the groups after intubation and skin incision (Table 2). However, all changes were within the clinically accepted range. Figure 3 shows changes in CVP during the operative time. There was no significant change in CVP in the two groups and no difference in CVP between the two groups.

Apgar scoring was significantly better (higher) in the ketofol group at 1 and 5 min (Table 4).

In terms of recall, hallucination, and PONV, no patient in either group experienced recall or hallucination and only one patient in the fentanyl propofol group experienced nausea and vomiting, treated with 10 mg metoclopramide intravenously.

Discussion

This study showed that a combination of ketamine and propofol (ketofol) is a safe and effective option for induction of anesthesia for cesarean section in parturients with severe cardiac disease. Ketofol produced a moderate clinically acceptable decrease in MAP (median value of 10%) in addition to a slight change in HR and CVP. Compared with propofol/fentanyl, it seems to be of comparable effectiveness and with a safer hemodynamic impact.

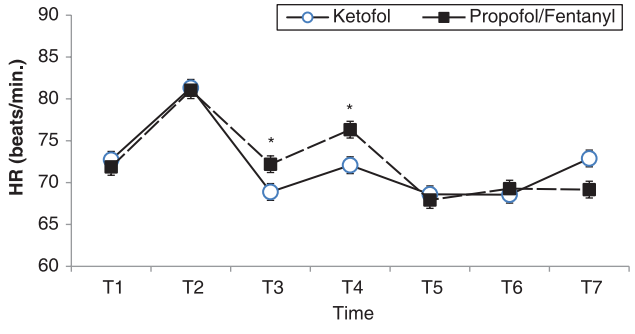
Anesthesia of cardiac patients undergoing cesarean section has always been a challenge for experienced anesthesiologists. A compromised cardiovascular system encounters an extra burden during pregnancy that increases late close to delivery. This is the situation during elective cesarean delivery, a compromised heart carrying an overload that will increase after delivery of the fetus secondary to relief of inferior vena cava obstruction and autotransfusion of about 500 ml from uterine contraction [9].

Rheumatic heart diseases during pregnancy are not uncommon, especially in developing countries such as Egypt [5]. Carapetis *et al.* [10] reviewed the worldwide burden of these diseases; they estimated a prevalence of at least 15.6 million cases of rheumatic heart disease, with a yearly 282 000 new cases and 233 000 deaths. They calculated a 1.8/1000 regional prevalence in Middle East and North Africa. In the current study, we included cases with rheumatic valvular heart lesions of NYHAC functional class II or III.

Both general and spinal anesthesia can be used for elective cesarean section in cardiac parturients. Spinal anesthesia is simple, with rapid onset and dense block [11]. However, to prevent intraoperative visceral pain, a level of anesthesia including T5 is required [12,13], which carries the risk of hypotension with a subsequent reduction of cerebral perfusion and unpleasant nausea and vomiting [14]. More severe and prolonged hypotension may cause loss of consciousness, with the risk of airway obstruction or aspiration and subsequent hypoxia. Inadequate uteroplacental perfusion may place the fetus at risk [15].

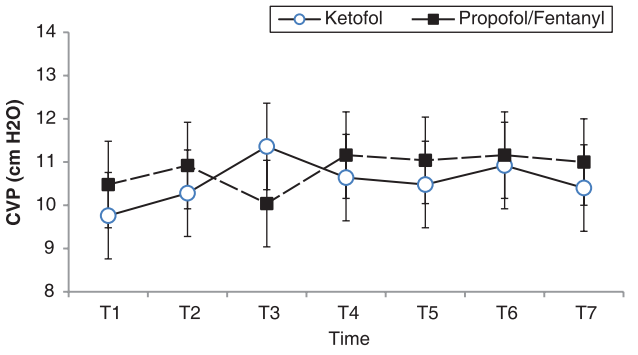
Pathophysiologically, hemodynamic changes are a reflection of a marked decrease in systemic vascular resistance compensated by increased stroke volume and HR [16]. Hemodynamic stability under spinal

Figure 2



Heart rate (HR) in the two groups studied (mean ± SD). *Significant difference between the two groups.

Figure 3



Central venous pressure (CVP) in the two groups studied (mean ± SD).

anesthesia can be achieved by titrated regional anesthesia by intravenous volume, phenylephrine infusion, and small repeated doses of intravenous oxytocin [17].

In patients with mitral stenosis, epidural anesthesia is a preferable choice because of slower onset of blockade, allowing controllable hemodynamic alterations. However, patients are also at risk of developing hypotension because of venous pooling. Prophylactic ephedrine and appropriate intravenous fluid administration are needed to maintain hemodynamic stability [18].

During general anesthesia, hemodynamic stability can be achieved if sympathetic stimulation associated with intubation, suction, and extubation is minimized and by avoidance of induction with drugs that commonly produce tachycardia. Blunting of hemodynamic response to stimulating events may be accomplished by the use of opioids. Controlled emergence is necessary to avoid postoperative tachycardia and increase in blood pressure. We believe that the opposing hemodynamic and respiratory effects of ketamine and propofol are a tempting option that enhances the practicality of this combination to ensure safety and efficacy, with a consequent reduction of the required dose of propofol to induce adequate sedation. The results of this study proved this assumption, which is supported by other investigations that utilized ketofol in other critical situations.

Prospective studies investigated the effects of propofol–ketamine in pediatric patients undergoing cardiac catheterization. Low-dose ketamine combined with propofol led to better preservation of MAP compared with propofol alone [19,20]. This combination was also proved to be safe in pediatric patients undergoing auditory brainstem response testing; it prevented the risk of respiratory depression because of propofol [21]. It was also safe and effective in pediatric patients undergoing burn dressing changes [22].

Another prospective, randomized trial included 90 adults to study the effects of ketamine addition to propofol on hemodynamic profile and laryngeal mask airway insertion conditions. Higher blood pressure was observed following the administration of ketamine compared with either fentanyl or saline. Ketamine was associated with less prolonged apnea than fentanyl [23]. Ketofol was tested in 114 procedural sedation and analgesia in emergency orthopedic procedures. It was found to be effective and safe for such painful procedures, with rapid recovery and satisfaction among both patients and staff [24]. Similar success of ketofol combination for procedural sedation and analgesia was reported in a prospective study of 219 pediatric patients. Few adverse events were observed [25].

Ketofol provided effective sedation in children undergoing bone marrow aspiration with rapid recovery and insignificant complications [26]. Ketofol also produced deep sedation as an adjunct to regional analgesia for lower limb surgery [27]. Ketofol maintained hemodynamic stability in oncology procedures [28,29].

Conclusion

The combination of ketamine and propofol seems to be an appropriate choice for anesthesia of critically ill rheumatic cardiac parturients undergoing cesarean section. It proved to be effective and hemodynamically safe for such a critical situation. Further larger randomized trials are required to confirm these findings.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Warncke T, Stubhaug A, *et al.* Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. Pain 1997; 72:99–106.

2 Bassett KE, Anderson JL, Pribble CG, *et al.* Propofol for procedural sedation in the emergency department. Ann Emerg Med 2003; 42:773–782.

3 Frizelle HP, Duranteau J, Samii KA comparison of propofol with a propofol-ketamine combination for sedation during spinal anesthesia. Anesth Analg 1997; 84:1318–1322.

4 Dobbenga-Rhodes YA, Prive AM Assessment and evaluation of the woman with cardiac disease during pregnancy. J Perinat Neonatal Nurs 2006; 20:295–302.

5 Taha NM, Mahmoud KS, Eisa MK, Darder A Structural heart disease in pregnancy in El-Minia localitiesEgypt Heart J2012[Epub ahead of print]

6 Bonow RO, Carabello BA, Kanu C, *et al.* ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2006; 114:e84–e231.

7 Ayoub CM, Jalbout MI, Baraka AS The pregnant cardiac woman. Curr Opin Anaesthesiol 2002; 15:285-291.

8 Aboeldahab H, Samir R, Hosny H, *et al.* Comparative study between propofol, ketamine and their combination (ketofol) as an induction agent. *Egypt J Anesth* 2011; 27:145–150.

9 Iyera GB, Durbridgeb J, Coxb M Management of the pregnant cardiac patient. Trends Anesth Crit Care 2011; 1:13–17.

10 Carapetis JR, Steer AC, Mulholland EK, Weber M The global burden of group A streptococcal diseases. Lancet Infect Dis 2005; 5:685–694.

11 Shibli KU, Russell IF A survey of anaesthetic techniques used for caesarean section in the UK in 1997. Int J Obstet Anesth 2000; 9:160–167.

12 Craft JB Jr, Roizen MF, Dao SD, Edwards M, Gilman R A comparison of T4 and T7 dermatomal levels of analgesia for caesarean section using the lumbar epidural technique. Can Anaesth Soc J 1982; 29:264–269.

13 Sarvela PJ, Halonen PM, Korttila KT Comparison of 9 mg of intrathecal plain and hyperbaric bupivacaine both with fentanyl for cesarean delivery. Anesth Analg 1999; 89:1257–1262.

14 Cesur M, Alici HA, Erdem AF, Borekci B, Silbir F Spinal anesthesia with sequential administration of plain and hyperbaric bupivacaine provides satisfactory analgesia with hemodynamic stability in cesarean section. Int J Obstet Anesth. 2008; 17:217–222.

15 Dresner M Haemodynamic stability and regional anaesthesia for caesarean section. Curr Anaesth Crit Care 2004;15:262–269.

16 Langesæter E, Dyer RA Maternal haemodynamic changes during spinal anaesthesia for caesarean section. Curr Opin Anaesthesiol 2011; 24:242–248.

17 Langesaeter E, Dragsund M, Rosseland LA Regional anaesthesia for a caesarean section in women with cardiac disease: a prospective study. Acta Anaesthesiol Scand 2010; 54:46–54.

18 Ziskind S, Etchin A, Frenkel Y, *et al.* Epidural anesthesia with the Trendelenburg position for cesarean section with or without a cardiac surgical procedure in patients with severe mitral stenosis: a hemodynamic study. J Cardiothorac Anesth 1990; 3:354–359.

19 Akin A, Esmaoglu A, Guler G, Demircioglu R, Narin N, Boyaci A Propofol and propofol-ketamine in pediatric patients undergoing cardiac catheterizationPediatr Cardiol. 2005; 26:553–557.

20 Kogan A, Efrat R, Katz J, Vidne, BA Propofol-ketamine mixture for anesthesia in pediatric patients undergoing cardiac catheterization. J Cardiothorac Vasc Anesth 2003;17:691–693.

21 Akin A, Esmaoglu A, Tosun Z, Gulcu N, Aydogan H, Boyaci A Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. Int J Pediatr Otorhinolaryngol 2005; 69:1541–1545.

22 Tosun Z, Esmaoglu A, Coruh A Propofol-ketamine vs propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. Paediatr Anaesth 2008; 18:43–47.

23 Goh PK, Chiu CL, Wang CY, Chan YK, Loo PL Randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol-saline on haemodynamics and laryngeal mask airway insertion conditions. Anaesth Intensive Care 2005; 33:223–228.

24 Willman EV, Andolfatto G A prospective evaluation of 'ketofol' (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med 2007; 49:23–30.

25 Andolfatto G, Willman E A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). Acad Emerg Med 2010; 17:194–201.

26 Da Silva PS, de Aguiar VE, Waisberg DR, Passos RM, Park MV Use of ketofol for procedural sedation and analgesia in children with hematological diseases. Pediatr Int 2011; 53:62–67.

27 Weatherall A, Venclovas R Experience with a propofol-ketamine mixture for sedation during pediatric orthopedic surgery. Paediatr Anaesth 2010; 20:1009–1016.

28 Chiaretti A, Ruggiero A, Barone G, *et al.* Propofol/alfentanil and propofol/ketamine procedural sedation in children with acute lymphoblastic leukaemia: safety, efficacy and their correlation with pain neuromediator expression. *Eur J Cancer Care (Engl)* 2009; 21:212–220.

29 Aouad MT, Moussa AR, Dagher CM, *et al.* Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. *Acta Anaesthesiol Scand* 2008; 52:561–565.