

RESEARCH ARTICLE

Pre-anesthetic Anxiety Level in Children with Congenital Heart Disease: Comparison between Maternal Presence during Anesthetic Induction and Midazolam Premedication

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Abstract

General anesthesia was needed by children with congenital heart disease (CHD) who underwent cardiac catheterization procedure and surgery. Pre-anesthetic anxiety in children with CHD can cause significant problems during induction of anesthesia which leads to negative postoperative outcomes. This study compared the role of maternal presence during anesthesia induction with midazolam premedication on pre-anesthetic anxiety level in children with CHD. Dr. Cipto Mangunkusumo National Hospital on April to September 2014. Forty-five CHD patients aged 2-5 years old who underwent cardiac invasive procedure were divided into P group (received midazolam premedication) and M group (had maternal presence during anesthesia induction). Modified Yale Pre-anxiety Scale (MYPAS) was used for measuring anxiety level in each patient during preoperative visit, on the time patient entered the procedure room and during induction of anesthesia. There was no significant difference of MYPAS scores between the two groups in all measurement times. The MYPAS score results were non-anxious (median score 23.4) and the highest was at induction of anesthesia. Inter-rater agreement test between 2 observers was good ($k > 0.5$). In conclusion, there was no significant difference between the effect of maternal presence during induction of anesthesia and midazolam premedication on pre-anesthetic anxiety level in children with CHD.

Keywords: pre-anesthetic anxiety, congenital heart disease, maternal presence, midazolam.

Peran Kehadiran Ibu selama Induksi Anestesia dengan Premedikasi Midazolam terhadap Tingkat Kecemasan Pra-anestesia Anak dengan Penyakit Jantung Bawan

Abstrak

Pembiusan umum diperlukan oleh pasien dengan penyakit jantung bawaan (PJB) pada saat kateterisasi atau pembedahan jantung. Kecemasan pra-anestesia dapat menimbulkan masalah saat induksi anestesia yang berdampak negatif pascapembedahan. Penelitian ini bertujuan untuk membandingkan efek premedikasi midazolam dan kehadiran ibu selama induksi anestesia terhadap tingkat kecemasan pra-anestesia anak dengan PJB. Penelitian dilakukan di RSUP Nasional Dr. Cipto Mangunkusumo National pada bulan April-September 2014. Uji klinis acak dilakukan pada anak dengan PJB usia 2-5 tahun. Subjek dibagi menjadi kelompok premedikasi midazolam (P) dan kelompok pendampingan ibu (I) menurut randomisasi blok. Tiap-tiap kelompok dinilai status mental dengan MINI KID dan tingkat kecemasan dengan MYPAS oleh dua observer yang telah dilatih sebelumnya. Tingkat kecemasan dinilai saat awal, masuk ruang tindakan dan saat induksi anestesia. Kedua kelompok diinduksi dengan anestetika inhalasi sevofluran. Tidak didapatkan perbedaan bermakna skor MYPAS di antara kedua kelompok pada ketiga waktu pengukuran. Skor MYPAS termasuk dalam kategori tidak cemas (median skor 23,4). Skor MYPAS tertinggi didapatkan saat induksi anestesia. Uji kesesuaian antara kedua observer didapatkan baik ($k > 0,5$). Kesimpulannya, tidak terdapat perbedaan yang bermakna antara premedikasi midazolam dan kehadiran ibu selama induksi anestesia pada kecemasan pra-anestesia anak dengan PJB.

Kata kunci: Kecemasan pra-anestesia, kehadiran ibu, penyakit jantung bawaan, midazolam

Introduction

Congenital heart disease (CHD) was found in 1% of child birth every year.¹⁻³ Two to three of these children need cardiac catheterization and cardiac surgery under general anesthesia in their lifetime.^{4,5} Pediatric patients with CHD often need repetitive invasive procedures or prolonged therapy.⁶ Separation from a parent or guardian when the patient enters the procedure room can be very difficult.^{4,7-9} Additionally, induction of anesthesia is a stressful procedure as well. Stress and anxiety during induction in CHD patients might induce sympathetic activity which can deteriorate the cardiovascular status.^{7,8,10-12}

Midazolam is the most common premedication used in pediatric anesthesia. In patients with CHD, midazolam has side effect potential toward cardiovascular function (decreased cardiac output and hypotension) and respiration (loss of airway reflexes and airway obstruction) with unpredictable variation of myocardial depression levels.^{17,18} Midazolam is used especially for CHD paediatric patients who are restless, uncooperative or suffer from hypercyanotic spell at the moment they enter the procedure room or separated from their parents.

Children with CHD tend to be more attached to their parents because of their limitation in sociability and the impact of the cardiac condition on daily activities. There are also negative influence due to parents' over attention and overprotective demeanors.^{9,19,20} In Asia, parenting method is dominated by mothers. The maternal role in providing comforts and supports while exposed with variable stress or new experiences is essential during the child's development.^{21,22} The aim of this study is to compare pre-anesthetic anxiety level in children with CHD between midazolam premedication and maternal presence during induction of anesthesia.

Methods

This prospective, randomized-controlled trial was conducted at Integrated Cardiac Care, Dr. Cipto Mangunkusumo General Hospital on April to September 2014, after approval from the Human Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia following the provisions of the Declaration of Helsinki. Written informed consents were obtained from the parents of participants or their legal guardians.

The accessible population of this study was children with CHD who were scheduled to undergo invasive cardiac procedure. Samples were taken

consecutively and divided into groups of midazolam premedication (P) and maternal presence (M). These groups were randomized by random alphabets with envelopes in blocks of 4. Sample size was calculated based on an unpaired numeric analytical study,^{27,28} with Modified Yale Preoperative Anxiety Scale (MYPAS) pre-anesthetic anxiety score in children with parental presence during induction of anesthesia was 42 ± 17 .⁶ A minimum sample size of 22 patients was needed for each group. Observers were anesthesiology residents who were trained to use MYPAS. There were two observers whom did not communicate to each other during the measurement of the anxiety level of the patients.

Inclusion criterion was children aged 2-5 years old who were scheduled to undergo invasive cardiac procedure with the agreement from parent(s) to abide the study rules. Exclusion criteria were the presence of hypoplastic left heart syndrome, other syndromes or congenital abnormalities involving central nervous system, any possibility of ventilation and/or intubation difficulty, mental retardation, psychosis, central nervous system disorder or disease, accompanied by other than the mother, severe anxiety causing uncooperative behavior, or with clinically anxious mothers. Drop out criteria included rejection or partial consumption of premedication, patients who entered the procedure room less than 30 minutes after premedication, mothers with hysteria/severe anxiety or became uncooperative before the induction of anesthesia, patients who became restless and uncooperative, occurrence of cardiorespiration emergency before the induction of anesthesia, or cancelled anesthesia induction.

All subjects were assessed with Mini International Neuropsychiatry Interview for Children and Adolescent (MINI KID) instrument, which had undergone validity and reliability tests before in Pediatric and Juvenile Psychiatric Division Department of Psychiatry Faculty of Medicine, Universitas Indonesia. MINI KID was used to assess mental status in children based on *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV. Subjects who suffered from any mental status were excluded.

Indonesian version of MYPAS was used to measure the anxiety level of children during preoperative visit, on the time patient entered the procedure room and during anesthesia induction. To increase the reliability, assessment of pre-anesthetic anxiety level in children with CHD was performed by the same observers (Figure 1).

Indonesian version of MYPAS had been validated before this study started. It was translated into “Bahasa Indonesia” followed by content validation performed by a panel of experts from Department of Anesthesiology and Intensive Care along with Department of Psychiatry, Universitas Indonesia. Validity and reliability testing of Indonesian version MYPAS were conducted on 30 children aged 2-5 years old without CHD who were scheduled to undergo general anesthesia for non-cardiac surgery.

Data were analyzed by Shapiro Wilk test.²⁹ Statistical test was performed with computer software, Statistical Product and Service Solution (SPSS) 21.0 for Windows. Hypothesis was tested by unpaired t-test on normal distribution to acquire score difference of pre-anesthetic anxiety level. Mann Whitney test was performed on data which was not normally distributed. Baseline anxiety level and characteristic data of the children with CHD were presented in percentages.

Results

The content and validity test resulted that MYPAS was valid. The reliability test concluded that two observers were reliable with a good clinical significance ($k=0.601$). Furthermore, cut-off point of anxiety level was set using these measures i.e iMYPAS score ≤ 30 means non-anxious and MYPAS score >30 means anxious.^{24,25}

There were 55 children acquired from the accessible population, 49 study subjects who met the inclusion criteria were obtained. From this number, 23 subjects included in the group receiving premedication (Group P) and 22 subjects included in the group accompanied with the mothers (Group M). Subject characteristic based on age, gender, type of CHD, history of invasive procedure in the hospital, history of anesthesia and invasive cardiac measures undertaken by both groups were shown in Table 1.

Table 1. Characteristic of Subject (n=45)

| Variables | Premedication (n=23) | Mother (n=22) | Total (n=45) |
|--------------------------------|----------------------|---------------|--------------|
| Age (years), median (min-max) | 3.4 (2-5.8) | 3.6 (2-5.8) | 3.4 (2-5.8)* |
| Gender | | | |
| Male (%) | 8 (34.8) | 9 (40.9) | 17 (37.2) |
| Female (%) | 15 (65.2) | 13 (59.1) | 28 (62.8) |
| Type of CHD | | | |
| Acyanotic (%) | 7 (30.4) | 9 (40.9) | 16 (35.6) |
| Cyanotic (%) | 16 (69.6) | 13 (59.1) | 29 (64.4) |
| Anesthetic procedure history | | | |
| Never (%) | 7 (30.4) | 13 (59.1) | 20 (44.4) |
| $\geq 1x$ (%) | 16 (69.6) | 9 (40.9) | 25 (54.6) |
| Invasive procedure history | | | |
| Never (%) | 5 (21.7) | 12 (53.9) | 17 (37.2) |
| $\geq 1x$ (%) | 18 (78.3) | 10 (46.1) | 28 (62.8) |
| Cardiac invasive procedure | | | |
| Diagnostic(%) | 6 (26.1) | 10(45.5) | 16 (35.6) |
| Transcatheter Intervention (%) | 5 (21.7) | 2 (9.1) | 7 (15.6) |
| Paliative surgery (%) | 3 (13.1) | 3 (13.6) | 6 (13.3) |
| Definitive surgery (%) | 9 (39.1) | 7 (31.8) | 16 (35.6) |

*Shapiro-Wilk test

There was no difference in baseline anxiety level with MYPAS score, whether at the time of admission to the procedure room or at the time of anesthesia induction in both groups, with *p* value>0.05 for both observer 1 and 2 (Table 2).

The inter-rater agreement between both observers resulted in no difference in the measurement, with Cohen’s kappa >0.5 (excellent and good clinical significance). Similarly, the measurement of anxiety level for both groups was shown in Figure 3.

Table 2. Anxiety Level of Subject

| Variables | Premedication Median (min-max) | Mother Median (min-max) | <i>p</i> |
|---|-----------------------------------|----------------------------|----------|
| Baseline anxiety | | | |
| Observer 1 | 23.4 (23.4-51.6) | 23.4 (23.4-55.0) | 0.630 |
| Observer 2 | 23.4 (23.4-56.6) | 23.4 (23.4-55.0) | 0.444 |
| Anxiety when entering the procedure room | | | |
| Observer 1 | 23.4 (23.4-70.0) | 23.4 (23.4-65.0) | 0.807 |
| Observer 2 | 23.4 (23.4-70.0) | 23.4 (23.4-65.0) | 0.934 |
| Anxiety at induction of anesthesia | | | |
| Observer 1 | 23.4 (23.4-76.6) | 23.4 (23.4-70.0) | 0.790 |
| Observer 2 | 23.4 (23.4-76.6) | 23.4 (23.4-73.4) | 0.781 |

*Mann Whitney test

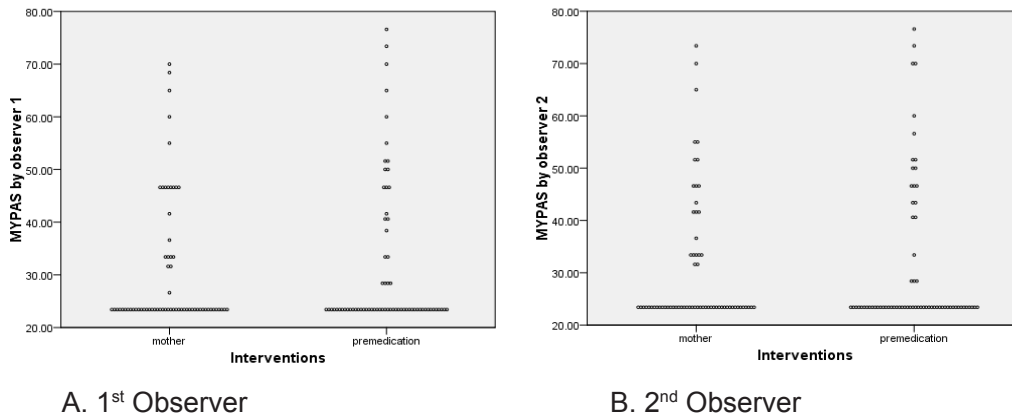


Figure 3. Diagram of Anxiety Level at P and M Groups

Changes of anxiety level in all three assessment periods were generally not significant. Although the median of the three assessments were equal, there was an increase in the anxiety level in the two groups based on both observers. This was shown as change of maximum value at each measurement time.

During the study, there were no side effects of midazolam premedication in the form of desaturation, bradypnea, respiration arrest, or cardiovascular disturbances such as hypotension,

arrhythmia, or cardiac arrest. One mother of the subject experienced hysteria and triggered the subject to cry and became uncooperative when entering the procedure room. Hence, the subject needed intravenous midazolam and was dropped out from the study.

Discussion

Children with CHD are vulnerable to experience pre-anesthetic anxiety.⁶ Premedication or parent’s presence along with good preanesthetic education

and preparation were expected to be able to reduce anxiety and improve children's cooperation. In this study, subjects were accompanied by their mothers. For Indonesian people, particularly Javanese and Sundanese ethnics, the relation between mother and child is stronger compared to father and child. Mothers have a major role of providing comfort and support when children are exposed to various stressors or new experiences e.g. hospitalization. In addition, when having children with congenital defects or in sickness, a mother's guilt can lead to overprotective behavior towards the child. This often causes children to be dependent on the maternal presence. The strong influence of mothers on these children can give advantages or disadvantages, e.g. when a mother has anxiety problems.²¹

Validity test showed that Indonesian version of MYPAS had a good content and construction validity. It also had a good reliability. In order to increase MYPAS reliability in this study, inter-rater agreement was conducted on the same observers, based on validity and reliability tests. Inter-rater agreement test at initial measurement, at the time of entering the procedure room and at induction of anesthesia resulted in good and excellent clinical significance.

In this study, there was no difference in baseline MYPAS score of anxiety between both treated groups ($p > 0.05$). Mean value of baseline MYPAS score in both groups was not significantly different (≤ 30) and included in category of non-anxious. At first, it was thought that the subjects were accompanied by the mother or other relatives, so that they felt safe and comfortable. However, this condition continued to the subsequent step.

At the time of entering the procedure room, there was no difference of MYPAS score in both groups. Mean value of MYPAS score increased from the baseline score. The MYPAS mean value was 30, which was classified as non-anxious. This result was different in comparison with other studies which found that the anxiety level significantly increased at the time of entering the procedure room.¹⁰ This study result indicated that the surrounding environment was comfortable for the subjects. This study showed that for pediatric patients, knowing the medical procedure that would be undertaken did not lead to anxiety. The environment played a more important role. Two subjects (one from each group) reached the extreme value when entering the procedure room. However, both baseline scores of these subjects were already in the category of anxious. It

was difficult to differ whether it was caused by stress due to the scheduled procedure or caused by trait anxiety.^{36,37}

Induction of anesthesia is known as one of the most stressful experience for a child during hospitalization.^{7-11,19,34,35} More than 50% of subjects in both group remained in non-anxious category at induction of anesthesia. Three subjects showed high anxiety level (MYPAS score > 70) at induction of anesthesia. Interestingly, two of them were from group P. This was not consistent with the study of Kain et al^{7,10} which showed that midazolam premedication were more effective in treating anxiety in children. Thus, the final score obtained was not able to ensure whether the increase of anxiety experienced by both patients was due to interaction with the pre-procedure atmosphere or due to the individual characteristic of the patients. Other studies showed that patients with higher anxiety level or high trait anxiety level would increase the level of anxiety at the time of anesthesia induction.^{36,37}

In this study, the maternal anxiety level was not assessed. Hence, it could not be proven whether the child's anxiety level was influenced by the maternal anxiety level or not. According to the observation, most of the mothers showed no anxiety, except the one who had hysteria and gave direct effect to the subject, which led to extreme increase of subject's anxiety level and ended up with exclusion from the study. Although it happened only in 1 out of 49 samples, but it seemed obvious that mother's behavior affected the child's anxiety level.

A limitation of this study was that MYPAS instrument was unable to measure the pre-anesthetic anxiety level in children age less than 2 years old. This study did not measure the maternal anxiety level in pediatric patient with CHD. Therefore, it could not be proven that maternal anxiety level might affect the child's anxiety level. The anxiety level in normal children or non-CHD patients who was going to undergo non-cardiac surgery could not represent the actual condition because the sample size for validity test was only based on minimum sample (30 children).

In conclusion, there was no significant difference in the pre-anesthetic anxiety level between the pediatric patients with CHD receiving premedication of oral midazolam with the pediatric patients who had CHD being accompanied by their mothers during anesthesia induction. The anxiety level in pediatric patients with CHD was included in non-anxious category. There was no significant difference

between the effect of premedication with midazolam and the maternal presence at the time of entering the procedure room toward the pre-anesthetic anxiety level in pediatric patients with CHD.

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References

- Davies LK, Knauf DG. Anesthetic management for patients with CHD. Dalam: Hensley FA, Martin DE, Penyunting. A practical approach to cardiac anesthesia. Edisi ke-4. Philadelphia: Lippincott Williams & Wilkins; 2008.p.375-439
- Menahem S, Poulakis Z, Prior M. Children subjected to cardiac surgery for CHD. Part 1-emotional and psychological outcomes. *Interact Cardiovasc Thorac Surg.* 2008;7:600-4.
- Oster ME, Riehle-Colarusso T, Simeone RM, Gurvitz M, Kaltman JR, McConnell, et al. Public health science agenda for congenital heart defects: report from a centers for disease control and prevention experts meeting. *J Am Heart Association.* 2013;2:1-10.
- LeRoy S, Elixson EM, O'Brien P, Tong E, Turpin S, Uzark K. Recommendations for preparing children and adolescents for invasive cardiac procedures: a statement from the American Heart Association Pediatric Nursing Subcommittee of the Council on Cardiovascular Nursing in collaboration with the Council on Cardiovascular Disease of the Young. *Circulation.* 2003;108:2550-64.
- Olsen M, Sorensen HT, Hjortdal VE, Christensen TD, Pedersen L. Congenital heart defects and developmental and other psychiatric disorders: a Danish nationwide cohort study. *Circulation.* 2011; 124:1706-12.
- Lee S, Yoo J-S, Yoo I-Y. Parenting stress in mother of children with CHD. *Asian Nursing Research.* 2007;1(2):116-24.
- Kain Z, Mayes LC, Wang S, Caramico LA. Parental presence during induction of anesthesia versus sedative premedication: Which intervention is more effective? *Anesthesiology.* 1998;89:1147-56.
- Kain Z, Fortier M. Psychological aspects of pediatric anesthesia. Dalam: Davis PJ, Cladis FP, Motoyama EK, Penyunting. *Smith's anesthesia for infants and children.* Edisi ke-8. Philadelphia: Elsevier Mosby, 2011.p.265-76.
- Kain Z, Caldwell-Andrews A, Wang S. Psychological preparation of the parent and pediatric surgical patient. *Anesthesiol Clin.* 2002;20:29-44.
- Kain Z, Mayes LC, Wang S, Caramico LA, Krivutza DM, Hofstadter MB. Parental presence and a sedative premedicant for children undergoing surgery, a hierarchical study. *Anesthesiol Clin.* 2000; 92:939-46.
- Kain Z, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: predictor and outcomes. *Arch Pediatr Adolesc Med.* 1996;150:1238-45.
- Wollin SR, Plummer JL, Owen H, Hawkins RMF, Materazzo M. Predictors of preoperative anxiety in children. *Anesth Intensive Care.* 2003;31:69-74.
- Krane EJ, Davis PJ, Kain Z. Preoperative Preparation. Dalam: Davis PJ, Cladis FP, Motoyama EK, Penyunting. *Smith's anesthesia for infants and children.* Philadelphia: Elsevier Mosby; 2011.p.277-92.
- Kain Z, Caldwell-Andrews A, Krivutza DM, Wang S, Weinberg ME, Gaal D. Trend in the practice of parental presence during induction of anesthesia and use of preoperative sedative premedication in the United States; Results of a follow up national survey. *Anesth analg.* 2004;98(2):1252-9.
- Jawaid M, Mushtaq A, Mukhtar S, Khan Z. Preoperative anxiety before elective surgery. *Neuroscienc.* 2007;12(2):145-8.
- Millan JV, Serrano JRB, Aguirre JMO. Anxiety in preoperative anesthetic procedure. *Cir Cir.* 2010:147-51.
- Arnold PD, Holtby HM, Andropulous DB. Anesthesia for the cardiac catheterization laboratory. Dalam: Andropulous DB, Stayer S, Rusel I, Mossad E, Penyunting. *Anesthesia for CHD.* Penyunting. Chichester: Blackwell Publishing; 2010.p.521-45.
- Diaz LK. Anesthesia for noncardiac surgery and magnetic resonance imaging. Dalam: Andropulous DB, Stayer S, Rusel I, Mossad E, Penyunting. *Anesthesia for CHD.* Edisi ke-2. Chichester: Blackwell Publishing; 2010. p.546-82.
- Wright KD, Stewart SH, Finley GA, Buffet-Jerrott SE. Prevention and intervention strategies to alleviate preoperative anxiety in children. *Behav Modif.* 2007; 31(1):52-79.
- Silva MMd, Schoen-Ferreira TH, Diogenes MSB, Carvalho AC. Behaviour problems in adolescents with cardiac disease: an exploratory study in a pediatric cardiology outpatient clinic. *Cardiol young.* 2011:1-9.
- Hakim MA, Supriyadi, Yuniarti KW. The contents of Indonesia child-parent attachment: Indigenous and cultural analysis. *ISSBD.* 2012;2(62):11-5.
- Hannallah RS, Rosales JK. Experience with parents presence during anaesthesia induction in children. *Can Anaesth Soc J.* 1983;30(3):286-9.
- Wright KD, Eisner A, Stewart SH, Finley GA. Measurement of preoperative anxiety in young children: Self-report versus observer-rated. *J Psychopath Behav Ass.* 2010;32:416-27.

24. Kain Z, Mayes LC, Cicchetti DV, Caramico LA, Spieker M, Nygren MM, et al. Measurement tool for preoperative anxiety in children: the Yale Preoperative Anxiety Scale. *Child Neuropsychol.* 1995;1:203-10.
25. Kain Z, Mayes LC, Cicchetti DV, A B, Finley J, Hofstadter MB. The Yale Preoperative Anxiety Scale: How does it compare to a gold standard ? *Anesth analg.* 1997;85:783-8.
26. Proczkowska-Bjorklund M, Berglund G, Ericsson E. Reliability and validity of the Swedish version of the Modified Yale Preoperative Anxiety Scale. *Acta Anaesth Scan.* 2012;56:491-7.
27. Sastroasmoro S, Ismael S. Dasar-dasar metodologi penelitian klinis. Edisi ke-3. Jakarta: Sagung Seto; 2008.
28. Dahlan MS. Besar sampel dan cara pengambilan sampel. Edisi ke-2. Jakarta: Salemba Medika; 2009.
29. Dahlan MS. Statistik Untuk Kedokteran dan Kesehatan. Edisi ke-4. Jakarta: Salemba Medika; 2009.
30. Soenarto RF, Kapuangan C. Premedikasi. Dalam: Soenarto RF, Chandra S, Penyunting. Buku ajar anestesiologi. Jakarta: Departemen Anestesiologi dan Terapi Intensif FKUI-RSCM, 2012. p.197-205.
31. Ramlan AAW. Anestesia Pediatrik. Dalam: Soenarto RF, Chandra S, Penyunting. Buku ajar anestesiologi. Jakarta: Departemen Anestesiologi dan Terapi Intensif; 2012.p.375-96.
32. Marelli AJ, Mackie AS, Ionescu-Iltu R, Rahme E, Pilote L. CHD in the general population: changing prevalence and age distribution. *Cir Cir.* 2007;115:163-72.
33. Ong L, Nolan RP, Irvine J. Parental overprotection and heart-focused anxiety with CHD. *Int J Behav Med.* 2011;18: 260-7.
34. Proczkowska-Bjorklund M. The process of anaesthetic induction with children. Linkoping: Linkoping University; 2009.p.1-53.
35. Ahmed MI, Farrell MA, Parrish K, Karla A. Preoperative anxiety in children risk factors and non-pharmacological management. *MEJ Anesth.* 2011; 21:153-70.
36. Finley GA, Stewart SH, Buffett-Jerrot S, Wright KD, Millington D. High levels of impulsivity may contraindicate midazolam premedication in children. *Can J Anesth.* 2006; 53(1):73-8.
37. Shin YH, Kim MH, Lee JJ, Choi SJ, Gwak MS, Lee AR, et al. The effect of midazolam dose and age on the paradoxical midazolam reaction in Korean pediatric patients. *Korean J Anesthesiol.* 2013;65(1):9-13.