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Original Article

Estimating BIS50 and BIS95 for lack of recall of music during recovery from sevoflurane balanced endotracheal anesthesia

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Abstract: Background: Studies concerning BIS levels and the probability of recall during endotracheal anesthesia are rare, since it would be harmful to patients if the depth of anesthesia was intentionally lightened. Present authors estimated BIS50 and BIS95 for lack of recall of music during recovery from sevoflurane balanced endotracheal anesthesia. Methods: This prospective cohort study was performed to estimate BIS50 and BIS95 for lack of recall of music during recovery from sevoflurane balanced anesthesia. Randomly selected songs were applied to the participants at different levels of BIS at PACU. This sequential trial consisted of two stages. In the first stage, pro-bit analysis of the up-and-down sequential portion of the study was used to estimate BIS50. In the second stage, the continual reassessment method was used to estimate BIS95. Results: A total of 69 patients completed the trial (n = 29 for the first stage and n = 40 for the second stage). BIS50 (95% CI) for lack of recall of music was estimated to be 84 (80.9-87.6), while BIS95 (95% CI) was estimated to be 79 (95% CI, 78.8-79.1). Conclusion: The current study revealed that BIS50 and BIS95 results, for lack of recall of music during recovery from endotracheal sevoflurane balanced anesthesia, were 84 and 79, respectively. This study also illustrates the value of CRM in BIS95-finding trials.

Keywords: Anesthesia, endotracheal, anesthesia recovery period, intraoperative awareness, prevention, and control, monitoring, bi-spectral index, music

Introduction

Recall of awareness is the postoperative recollection of events occurring during general anesthesia. Patients experiencing this find it to be a terrible experience. Some go on to develop post-traumatic stress disorder [1]. It has been established that BIS is closely correlated with the concentration of anesthetics and hypnotic state [2-4]. Many studies have indicated that BIS-guided anesthesia reduces the risk of awareness in patients undergoing endotracheal general anesthesia [5, 6]. Most studies about the relationship between BIS levels and probability of recall studies have been performed on volunteers under intravenous sedation or patients under regional anesthesia, combined with intravenous sedation [3, 4, 7, 8]. BIS levels between 40 and 60 are considered suitable for surgical anesthesia, ensuring no awareness [9]. However, some patients had no response to doctor's orders when the BIS index increased to over 70 or 80 during recovery from sevoflurane balanced endotracheal anesthesia. The BIS level when patients begin to receive auditory messages and form memory before being wide awake remains unknown. To evaluate this vulnerable BIS level, the current study tested music recall on clinical patients during recovery from endotracheal anesthesia.

The up-and-down study design method has been widely applied to determine doses or concentrations to produce an effect in half of the subjects [10, 11]. This approach is suitable for estimating ED50, but not ED95, which has more clinical importance. The continual reassessment method (CRM) is an approach to the design and analysis of Phase 1 clinical trials for cancer treatments [12]. Recently, several studies have reported the use of CRM for ED95 dose-finding in regional block [13-15]. The cur-

rent study conducted a trial using the up-and-down method and CRM to estimate the BIS50 and BIS95 for lack of recall of music in PACU.

Materials and methods

Recruitment

This prospective cohort study was conducted at a tertiary hospital with more than 30,000 patients, under general anesthesia, admitted for elective surgery per year. This study was registered on July 23, 2017, in the Chinese Clinical Trial Registry (ID: ChiCTR-OPN-170 12097). The registration information can be found on the following website: http://www.chictr.org.cn/showproj.aspx?proj=20262. The Ethics Committee of the First Hospital of Jilin University, Changchun, China, approved the study on June 30, 2017 (Approval No. of Ethics Committee: AF-IRB-032-04). Written informed consent was obtained from all patients prior to enrollment. Patients were told that they would be provided with headphones to listen to music during recovery. Between July 26, 2017, and October 21, 2017, a total of 76 subjects, American Society of Anesthesiologists (ASA) stage I-II patients aged between 18 and 64 years, undergoing abdominal surgery with muscle relaxant endotracheal anesthesia, were referred by the anesthesiologist for initial screening. Patients with impaired cognition, auditory acuity, history of brain surgery, or history of strokes were excluded from the study.

General anesthesia protocol

All patients received general anesthesia with tracheal intubation. Anesthesia was induced with fentanyl 2 μg/kg, propofol 1-2 mg/kg, and cisatracurium 0.15 mg/kg. it was maintained with propofol 5-12 mg/kg/h and inhalation of sevoflurane 1.5-3%, remifentanil 0.25-4 μg/kg/min, and cisatracurium 3 μg/kg/min. After surgery, fentanyl 2 μg/kg and paracetamol 1 g were given.

Perioperative monitoring included ECG, pulse oximetry, blood pressure, capnography, and BIS index (BIS VISTATM, Covidien Company, US). Depth of sedation was adjusted according to BIS number (40-60) during the operation. When surgical procedures were completed, all intravenous infusion of anesthetics and sevoflurane inhalation were discontinued. The patients were transferred to PACU. During the 1-2 minutes of the PACU transferring process, ventilation was maintained through a bag respirator. ECG, pulse oximetry, and blood pressure were monitored by portable monitors. Upon arrival at the PACU, mechanical ventilation was resumed. ECG, BIS index pulse oximetry, and blood pressure were again monitored.

Music intervention protocol

Blinding: The first investigator (Dr. Teng) provided a randomly chosen song track (1 from 6) to the patients via headphones. Songs were selected from the most well-known fragments of theme music of Chinese Four Great Classical Novels and the Chinese National Anthem. These are well known by almost every adult in China. Music was initiated upon arrival at PACU and stopped when BIS reached the target value. Another investigator, Dr. Wang, blinded to the BIS level, administered questionnaire surveys at 10 minutes after extubation.

Recall of music assessment

Patients were queried 10 minutes after extubation.

Questions included: What was the last thing you remember before going to sleep? What was the first thing you remember when you woke up? Can you recall anything between? Did you dream while you were asleep? Did you hear any music while you were asleep? If yes, could you recall the name or melody of the song? The following two kinds of results were considered indicative that patients had remembered the music. One, the patient reported that he or she had heard music and could recall the name or melody. Two, the patient reported that he or she had heard music but could not recall the name or melody. However, they could select the correct song from the six randomly played tracks.

BIS level allocation

The study was divided into two stages, as shown in **Figure 1**.

Stage 1. The first stage was used to determine the BIS50 and a priori probabilities of lack of recall of 0.5, 0.75, 0.90, 0.95, 0.98, and 0.99, respectively, using the up-and-down method and pro-bit regression. The patients were set to hear a piece of popular music (1 through 6)

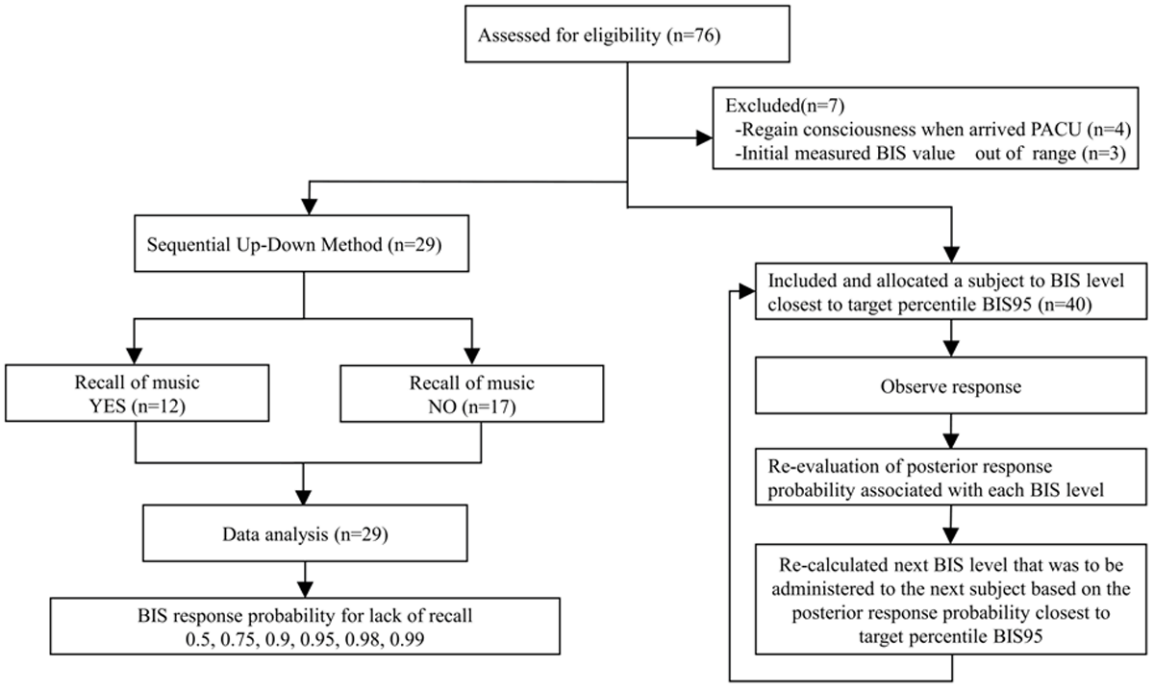

Figure 1. Schematic representation of the up-and-down and CRM design.

through headphones at different BIS intervals. The melody was randomly played within a specified BIS interval. The initial BIS level during which music was played was ≤65.

The next target BIS level for the cessation of music was selected using results from the previous patient. If that person remembered hearing music or if the patient regained consciousness and was extubated before the BIS value reached the target value, the target BIS value at which he or she ceased hearing music was decreased by 5 for the next patient. If the previous patient did not remember the music, then the next target BIS level was increased by 5.

Stopping rules: Establishing stopping rules required the recruitment of more than 20 patients, with at least six turning points in the same direction of the sequential allocation response graph [16].

Stage 2. The second stage of the study was to find a more precise BIS95 to prevent the recall of music during recovery from general anesthesia. The continual reassessment method was employed.

This study set out to recruit 40 patients, aiming to obtain a reliable estimate of the BIS95 for lack of recall of music. The starting BIS level was predetermined using a priori estimates based on results from Stage 1. Subsequent BIS levels were allocated based on the CRM. Results for each cohort were, in turn, conveyed to one of the researchers (Dr. Teng). He used the BCRM package in R software to estimate the target BIS value in the next cohort of patients.

Statistical analysis

Personal and surgical data are presented as medians (interquartile and range) or percentages. The BIS50 for lack of recall of music and a priori probabilities of lack of recall of 0.5, 0.75, 0.90, 0.95, 0.98, and 0.99 were estimated through pro-bit analysis from data from the up-and-down method. The ED95 dose was defined as the 5th percentile of the dose-failure relationship [14]. This study defined BIS95 for lack of recall as the recall probability closest to the 0.05 target. Moreover, this study chose k = 6 BIS levels, while corresponding recall probabilities were 0.5, 0.25, 0.10, 0.05, 0.02, and 0.01. The CRM was set up to assign new BIS levels after each cohort of two subjects. Accurate methods were used to estimate the quantiles of posterior distribution. The first cohort was administered the BIS level correspo-

Table 1. Characteristics of patients (n, number; SD, standard deviation)

Variable	Total number of patients n = 69
Age (y) [mean (range)]	46.74 (20-64)
Gender, male [n (%)]	33 (48)
Wt (kg) [mean (SD)]	63.5 (11.8)
Height (m) [mean (SD)]	1.65 (0.08)
Duration of anesthesia (min) [mean (SD)]	82.4 (37.3)
Duration of surgery (min) [mean (SD)]	59.3 (30.8)
Duration of music (min) [mean (SD)]	12.8 (5.7)

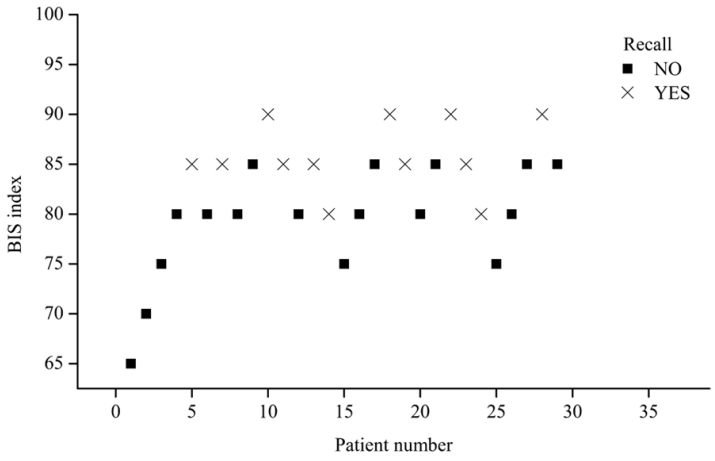

Figure 2. Sequential allocation graph to show the series of recall and lack of recall in the up-and-down study.

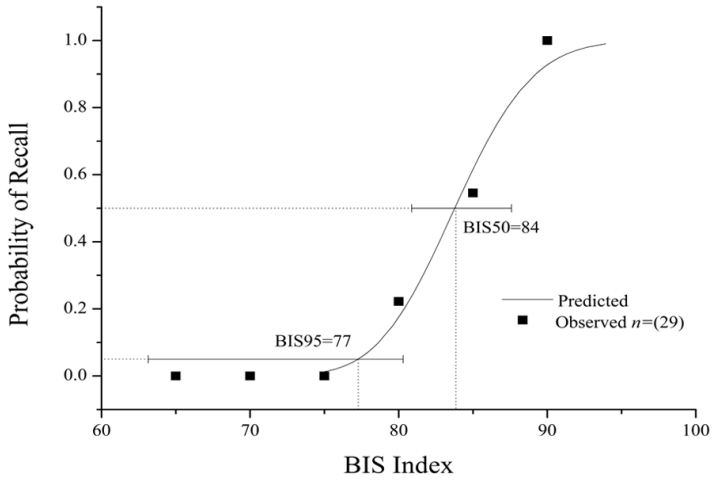

Figure 3. Pro-bit regression of the probability of recall of music and BIS index. Horizontal bars denote 95% CI for BIS50 and BIS95.

nding to the best guess of the BIS95. This was based on the first stage of the study. For each further cohort of two, the probabilities were re-estimated with an updated recall probability closest to the 0.05 target, chosen as the current BIS95. The CRM continued until the planned number of 40 subjects was reached or the estimated probability of response was either too low or too high for all dose levels [17]. BIS-finding allocation was performed using the BCRM package (http://www.jstatsoft.org/v54/i13/) of the R software version 3.3.3 (R CRAN, Vienna, Austria). Other data, including sex, age, weight, height, duration of anesthesia, duration of surgery, and duration of music, were analyzed using SPSS 22 for Windows (SPSS Inc., US).

Results

A total of 76 patients were enrolled in the study. Seven patients were excluded (four patients were excluded because they regained consciousness upon arrival at the PACU and three because the initial measured BIS index was outside the target range) (**Figure 1**). A total of 69 patients were recruited and completed the study, including 29 patients in the up and down study and 40 in the CRM study. Personal and surgical characteristics of the patients recruited for the study are shown in **Table 1**.

During the up-and-down portion of the trial, 12 patients experienced recall while 17 did not. **Figure 2** shows the sequence of recall and lack of recall. Using pro-bit regression (**Figure 3**), the BIS50 (95% CI) was 84 (80.9-87.6). Probabilities of lack of recall of music were 99%, 98%, 95%, 90%, 75%, and 50% for BIS index values of 75, 76, 77, 79, 81, and 84, respectively (**Table 2**).

During the CRM stage, 40 patients were recruited. There was recall in 3 patients and no recall in 37 patients. At the end of the trial, the actualized probabilities of lack of recall of music associated with each BIS

Table 2. Dose-response data for BIS index and recall of music with pro-bit regression in the up-and-down study

Parameter	Recall probability	BIS index	Lower 95% confidence interval	Upper 95% confidence interval
BIS 95	.01	74.7	56.2	78.6
	.02	75.7	58.9	79.3
	.05	77.3	63.1	80.3
	.10	78.6	67.2	81.3
	.25	81.0	74.2	83.3
BIS 50	.50	83.8	80.9	87.6

Table 3. Posterior estimated BIS-response curve for lack of recall of music in CRM study

BIS index			75	76	77	79	81	84
Working model for lack of recall			0.99	0.98	0.95	0.90	0.75	0.5
COHORT	BIS	RESPONSE	Updated Estimated Probability of Response					
1	77	0,0	1.00	1.00	0.98	0.96	0.86	0.62
2	79	0,0	1.00	1.00	0.99	0.98	0.90	0.68
3	79	0,0	1.00	1.00	1.00	0.98	0.92	0.71
4	81	0,1	1.00	0.99	0.97	0.93	0.80	0.55
5	79	0,0	1.00	0.99	0.98	0.94	0.82	0.58
6	79	0,0	1.00	0.99	0.98	0.95	0.84	0.60
7	79	0,0	1.00	1.00	0.98	0.96	0.86	0.62
8	79	0,0	1.00	1.00	0.99	0.96	0.87	0.64
9	79	0,0	1.00	1.00	0.99	0.97	0.88	0.65
10	79	0,0	1.00	1.00	0.99	0.97	0.88	0.66
11	79	0,0	1.00	1.00	0.99	0.97	0.89	0.67
12	79	0,1	1.00	0.99	0.97	0.94	0.81	0.56
13	79	0,0	1.00	0.99	0.98	0.94	0.82	0.58
14	79	0,0	1.00	0.99	0.98	0.95	0.83	0.58
15	79	0,0	1.00	0.99	0.98	0.95	0.83	0.59
16	79	0,0	1.00	0.99	0.98	0.95	0.84	0.60
17	79	0,0	1.00	0.99	0.98	0.96	0.85	0.61
18	79	0,0	1.00	1.00	0.98	0.96	0.85	0.61
19	79	0,1	1.00	0.99	0.97	0.93	0.81	0.56
20	79	0,0	1.00	0.99	0.97	0.94	0.81	0.57

Bold includes the estimated BIS95 after the inclusion of each cohort. esponse = 0 means no recall; response = 1 means recall.

index 75, 76, 77, 79, 81, and 84, were 100%, 99%, 97%, 94%, 81%, and 57%, respectively (**Table 3**). The response probability associated with BIS index 79 was 94% (95% credibility interval: 83-98%). The probability associated with BIS index 76 was 99% (95% credibility interval: 95-100%). It seems that the BIS index associated with a 95% response lies between BIS index values 79 and 76. Based on these data, the BIS level closest to the BIS95 was estimated to be 79 (95% CI, 78.8-79.1).

Discussion

This study found that patients were able to gain auditory recall when the BIS level was above 79, during recovery from sevoflurane balanced endotracheal anesthesia. A BIS index below 79 ensured lack of recall of music closest to the response probability of 0.95 (BIS95), giving the patient a probability of 0.50 (BIS50) of remembering music played when the BIS index increased to 84.

It is difficult to investigate the relationship between BIS levels and the probability of recall during endotracheal anesthesia. It can be harmful to patients if the depth of anesthesia is intentionally lightened. It is neither palatable to patients nor consistent with ethical standards. For this reason, previous studies have mainly focused on observations from volunteers under intravenous sedation or patients under regional anesthesia, combined with intravenous sedation [3, 4, 8]. However, the situation differed from volunteers under intravenous sedation and clinical anesthesia as to whether tracheal intubation was applied. Explicit recall occurs mainly in patients given general anesthesia with a laryngeal mask airway, tracheal intubation, or jet ventilation [18]. Thus, the current study investigated auditory recall in patients during recovery from endotracheal anesthesia. Furthermore, this method is more palatable to patients. Listening to music would be harmless, increasing satisfaction and improving the experience [19, 20].

Table 4. Comparison of the BIS95 and 95% CI to that of previous studies

BIS95 (95% CI)	Anesthesia intervention	Participants	Statistical method	Reports
42 (13-71)	Isoflurane	Volunteers	Covariance matrix of logistic regression	Glass 1997 [7]
68 (59-78)	Midazolam	Volunteers		
77 (72-83)	Propofol	Volunteers		
64 (57-71)	Combined	Volunteers		
79 (70-88)	Propofol	Volunteers	Covariance matrix of logistic regression	Iselin 1998 [8]
67 (51-83)	Propofol and alfentanil	Volunteers		
77 (63.1-80.30)	Intravenous-inhalation combined anesthesia	Patients under endotracheal anesthesia	In stage 1 of the study (up-and-down part), using pro-bit analysis to estimate BIS 95	Stage 1 of our study
79 (78.8-79.1)	Intravenous-inhalation combined anesthesia	Patients under endotracheal anesthesia	Continual Reassessment Method	Stage 2 of our study

Dixon's up-and-down method [21] was established in 1948. It has become widely used in anesthetic dose identification studies [10, 11, 22, 23]. This method may be used to provide an accurate estimate of the ED50. However, it is not suitable for estimating ED95, which has more value in clinical practice [24]. Up-and-down methods are concentrated in the 16-84% response range of the dose-response curve. ED95 estimated by up-and-down methods have larger credibility intervals [13]. The continual reassessment method was first proposed in 1990 [12]. It has been widely applied for ED95 dose-finding in oncology trials [25, 26]. Recently, some anesthesiologists have used the CRM in anesthesia dose-finding studies [13-15, 27, 28]. The current study found the CRM to be a convenient and efficient way to estimate BIS95. The credibility interval of BIS95, estimated by CRM in this study, is more precise than estimating BIS95 using pro-bit analysis. This was performed in stage 1 of the present up-and-down study and previous studies [7, 8] (**Table 4**).

It has been reported that awareness occurring during the recovery period is around 18% of total awareness cases [29]. The current study demonstrated that the patient might be vulnerable to receive auditory message and gain recall when the BIS index was over 79. Effort should be made to make the auditory circumstance around the patients contain informative and conciliative words instead of noisy or misguided words, ensuring a safe feeling and a good experience when recovering from sevoflurane balanced endotracheal anesthesia, especially when BIS index is over 79. This result might also have some implications for sedative management of patients under mechanical ventilation in intensive care units.

There were some limitations to the present study, however. 1) Sedation was not controlled during recovery and the BIS index increased rapidly in a few patients. Proper methods should be applied to slow down increasing rates of BIS in further studies; 2) Awareness contains both auditory and somatosensory phases. However, this study merely investigated auditory recall. Thus, the results might be partial. Additional indicators should be included in future studies.

Conclusion

In conclusion, the present study investigated the relationship between BIS levels and probability of lack of recall of music during recovery from endotracheal anesthesia. This study found the BIS95 of lack of recall to be 79 and the BIS50 to be 84. BIS of more than 79 indicates that the patient might be vulnerable to receive auditory message and gain recall. This study suggests that the CRM might be a suitable method for studying BIS95.

Disclosure of conflict of interest

None.

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References

[1] Moerman N, Bonke B, Oosting J. Awareness and recall during general anesthesia. Facts and feelings. Anesthesiology 1993; 79: 454-64.

[2] Leslie K, Sessler DI, Schroeder M, Walters K. Propofol blood concentration and the Bispec-

tral Index predict suppression of learning during propofol/epidural anesthesia in volunteers. Anesthesia Analg 1995; 81: 1269-74.
[3] Liu J, Singh H, White PF. Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. Anesthesiology 1996; 84: 64-69.
[4] Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anesth Analg 1997; 84: 185-9.
[5] Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004; 363: 1757-1763.
[6] Mathews DM, Rahman SS, Cirullo PM, Malik RJ. Increases in bispectral index lead to interventions that prevent possible intraoperative awareness. Br J Anaesth 2005; 95: 193-6.
[7] Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 1997; 86: 836-47.
[8] Iselin-Chaves IA, Flaishon R, Sebel PS, Howell S, Gan TJ, Sigl J, Ginsberg B, Glass PS. The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the Bispectral Index. Anesth Analg 1998; 87: 949-55.
[9] Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, Manberg P. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology 1997; 87: 808-15.
[10] Beale N, Evans B, Plaat F, Columb MO, Lyons G, Stocks GM. Effect of epidural volume extension on dose requirement of intrathecal hyperbaric bupivacaine at caesarean section. Br J Anaesth 2005; 95: 500-3.
[11] Gupta PK, Pace NL, Hopkins PM. Effect of body mass index on the ED50 volume of bupivacaine 0.5% for supraclavicular brachial plexus block. Br J Anaesth 2010; 104: 490-5.
[12] O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics 1990; 46: 33-48.
[13] Gupta PK, Chevret S, Zohar S, Hopkins PM. What is the ED95 of prilocaine for femoral nerve block using ultrasound? Br J Anaesth 2013; 110: 831-6.
[14] Kant A, Gupta PK, Zohar S, Chevret S, Hopkins PM. Application of the continual reassessment method to dose-finding studies in regional anesthesia: an estimate of the ED95 dose for 0.5% bupivacaine for ultrasound-guided supraclavicular block. Anesthesiology 2013; 119: 29-35.
[15] Jaeger P, Jenstrup MT, Lund J, Siersma V, Brondum V, Hilsted KL, Dahl JB. Optimal volume of local anaesthetic for adductor canal block: using the continual reassessment method to estimate ED95. Br J Anaesth 2015; 115: 920-6.
[16] Dixon WJ. Staircase bioassay: the up-and-down method. Neurosci Biobehav Rev 1991; 15: 47-50.
[17] Zohar S, Chevret S. The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies. Stat Med 2001; 20: 2827-43.
[18] Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. Lancet 2000; 355: 707-711.
[19] Easter B, DeBoer L, Settlemyre G, Starnes C, Marlowe V, Tart RC. The impact of music on the PACU patient's perception of discomfort. J Perianesth Nurs 2010; 25: 79-87.
[20] Heitz L, Symreng T, Scamman FL. Effect of music therapy in the postanesthesia care unit: a nursing intervention. J Post Anesth Nurs 1992; 7: 22-31.
[21] Dixon WJ, Mood AM. A Method for Obtaining and Analyzing Sensitivity Data. Publications of the American Statistical Association 1948; 43: 109-126.
[22] Davidson AJ, Wong A, Knottenbelt G, Sheppard S, Donath S, Frawley G. MAC-awake of sevoflurane in children. Paediatr Anaesth 2008; 18: 702-7.
[23] Frawley G, Skinner A, Thomas J, Smith S, Ropivacaine spinal anesthesia in neonates: a dose range finding study. Paediatr Anaesth 2007; 17: 126-32.
[24] Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a precis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology 2007; 107: 144-52.
[25] Saji S, Toi M, Morita S, Iwata H, Ito Y, Ohno S, Kobayashi T, Hozumi Y, Sakamoto J. Dose-finding phase I and pharmacokinetic study of capecitabine (Xeloda) in combination with epirubicin and cyclophosphamide (CEX) in patients with inoperable or metastatic breast cancer. Oncology 2007; 72: 330-7.
[26] Peereboom DM, Supko JG, Carson KA, Batchelor T, Phuphanich S, Lesser G, Mikkelsen T, Fisher J, Desideri S, He X, Grossman SA; New Approaches to Brain Tumor Therapy (NABTT) Consortium. A phase I/II trial and pharmacoki-

netic study of ixabepilone in adult patients with recurrent high-grade gliomas. J Neurooncol 2010; 100: 261-8.
[27] Treluyer JM, Zohar S, Rey E, Hubert P, Iserin F, Jugie M, Lenclen R, Chevret S, Pons G. Minimum effective dose of midazolam for sedation of mechanically ventilated neonates. J Clin Pharm Ther 2005; 30: 479-85.
[28] Zeidan A, Mazoit JX. Minimal alveolar concentration of sevoflurane for maintaining bispectral index below 50 in morbidly obese patients. Acta Anaesthesiol Scand 2013; 57: 474-9.
[29] Pandit JJ, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N, Mackay JH, Nimmo AF, O'Connor K, O'Sullivan EP, Paul RG, Palmer J, Plaat F, Radcliffe JJ, Sury MR, Torevell HE, Wang M, Hainsworth J, Cook TM; Royal College of Anaesthetists; Association of Anaesthetists of Great Britain and Ireland. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth 2014; 113: 549-559.