PERIODICUM BIOLOGORUM
VOL. 113, No 2, 181–185, 2011

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Original scientific paper/new guidelines

Comparison of needed end-tidal concentration of sevoflurane in children with balanced intravenous intraoperative analgesia versus epidural caudal intraoperative analgesia: prospective randomized trial

[1]MILENA KREMESEC
[1]ŠPELA ŠTUPNIK
[1]MENSUR SALIHOVIĆ
[2]STELA MARIĆ
[1]VESNA NOVAK JANKOVIČ
[1]VESNA PAVER ERŽEN

[1]University Medical Centre Ljubljana, Department of Anaesthesiology and Intensive Therapy, Ljubljana, Slovenia

[2]University Hospital Center »Sestre milosrdnice« Clinic for tumors, Department of Anaesthesiology, Zagreb, Croatia

Correspondence:
Milena Kremesec
Department of Anaesthesiology and Intensive Therapy, University Medical Centre Ljubljana, Ljubljana, Slovenia
E-mail: milena.kremesec@gmail.com

Key words: epidural caudal anaesthesia, sedative effects, sevoflurane, alfentanil, BIS, children

Received March 16, 2011.

Abstract

Background and Purpose: *It was already shown that neuroaxial anaesthesia has sedative effects. The scope of our study was to find out whether the combined caudal epidural block with 0.19% bupivacaine decreases the sevoflurane requirement because of its synergistic hypnotic effect in comparison to balanced anaesthesia with intravenous alfentanil and sevoflurane in children.*

Materials and Methods: *Forty boys aged 1–7 years were included in the study; they were undergoing elective orchidopexy. Children were randomized in two groups: A (caudal block) and B (IV analgesia with opioid). Each child in group A received a caudal epidural block in a dosage of 0.19% bupivacaine 2.5 mg/kg. In group B the loading dose of alfentanil was 20 μg/kg, followed by intermittent doses of 10–20 μg/kg. Anaesthesia hypnosis was controlled by the clinical parameters and by the Bispectral Index monitor (BIS). We measured end-tidal sevoflurane concentration (sevoE) at 5-minute intervals. The aim was to maintain the BIS values near 50 through increments or decrements in sevoflurane concentration.*

Results and Conclusion: *No difference in end-tidal sevoflurane concentration (sevoE) values was observed between the two groups. We do suppose that due to the low level of caudal block we could not confirm synergism between caudal epidural block with local anaesthetic and sevoflurane.*

INTRODUCTION

For more than 20 years it has been common practice to combine epidural analgesia with general inhalational anaesthesia in children, whenever the patient's conditions and surgical procedure as well as anaesthetist's skills are suitable for epidural blocks or a continuous infusion of local anaesthetic. Local anesthetics applied on nerve cause a reversible but complete block of pain transmission, and the deafferentation has been developed at the neuroaxial use *(1, 2)*. This could reduce the inhalation anaesthetics requirement, needed to suppress somatic movements in response to surgery, as well as the cardiovascular response to painful surgical stimulations. Some authors demonstrated that neuroaxial blocades have also direct sedative effects *(2, 3, 4, 5, 6)*.

The anaesthesia hypnosis has to be deep enough to prevent pharyngeal and laryngeal reflexes caused by the inserted laryngeal mask (or endotracheal tube) and to prevent awareness throughout the surgical procedure *(7, 8, 9)*.

The aim of our study was to determine if epidural caudal bupivacaine decreases the sevoflurane requirement in comparison to balanced anaesthesia using sevoflurane and alfentanil. Adequate anaesthesia hypnosis was measured by the BIS and by the clinical parameters.

PATIENTS AND METHODS

This parallel randomized study was approved by the local ethics committee, and informed consent in writing was obtained from children's parents from 1–7 years of age and up to 20 kg in body weight. The children included in the study were rated in American Society of Anaesthesiologists (ASA) physical status I, and were undergoing elective orchidopexy. Children were randomized in two groups, planning 20 children in each group: A (caudal block) and B (IV analgesia with opioid). We processed a simple randomization with paper sheets numbered from 1 to 40, and put them in a box. Patients with even numbers were allocated into group A, and those with odd numbers into group B. The sheets were put in custody of the matron in the Pediatric Department and subsequently used for the scheduled purposes.

The exclusion criteria have been applied to children with known allergies and/or local skin lesions or infection in the sacrococcygeal area. We also explained verbally all procedures to the parents in the presence of their child *(10, 11)*. Elective orchidopexy procedures were performed at the Children Surgery Department of the University Medical Centre Ljubljana. The same team carried our surgical operations as well as anaesthesia.

All boys were premedicated orally with midazolam in a dosage of 0.4 mg/kg body weight. Before the induction of anaesthesia, ECG electrodes, a cuff for noninvasive blood pressure, and a sensor for pulse oximetry were applied. Inhalation induction of anaesthesia with sevoflurane via facial mask, connected to the breathing system of the »Cato« respirator Draeger, was performed with sevoflurane in 50% oxygen/N_2O gas mixtures. Sevoflurane was increased gradually to 7% by using the step by step method.

After loss of consciousness, IV access was obtained, the laryngeal mask airway (LMA Classic^{TM} Laryngeal Mask Company Limited, Seychelles) was inserted and the sevoflurane concentration was decreased to 4% in group A and to 2% in group B; after LM insertion, frontotemporal children's BIS Quattro electrodes (Aspect Medical System A-2000^{TM}, Newton, USA) were applied, according to the written instructions for the procedure, and connected to the BIS$_{TM}$ monitor (XP Aspect Medical System, Newton, MA, USA) with integrated software for children. Manual ventilation was performed at higher concentrations of sevoflurane in induction, as well as after the LMA insertion. Each child in group A received on its left side position a caudal epidural block in a dose of 2.5 mg/kg as diluted concentration of 0.19% of bupivacaine; after the blocade the sevoflurane concentration was decreased to 2%. Surgical incision started 15 minutes after the caudal blockade, and analgesia was checked via puncture with an intradermal needle at the Th 12 level. In the group B the loading dose of alfentanil was 20 μg/kg (3–5 minutes before surgical skin incision) followed by intermittent doses of 10–20 μg/kg, as needed, regarding all clinical parameters that we measured. In both groups, anaesthesia was maintained with a mixture of 50% oxygen/N_2O and sevoflurane. All children received an infusion of 0.9% saline solution (3 mL/kg/h).

The following values were measured continuously in 5-minute intervals: heart rate, systolic-, diastolic- and mean arterial pressure; pulsoxymetrie (Draeger oxymeter), end-tidal carbondioxyde (Draeger Capnograph), as well as concentration of inhalation anaesthetic (Draeger gas detectors) were performed. In 5-minute intervals we also monitored BIS values, and for calculation purposes of statistical values we considered the highest and the lowest value per interval. We tried to maintain the BIS values near 50 through increments or decrements (up and down method) in sevoflurane concentration.

For the expected effect size in sevoE $\theta = -0.5$ with 80% power of the test and significance level of $\alpha = 0.05$ 16 patients per group are required with the assumption that the data will be approximately normally distributed with standard deviation (SD) of $\sigma = 0.5$. We included 20 patients per each group (n=20).

Values are expressed as the mean ± SD or as mediana with interquartile range.

With exploratory data analysis we used graphical plots and Shapiro-Wilk test to confirm normal distribution.

Continuous variables were compared using Student t-test for normally distributed variables and the Mann--Withney test for non-normally distributed variables.

Ten intervals were used to bridge the differences between time length for each operation (D_i, 1.10).

To determine the effect of the sevoE on one subject and compared to among all subjects, we used Repeated Measures Analysis of Variance, using the Greenhouse--Geisser correction.

Pearson test was used to determine correlation between sevoE and age and BISmax.

p values ≤0.05 were considered to indicate statistical significance.

All analyses were compared using SPSS 14.0.

RESULTS

The groups were well balanced for age, body weight, time of operation procedures (Table 1). In group A there were 16 children of 1 to 3 years of age, and in group B 13.

TABLE 1

Patient characteristics, time of operation, end-tidal sevoflurane concentration (sevoe), heart rate (hr), mean arterial pressure (map), bis min and bis max.

	Group A (n=20)	Group B (n=20)	P
age (months)	23 (17–36)	31 (21–44)	0.176
Body weight (kg)	14 ± 3	15 ± 3	0.36
Time of operation (min)	55 ± 19	51 ± 18	0.415
sevoE (% vol.)	2.2 ± 0.5	2.3 ± 0.5	0.694
HR (beats/min)	114 ± 16	125 ± 17	0.047
MAP (mmHg)	59 (55–64)	67 (63–71)	0.003
BIS min	49 ± 5	47 ± 6	0.251
BISmax	56 ± 5	54 ± 5	0.260

n = number of patients, Values of variables are shown as average ± SD or the median (interquartile range), Probability level of <0.05 was considered as significant

Mean (SD) of concentration of end-tidal sevoflurane was 2.2 ± 0.5 in the caudal block group; and 2.3 ± 0.5 in the intravenous opioid analgesia group (p=0.7).

In both groups we found a statistically significant negative correlation between end-tidal sevoflurane concentrations and age of children (p<0.001).

We found no significant correlation between end-tidal sevoflurane concentration and the highest values of BIS, nor with sevoE and heart rate.

In group A, contrary to group B, we found a statistically significant negative correlation between end-tidal sevoflurane concentration and mean arterial blood pressure (MAP) (p=0.02).

We found a negative correlation between BIS values and the age of the children, statistically significant only in group A; higher BIS values of younger children with higher sevoE concentration.

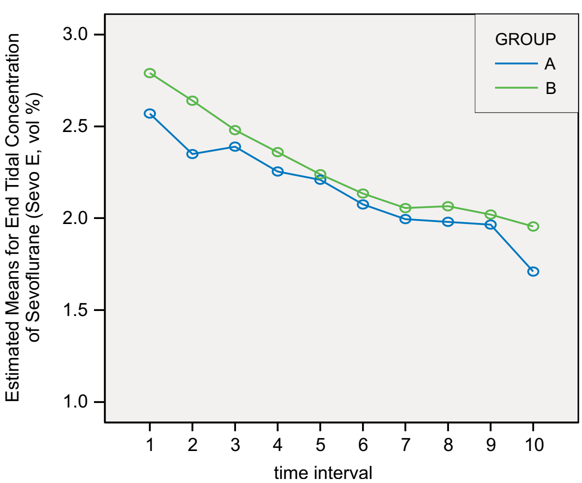

Figure 1. *Estimated means for End tidal concentration of sevoflurane in each time interval: groups A and B. Sevo E values were significantly different within subject during time interval in both groups (F(3.299, 342)=7.67, p<0.001) while we did not find significant changes between subjects (F(1, 38)=0.801, p=0.376).*

DISCUSSION

In this trial we could not prove that, in the observed time, the local anaesthetic given epidurally in the caudal space in boys that were undergoing elective orchidopexy had anaesthesial synergistic hypnotic effect.

Concentrations of sevoflurane in combination with caudal analgesia in group A compared to balanced anaesthesia (sevoflurane and alfentanil) in group B, considering the required adequate depth of anaesthesia controlled with usual clinical signs and measured by the BIS

TABLE 2

Correlation of end-tidal sevoflurane concentration (sevoe) considering age of children, with bis max, mean arterial pressure (map) and heart rate (hr) in groups a and b, and correlation of bis (minimal and maximal values) with age.

	group A	group B
sevoE/age		
r	–0.444	–0.293
p	<0.001	<0.001
sevoE/BISmax		
r	0.066	0.017
p	0.355	0.812
sevoE/MAP		
r	–0.162	–0.097
p	0.022	0.170
sevoE/ HR		
r	0.076	0.004
p	0.283	0.954
age/BISmin		
r	–0.467	–0.271
p	0.038	0.274
age/BISmax		
r	–0.611	–0.219
p	0.004	0.353

Correlations are expressed with Pearson test r (r), with corresponding probability (p).

monitor, were not statistically significantly lower (Table 1), despite the fact that Figure 1 shows that the mean values of the end-tidal concentration of sevoflurane at each time interval for groups A and B were higher in all time intervals in group B.

Based on the studies which proved a sedative effect of local anaesthetic given epidurally, we however expected a statistically significant lower concentration of sevoflurane with the epidural caudal block *(2, 3, 6)*.

Local anaesthetic given epidurally blocks somatic afferent impulses and should decrease the neuron firing rate in the pontine reticular system. This could lower the level of consciousness and consequently decrease the need for general anaesthetics *(2–4)*. Local anaesthetic given epidurally diffuses in cerebrospinal fluid (CSF), and because of its pulsation it is spread throughout cerebrospinal fluid compartments in both directions. Some authors raise the issue as to whether subanaesthetic concentrations of local anaesthetic could influence the electrical activity of higher neural centers and thereby decrease the measured BIS values *(2)*.

Vladic *et al*. studied the inulin distribution between various CSF compartments after its injection into the cisterna magna or lateral ventricle in dogs. After some hours the concentration of inulin increased in lumbar subarachnoid space *(12)*. This study raised a question how much time local anaesthetic needs to reach higher level of central nervous system after neuroaxial administration. In 1998 Gentili *et al*. proved that high spinal block had a synergistic effect on sedation highly dependent on the level of application of local anaesthetic *(5, 13)*. Reinoso-Barbero study which included twenty six children from 2–15 years of age found out lower concentrations of sevoflurane due to a synergistic effect of the local anaesthetic given epidurally in terms of anaesthetic hypnosis which was also controlled by BIS *(3)*.

The use of BIS monitor has been reported to have decreased the incidence of anaesthesia awareness. Awareness during anesthesia is namely a serious complication with potential long-term psychological consequences *(8, 9)*.

BIS monitor translates electroencephalographic data from forehead electrodes into a nominal scale of 0 (flat line EEG) to 100 (awake). BIS values from 40 to 60 are considered being in the range of anaesthetic hypnotic state. To prevent wakefulness in children, Davidson suggested that the BIS should be maintained even below 50 *(14)*. Most authors agree that BIS monitor is a useful tool in modern anaesthesiology for maintaining anaesthesia individually, with regard to age, sex, body weight and the complete health status of a patient, as well as the technique of anaesthesia applied *(15–17)*. Notwithstanding the above, some authors doubt about validity of BIS measurement anaesthesia hypnosis especially not only in children but also in adult population *(18–23)*. As brain maturation and synapse formation continues after birth up to 5 years of age, the validity of BIS monitor in children is therefore questionable *(18–20)*. According to some authors, BIS monitor is helpful in pediatric anaesthesia *(14, 18, 24)* but would probably need to be adapted to individual patient's age.

In our study, the correlation between the end-tidal sevoflurane concentration (sevoE) and age of children in both groups showed that this correlation is negative and statistically significant for both groups (group A $r=-0.444$, $p<0.001$; and group B $r=-0.293$, $p<0.001$) as it had been expected (Table 2).

Heart rate and blood pressure are two important clinical parameters of antinociception during anaesthesia. In our study, mean values of heart rate and blood pressure were for all time intervals statistically lower in the group with the caudal block (group A) compared to the group with intravenous analgesic (group B) ($p=0.047$; $p=0.003$), but seven children in group B got atropine after alfentanil and no child in group A (Table 1). We found a statistically significant negative correlation between the concentration of the end-tidal sevoflurane concentration (sevoE) and mean arterial blood pressure in group A ($p=0.022$) (Table 2). Regarding blood pressure and heart rate and immobility of children (movement), we could lower the concentration of inhaled sevoflurane, but the BIS values showed a tendency to go upwards, indicating a shift from a level of anaesthesia to a level of sedation, or possibly even a level of awareness *(14)*. Literature and clinical observations already showed that blood pressure and heart rate are not reliable parameters of the hypnotic state during anaesthesia *(25)*. Immobility without the use of muscle relaxants during surgery as it was the case in our study is a useful clinical parameter of adequate depth of anaesthesia *(26)*.

After applying the pediatric BIS electrodes and after the blocade respectively, we decreased the sevoflurane concentration with the aim of reaching BIS in the range of 40–60, while maintaining the clinical parameters of the depth of anaesthesia. Regulation of BIS values was difficult because of their highly volatile oscillations. After reducing the concentration of sevoflurane, BIS values in some children stayed very low and then suddenly elevated. The oscillation of BIS, measured at 5-minute intervals – with changes observed from 26–60, would show that the level of anaesthesia hypnosis changed instantly from deep stage to the upper limit of anaesthetic hypnosis. High oscillations also appeared in the phase of absence of surgical intervention and with the same concentrations of sevoflurane (while we were waiting for the surgeon). The highest oscillations were observed in the younger children. We also observed paradoxical oscillations of BIS from 70–45 with very low end-tidal concentration of sevoflurane (sevoE 0, 5–0,2%) in the phase of awakening. These observations are similar to the observations of other investigators whose opinion about validity of the use of BIS monitor as a measurement of the level of anaesthesia hypnosis in children even up to five years of age is limited *(18, 19, 27)*.

As proportions of size of the heads in children of different age can be important, perhaps there should be more different sizes of pediatric electrodes.

Probably we could not confirm synergism between the local anaesthetic and sevoflurane because of the low level of caudal block. As oscillations of BIS values were observed in both groups, we believe that they are not decisive for the results.

REFERENCES

1. LANIER W L, IAIZZO P A, MILDE J H, SHARBROUGH F W 1994 The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. *Anesthesiology 80:* 392–401
2. HODGSON P S, LIU S S 2001 Epidural Lidocaine Decreases Sevoflurane Requirement for Adequate Depth of Anesthesia as Measured by the Bispectral Index Monitor. *Anesthesiology 94:* 799–803
3. REINOSO-BARBERO F, MARTINEZ-GARCIA E, HERNÁNDES-GANCEDO MC, SIMON AM 2006 The Effect of epidural bupivacaine on maintenance requirements of sevoflurane evaluated by bispectral index in children. *Eur J Anaesthesiol 23:* 460–4
4. CASATI L, FERNÁNDEZ-GALINSKI S, BARRERA E, POL O, PUIG M M 2002 Isoflurane requirements During Combined General/ Epidural Anesthesia for Major Abdominal Surgery. *Anesth Analg 94:*1331–7
5. GENTILI M, CHAU HUU P, ENEL D, BONNET H, BONNET F 1998 Sedation depends on the level of sensory block induced by spinal anaesthesia. *Br J Aanaesth 1:* 970–1
6. XIAO W J, DENG X M, TANG G Z, LU M P, XU K L 2002 Caudal anesthesia reduces the minimum alveolar concentration of enflurane for laryngeal mask airway removal in boys. *Can J Anesth 49:* 194–7
7. DAVIDSON A J 2007 Monitoring the anesthetic depth in children – un update. *Curr Opin Anasthesiol 20:* 236–43
8. DAUNDERER M, SCHWENDER D 2004 Unwanted wakefulness during general anesthesia. *Anaesthesist 53:* 581–94
9. ENGELHARDT T, MCCHEYNE A, BISSONNETTE B 2007 Awarenes during pediatric anesthesia – what is the position of european pediatric anesthesiologists? *Padiatr Anesth 17:* 1066–70
10. KRANE E J 2002 The Ethics of Regional Anesthesia in Anesthetized Children. *Tech Reg Anesth Pain Manag 6:* 90–4
11. SØREIDE E, LJUNGQVIST O 2006 Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions. *Best Pract & Res Clin Anaesthesiol 20:* 483–91
12. VLADIĆ A, KLARICA M, BULAT M 2009 Dynamics of distribution of ^{3}H-inulin between the Cerebrospinal fluid compartments. *Brain Research 1284:* 127–35
13. YANG M K, KIM J A, AHN H J, CHOI D H 2007 Influence of the baricity of a local anaesthetic agent on sedation with propofol during spinal anaesthesia. *Br J Anaesth 98:* 515–8
14. DAVIDSON A J, KWOK T 2008 Performance of BIS in children using the paediatric BIS Quattro sensor. *Anaesth Intensive Care 36:* 807–13
15. MORIMOTO Y, OKA S, MII M, SHINJO Y, YAMASHITA A, GOHARA T, MATSUMOTO M, SAKABE T 2002 Efficacy of bispectral index monitoring in improving anesthetic management, economics, and use of the operating theater. *Masui 51:* 862–8
16. JOHANSEN J W, SEBEL P S 2000 Develpment and clinical application of electoencephalographic bispectrum monitoring. *Anesthesiology 93*: 1336–44
17. KISSIN I 2000 Depth of Anesthesia and Bispectral Index Monitoring. *Anesth Analg 90:* 1114–7
18. WALLENBORN J, KLUBA K, OLTHOFF D 2007 Comparative evaluation of Bispectral Index and Narcotrend Index in children below 5 years of age. *Paediatr Anaesth 17:*140–7
19. WATCHA M F 2001 Investigations of the Bispectral Index Monitor in Pediatric Anesthesia: First Things First. *Anesth Analg 92:* 805–7
20. RODRIGUEZ R A, HALL L E, DUGGAN S, SPLINTER W M 2004 The bispectral index does not correlate with clinical signs of inhalational anesthesia during sevoflurane induction and arousal in children. *Can J Anesth 51:* 472–80
21. RUSSEL I F 2007 A similar BIS value does not mean a similar depth of anaesthesia. *Br J Anaesth 99*: 592–600
22. MANYAM S C, GUPTA D K, JOHNSON K B, WHITE J L, PACE NL, STAT M, WESTENSKOW D R, EGAN T D 2007 When Is a Bispectral Index of 60 too Low? *Anesthesiology 106:* 472–83
23. LYSAKOWSKI C, DUMONT L, PELLEGRINI M, CLERGUE F, TASSONYI E 2001 Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and Bispectral Index during propofol induction of anesthesia. *Br J Anaesth 86:* 523–7
24. BANNISTER C F, BROSIUS K K, SIGL J C, MEYER B J, SEBEL P S 2001 The effect of bispectral index monitoring on anesthetic use and recovery in children anesthetized with sevoflurane in nitrous oxide. *Anesth Analg 92:* 805–7
25. SICE P J A 2005 Depth of Anaesthesia. Update in Anaesthesia (accessed September 15, 2010). Available from: http://www.nda.ox.ac.uk/wfsa/html/u19/u1910_01.htm, 19.
26. HAMEROFF S R 2006 The Entwined Mysteries of Anesthesia and Consciousness. *Anesthesiology 10:* 400–12
27. KIM H S, OH AY, KIM C S, KIM S D, SEO K S, KIM J H 2005 Correlation of bispectral index with end-tidal sevoflurane concentration and age in infants and Children. *Br J Anaesth 95:* 362–6