Effect of 2,6-diisopropylphenol and 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy) propane as Anesthetic

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Sevoflurane (2,2,2-trifluoro-1-[trifluoromethyl]ethyl fluoromethyl ether or $C_4H_3F_7O$), with a molar mass 200.055 g/mol, also called fluoromethyl, is a highly fluorinated methyl isopropyl ether with general anesthetic property, available for clinical practice for about 30 years. Sevoflurane is a sweet-smelling, non-flammable and it is used for induction and maintenance of general anesthesia. Together with desflurane, it is replacing isoflurane and halothane in modern anesthesiology. Propofol (2,6-diisopropylphenol or $C_{12}H_{18}O$), with a molar mass 178.271g/mol is an alkylphenol derivative formulated for induction and maintenance (in some cases) of general anesthesia, sedation and hypnosis and acting as an intravenous anaesthetic drug, having largely replaced sodium thiopental because recovery from propofol is more rapid and clear. The present study provide evidence for further dates to develop and optimize the method of sedation which combining with spinal anesthesia to be safe and offer a comfortable awakening for all the pediatric patients. To intravenous maintenance sedation with Propofol is likely to be the solution to prevent emerge delirium in younger children undergoing spinal anesthesia and it's worth studying

Keywords: 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane, gamma-aminobutyric acid, 2,6-diisopropylphenol, monitored anaesthesia, spinal anesthesia, bupivacaine

There are numerous studies in the literature relating to comparison between Sevoflurane and Propofol as anesthetic agents for induction or/and maintaining of general anesthesia, for sedation in patients undergoing imagistic procedures or as adjuncts to regional anesthetic techniques. Spinal anesthesia is not so popular nowadays among the regional anesthetic techniques used in children. However spinal anaesthesia is perhaps one of the oldest and most studied modalities for providing pain relief in patients undergoing surgery. More than a hundred years ago, August Bier was the first surgeon who performed and reported the successful use of spinal anesthesia in an 11 year old child.

The interest for spinal anesthesia in pediatric patients seems to increase though in the past few years [1]. This technique can be successfully used for a variety of general, urologic and orthopedic procedures. It proved to be a valid alternative because it is simple, not requiring the instrumentation of the airways, facilitates the postoperative care and is the most suitable technique when general anesthesia should be avoided (emergencies, full stomach). [2]. But spinal anesthesia in children always requires additional perioperative sedation for younger children.

This study investigates the effects of the monitored anaesthesia care inhalatory sedation using Sevoflurane versus intravenous sedation with Propofol added for spinal anaesthesia in young children. Monitored anesthesia care sedation in this case refers to a conscious sedation in connection with a regional anesthetic technique which allows the patient to preserve normal protective reflexes and concerns the monitoring of the cardiovascular functions [3].

Sevoflurane

This drug has a chemical formula 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)propane and structural formula presented in figure 1 and it is a colourless non-flammable liquid with a non-irritant odour. It is stable at room temperature and has a boiling point of 58.6°C and a vapor pressure of 157 mm Hg so it can be used in standard vaporizers [4].

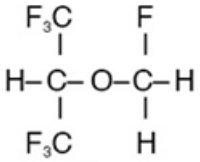

Fig. 1. Chemical formula of Sevoflurane

Sevoflurane has a blood: gas partition coeficient of 0.69 and its minimal alveolar concentration (MAC) - the percentage that is necessary to prevent movement in 50% of patients during skin incision - for adults is 2.1% (table 1). MAC values for pediatric patients aged between 1 and 3 years old is 2.8% Sevoflurane in oxygen and 2.0% Sevoflurane in 40% oxygen and 60% nitrous oxide.

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Table 1
PHYSICOCHEMICAL PROPERTIES OF THE INHALATORY AGENT SEVOFLURANE

Agent	Sevoflurane
Formula	$C_4H_3F_7O$
Blood/gas partition coeficient	0.69
Fat/blood partition coeficient	47.5
Boiling point	58.6°C
MAC adult	2.1 %
MAC 1-3 years	2.8 %
Vapor pressure	157 mmHg
Water solubility	Very slightly soluble
Recover as metabolite	2 – 5 %

The low solubility of sevoflurane in blood result in alveolar concentrations which rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. As an induction and maintenance agent for surgery in children, sevoflurane provides rapid induction and emergence from anaesthesia [5]. Studies have shown a significantly higher incidence of emerge delirium with sevoflurane [6]. The rapid elimination of sevoflurane also facilitates earlier awareness of postoperative pain.

Because of its pleasant odor, the absence of irritation to the airways and maintenance of stable hemodynamics, sevoflurane is the agent of choice for inhalational induction in children.

Metabolism of Sevoflurane on reaction with warm soda-lime release an important degradation product fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether also known as pentafluoroisopropanyl fluoromethyl ether (PEE) or *compound A*. Experimental studies reported that *compound A* may be nephrotoxic. But clinical experience doesn't concerns over the potential nephrotoxicity of the sevoflurane toxic product *compound A* because no renal impairment has been documented in children receiving sevoflurane in clinical trials [7, 8].

Propofol

This drug has a chemical formula 2,6-diisopropylphenol and structural formule is presented in tigure 2 and it is a sedative-hypnotic short-acting anesthetic agent that facilitates inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA). It is indicate in sedation for surgical procedures alone or in combination with regional anesthesia in adults and children > 1 month [9].

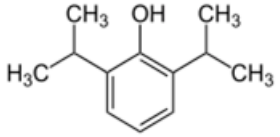

Fig. 2. Chemical structure of Propofol

Propofol short action is due to redistribution from the central nervous system to other tissues, the distribution half-life being 2-8 min. Recovery is not prolonged following repeated doses and this is due to metabolism rather than redistribution. It is metabolised in the liver by conjugation to glucuronide and sulphate but and by extrahepatic mechanisms and is excreted in urine mainly as inactive metabolites.

Propofol is slightly soluble in water (table 2) but has high lipophilicity and that is why it is currently available as an white oil-in-water lipid emulsion with soybean oil. Therefore patients could feel pain on the site of injection [10, 11]. Lidocaine is commonly mixed with propofol to reduce its incidence and severity [12, 13].

Table 2
PHYSICOCHEMICAL PROPERTIES OF THE INTRAVENOUS AGENT PROPOFOL

Agent	Propofol
Molecular formula	$C_{12}H_{18}O$
Molecular weight	178.275 g/mol
Water solubility	124 mg/dL
Distribution half life	2 – 8 min.

Experimental part

Material and method

This prospective, observational, unrandomised study included 378 pediatric patients aged 1 to 3 years old, with anesthetic risk - American Society of Anesthesiologists (ASA) I to III (healty patients or patients with mild or severe but not incapacitating systemic disease) who underwent lower abdominal or orthopedic surgery lasting between 30 and 60 min, performed under spinal anaesthesia, within May 2016 and May 2018 in the Children's Emergency Hospital of Galati.

The study exclusion criteria were the following:

- longer than estimated procedures where the anesthesia was prolonged by general anesthesia with endotracheal intubation;
- patients aged less than 12 months (who received subarachnoidian anesthesia with inhalatory sedation),
- children above 3 years old (all the patients were premedicated with Ketamine and sedation was maintained using Propofol infusion)
- emergency patients who received spinal anesthesia without sedation, on the grounds of a full stomach.

To facilitate technique, to comfort the child, to increase parents acceptability for the method, spinal anesthesia was combined with intravenous or inhalatory sedation which started preoperatively and continued during the surgery.

The parents were informed before the surgery and they were required to check in a questionnaire the type of anesthesia they chose for their child, upon being explained all the anesthetic techniques with their specific risks and benefits, and the anesthesiologist's decision took their choice into account whenever possible. It was by common agreement that the informed consent of one of the parents concerning the child's anesthesia was signed in the paper [14].

A lot of 206 children were premedicated intravenously before the lumbar puncture in the parent's presence. Topical anesthesia was provided by EMLA cream (containining two local anesthetic substances: lidocaine and prilocaine) 30 minutes before for the intravenous acces. During surgery these patients were continuously sedated with Propofol at an infusion rate: 5-6 mg/body weight/h on automatic syringe dispenser adjusted according to the response of the patient or supplemented by bolus administration of up to 1 mg/bw if a rapid increase of dept sedation was required.

A group of 172 children were given an inhalatory agent Sevoflurane before and during the surgical procedure (MAC 2.8% Sevoflurane in oxygen). They were those patients with exaggerated psychological response to needles or to hospital environment who received inhalatory sedation for the intravascular access.

During the study the following data were recorded and documented: children's demographic data, anesthetic risk - ASA physical status, surgical pathology, duration of surgery, variation of hemodynamic and respiratory parameters, intraoperative behaviour and eventual postanesthetic complications or drug-induced side effects [15].

The data were statistically analyzed and the results reported as absolute values, percentages or means with

standard deviations. For continuous variables, the results were reported as absolute values, average and standard deviation. The graphic representation was performed by Microsoft® Excel® 2010 (Microsoft® Corporation, USA). SPSS was used as statistic soft. p value Â 0.05 was considered as statistically significant. The data obtained were compared to the data in specialized literature.

The study fulfils the medical, ethical and deontological criteria, according to the Romanian legislation, and is approved by the Faculty of Medicine and Pharmacy Ethic Comission of Dunarea de Jos University of Galati [16].

Results and discussions

Of the total 1145 anesthetic procedures, 469 (40.96%) were performed under general anesthesia with endotracheal intubation (GA ETI), 298 (26.02%) were under inhalatory or intravenous general anesthesia with mask (GA mask) and 378 (33.01%) were spinal anesthesias (SA), from which 172 (15.02%) were associated with Sevoflurane sedation and 206 (17.99%) were associated with Propofol sedation. Figure 3 shows the types of anesthesia used in children. About a third of the anesthesias performed within two years for scheduled or emergency surgeries on pediatric patients in the children's hospital where the study was conducted were spinal anesthesias.

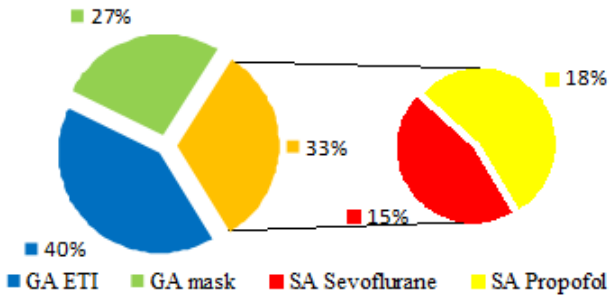

Fig. 3. Types of anesthesia

Spinal anesthesia was chosen due to the preference of the anesthesiologists, as well as the parents' option for this method, expressed by checking a box on the pre-anesthetic consultation form. The parents who did not select this anesthetic technique for their children motivated it by the children's anxiety, the lumbar placement of the puncture spot in the proximity of the spinal marrow and the fear of complications (postoperative headaches or lower limbs pareses/ paralysis).

The lumbar puncture was performed in the lateral decubitus or sitting position, according to the anatomical peculiarities specific to the child and the topography of the surgical intervention. Local anesthetic was in all cases Bupivacaine spinal heavy 0.5% dosage of 0.5-1 mg/bw alone or associated with epinephrine for a prolonged duration of anesthesia. During the lumbar puncture, children didn't oppose the manipulation of the lumbar spine and after 10-15 min waiting time sensitive and motor block for surgery was considered adequate for surgery.

It was noticed that the spinal anesthesia carried out to the pediatric patient who had undergone analgosedation before the procedure increases tolerance to the maneuver offering an absolute comfort to the patient, to the anesthetist and to the surgeon, who benefited from a good muscle relaxation during the surgery.

Abdominal surgery counted 299 cases (79.10%) of appendicitis, peritonitis, hernias, male specific pathology (hydrocele, varicocele, testicular ectopy, hypospadias) and 79 cases (20.89 %) of orthopedic surgery (fractures, equine varus foot, limb inequalities) (fig. 4).

Spinal anesthesia in young children always requires additional perioperative sedation. Optimum monitored anesthesia care sedation must provide a deep and secure sedation, not to reduce or anulate the advantages of spinal anesthesia by the side effects of adding agents and increase children and parents' acceptability for the anesthetic tehnique.

The patients were monitored during the surgery by means of the Ramsay sedation scale (table 3) - level 4 was considered acceptable, i.e. sleeping, easy to wake patient; awakening, the oxygen saturation of arterial blood, respiratory rate (RR), blood pressure (BP) and heart rate (HR) (table 4).

Table 3

RAMSAY SEDATION SCALE [17]

Awake, anxious and/or crying	1
Awake, tranquil, oriented	2
Tired, sleepy, immobile, indifferent	3
Asleep but easy to awaken	4
Asleep but difficult to awaken	5

Table 4

NORMAL VALUES OF HEMODYNAMIC AND RESPIRATORY PARAMETERS [18]

Age (years)	BP (mmHg)	HR (beats/min)	RR (cycles/min)
1 – 2	94/53	105±16	26±4
2 – 3	95/56	93±12	25±4

Biological parameters such heart rate (HR), systolic blood pressure (SBP) and respiratory rate were monitored preoperatively (preop), postanesthetic (postan), intraoperatively (intraop) and postoperatively (postop), (figs. 5 and 6) and recorded in the patient observation chart.

Both hypnotic drugs offered the same acceptable level of sedation, some but no significant statistic fluctuations of the heart rate, the blood pressure and the respiratory rate [p -value as sig. (2-tailed) > 0.05] (table 5).

Pediatric patients who were sedated with Sevoflurane experienced a short time to emergence but in 88 cases (23.28%) was recorded emerge delirium. Among those

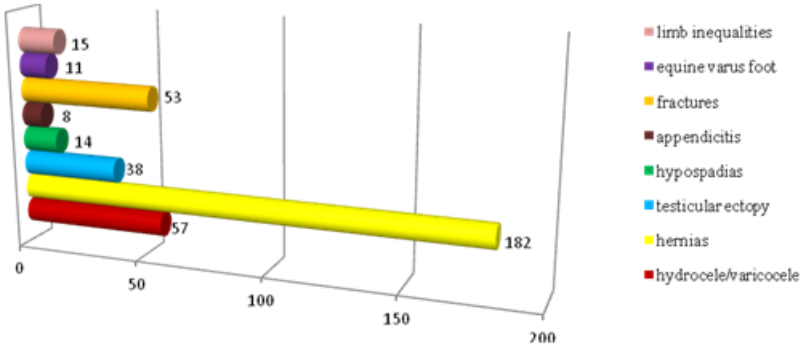

Fig. 4. Number of cases for different surgical pathologies

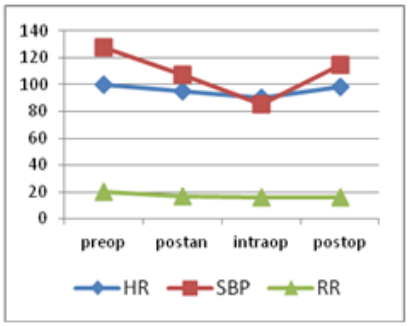

Fig. 5. Comparative parameter variations (SA associating Sevoflurane sedation)

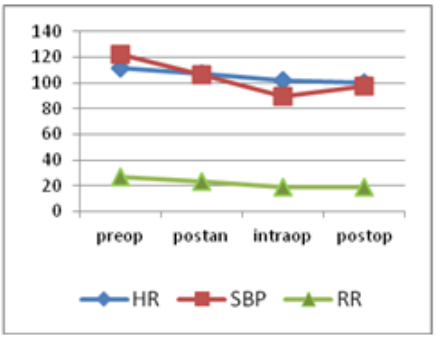

Fig. 6. Comparative parameter variations (SA associating Propofol sedation)

sedated with Propofol, 41 patients (10.84%) presented purposeless movements during surgery, but they had a light awakening. In the studied pediatric population, another complication was minor and easy to manage (eg. insignificant decreasing of the blood pressure or infrequent postoperative nausea and vomiting,).

Because of its pleasant odor, the absence of irritation to the airways and rapid induction and emergence, sevoflurane is considered the agent of choice for inhalational induction in children.

Increasing concentrations of sevoflurane can produce decreases in blood pressure immediately corrected by decreasing the inspiratory concentration of sevoflurane. However cautions are required in hypovolemic patients [19, 20].

Sevoflurane has a good safety profile pre- and intraoperatively but the delirium awakening disturb the child, the parents and recovery staff [21, 22]. Pediatric patients are inconsolable in the recovery room. A recent study published online in February 2019, conducted by Xiaole et al. concluded that propofol can be used to prevent emergence agitation after Sevoflurane in pediatric patients [23].

Propofol is the sedative-hypnotic substance that by interaction with the main inhibitor neurotransmitter at the level of the central nervous system provides good and safe intraoperative sedation, light awakening and is easily controllable by automatic syringe titration. It requires higher doses in children than in adults [24]. After propofol sedation the cognitive functions recover fast and vomiting is also prevented.

Sporadically appear undesirable movements of the head or upper limbs during the surgery [25]. Awarness is not common in patients under 5 years old [26].

There is no evidence that propofol induces neurotoxicity in humans [27], and the propofol related lypid syndrome, that is more likely to appear in pediatric population, occurs in high doses exceeding 4 mg/bw/h administered for over 24 hours [28]. Younger children are more resistant to the respiratory depressant effects of the Propofol and special

Table 5

PAIRED SAMPLES TEST ANALYSIS

	Paired Differences				
	95% Confidence Interval of the Difference				
	Lower	Upper	t	df	Sig. (2-tailed)
HR Sevoflurane – HR Propofol	-5.32956	4.84956	-.095	49	.925
SBP Sevoflurane – SBP Propofol	-3.34576	2.78576	-.184	49	.855
RR Sevoflurane – RR Propofol	-1.35442	.75442	-.572	49	.570

care for children with associated autoimmune disorders is needed [29]

Propofol is the most effective drug for intravenous monitored anesthesia care sedation in children undergoing spinal anesthesia [30].

Conclusions

Both hypnotic drugs used for monitored anesthesia care sedation in pediatric patients undergoing spinal anesthesia, intravenous Propofol and inhalatory Sevoflurane, offer acceptable levels of sedation, hemodynamic and respiratory stability intraoperatively and a short time to induction and emerge, children being able to respond commands soon in the recovery room.

The limitation of our study was the impossibility to determine the blood Propofol concentrations in the same way we measured volatiles. Undesirable side effects, such as decreases in blood pressure could occur at higher blood concentrations of Propofol from bolus dosing or rapid increases in infusion rates.

The result from the present study provide evidence for further studies to develop and optimize the method of sedation which combining with spinal anesthesia to be safe and offer a comfortable awakening for all the pediatric patients. Sevoflurane inhalatory induction swiched to intravenous maintenance sedation with Propofol is likely to be the solution to prevent emerge delirium in younger children undergoing spinal anesthesia and it's worth studying.

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