Egyptian Journal of Anaesthesia (2014) **30**, 325–329

HOSTED BY

ELSEVIER

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Safety and consumption of sevoflurane versus desflurane using target controlled anesthesia in children

Hossam Z. Ghobrial *, **Ayman A. Ghoneim**

National Cancer Institute, Cairo University, Egypt

Received 30 November 2013; accepted 19 March 2014
Available online 21 April 2014

KEYWORDS

Sevoflurane;
Desflurane;
Target controlled anesthesia;
Zeus machine;
Auto control mode

Abstract *Background:* Recently a concept of target controlled inhalational anesthesia (TCA) is introduced in which the fresh gas flow and its composition are automatically delivered to the patients with the least possible flow. The aim of this study is to compare safety, consumption and cost of both sevoflurane and desflurane when delivered by target controlled anesthesia (TCA) using fully closed circuit conditions.

Patient and method: After approval of the hospital review board and obtaining parental informed consent, 60 pediatric patients aged 2–12 were selected. The patients were classified into two groups according to the anesthetic used S Group (n = 30) in which sevoflurane D Group (n = 30): in which desflurane was used. Both were delivered by auto control mode of Zeus machine. Anesthetic agent and O_2 consumption, cost and number of adjustments were assessed. Blood samples were obtained preoperatively and at 24, 48 and 72 h after the end of surgery for measuring serum creatinine, BUN, AST and ALT. Twenty-four hour urine samples were collected for 3 consecutive days to measure glucose, microprotein and creatinine for the estimation of creatinine clearance.

Results: This study revealed that sevoflurane group had a lower O_2, anesthetic consumption and cost than desflurane group. Also both groups had higher levels of serum urea and creatinine together with urinary microproteins and glucose in the first three post-operative days compared to preoperative values which indicates minor tubular insult. However there was no statistically significant difference between the two groups.

Conclusion: Sevoflurane is as safe as desflurane when delivered by auto control mode of Zeus machine with decreased anesthetic consumption and cost.

* Corresponding author. Address: Anesthesia Department, National Cancer Institute, Cairo University, 1 Fom Elkhalig Square, Cairo 13669, Egypt. Tel.: +20 1002412343.
E-mail address: hossam_zarif@yahoo.com (H.Z. Ghobrial).

Peer review under responsibility of Egyptian Society of Anesthesiologists.

 http://dx.doi.org/10.1016/j.egja.2014.03.003

1. Introduction

Low flow anesthesia has various advantages which include decreased consumption of medical gases and volatile anesthetics with its economic impact, reduction of anesthetic gas loss into the atmosphere with its environmental impact and finally conservation of temperature and humidity of the airway [1].

More recently a concept of target controlled inhalational anesthesia (TCA) is introduced in which the fresh gas flow and its composition are automatically delivered to the patients with the least possible flow. Theoretically target controlled anesthesia has many advantages in inhalational anesthesia practice which include decreased time to achieve a desired alveolar anesthetic gas concentration together with decreased overshoots and fluctuation of anesthetic agent. Another advantage is that the need for repeated anesthetic adjustments is markedly minimized decreasing the work of anesthetist. [2].

Modern anesthesia machines that implemented the target controlled concept has an auto control mode that deliver target controlled anesthesia with a fully closed circuit through blower-driven ventilator, an electronically-controlled gas and vapor delivery system and a servo-controlled valve system [3].

The last generations of halogenated anesthetics (desflurane and sevoflurane) have certain pharmacokinetic and pharmacodynamic properties which have been greatly magnified in minimal flow states. These anesthetic agents have low potency and low solubility in tissues, which fastens equilibration between concentrations of the alveoli and the brain. This makes these agents ideal for minimal flow and closed circuit conditions; hence, their Minimum Alveolar Concentration (MAC) in the inspiratory mixture is easily reached [4].

Despite being synthesized before the 1970s, one of the major barriers to their use is the high cost together with greater amount of agent required. This is evident in desflurane which has the highest MAC known among all anesthetic agents increasing its consumption and overall cost [4].

The side effects of accumulated volatile substances as an outcome of metabolism of sevoflurane are another aspect to be considered and may add to barriers of its use in minimal flow conditions [5].

The aim of this study is to compare safety, consumption and cost of both sevoflurane and desflurane when delivered by auto-control mode of Zeus machine that deliver target controlled anesthesia (TCA) using fully closed circuit conditions.

2. Patients and methods

After approval of the hospital review board and obtaining parental informed consent, 60 pediatric patients aged 2–12 and ASA status I–II with normal liver and kidney function scheduled for procedures longer than two hours duration in children's cancer hospital of Egypt were included in this study.

2.1. Anesthetic management

After arrival of the patients in the holding area, I.V cannula was inserted; midazolam 0.2 mg kg^{-1} and atropine 0.02 mg kg^{-1} were administered intravenously for anxiolysis. Patients then were transferred into the operating theatre and the non invasive monitoring including electrocardiogram, non-invasive blood pressure, pulse oximetry, axillary temperature and bispectral index (BIS) was used to estimate hypnosis. All patients had warming blanket to maintain a body temperature between 34 and 36 °C throughout surgery. Anesthesia was induced with propofol (2.5 mg kg^{-1}), atracurium (0.5 mg kg^{-1}), and fentanyl (2 μg kg^{-1}). After endo-tracheal intubation, the patient's lungs were mechanically ventilated with volume-controlled mode in order to maintain an end-tidal CO_2 between 30 and 36 mmHg, with O_2/air, with an inspired O_2 concentration of 50%. The anesthesia machine used (Zeus®, Draeger, Luebeck, Germany) utilizing target controlled anesthesia (TCA) through the autocontol mode.

2.2. Study settings

The patients were classified into two groups according to the anesthetic used:

S Group (n = 30)**:** in which sevoflurane was delivered by auto control mode of Zeus machine.

D Group (n = 30)**:** in which desflurane was delivered by auto control mode of Zeus machine.

In both groups, during maintenance, the administered end tidal concentration of agent used was readjusted in order to maintain the BIS value between 40 and 60 units. Adequate neuromuscular blockade was achieved using atracurium boluses at 0.15 mg kg^{-1} every 20 min.

During skin closure, anesthetic was discontinued and the patient received 100% O_2. At 25% recovery of the first response to train-of-four stimulation, neuromuscular blockade was reversed by neostigmine (4 μg kg^{-1}) and atropine (15 μg kg^{-1}).

2.4. Measured and recorded parameters

1. Anesthetic agent and O_2 consumption, cost and number of adjustments:

Sevoflurane, desflurane and O_2 consumption were obtained and recorded from the integrated Zeus delivery system and calculated as per hour consumption. Cost is calculated as per hour cost by Egyptian pound. Also the number of adjustments needed to maintain the BIS value between 40 and 60 units were recorded.

2. The laboratory variables:
   - Renal function

A. Standard renal biomarkers

Blood samples were obtained preoperatively and at 24, 48 and 72 h after the end of surgery for measuring serum creatinine and BUN. Normal values are defined by the commercial laboratory. Results are expressed in conventional units.

B. Specific renal biomarkers

Twenty-four hours urine samples were collected for 3 consecutive days to measure glucose, protein in urine as sensitive

indicators for renal tubular insult. Creatinine was also measured in urine for estimation of creatinine clearance.

- Hepatic function

Blood samples were obtained preoperatively and at 24, 48 and 72 h after the end of surgery for measuring aspartate aminotransferase [AST] and alanine aminotransferase [ALT] using automated chemistry system.

2.5. Statistical analysis

Data collected were revised, coded, tabulated and introduced to a personal computer (PC) for statistical analysis. Qualitative data presented in the form of frequency tables (number and percent). Quantitative data presented in the form of means and SD.

Normality of distribution of variables was tested using one sample Kolmogorov Smirnov test. Differences between groups were assessed using the Student's t test for normally distributed data and Mann Whitney U test for non-normal distributed data. The chi-square test was used to compare the differences of categorical variables between groups. Paired-samples t test for normal and Wilcoxon test for non-normal distributed data were used to analyze changes from preanesthesia to postanesthesia at 24, 48, and 72 h. SPSS (Statistical Package for Social Science) version 16 was used for statistical analysis. A p value < 0.05 was considered statistically significant.

3. Results

As regards patients' demographics, mean age, weight, sex, duration of surgery and MAC-hour results were comparable in both groups. There was no statistically significant difference between the groups (Table 1).

O_2 and anesthetic agent consumption, cost and number of adjustments were significantly lower in S group than in D group (Table 2).

In both groups serum creatinine levels postanesthesia were significantly higher than preanesthetic values at all assessment time points. In S group, preanesthetic creatinine value was 0.29 ± 0.13 vs. 0.52 ± 0.14, 0.47 ± 0.13 and 0.44 ± 0.14 at 24, 48, and 72 h, respectively, whereas in D group, preanesthetic creatinine value was 0.26 ± 0.12 vs 0.48 ± 0.09, 0.46 ± 0.11 0.44 ± 0.09 at 24, 48, and 72 h, respectively. However, there was no significant difference between both groups regarding creatinine level all over the study period. Also serum BUN values postanesthesia were significantly higher than pre-anesthetic values in both groups at all assessment time points. In S group, preanesthetic value was 6.2 ± 2.9, vs 7.4 ± 2.6, 7.2 ± 2.7 and 8.4 ± 3.1 at 24, 48, and 72 h, respectively, while in D group, preanesthetic value was 4.7 ± 2.3 vs 6.3 ± 2.4, 6.9 ± 2.6 and 8.4 ± 2.1 at 24, 48, and 72 h, respectively. However, there were no significant differences between both groups regarding BUN level at assessment time points of the study period.

There were no statistically significant differences between both groups regarding twenty-four hour creatinine clearance level at any time throughout the study period. In S group, preanesthetic value was 127.1 ± 37.4 vs 144.2 ± 25.6, 141.2 ± 39.1 and 140.2 ± 46.1 at 24, 48, and 72 h, respectively,) and in D group, preanethetic value was 143.8 ± 22.4 vs 135.4 ± 23.8, 137.1 ± 19.46 and 147.3 ± 15.6 at 24, 48, and 72 h, respectively.

Twenty-four hour urinary protein and glucose levels were significantly higher from the pre-anesthetic values in both groups at 24, 48, 72 h (Tables 3 and 4). However, there were no statistically significant differences between both groups regarding twenty-four hour urinary proteins (The 2 groups comparison had p values of: 0.09, 0.13, 0.06 at 24, 48, 72 h, respectively) (Table 3). Also glucose levels showed no significant differences at all assessment time points through the study

Table 1 Patient's demographic data in the studied groups.

Variables	S group $n = 30$	D group $n = 30$	P value
Age (years)	7.5 (3.9–10.8)	9 (6.6–12)	0.13
Male/female	16/14	14/16	0.20
Weight (kg)	23 (15.1–29.5)	21 (18–38.5)	0.66
Duration of anesthesia (h)	5.3 ± 1.6	5.1 ± 2.97	0.81

Data are presented as mean ± SD, median (range) and ratio.

Table 2 O_2 anesthetic consumption, cost and number of adjustments among the studied groups.

Variables	S group $n = 30$	D group $n = 30$	P value
O_2 consumption (L/h)	15.65 ± 4.9	117.4 ± 30.6	< 0.001
Agent consumption (ml/h)	3.1 ± 1.3	16.4 ± 7.1	< 0.001
Cost (Egyptian pound/h)	13.4 ± 4.6	33.6 ± 6.7	< 0.001
Number of adjustments	3.65 ± 0.75	5.45 ± 1.9	< 0.001

Results are represented as mean ± SD.

Table 3 Twenty-four hour urinary protein level in both studied groups.

	S group $n = 30$	D group $n = 30$
Pre-anesthesia	32(15–86)	73(22–108)
24 h	65(40.5–187.5)*	189.5(44.75–262.5)*
48 h	64(28.5–205)*	260(27.25–406.5)*
72 h	52(26.3–172.8)**	173(35–227.5)*

Data are presented as median (inter-quartile range).
Normal range of urinary proteins in 24 h = 0–150 mg/day.
* $P < 0.001$ in comparison with pre-anesthetic level.
** $P = 0.01$ in comparison with pre-anesthetic level.

Table 4 Twenty-four hour urinary glucose level in both studied groups.

	S group $n = 30$	D group $n = 30$
Pre-anesthesia	5(0–14.25)	12.5(0–20)
24 h	21(12.25–52.25)*	44(28–52.8)*
48 h	19.5(14.25–36.5)*	33(14.3–60)*
72 h	14.5(10.5–22)†	19(15–39.5)†

Data are presented as median (inter-quartile range).
$P < 0.001$ in comparison with pre-anesthetic level.
Normal range of urinary glucose = 0–20 gm/day.
† $P = 0.004$ in comparison with pre-anesthetic level.

period, where the p values were 0.14, 0.44, 0.15 at 24, 48, 72 h, respectively (Table 4).

Serum AST and ALT levels were not significantly different from the pre-anesthetic values in either group all over the study period. Also, there were no statistically significant differences between both groups regarding serum AST and ALT values at any time through the study period (Fig. 1).

4. Discussion

This study revealed that sevoflurane group had a lower O_2, anesthetic consumption and cost than desflurane group. Also, both groups had higher levels of serum urea and creatinine together with urinary microproteins and glucose in the first 3 post operative days compared to preoperative values which indicates minor tubular insult. However, there was no statistically significant difference between the two groups. It is worthy to mention that by the 3rd day all values were within normal values in both groups.

Sofie et al. compared desflurane consumption during auto-control mode of Zeus machine and conventional anesthesia machine with low fresh gas flow and concluded that desflurane consumption was higher in auto control mode [6]. Another study for cost analysis of two anesthetic machines: "primus" and "zeus" showed that the consumption of sevoflurane and isoflurane is also higher in auto control mode [7], and this was contrary to a study by Lortat et al. who assessed clinical and pharmaco-economic benefits of TCA showed decreased desflurane consumption in auto control mode [8].

In the present study, the higher consumption of desflurane may be due to the higher MAC that needs more time by the machine to reach the target expired setting of desflurane with more oxygen and desflurane consumption. Also, because of the automatic control of fresh gas and volatile agent flow, any change in the targeted concentration of volatile agent in the circle system was achieved using maximum fresh gas flow rates of oxygen for rapid equilibration. This means that with each adjustment to the desired inspired expired anesthetic agent, the circle system became more toward higher flows as open breathing circuits with higher oxygen and agent consumption [7]. In our study, higher number of adjustments was reported with desflurane that also may add to higher desflurane consumption.

Lately in the last century, there was controversy about safety of low flow sevoflurane due to accumulation of toxic metabolite in the anesthetic circuit, however many literatures supports its safety. A retrospective study evaluated pooled renal laboratory data from 22 different clinical trials that compared sevoflurane with isoflurane, enflurane, or propofol. The trials examined postoperative changes in serum creatinine and blood urea nitrogen levels from a total of 3436 adult surgical patients. The incidences of increased serum creatinine and blood urea nitrogen concentrations were similar among patients administered sevoflurane and those administered control drugs. Additionally, no trends specific to sevoflurane were observed as regard to postoperative serum creatinine concentration with the fresh gas flow rate and concurrent treatment with nephrotoxic antibiotics, or type of carbon dioxide absorbent [9].

In another study, 17 patients with stable renal insufficiency were anesthetized with sevoflurane or isoflurane at a total flow

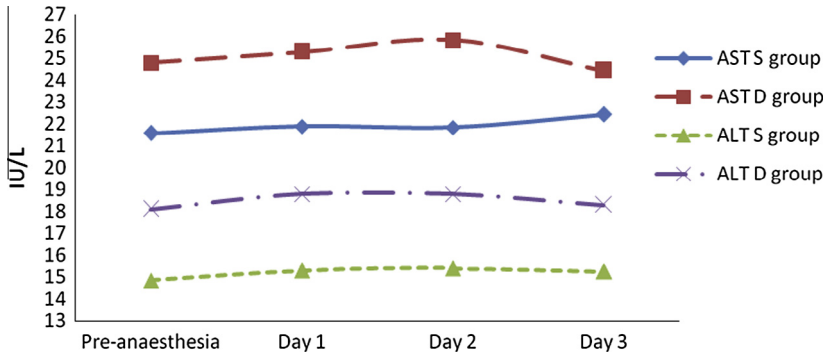

Figure 1 Serum AST and ALT in groups of patients under investigation.

of 1 L/min. Renal function was assessed with serum creatinine and blood urea nitrogen. The results showed no significant changes in blood urea nitrogen levels, serum creatinine concentrations, or creatinine clearance after anesthesia within each group [10]. Even in cirrhotic patients who are prone to renal dysfunction after anesthesia, [11] concluded that sevoflurane did not seem to impair post-operative renal function.

Also recently, Sahin and coworkers [12] evaluated the effect of moderate duration low-flow sevoflurane on renal and hepatic functions in 80 patients, with an operation time of 120–240 min. They reported similar results to the current study. They found that postoperative serum BUN, creatinine and urine glucose were significantly higher from the preoperative values. However, all values were within the normal range.

In 80 children aged 5–15 years, no significant effect on renal and hepatic functions was found after low flow sevoflurane anesthesia [13]. Many factors common to anesthesia and surgical procedures have been concerned in the cause of renal dysfunction/injury. Antibiotics, surgical stress, preexisting renal disease, intraoperative blood pressure, site of surgery, and anesthetics are some of the suggested factors.

It is suggested in the current study that an additional factor which adds to sevoflurane safety with auto control mode of Zeus is the automatic flushing that occurs with each anesthetic agent adjustment increasing the flow toward open circuit that may wash any toxic metabolite in the circuit.

In conclusion, sevoflurane is as safe as desflurane when delivered by auto control mode of Zeus machine with decreased anesthetic consumption and cost.

Conflict of interest

None declared.

References

[1] Baum JA. Low flow anaesthesia. The theory and practice of low flow, minimal flow and closed system anaesthesia. 2nd ed. Oxford: Butterworth-Heinemann; 2001.

[2] Schober P, Loer SA. Closed system anaesthesia – historical aspects and recent developments. Eur J Anaesthesiol 2006;23:914–20.

[3] Lortat-Jacob, Billard V, Buschke W, Servin F. Assessing the clinical or pharmaco-economical benefit of target controlled desflurane delivery in surgical patients using the Zeus anaesthesia machine. Anaesthesia 2009;64:1229–35.

[4] Brattwall M, Warrén-Stomberg M, Hesselvik F, Jakobsson J. Brief review: theory and practice of minimal fresh gas flow anesthesia. Can J Anaesth 2012;59(8):785–97.

[5] Kharasch ED, Frink Jr EJ, Artru A, Michalowski P, Rooke GA, Nogami W. Long-duration low flow sevoflurane and isoflurane effects on postoperative renal and hepatic function. Anesth Analg 2001;93:1511–20.

[6] De Cooman Sofie, De Mey Nathalie, Dewulf Bram BC, Carette Rik, Deloof Thierry, Sosnowski Maurice, De Wolf Andre M, Hendrickx Jan FA. Desflurane consumption during automated closed circuit delivery is higher than when a conventional anesthesia machine is used with a simple vaporizer O_2–N_2O fresh gas flow sequence. BMC Anesthesiol 2008;8:4.

[7] Hinz Jose, Rieske Nadine, Schwien Bernd, Popov Aron F, Mohite Prashant N, Radke Oliver, Bartsch Armin, Quintel Michael, Züchner Klaus. Cost analysis of two anaesthetic machines: "Primus®" and "Zeus®". BMC Res Notes 2012;5:3.

[8] Lortat-Jacob B, Billard V, Buschke W, Servin F. Assessing the clinical or pharmaco-economical benefit of target controlled desflurane delivery in surgical patients using the Zeus anaesthesia machine. Anaesthesia 2009;64:1229–35.

[9] Mazze RI, Callan CM, Galvez ST, Delgado-Herrera L, Mayer DB. The effects of sevoflurane on serum creatinine and blood urea nitrogen concentrations: a retrospective, twenty-two-center, comparative evaluation of renal function in adult surgical patients. Anesth Analg 2000;90:683–8.

[10] Higuchi H, Adachi Y, Wada H, Kanno M, Satoh T. The effects of low-flow sevoflurane and isoflurane anesthesia on renal function in patients with stable moderate renal insufficiency. Anesth Analg 2001;92(3):650–5.

[11] Song JC, Zhang MZ, Wu QC, Lu ZJ, Sun YM, Yang LQ, Yu WF. Sevoflurane has no adverse effects on renal function in cirrhotic patients: a comparison with propofol. Acta Anaesthesiol Scand 2013;57(7):896–902.

[12] Sahin SH, Cinar SO, Paksoy, Sut N, Ob S. Comparison between low flow sevoflurane anesthesia and total intravenous anesthesia during intermediate-duration surgery: effects on renal and hepatic toxicity. Hippokratia 2011;15(1):69–74.

[13] Isik Y, Goksu S, Kocoglu H, Oner U. Low flow desflurane and sevoflurane anaesthesia in children. Eur J Anaesthesiol 2006:60–4.