Evaluation of Target-Controlled Inhalational Anesthesia in Pediatrics Using the Newly Introduced Zeus Anesthesia Workstation: A Prospective Clinical Study

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Abstract

Background: The optimal inhalational induction should provide titration of inhaled anesthetics to imply a fast and reliable alteration without overshooting the targeted inhaled agent concentration and involves a stable desired drug level. The recent option of target-controlled inhalation anesthesia was made possible by the introduction of Zeus anesthesia workstation. The aim of this study was to evaluate the target-controlled inhalational anesthesia in pediatrics using the Zeus anesthesia machine in comparison to the classic technique with the conventional anesthesia machine using sevoflurane.

Methods: In this prospective, controlled, clinical study, we randomized 40 children undergoing elective oncological surgery under general anesthesia into 2 equal groups to receive either target-controlled inhalational induction with sevoflurane through Zeus anesthesia machine [Target-controlled group (TC)], or to be induced classically with inhalation of sevoflurane through Fabius-CE conventional anesthesia machine (control group). Time to loss of conscious, wash in, washout times, time to target ETsevo and emergence time were recorded. Number of adjustments to reach the target sevoflurane concentration and overshooting was also recorded.

Results: Mean time to attain and maintain target concentration (time to target TT) was significantly shorter in the target controlled group (TC 104±24.6 sec Vs control 210±19.8 sec). A significantly longer emergence time was obtained in the control group (16.1±2.4min) versus (7.8±2.6min) in TC group. In addition number of adjustments to target ETsevo was higher in control group (7±1.5 in control group Vs 1±0.5 in TC group). Overshooting to a mean ETsevo of 4.9±0.1% occurred in the control group after 3 min of induction, whereas no overshooting occurred in the TC group. Mean wash in time as well as mean time to loss of conscious (TLOC) did not differ significantly in either group.

Conclusion: The target controlled inhalational anesthesia using the auto-control mode of the Zeus® apparatus allowed a very fast and reliable induction of sevoflurane in pediatrics with no overshoot. It also allowed minimal or no anesthetist intervention in reaching the target end-tidal sevoflurane concentration. Reduced emergence time as a result of very rapid washout times was also remarkable compared to conventional anesthesia machine.

Key Words: Target-controlled inhalation – Auto-control mode – Zeus anesthesia machine – Pediatric – Sevoflurane.

Introduction

INHALATION agents are the cornerstone of pediatric anesthesia, as children are often induced by mask before venous access is obtained. Inhalation anesthesia is still considered to be the gold standard by the overwhelming majority of pediatric anesthesiologists world-wide. The potent inhalational anesthetic, sevoflurane has dominated anesthetic inductions in children for decades providing smooth induction of anesthesia with excellent outcomes. The higher costs are probably the main reason for not completely switching from halothane to sevoflurane world-wide [1,2].

The optimal inhalational induction should provide titration of inhaled anesthetics to imply a fast and reliable alteration without overshooting the targeted inhaled agent concentration and involves a stable desired drug level. The conventional anesthesia machine with a classically applied out-of-circle vaporizer, implies that a fast adjustment of inhaled agent concentration is only feasible by increasing the FGF resulting in a possible overshoot in inhaled agent concentrations and increased consumption [3]. The conflict between reducing agent consumption by minimizing the fresh gas flow (FGF) and gradually reaching the difference between the actual drug concentration and the target drug level would be only possible by uncoupling agent delivery and FGF. Using a principle

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where an agent is directly delivered into the breathing circle system independent of FGF theoretically allows fastest alteration of agent concentration and its minimal consumption [4].

However, a recently launched anesthesia workstation allow target-controlled inhalation anesthesia (TCIA) using this principle: the Zeus® anesthesia workstation (Dragér Medical, Lübeck, Germany). In adults target-controlled inhalation induction (TCII) was successfully performed with the Zeus anesthesia machine [5].

Zeus anesthesia machine was recently introduced in Egypt in Children’s Cancer Hospital (CCHE) Therefore; the aim of this study was to evaluate the target-controlled inhalational anesthesia in pediatrics using the Zeus anesthesia machine in comparison to the classic technique with the conventional anesthesia machine using sevoflurane.

Material and Methods

The zeus® apparatus:

The Zeus® apparatus is multifunctional in both administration modes for inhaled anesthetics and in ventilation modes. For drug delivery, two control modes are possible, fresh gas control (FGC) and auto-control (AC). In FGC mode, a classical ventilator with capacity for low-flow and an out-of-circle vaporizer is emulated and no automated system is active. FGF and oxygen concentration are set manually, emulating the use of classical rotameters. In AC mode, multiple computerized closed-loop feedback systems can be turned on. In the AC mode with minimal FGF (e.g. 1 liter/min), the clinician sets a targeted end-tidal concentration of inhaled anesthetic and the volatile anesthetic feedback control will obtain and maintain this targeted end-tidal concentration as accurate as possible. In full AC mode, also called ‘uptake mode’, anesthetic delivery, inspiratory oxygen concentration and FGF are feedback-controlled.

FGF is therefore minimized towards closed-circuit conditions and will only add the required quanta of oxygen, nitrous oxide or air to maintain a given set gas mixture.

The breathing system of the Zeus® apparatus follows the basic structure of a classical rebreathing system (circle system), as shown in Fig. (1). The ventilator consists of an electronic driven and controlled compressor turbine placed in the inspiratory limb.

Direct Injection of Volatile Anesthetic (DIVA) module; (which replaced the conventional vaporizer) is the anesthetic metering unit, which meters volatile anesthetics and FGF. The metering unit stores a quantity of anesthetic liquid. The selected volatile anesthetic is injected into a heated vaporizing chamber and the vapour is delivered to the breathing system via the supply unit using a heated pipe. Depending on the ventilator control mode, the supply unit either directly injects (auto-control (AC) mode) the saturated agent vapour into the breathing system or mixes it with the fresh gas first (fresh gas control (FGC) mode).

The fabius®-CE apparatus:

The fabius®-CE anesthesia machine (Dragér Medical, Lübeck, Germany) consists of an electrical piston-driven ventilator, an electronic mixed gas control unit and out-of-circle vaporizer to deliver the volatile anesthetic. The breathing system of the fabius®-CE apparatus is a classical rebreathing system (circle system).

Fig. (1): Schematic view of the Zeus breathing system.
Patients and methods:

After approval from research committee of our hospital and obtaining parental consents, 40 children aged 1-12 years, ASA I-III undergoing elective oncological surgery under general anesthesia were included in this prospective, randomized, controlled, clinical study. Cases with significant cardiorespiratory, renal, hepatic dysfunction were excluded. Other exclusion criteria were: expected difficult intubation, full stomach and neurological impairment. Premedication with oral midazolam 0.2mg/kg was given in the preoperative holding area. Cases were randomly allocated into 2 equal groups to receive either target-controlled inhalational induction with sevoflurane through Zeus anesthesia machine [Target controlled group (TC) group n=20 patient], or to be induced classically with inhalation of sevoflurane through Fabius-CE conventional anesthesia machine (control group n=20 patient). Heart rates (HR), electrocardiogram (ECG), pulse oximetry (SpO2), noninvasive mean arterial pressure. (MAP), end-tidal carbon dioxide (ETCO2), inspired sevoflurane concentration and ETSevo concentration were monitored. After pre-oxygenation with 100% oxygen, the target end-tidal sevoflurane (ETSevo) was set at 4% in the TC group without priming of the circuit using the auto-control mode (AC) with minimal FGF (1L/min). When the expired ETSevo reached 4%, the target was set to keep it at this value. In the control group induction was initiated with sevoflurane at 8% (Over pressure technique without priming of the circuit) until ETSevo reaches 4% then the vaporizer was adjusted to maintain ETSevo at this level. The fresh gas flow was adjusted according to the child’s body weight with a minimum of 1L/min. In both groups, after loss of consciousness IV line was inserted and fentanyl 2 g/kg was injected, when the child became apneic controlled ventilation was initiated to obtain tidal volume of 10ml/kg to compensate for facial mask and tubing dead space and to monitor accurately ETSevo concentration. Atracurium 0.5mg/kg was given; three minutes later endotracheal tube was introduced. Maintenance was done by air-oxygen mixture (50% oxygen +50% air). During maintenance, the end-tidal sevoflurane was adjusted to 2% in both groups. At the end of surgery, termination of sevoflurane administration by setting the target end-tidal sevoflurane to 0% in the TC group and the vaporizer was shut off in the control group, washout-times were measured. Ventilation as well as FGF settings were maintained unchanged all through the operation until spontaneous respiration commenced and extubation was done in both groups.

Recorded parameters:

Heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO2), end-tidal carbon dioxide (ETCO2), inspired sevoflurane concentration (Fisevo%) and end-tidal sevoflurane (ETSevo%) concentration were recorded every 1min during induction and every 5 min thereafter. Number of adjustments to obtain and maintain the target ETSevo during induction. Overshoot during induction which is the highest value in end-tidal sevoflurane concentration when aiming for 4%. Duration of overshoot during induction i.e. period of time (sec) during which ETSevo is above target concentration. Sevoflurane consumption during induction is the volume in ml consumed during induction as measured by the machine (only in Zeus). All potential adverse effects were recorded.

Time measurements in seconds:

Wash in time; defined as time to first appearance of sevoflurane in the inspiratory circuit. Time to target (TT); defined as time to reach end-tidal sevoflurane a stable target concentration of 4%. Time to loss of consciousness (TLOC); defined as time to loss of eyelash reflex. Times to 25, 50, 75 and 90% wash-out; defined as the seconds needed after setting target end-tidal concentration to 0% to reach 25, 50, 75 and 90% reduction of ETSevo concentration respectively, (ETSevo to reach 1.5%, 1%, 0.5%, 0.2% concentration respectively). Emergence time defined as time to eye opening, first purposeful movement or first cry (whichever is earlier).

Statistical analysis:

Data was presented as mean and standard deviation for quantitative variables. Comparison between groups was done using Student’s t-test for qualitative variables, while repeated measure analysis of variance (ANOVA) was used for repeated measures of HR, MAP, SpO2, ETCO2, ETSevo% and Fisevo% followed by post hoc t test with Bonferroni correction for multiple comparisons as appropriate. The chi square test was used for comparison of gender. Data obtained from the study was analyzed using the software SPSS (Statistical package for social science) version 11.0. A p value <0.05 was considered statistically significant.

Results

This prospective study was carried out at Children’s Cancer Hospital of Egypt in the period between November 2007 to June 2008. All allocated cases completed the study. The two groups showed no significant difference as regard mean age; weight
and duration of surgery. The distribution of sex and ASA status was similar also (Table 1).

There were no significant difference in respect to heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO\textsubscript{2}), end-tidal carbon dioxide (ETCO\textsubscript{2}) among the two studied groups, although mean MAP was slightly lower in the control group but this mild difference was not significant statistically (Table 2).

Mean wash in time as well as mean time to loss of conscious (TLOC) did not show any significant difference between the two groups. Whereas mean time to attain and maintain target concentration (time to target TT) was significantly shorter in the target controlled group in comparison to control group (TC 104±24.6 Vs control 210±19.8) (Table 3).

Mean emergence time was significantly longer in the control group versus the TC group [966±144 sec (16.1±2.4min) in control Vs 468±156 sec (7.8±2.6min) in TC] (Table 3), as the FGF settings were maintained unchanged till the end of surgery except for one case where the FGF was increased to 6L/min due to persistent hypotension toward the end of the surgery and rapid washout was required. The emergence time in this case was 450 sec. (This case was excluded from emergence time and washout times’ analysis of control group results).

Number of adjustments to reach and maintain the target ETsevo was higher significantly in the control group in comparison to the TC group (1 ±0.5 in TC group Vs 7±1.5 in control group). Overshooting to a mean ETsevo of 4.9±0.1% occurred in the control group after 3 min of induction and the ETsevo exceeded the targeted value for 60±4.7 sec during induction before returning to target value and stability (Fig. 2). On the contrary the target controlled group didn’t show any overshooting of ETsevo % during induction (Fig. 3).

Times to 25, 50, 75 and 90% wash-out are presented in Fig. (4) and showed statistically significant delay in washout times in the control group in comparison to target controlled group at all recorded percentages. No significant complications were noted in any patient of the two groups apart of one case in TC group who developed agitation during mask ventilation and resolved with the administration of fentanyl. The mean consumption of sevoflurane during induction in the TC group as measured by Zeus anesthesia machine was 10.8±0.6 ml. Sevoflurane consumption couldn’t be measured in control group.

### Table (1): Patients demographic characteristics, duration of surgery (min) and distribution of sex and ASA status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TC group (n=20)</th>
<th>Control group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>3.9±2.1</td>
<td>4.6±1.9</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>14.6±2.5</td>
<td>15.3±1.1</td>
</tr>
<tr>
<td>Male/female</td>
<td>14/6</td>
<td>12/8</td>
</tr>
<tr>
<td>ASA I/II/III</td>
<td>4/9/7</td>
<td>6/8/6</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>166±29.8</td>
<td>180±25</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD.

### Table (2): Mean values of mean arterial pressure (MAP), heart rate (HR), oxyhemoglobin saturation (SpO\textsubscript{2}), and end-tidal CO\textsubscript{2} tension (EtCO\textsubscript{2}) in the two studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TC group (n=20)</th>
<th>Control group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>93.4±8.4</td>
<td>88.0±10.4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>127.8±15.9</td>
<td>129±8.5</td>
</tr>
<tr>
<td>SpO\textsubscript{2} (%)</td>
<td>98.1±1.0</td>
<td>98.5±1.2</td>
</tr>
<tr>
<td>EtCO\textsubscript{2} (mm Hg)</td>
<td>35.6±4.9</td>
<td>34.4±5.1</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD.

### Table (3): Different time phases during anesthesia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TC group (n=20)</th>
<th>Control group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wash in time (sec)</td>
<td>26.4±2.5</td>
<td>28±2.7</td>
</tr>
<tr>
<td>TLOC (sec)</td>
<td>80±14.6</td>
<td>84±17.4</td>
</tr>
<tr>
<td>TT (sec)</td>
<td>104±24.6</td>
<td>210±19.8*</td>
</tr>
<tr>
<td>Emergence time (sec)</td>
<td>468±156</td>
<td>966±144*</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD. *p<0.05 in comparison to TC group. TT= Time to target. TLOC= Time to loss of conscious.

![Graph](image-url)
where inhalational anesthetics are administered without additional costs [7].

Recently, the new anesthesia machine (Zeus ®, Dragèr Medical, Lübeck, Germany) is currently using the principle of independence of agent delivery upon the FGF. Anesthetic and fresh gas delivery is feedback-controlled by using direct injection into the breathing circle. In this study we have chosen to use the auto-control mode with minimal flow to evaluate the automatic control system in target controlled inhalational anesthesia, and the minimal flow (FGF=1L/min) was used as compound A may accumulate in the breathing system, and the recommendation that sevoflurane not to be administered with fresh gas flows lower than 1.0 l/min [8]. The first study on TCII with sevoflurane was performed with the Zeus apparatus in adults [8]. In that study TCII was successfully performed with sevoflurane highlighting several points as stability, accuracy and simplicity of the technique. The wash in time in our study was comparable between the two groups (26.4 ± 2.5 sec in TC group Vs 28±2.7 in control group) but was shorter than that reported in the adult study (36 sec) which may be explained by smaller volume of pediatric hoses taking less time to saturate the inspiratory circuit. Our results as regard time to loss of conscious was similar to that reported in adults’ target controlled inhalation induction [5]. Loss of conscious time was shorter in our study in TC group (80±14.6 sec) than a previous study using incremental induction with sevoflurane in neonates (116 sec) [9]. While Sigeston, et al. performed rapid inhalation induction with the use of 8% sevoflurane and 66% N2O in pediatrics; loss of conscious time was a little bit shorter (72 sec) in the sevoflurane group [10] than that encountered in our study and that may be explained by the addition of nitrous oxide denoting that target controlled inhalational induction is almost as rapid as induction by over pressure technique and the addition of N2O may add to its rapidity. Time to target fraction of sevoflurane 4% was obtained in adults after 130±19s, however, in this study it took only 104±24.6 sec in the target controlled TC group to reach a stable ETsevo concentration of 4%. This rapid rise of the alveolar concentrations of inhalation agents can be expected in pediatric patients compared to adults because alveolar ventilation in younger patients is high compared to their functional residual capacity. Whereas the target ETsevo was obtained in the control group after 210 ± 19.8 sec, this was preceded by a period of overshoot (to a mean ETsevo of 4.9±0.1 %) during induction. The mean duration of overshoot was for 60±4.7

**Fig. (3):** Mean end-tidal versus mean inspired sevoflurane concentration in target controlled group during induction.

**Fig. (4):** Time to percentage washout of sevoflurane in the two studied groups.

**Discussion**

Automatic closed-loop control is a system that processes information coming from the patient and the anesthesia system, compares it to a set point that defines the target output level and uses the difference to adjust the output so that the targeted set point is reached and maintained [6]. Since the ideal variable for the control of anesthetics is still searched for, anesthetists use the most famous indirect variable which is the mean arterial pressure. Another easily measurable variable is the end-tidal concentration of inhalational agents. It closely represents the brain concentration of the anesthetic agent and is available in virtually every location
sec before returning to target concentration of 4%. These results coincide to those reported in an in-vitro study comparing the time course of sevoflurane or desflurane end-tidal concentrations in FGC mode from the Zeus apparatus with the classical Primus system [11]. In both anesthesia machines, FGC mode resulted in the largest initial overshoot in end-tidal concentration and this was similar to what occurred in our control group. In the TC group we used the auto-control mode and the results showed the shortest time to target ETsevo, no overshoot and a significant decrease in number of adjustments to reach the target concentration denoting that in this mode, the inhaled anesthetics are feedback-controlled independent from the FGF, so rapid changes in concentrations are possible [11]. The possibility of overshooting the target concentration may result in increased incidence of side effects mainly hypotension; however the mild decrease in the mean MAP that occurred in the control group was statistically insignificant. The significant decrease in number of adjustments to reach and maintain the target ETsevo in the TC group in comparison to the control group (1 ±0.5 in TC group Vs 7± 1.5 in control group) was very much comparable to the results of the in-vitro study concluding that only few steps were required to guide drug administration in AC mode, in contrast to the manually controlled, where continuous changes in agent titration are required to reach and maintain a targeted concentration [11]. Also a previous study using automatic feedback control system to adjust end-tidal isoflurane concentration reported that it was generally faster, more stable and more accurate than human control [7]. As regard washout times our results showed statistically significant delay in washout times in the control group in comparison to target controlled group at all recorded percentages (Fig. 4). That was apparent and explained in the study of time course in-vitro comparison between the Zeus apparatus with the classical Primus system in different control modes where the AC mode was always faster in decreasing agent content of the system than fresh gas control mode in the classic anesthesia machine, revealing the ability of the auto-control mode to maximizes FGF to enhance flushing of the breathing system until the new set value is reached [11]. That would also explain the reduction in emergence time in the TC group significantly than control group (Table 3) (as we didn’t increase the FGF in either groups towards the end of surgery, which is the only feasible way to enhance agent washout in fresh gas mode). The elongated emergence time in the control group 16.1 ±2.4 min was similar to the results of O’Brien et al. were the emergence time (limb move) of the sevoflurane group (18:44 min: sec) was longer than other groups [9]. That could be partly explained by absence of MAC tailoring towards the end of surgery and that was also our practice in this study. The mean consumption of sevoflurane during induction in the TC group was 10.8±0.6 ml and this was in the same range reported in the adults using target controlled inhalation induction (12.3 ±2.6 ml) [8]. In another study performing rapid induction with 8% sevoflurane, the agent consumption during induction was 8.5 ml [12]; but the insertion of laryngeal mask in that study shortened the induction time to 140 sec explaining this reduced consumption.

In conclusion the target controlled inhalational anesthesia using the auto-control mode of the Zeus® apparatus allowed a very fast and reliable induction of sevoflurane in pediatrics with no overshoot. It also allowed minimal or no anesthetist intervention in reaching the target end-tidal sevoflurane concentration. Thus freeing the anesthetist hands’ for other tasks of anesthesia care. Reduced emergence time as a result of very rapid washout times was also remarkable compared to conventional anesthesia machine. The use of the auto-control mode may optimize the course of volatile anesthetic improving patient safety, reducing anesthetist repetitive tasks. The attractive option of closed circuit conditions to reduce the cost of inhalational agents and gases is very much highlighted with the availability of the “uptake mode” in the Zeus® apparatus and the need for detailed studies in this aspect is to be recommended.

References
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