Journal of Clinical Monitoring and Computing (2018) 32:623–627
https://doi.org/10.1007/s10877-018-0138-z

ORIGINAL RESEARCH

# Use of the MIRUS™ system for general anaesthesia during surgery: a comparison of isoflurane, sevoflurane and desflurane

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Received: 27 November 2017 / Accepted: 2 April 2018 / Published online: 9 April 2018


**Abstract**

The MIRUS™ system enables automated end-expired control of volatile anaesthetics. The device is positioned between the Y-piece of the breathing system and the patient's airway. The system has been tested in vitro and to provide sedation in the ICU with end-expired concentrations up to 0.5 MAC. We describe its performance in a clinical setting with concentrations up to 1.0 MAC. In 63 ASA II–III patients undergoing elective hip or knee replacement surgery, the MIRUS™ was set to keep the end-expired desflurane, sevoflurane, or isoflurane concentration at 1 MAC while ventilating the patient with the PB-840 ICU ventilator. After 1 h, the ventilation mode was switched from controlled to support mode. Time to 0.5 and 1 MAC, agent usage, and emergence times, work of breathing, and feasibility were assessed. In 60 out of 63 patients 1.0 MAC could be reached and remained constant during surgery. Gas consumption was as follows: desflurane ($41.7 \pm 7.9$ ml $h^{-1}$), sevoflurane ($24.3 \pm 4.8$ ml $h^{-1}$) and isoflurane ($11.2 \pm 3.3$ ml $h^{-1}$). Extubation was faster after desflurane use (min:sec): desflurane 5:27 ± 1:59; sevoflurane 6:19 ± 2:56; and isoflurane 9:31 ± 6:04. The support mode was well tolerated. The MIRUS™ system reliable delivers 1.0 MAC of the modern inhaled agents, both during mechanical ventilation and spontaneous (assisted) breathing. Agent usage is highest with desflurane (highest MAC) but results in the fastest emergence. *Trial registry number*: Clinical Trials Registry, ref.: NCT0234509.

**Keywords** Inhalation drug administration · Isoflurane · Sevoflurane · Desflurane

## 1 Introduction

In 2013, the MIRUS™ (Pall Medical, Dreieich, Germany) was introduced, primarily intended for inhalational sedation of critically ill patients in the ICU. This device controls the delivery of volatile anaesthetics (VA) to target values automatically and independently of the breathing parameters set on the ventilator [1]. The automated control of the end-tidal VA concentration is the main difference compared with the AnaConDa™ (Sedana Medical, Uppsala, Sweden), another device that has been used > 10 years to deliver inhaled agents to sedate patients in the ICU [2]. The reflectors, which are used to conserve VA, are similar in both systems. The MIRUS™ as well as the AnaConDa™ can be used to deliver isoflurane (ISO) and sevoflurane (SEVO), but desflurane (DES) can only be administered with the MIRUS™.

While the MIRUS™ has been tested in vitro and to provide sedation in the ICU with end-expired concentrations up to 0.5 MAC, it has not been evaluated with high VA concentrations in a clinical setting. We investigated its performance during surgery with concentrations up to 1.0 MAC to test its functionality. Time to 0.5 and 1.0 MAC, agent usage, emergence times, work of breathing and feasibility were assessed.

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## 2 Methods

This investigation was conducted in a German University Hospital (St. Elisabeth Hospital, Ruhr-University Bochum). It was approved by the local ethics committee (registration number 4780-13) and registered with Clinical Trials

Registry (ref.: NCT0234509). Written informed consent was obtained from all patients prior to their inclusion.

### 2.1 Patients

Patients undergoing elective hip or knee replacement surgery under general anaesthesia during October–December 2014 were included in this prospective, randomised and controlled observation. Inclusion criteria were ASA I–III, age 18–80 years and application of VA. Exclusion criteria were regional anaesthesia, total intravenous anaesthesia and any neuromuscular disease.

### 2.2 Anaesthesia and study protocol

Patients obtained 3.75–7.5 mg midazolam orally for premedication. Anaesthesia was induced with 0.2 µg $kg^{-1}$ sufentanil, 2 mg $kg^{-1}$ propofol and 0.5 mg $kg^{-1}$ atracurium or 1 mg $kg^{-1}$ succinylcholine to facilitate intubation with a cuffed tube. Cuff pressures ranged between 20 and 30 cm $H_2O$ and were kept constant by a VBM manometer. The anaesthesia machine (Cicero™; Draeger Medical, Lübeck, Germany) was replaced by an ICU ventilator (PB-840, Metronic, Dublin, Ireland) and connected to an anaesthesia gas scavenging system (AGS, Draeger medical, Lübeck, Germany).

Blood pressure was measured every 3 min by a suitable blood pressure cuff (non-invasive measurements). Systolic values below 100 mmHg were treated by norepinephrine application during anaesthesia as necessary. The inspiratory VA concentration during wash-in can be varied (slow, moderate or high), influencing the speed needed to reach an end-expired target value. This is expressed by symbols such as "tortoise", "hare" or "cheetah". Here, the wash-in speed was set at 'hare' (moderate) for all patients. The tidal volume was 8 ml $kg^{-1}$ ideal body weight on a controlled mechanical ventilation (CMV) mode with an $FiO_2$ of 0.8. The times needed to reach 0.5 MAC and 1.0 MAC end-expired were recorded. If the MIRUS™ was unable to reach the target values or remained at < 0.5 MAC for longer than 5 min, MIRUS™ was stopped and patients received a total intravenous anaesthesia for surgery. After 1 h, a spontaneous breathing trial was performed by halving the respiratory rate and use of proportional assist ventilation (PAV), a mode of synchronized partial pressure support. The pre-set support was 50%, which means that half of the patient's elastic and resistive loads were compensated by the ventilator. All patients had a TOF ratio equal to or > 90% measured by a TOF-Watch® SX (Organon, Dublin Ireland). Work of breathing, compliance and resistance were determined by the ventilator at the beginning of PAV mode, after 30 min and shortly before extubation [3]. The rapid shallow breathing index (ratio of respiratory frequency to tidal volume) was calculated. As soon as the respiratory rate exceeded 14 breaths per minute or the end-tidal $CO_2$ was < 35 mmHg, a bolus of 5 µm sufentanil was given. At the end of surgery, MAC was set to 0.0. The MIRUS™ reflector was not removed. Time to extubation, first eye opening, hand squeezing, specifying birthdate and discharge from the recovery room were recorded. VA consumption was calculated by the MIRUS™ system.

### 2.3 Statistical analysis

The patient's allocation to group ISO, SEVO or DES was random (closed envelope method). SPSS statistics 22 (IBM, Ehningen, Germany) was used for calculation. A descriptive analysis was performed to determine frequencies, mean and median. The Chi square or the Fisher Exact test were performed on qualitative data, when the sample size was too small. For qualitative data, mean comparison was calculated with an analysis of variance (ANOVA). Nonparametric Kruskal–Wallis tests were performed, when the sample size was too small, or data demonstrated a non-Gaussian distribution. The level of significance was set as a two-sided test with an error probability < 5%. Significant differences were further investigated by a 2 by 2 comparison with Bonferroni correction.

## 3 Results

### 3.1 Patient characteristics

A total of 63 patients were enrolled in this prospective investigation. Three patients were excluded (DES: n = 2; ISO: n = 1), because 1.0 MAC could not be reached by MIRUS™ within 5 min. Age, height, weight, ideal body weight, sex and the kind of surgery of the remaining 60 patients were comparable between the groups (Table 1).

### 3.2 Wash-in times and VA consumption

Durations of anaesthesia and surgery were comparable in all groups. The time needed to reach 0.5 MAC was shortest in group ISO and longest in group SEVO. However, the time needed to reach 1.0 MAC did not differ significantly among the groups (Fig. 1). The highest VA consumption was seen in group DES, followed by SEVO and ISO (Table 1).

### 3.3 Proportional assisted ventilation mode

The MIRUS™ system has a total dead space of 100 ml (50 ml filter, 50 ml reflector). During PAV mode, work of breathing (WOB) was within a normal range with no significant differences among the groups ([J/L]; ISO: $0.96 \pm 0.34$; SEVO: $0.88 \pm 0.29$; DES: $0.75 \pm 0.18$; $p = 0.068$). This also applies to the pulmonary compliance ([ml $mbar^{-1}$]; ISO:

**Table 1** Patient characteristics and agent usage

| | Isoflurane | Sevoflurane | Desflurane | p-Value |
|---|---|---|---|---|
| Patients (n) | 20 | 20 | 20 | 1.0 |
| Age (years) | 67 [60.3–75.5] | 73 [62.3–76.0] | 71 [65.8–77.0] | 0.078 |
| Height (cm) | 168 ± 9 | 171 ± 8 | 172 ± 9 | 0.358 |
| Weight (kg) | 79 ± 13 | 84 ± 21 | 83 ± 14 | 0.592 |
| Ideal body weight (kg) | 62 ± 10 | 64 ± 9 | 64 ± 10 | 0.710 |
| Sex (m/f) | 10/10 | 10/10 | 7/13 | 0.545 |
| Surgery (knee/hip replacement) | 8/12 | 7/13 | 12/8 | 0.189 |
| Duration of anaesthesia (min) | 115 ± 28 | 108 ± 14 | 111 ± 30 | 0.392 |
| Duration of surgery (min) | 92 ± 30 | 83 ± 14 | 81 ± 31 | 0.632 |
| Time MAC 0.0–0.5 (min:sec) | 1:05 ± 00:41 | 2:25 ± 1:48 | 1:20 ± 0:37 | 0.002*,§ |
| Time MAC 0.5–1.0 (min:sec) | 1:20 ± 1:20 | 2:43 ± 2:59 | 3:24 ± 4:43 | 0.144 |
| MAC 1.0 → vol% VA (CMV) | 0.97 ± 0.07 | 1.45 ± 0.18 | 5.17 ± 0.50 | < 0.001#,§ |
| MV ($l\ min^{-1}$) (CMV) | 6.3 ± 1.1 | 7.1 ± 0,9 | 6.2 ± 1.1 | 0.016§ |
| MV ($l\ min^{-1}$) (PAV) | 6.1 ± 2.0 | 7.2 ± 2.6 | 5.6 ± 1.8 | 0.068 |
| $etCO_2$ (mmHg) (CMV) | 35.6 ± 3.3 | 35.0 ± 4.2 | 35.2 ± 3.5 | 0.876 |
| $etCO_2$ (mmHg) (PAV) | 41.6 ± 4.7 | 39.8 ± 5.9 | 42.3 ± 6.6 | 0.362 |
| Agent usage MAC 1.0 ($ml\ h^{-1}$) (CMV) | 11.2 ± 3.3 | 24.3 ± 4.8 | 41.7 ± 7.9 | < 0.001#,§ |

Patient characteristics were comparable between the groups. Time to reach 0.5 MAC, MAC itself, as well as gas consumption were significantly different between the groups (*isoflurane vs. sevoflurane; #isoflurane vs. desflurane; §sevoflurane vs. desflurane). Values are presented as mean (standard deviation or IQR [25.–75.]) or number

*CMV* controlled mechanical ventilation, *PAV* proportional assist ventilation, *MV* minute volume, *VA* volatile anaesthetic, *MAC* minimum alveolar concentration

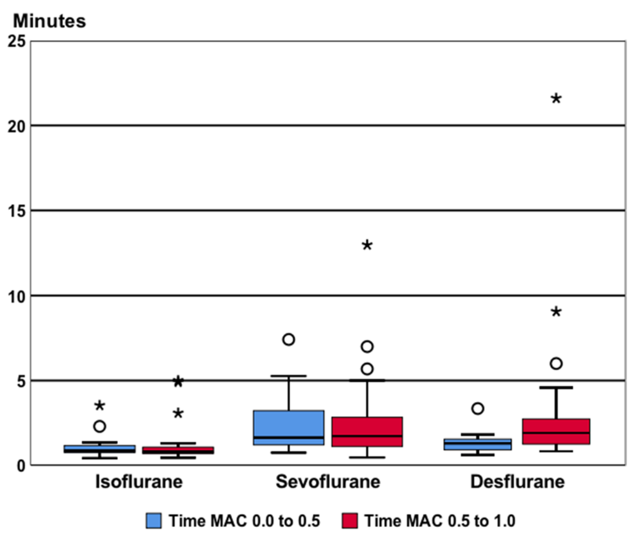


**Fig. 1** Wash-in times. The time needed to reach 0.5 MAC was shortest in group ISO and longest in group SEVO (blue). Pink boxes represent the time needed to increase MAC from 0.5 to 1.0, which was not significantly different among the groups. Median (horizontal black lines), 1st and 3rd quantile (upper and lower end of the boxes), the 95% interval (horizontal black lines) and statistical outliers (circles: outside the 95% interval; stars: values, which are three times higher than the corresponding box) are presented

65 ± 22; SEVO: 61 ± 19; DES: 67 ± 20; p = 0.629), to the airway resistance ([$mbar\ l^{-1}\ s^{-1}$]; ISO: 7.1 ± 3.2; SEVO: 6.2 ± 2.1; DES: 7.5 ± 3.3; p = 0.389) and to the rapid shallow breathing index (ISO: 26 ± 17; SEVO: 25 ± 10; DES: 28 ± 17; p = 0.766).

### 3.4 Recovery times

Recovery from anaesthesia was quickest in group DES throughout all measured parameters, including time to extubation (Table 2).

## 4 Discussions

The MIRUS™ was originally designed for the application of VA in the ICU. It consists of a 'control unit', which monitors gas concentration, pressure, flow and VA application, and a 'MIRUS™ Exchanger'. The 'Exchanger' is a VA carbon reflector, which works as a heat moisture exchanger and eliminates particles as well as microorganisms. Comparable to anaesthesia ventilators (e.g. Aisys, Zeus or FLOW-i), the MIRUS™ enables an automated end-tidal target-controlled VA application [1]. This feature is up to now not used in ICU ventilators.

As far as we know, MIRUS™ has not yet been investigated with high concentrations of ISO, SEVO and DES (1.0 MAC) in an operating room setting. Our findings indicate that the MIRUS™ delivers high VA concentrations reliably

**Table 2** Recovery times

| | Isoflurane (n = 20) | Sevoflurane (n = 20) | Desflurane (n = 20) | p-Value |
|---|---|---|---|---|
| Extubation (min:sec) | 9:31 ± 6:04 | 6:19 ± 2:56 | 5:27 ± 1:59 | 0.006*,# |
| Open eyes (min:sec) | 10:11 ± 4:40 | 7:42 ± 3:18 | 6:24 ± 2:27 | 0.007*,# |
| Squeeze hand (min:sec) | 11:17 ± 5:11 | 9:30 ± 4:02 | 7:38 ± 2:32 | 0.029# |
| Tell birthday (min:sec) | 15:10 ± 7:02 | 12:33 ± 4:43 | 9:41 ± 3:35 | 0.023# |
| Discharge from the recovery room (min) | 57 ± 21 | 42 ± 15 | 43 ± 15 | 0.014*,# |

Recovery from anaesthesia was quickest in group DES throughout all measured parameters (*isoflurane vs. sevoflurane; #isoflurane vs. desflurane). Values are mean ± standard deviation

during mechanical ventilation and spontaneous breathing. Target concentrations were mostly reached within 5 min. Three times, leakages occurred and MIRUS™ was stopped prior to surgery. We choose moderate speed for VA injection only, although the system offers three injection modes. Consequently, wash-in times can be varied, depending on the patient's individual needs. Mean wash-in time with moderate speed of VA injection was shorter than previously described for the AnaConDa™ (13.5 ± 2.7 min), when it was inserted in a circle system and manually adjusted to achieve an end-tidal SEVO concentration of 1.5% in an operating room setting [2]. An explanation might be, that MIRUS™ applies the VA punctually at the beginning of inspiration (when the flow is highest), thus allowing the VA to reach the alveoli before being delivered to the circuit and washed-out with the next expiration.

During spontaneous breathing using the PAV mode after 1 h of surgery, the WOB was still within a normal range, although the device's total dead space is at least 100 ml [4]. Airway compliance, resistance and the rapid swallow breathing index were in normal ranges, too.

Gas consumption primary depends on the MAC, which is lowest for ISO. Up to now, data on VA consumption of the MIRUS™ system are rare and comparisons can hardly be made. In 2014, a benchmark study was published, stating that 40 ml $h^{-1}$ DES would be needed to maintain an expired fraction of 6.0–6.6% [1]. A case report presented a consumption of 53 ml $h^{-1}$ DES to maintain DES at 3.3–3.8% end-expiratory in a woman with ARDS [5]. In a recently published study, SEVO consumption was 7.89 ml $h^{-1}$ for a MAC of 0.45, corresponding to an expired SEVO fraction of 0.76 ± 0.18% during short term ICU sedation [6]. We assume that the amount of VA, which is necessary for sedation (0.5 MAC), would be less than half of the amount used for anaesthesia (1.0 MAC), because the system's reflection efficiency is highest at lower end-expiratory concentrations between 0.2 and 1.0%, which are commonly used in the ICU [1].

Awakening after surgery was quickest after DES exposure (5.27 min) with the reflector within the breathing system. Romagnoli et al. reported an awakening time of approximately 4 min after SEVO application, but disconnected the reflector from the breathing system [6]. Here, awakening after use of SEVO with the reflector within the breathing system lasted 2.5 min longer. Consumption of ISO was lowest, but recovery times lasted significantly longer compared to SEVO and DES.

In summary, in a small group of ASA II–III patients undergoing orthopaedic surgery, the MIRUS™ was able to attain and maintain 1.0 MAC of ISO, SEVO and DES in the end-expired gas. During spontaneous assisted ventilation, WOB was within a normal range. These findings are encouraging to further explore the use of MIRUS™ for anaesthesia and sedation.

**Author contributions** MB: study design, experimental setup, statistical analysis, writing up the first draft of the manuscript, study coordinator and guarantor. DD: experimental setup, data collection. VV: study design, data collection. LP: writing up the first draft of the manuscript, review and editing. BJ: data collection. AM: study design, experimental setup, interpretation of data. HB: interpretation of data. HV: patient recruitment, review and editing of the manuscript. PG: patient recruitment, study design, experimental setup, data analysis. TPW: study design, review and editing of the manuscript. JH-N: study design, statistical analysis, writing up the first draft of the manuscript, review and editing. All authors have read and approved the final draft. All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Funding** The MIRUS™ system was kindly provided by the manufacturer (Pall Medical, Dreieich, Germany).

## Compliance with ethical standards

**Conflict of interest** Bellgardt und Herzog-Niescery received speakers honoraria from Pall Medical, Dreieich, Germany. The other authors declare that they have no conflict of interest.

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