Spontaneous breathing for managing analgesia during balanced anesthesia with remifentanil and desflurane: a prospective, single center randomized controlled trial

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Abstract

The main goal of anesthesiology is to achieve the best level of analgesia and a fast recovery of consciousness following anesthesia. The preservation of spontaneous breathing during general anesthesia with anesthetic gases is practiced by many anesthetists. However, very few studies have dealt with these positive properties of volatile anesthetics such as sevoflurane or desflurane. Remifentanil is a very short half-life opiate that combines sufficient intra-operative analgesia with a fast post-operative recovery time. We tested the hypothesis that spontaneous breathing can reduce overdosing with remifentanil during desflurane anesthesia. In this prospective, single center, multiple anesthetist study, 30 patients were randomized into two groups (volume-controlled ventilation mode and spontaneous breathing). The spontaneous breathing group showed a significantly lower post-operative pain level than the volume-controlled ventilation mode group. Furthermore, less remifentanil as well as less piritramide was needed in the spontaneous breathing group compared with volume-controlled ventilation mode. It was possible to achieve spontaneous breathing in all patients with 0.6 minimum alveolar concentration desflurane, in order to control the remifentanil rate and prevent an overdose. All spontaneous breathing patients had low intra- and post-operative pain levels and the need for analgesics was equal to or lower than that in the volume-controlled ventilation mode group. By reducing the intra-operative amount of opiates, both the post-operative pain and the amount of post-operative analgesia required can be reduced. A balanced anesthesia with spontaneous intra-operative breathing is needed to determine the required amount of opiates. This study was approved by the Ethic Committee of the Ruhr-University of Bochum (approval No. 2435) in September, 2004.

Key words: balanced anesthesia; BIS; bispectral index; desflurane; minimum alveolar concentration; remifentanil; spontaneous breathing for management analgesia; volatile anesthetics

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Introduction

Other than the patient's safety during an operative intervention, the main goal of anesthesiology is to achieve the best level of analgesia and a fast recovery of consciousness after anesthesia.[1] The preservation of spontaneous breathing during general anesthesia with anesthetic gases is practiced by many anesthetists. However, very few studies have dealt with these positive properties of volatile anesthetics such as sevoflurane or desflurane. Anesthesiologists agree that reaching the optimal level of analgesia is in conflict with the goal of a fast recovery of consciousness. The main reason for this is the respiratory depressant effect of opiates, which are necessary for analgesia. To combine sufficient intra-operative analgesia with a fast recovery time, remifentanil as an opiate with a very short half-life was developed.[2,3] In contrast to other opiates, remifentanil is degraded by non-specific esterases and has a half-life of less than four minutes. Additionally, its degradation products are not clinically relevant due to their very light analgesic potency which is 300 to 4600 times less than the potency of remifentanil itself.[2,4] Consequently, in contrast to fentanyl and sufentanil, even after several hours of infusion no cumulative effect can be observed after the usage of remifentanil.[5] Due to these characteristics, while remifentanil is an easy to handle opiate during the operation, it does require additional attention for post-operative analgesia.

Even though great progress has been made in the field of post-operative analgesia, patients still suffer from insufficient intra- and post-operative analgesia. Later, different concepts were developed attempting to optimize post-operative analgesia in patients who underwent intra-operative treatment with remifentanil. Kochs et al.[6] tried additional applications of morphine or fentanyl 25 minutes before the end of the operation. Neither this, nor other similar concepts by other research groups, led to improved post-operative analgesia.[7-9] Additionally, studies in which the remifentanil application was prolonged after waking up the patient using a dosage between 50 to 230 ng/kg per minute failed due to respiratory depression.[10-12]

Based on this background, we sought a novel concept to fulfill both requirements: the preservation of the beneficial effects of remifentanil, and the minimization of post-operative pain after the usage of remifentanil. We tested the hypothesis

that spontaneous breathing can reduce overdosing with remifentanil during desflurane anesthesia. To do this, we tried to optimize analgesia without reaching the level of respiratory depression. The second aims were the consumption of remifentanil, depth of anesthesia, end-tidal CO_2 levels, wake-up time, pain score using the Visual Analog Scale (VAS), and usage of piritramide and oxygen saturation. In all patients the wake-up time was monitored. We evaluated the time point when patients opened their eyes, were able to move their hands and were able to reproduce their date of birth.

Subjects and Methods

This is a single blinded prospective, single center, multiple anesthetist study. Between November 2004 and January 2005, 56 patients awaiting an orthopedic or traumatological operation at St. Josef-Hospital, which did not require muscle relaxation, were included in the study (**Figure 1**). Multiple variables such as demographics, performed operative procedure, number of required doses of piritramide after the operation, blood gas analysis, pain score and duration of post-operative monitoring were compared between the two groups. Inclusion criteria were balanced anesthesia and orthopedic or traumatological operation is needed. Exclusion criteria were patients younger than 18 years, pregnancy, operative procedures requiring a relaxant or additional local anesthesia, body mass index greater than 35 kg/m^2, kidney or liver insufficiency, neurological disease, allergic reactions to desflurane, remifentanil or piritramide.

This study was approved by the Ethic Committee of the Ruhr-University of Bochum (approval No. 2435) in September, 2004. Patients were informed about the study modalities at least one day before the operation, were asked for an agreement to participate in this study and signed a declaration of consent. The VAS to quantify post-operative pain was then explained to the patients. Every patient received 7.5 mg midazolam (Dormicum, Roche, Basel, Switzerland) as premedication on the ward. After arrival in the holding area, patients were connected to a monitoring device to track vital parameters. The patients were then equipped with a 22G venous cannula for administration of intravenous medication. Shortly before the operation starting time, the patients were transferred to the operation room and anesthesia was commenced with the administration of 2.0 to 2.5 mg/kg propofol (Disoprivan, AstraZeneca, Wedel, Germany) followed by intubation and randomization (via envelope managed by the hospital pharmacist) to one of the two study groups (1:1). Randomization was performed following induction of anesthesia just prior to the start of the operation.

All patients received 0.6 minimum alveolar concentration desflurane (Suprane, Baxter, Unterschleißheim, Germany) automated controlled by the anesthesia machine Zeus (Dräger Medical, Lübeck, Germany).

The volume-controlled ventilation mode group (VC group) received remifentanil (Ultiva, GlaxoSmithKline, Hamburg, Germany) at a dose of 100 to 400 ng/kg per minute applied continuously via syringe pump with a concentration of 1.0 mg/50 mL and was ventilated by the ventilator Zeus using the volume-controlled ventilation mode. In the spontaneous breathing group (SB group) was established by adjusting the remifentanil dose depending on the end-tidal CO_2 level. In the SB group the patients were ventilated using the pressure support mode of the ventilator. The support pressure was adjusted to a maximum of 10 mbar (1 mbar = 0.1 kPa) and the positive end-expiratory pressure to 5 mbar. An end-tidal CO_2 level of up to 8 kPa was tolerated to give the patients a strong trigger to start spontaneous breathing as soon as possible. Once spontaneous breathing started, CO_2 levels were regulated to a level of 6 kPa; this was done by increasing the remifentanil administration if end-tidal CO_2 levels dropped below this level and by down-regulation if end-tidal CO_2 levels were above this level. At the end of the operation one capillary blood gas analysis was taken and the remifentanil infusion was continued at the same level for post-operative analgesia. Desflurane was discontinued to bring an end to the anesthesia. The remifentanil infusion was also then discontinued once the patient reached the post-operative care unit. The depth of anesthesia was measured using the bispectral index (BIS; BIS® XP monitor; Aspect Medical Systems, Norwood, MA, USA; electrode impedance was kept below 5 kΩ).

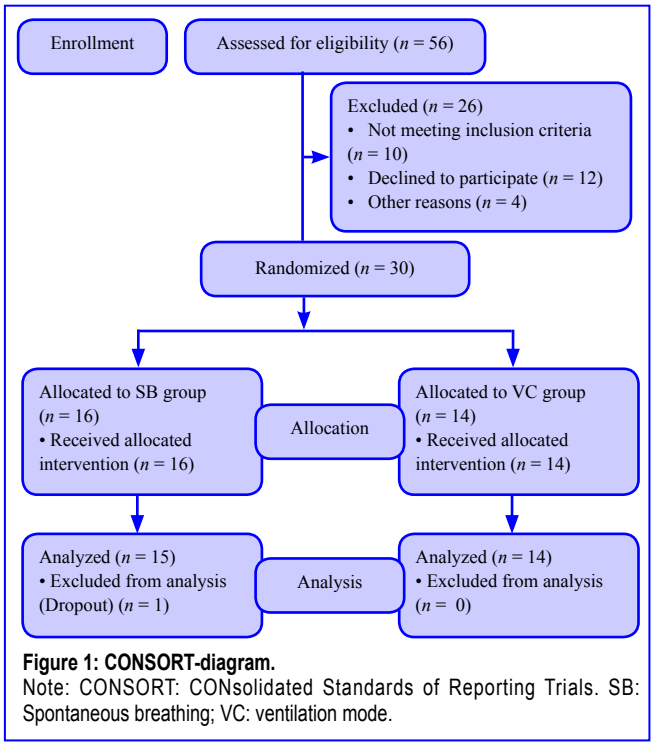

Figure 1: CONSORT-diagram.
Note: CONSORT: CONsolidated Standards of Reporting Trials. SB: Spontaneous breathing; VC: ventilation mode.

In the VC group patients underwent controlled ventilation and their breathing was adjusted to an end-tidal CO_2 level of 5.3 kPa. The remifentanil dose was adjusted between 100 to 400 ng/kg per minute to prevent effective spontaneous breathing. At the end of the operation remifentanil as well as desflurane were stopped to wake the patient up.

Every patient received a 2.5 g of metamizole (Novalgin, Sanofi-Aventis, Frankfurt am Main, Germany) close to the end of the operation to prevent post-operative pain.

During transportation to the patient holding area and at the time of arrival in the patient holding area, patients were asked to indicate their pain level on a VAS (0 to 10; 0 = no pain and 10 = maximum imaginable pain). On indicating two points

or more, a bolus of 3.75 mg piritramide (Dipidolor, Janssen-Cilag, Neuss, Germany) was offered.

During the time spent in the patient holding area patients were asked every 10 minutes to indicate their pain level using the VAS and were questioned regarding emesis and shivering. Every patient was also questioned regarding pain, emesis and shivering during the first post-operative day on the ward.

Emesis was treated with antiemetics and shivering with heated blankets. The time and amount of all administered substances and care were documented.

Data collected during the operation was protocolled manually in a case report file. From the point of intubation, the following data were collected every 5 minutes: "Spontaneous-Breathing-Index" (from 0 to 3; 0 = no spontaneous breathing, 1 = starting to breathe spontaneously < 20% of minute volume or pressure support > 1 kPa, 2 = mostly breathing spontaneously: less the 50% of minute volume and pressure support ≤ 1 kPa, 3 = constantly breathing spontaneously: > 50% of minute volume and pressure support ≤ 1 kPa), CO_2, tidal volume, frequency of breathing, oxygen saturation. Clinical parameters were saved electronically every three seconds.

Data collection and subsequent statistical analysis were performed with MS Excel for Windows (MS Office 2003, Version 11, Redmond, WA, USA) and SPSS for Windows (Version 14, SPSS Inc., Chicago, IL, USA). A power analysis was performed (power > 80%) and a total amount of $n = 30$ patients was defined. Statistical tests of significance were performed and a P-value < 0.05 was assumed to be statistically significant. Continuous variables were analyzed using a two-tailed Student's t-test for independent samples. Categorical or dichotomous data are presented in number (percentage) and were compared using the Chi-square test.

Results

Demographic data of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

No significant differences were found between the two groups regarding age, sex, height and weight (**Table 1**).

Duration of the operation and anesthesia of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

All patients included in this study underwent an orthopedic or trauma surgery. The operations included 15 decompressions of the lumbar spine in degenerative spinal stenosis, 6 arthroscopies of the knee, 2 lumbar discectomies and 6 other orthopedic or traumatic operations. Concerning the duration of the operation (incision until last stitch) and the duration of the anesthesia (intubation until extubation) no significant differences were found between the two groups (**Table 1**).

Drugs use for orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

No significant differences were observed in the desflurane consumption between two groups. However, the remifentanil dose was significantly lower in the SB group – even though the remifentanil infusion was continued after waking up the patient. The patients of SB group needed only approximately half of the remifentanil dose compared to the VC group (P = 0.040). Additionally, we observed that the VC group needed significantly higher doses of piritramide as pain medication after the end of the operation (**Table 2** and **Figure 2**).

Depth of anesthesia of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

Even though there was a small tendency to higher BIS values in the VC group no significant differences could be observed. No signs of awareness or spontaneous movements were observed in any patient intra-operatively (**Table 2**).

Vital parameters of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

No significant differences were observed relating to heart rate and mean arterial pressure (**Table 2**).

Table 1: Demographics of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

	Spontaneous breathing group (n = 15)	Volume-controlled ventilation mode group (n = 14)	P-value
Age (yr)*	54±14	56±15	> 0.05
Sex (female:male)#	9:6	4:10	> 0.05
Height (cm)*	171±13	174±8	> 0.05
Weight (kg)*	77±12	83±14	> 0.05
Type of surgery#			
Decompressions of the spine	7	8	> 0.05
Arthroscopies of the knee	5	1	> 0.05
Discectomies of the spine	1	1	> 0.05
Other orthopedic or traumatic surgery	2	4	> 0.05
Duration of the surgery (h)*	1.05±0.58	1.25±1.09	> 0.05
Duration of the anesthesia (h)*	1.70±0.78	1.95±1.10	> 0.05

Note: *Data are expressed as the mean ± SD and were analyzed by two-tailed Student's t-test. #Data are expressed as the number and were analyzed by Chi-square test.

Table 2: Drugs use for orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

	Spontaneous breathing group (n = 15)	Volume-controlled ventilation mode group (n = 14)	P-value
Midazolam 7.5 mg (number of medications) #	13	11	> 0.05
Mivacurium (mg/kg) *	0.19±0.03	0.25±0.19	> 0.05
Propofol (mg/kg) *	2.26±0.24	2.44±0.52	> 0.05
Desflurane (MAC h) *	0.97±0.54	1.16±0.73	> 0.05
Remifentanil (mg) *	0.79±0.38	1.61±1.43	0.040
Metamizole 2.5 g intravenous injection (n) #	15	14	> 0.05
Piritramide (mg) *	2.0±3.1	21.6±17.3	< 0.001
Paracetamol 1 g intravenous injection (n) #	1	1	> 0.05
Metoclopramide 10 mg (number of medications) #	2	3	> 0.05
Visual Analog Scale*	2.5±2.2	6.4±1.8	< 0.001
Bispectral Index*	45±13	48±6	> 0.05
Heart rate (beat/min)*	65±6	64±9	> 0.05
Mean arterial pressure (mmHg)*	77±10	77±6	> 0.05

Note: *Data are expressed as the mean ± SD and were analyzed by two-tailed Student's t-test; #Data are expressed as the number and were analyzed by Chi-square test. MAC: Minimal alveolar concentration.

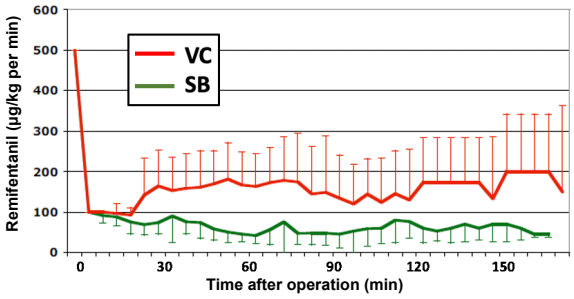

Figure 2: Dosage of remifentanil intra-operative (infusion start until end of operation) of orthopedic or traumatological patients under desflurane anesthesia with/without SB.
Note: Data are expressed as the mean ± SD. SB: Spontaneous breathing; VC: ventilation mode.

Wake-up time of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

The patients of the SB group took slightly longer to arrive in the holding area (SB *vs*. VC: 16.73 ± 4.87 minutes *vs*. 14.12 ± 3.87 minutes, $P > 0.05$). Even though there was a slight tendency to a faster wake-up in the SB group, no significant differences could be found between the two groups (open eyes SB *vs*. VC: 3.77 ± 1.38 minutes *vs*. 4.07 ± 1.53 minutes, $P > 0.05$).

Impact desflurane anesthesia with/without spontaneous breathing on the surgical procedure

No surgeon became aware of the spontaneous breathing of a patient. None of the surgical procedures were affected in any way through the department of anesthesiology.

Blood gas analysis of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

Capillary blood gas analysis showed significantly lower pH levels and higher CO_2 levels in the SB group compared with VC group (**Table 3**).

Post-operative pain of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

Post-operative pain was significantly lower in the SB group compared to the VC group ($P < 0.001$). The relative dose of piritramide given was also highly significantly lower for the SB group *vs*. the VC group ($P < 0.001$). As a result of the lower pain levels of the SB group, these patients were transferred to a regular ward faster than the patients of the other group (SB: 72 ± 20 minutes *vs*. 115 ± 72 minutes; $P = 0.034$).

Discussion

In 1997, Wilhelm et al.[13] published a multicenter study to evaluate the necessary dose of remifentanil to achieve sufficient analgesia during operative procedures. They found that an average infusion rate of 200 ng/kg per minute was necessary to maintain sufficient analgesia in most patients. These results were confirmed by other studies.[14,15] However, in our study we found that the patients of the SB group required dramatically lower doses of remifentanil (85.7 ng/kg per minute) than described in the literature. The dose of remifentanil was reduced in our experimental set-up until spontaneous breathing started. Even though we used such low doses of remifentanil, we did not observe clinical signs of awareness such as an increase in blood pressure, the heart rate or the BIS value. The mean arterial pressure was 77 mmHg in both groups. The heart rate was 65 beats/min in the SB group and 64 beats/min in the VC group. Additionally, we observed a very stable hemodynamic situation in both patient groups. Both groups received equal amounts of infusions and medications such as Akrinor and atropine. This indicates that even low doses of remifentanil are sufficient to block hemodynamic reactions due to pain during surgical intervention.

Guignard et al.[16] found in their studies that after continuous propofol infusion of 4 mg/kg per minute, additional remifentanil infusion did not have an effect on the BIS values unless an additional pain stimulus was applied. The authors

Table 3: Blood gas analysis of orthopedic or traumatological patients under desflurane anesthesia with/without spontaneous breathing

	Spontaneous breathing group (n = 7)	Volume-controlled ventilation mode group (n = 9)	P-value
Fraction of inspired oxygen	0.43±0.05	0.42±0.02	> 0.05
pH	7.30±0.03	7.40±0.02	< 0.001
Partial pressure of carbon dioxide (kPa)	7.3±0.6	5.6±0.5	< 0.001
Partial pressure of oxygen (kPa)	24±4	22±7	> 0.05
Oxygen saturation (%)	98.6±0.3	98.7±0.4	> 0.05
Base excess (mM)	0.5±1.6	0.9±1.7	> 0.05

Note: Data are expressed as the mean ± SD, and were analyzed by two-tailed Student's t-test.

concluded that BIS does not measure analgesia directly, but that an increase of the BIS value might be a reaction to pain. According to the manufacturer of the BIS-Monitor, BIS values between 40–60 are ideal values for surgical interventions. Even though the volume-controlled ventilation group showed a tendency to higher BIS values, the results stayed within this range – again indicating a sufficient depth of sedation. Guignard et al.[17] also reported increased post-operative pain and morphine consumption when using relatively large doses of intra-operative remifentanil. They concluded remifentanil causes acute opioid tolerance and hyperalgesia, which matches with our findings. This opioid-induced hyperalgesia has also been described by Lee et al.[18] However, the molecular mechanism remains unclear. Theories vary, e.g. neuroplastic changes in the nerval system causing sensitization of pronociceptive pathways. Hood et al.[19] published similar results stating an acute opioid exposure is associated with enhanced hypersensitivity for hours after exposure. At the same time, we found no significant differences in the wake-up time between the two experimental groups. This indicates that even though a reduction of the opiate dose seems to be safe without putting patients at risk of awareness, it has no effect on the time taken to regain consciousness.

As expected, our blood gas analysis showed significantly higher CO_2 levels in the SB group. The reason for this is that it was necessary to increase the CO_2 blood levels to trigger spontaneous breathing during anesthesia. As a result of increased CO_2 levels, we also observed significantly lower pH levels in the SB group. To limit these necessary side effects, we ventilated the SB group using the pressure support mode of the ventilator. The support level was adjusted up to a level of 10 mbar to maintain a tidal volume of 8 mL/kg. Additionally, the remifentanil dose was adjusted continuously to maintain a sufficient level of analgesia and at the same time to reduce opiate-induced respiratory depression.

Another important target parameter of the study was the post-operative pain level. Remifentanil is known as an opiate which is effective for a very short time period.[2] Accordingly, as soon as remifentanil is discontinued, patients do not have sufficient analgesia and usually require an alternative pain killer. To our knowledge, in this study for the first time the patient-individual opiate dose was determined by establishing spontaneous breathing during anesthesia. This level was continued after anesthesia and after regaining consciousness. These findings match the results of Meijer et al.' study,[20] who described similar results, e.g. 30% less remifentanil consumption in nociception level guided analgesia during major abdominal surgery.

In conclusion, it is possible for patients to breathe spontaneously during volatile anesthesia with desflurane. Overdosing with opioids, with the side effects of circulatory depression and postoperative hyperalgesia, can be avoided. The quality of the anesthesia can be improved. Especially in analgosedation in intensive care, avoiding overdosing is an important goal.[21,22] When using anesthetic gases, the depth of sedation can be measured using the end-tidal gas concentration and controlled precisely. While the patient is unconscious, it is not possible to use scores to measure pain. By monitoring the frequency of spontaneous breathing, it is possible to measure the effect of opioids and to control them adequately. Future research is still needed with a focus on other surgical procedures and in ICU sedation settings. Furthermore, similar studies should use different volatile anesthetics to confirm our results.

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Author contributions
Study design and data analysis: AM, MB; study implementation and statistical analysis: AM; data collection: AM, MB, HV; manuscript writing: MW; manuscript revision: MT, TL, TPW. All authors revised the manuscript and approved the final version.

Conflicts of interest
There is no potential conflict of interest of the authors.

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Institutional review board statement
This study was approved by the Ethic Committee of the Ruhr-University of Bochum (approval No. 2435) in September, 2004.

Declaration of patient consent
The authors certify that they have obtained patients consent forms. In the form, patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published.

Reporting statement
The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement.

Data sharing statement
Datasets analyzed during the current study are available from the

corresponding author on reasonable request.

Plagiarism check

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Peer review

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