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Effective Target Concentration of Sufentanil Combined With Sevoflurane Anesthesia for Abdominal Surgery: A Dose-Response Study

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This study was designed to investigate the effects of target-controlled infusion (TCI) of sufentanil with sevoflurane anesthesia on hemodynamics and postoperative recovery of abdominal surgery. Target-controlled infusion of opioid analgesics provides efficient drug use, allowing an accurate achievement of the desired analgesia level and fewer overdose-induced adverse effects. A total of 80 patients receiving abdominal surgery (surgery for gastric cancer or colorectal cancer) were divided into 4 groups to receive anesthesia with sevoflurane accompanied with different doses of sufentanil (0.4, 0.6, 0.8, or 1.0 ng/mL). Systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, times to recovery of spontaneous respiration, eye opening, extubation, and orientation were recorded. Hemodynamic measurements were compared among groups. Comparison between the 2 groups of subjects was made with one-way analysis of variance (ANOVA), LSD-*t* test, or χ^2 test. Although sufentanil at 0.8 and 1.0 ng/mL maintained stable perioperative hemodynamics, the higher dose was associated with increased incidence of bradycardia following intubation (10/19 cases, 52.6%; $P < 0.05$). Additionally, no differences were observed in the incidence of hypotension, hypertension, or tachycardia between groups ($P > 0.05$). Increased dose of sufentanil was associated with delayed postoperative recovery. These results demonstrate that TCI at 0.8 ng/mL sufentanil accompanied with sevoflurane anesthesia is a suitable anesthetic regimen for abdominal surgery.

Key words: Sufentanil – Sevoflurane – Target-controlled infusion – Hemodynamics and postoperative recovery

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Modern anesthetic techniques aim at providing rapid induction, stable perioperative hemodynamics, rapid recovery, and a decreased incidence of postoperative complications. Target-controlled infusion (TCI) of anesthetic and analgesic drugs makes these goals achievable through maintaining the minimal effective concentration of drugs.[1]

Target-controlled infusion of opioid analgesics provides efficient drug use, allowing an accurate achievement of the desired analgesia level and fewer overdose-linked adverse effects.[2,3] Sufentanil is reported to be more potent than fentanyl.[4] In addition, remifentanil is demonstrated to be associated with an increased incidence and severity of cough than sufentanil and fentanyl.[5] Emerging lines of evidence reveal that TCI of sufentanil can be efficiently administrated during cardiac surgery.[6] Moreover, TCI of sufentanil is demonstrated to be more effective than the intraoperative combination of remifentanil TCI infusion with a morphine bolus for postoperative pain relief following major abdominal surgery.[7] The combined administration of a volatile anesthetic such as sevoflurane and infusion of an opioid such as sufentanil is a widely used anesthesia procedure.[8] However, the effective target concentration of sufentanil that can be combined with sevoflurane for abdominal surgery has not been clearly defined. Additionally, its effects on perioperative hemodynamics and postoperative recovery were not clearly illustrated.

The aim of the present study was to determine the effective target plasma concentration of sufentanil that can be combined with sevoflurane for anesthesia for abdominal surgery, to produce stable hemodynamics and favorable recovery with minimal postoperative complications.

Materials and Methods

Patients

The study was performed in Taizhou Hospital between November 2008 and May 2009. A total of 80 patients having American Society of Anesthesiologists (ASA) physical status I or II and undergoing elective abdominal surgery for gastric cancer or colorectal cancer were included in the study. Patient age was between 21 and 62 years and weight between 43 and 89 kg. Subjects were randomly divided into the following 4 groups: group A ($n = 22$); B ($n = 21$); C ($n = 18$); and D ($n = 19$), to receive 0.4, 0.6, 0.8, or 1.0 ng/mL sufentanil for anesthesia induction. Group assignment was performed by drawing lots. Patients who had heart failure, lung dysfunction, brain disease, history of drug addiction, or excessive alcohol intake were excluded. Pregnant and lactating women were also excluded. All participants who met the eligibility criteria were recruited after signing an informed consent. The study was approved by the ethics committee at Taizhou Hospital.

Anesthesia procedure

Patients were intravenously injected with midazolam 0.04 mg/kg 30 minutes prior to anesthesia. Following intravenous cannulation, patients were given lactated ringer's solution at a rate of 8 to 10 mL/kg/h. An anesthesia monitor (Cardiocap 5, GE Healthcare, Waukesha, Wisconsin) was used for monitoring continuous arterial blood pressure (ABP), electrocardiogram (ECG), heart rate (HR), and plethysmographic oxygen saturation (SpO_2). The bispectral index (BIS) was recorded using an electroencephalogram (EEG) monitor (Aspect Medical Systems, Medtronic Operational Headquarters, Minneapolis, Minnesota). Target controlled infusion of anesthetic drugs was administered using a commercial system (TCI2-II, SLGO, Beijing, China). Anesthesia was induced using 5% sevoflurane in an oxygen flow of 4 L/min. Once the BIS value was reduced to 60, intubation was facilitated by intravenous infusion of 0.15 mg/kg vecuronium. Anesthesia was maintained with sevoflurane and sufentanil. Sevoflurane concentration was adjusted to maintain a BIS value between 45 and 55. Sufentanil TCI was adjusted to maintain the target plasma level between 0.4 to 1.0 ng/mL according to the patients' group. The plasma level of drugs was measured automatically using the TCI system. Muscle relaxation was achieved by intermittent intravenous administration of vecuronium (0.04 mg/kg). Sufentanil infusion was maintained until 45 minutes prior to the end of the operation and the administration of sevoflurane was stopped at the end of skin closure. By the end of surgery, anesthetic gases were washed out with an oxygen flow of 5 L/min. Neostigmine (2.5 mg) and atropine (1.25 mg) were used to reverse the nondepolarizing muscle relaxant.

In addition, patients received additional boluses of ephedrine (6 mg), in the event that the mean arterial pressure (MAP) was lower than 30% of baseline value; or additional boluses of urapidil (12.5 mg) were applied when MAP was higher than 30% of baseline value. Patients received atropine (0.5 mg) when HR was less than 50 beats/min, or

Table 1 Patient demographic data

Group	n	Sex, M/F	Age, y	Weight, kg	Height, cm	Operation time, min
A	22	10/12	46 ± 4	60 ± 7	164 ± 8	130 ± 21
B	21	8/13	47 ± 8	59 ± 8	164 ± 6	128 ± 23
C	18	9/9	45 ± 7	59 ± 10	165 ± 7	136 ± 19
D	19	9/10	46 ± 6	60 ± 8	166 ± 10	129 ± 25

A total of 80 patients having ASA physical status I or II and undergoing elective abdominal surgery were included. Patients in groups A, B, C, and D received 0.4, 0.6, 0.8, or 1.0 ng/mL sufentanil, respectively, for anesthesia induction.

Data were expressed as number of patients or mean ± SD or number. There were no significant differences between the 4 groups.

esmolol (20 mg) when HR was greater than 100 beats/min.

Hemodynamic evaluation

We recorded MAP and HR prior to the induction of anesthesia (baseline, T0), immediately before tracheal intubation (T1); at intubation (T2); 5 minutes (T3) and 10 minutes (T4) after intubation; during skin incision (T5); peritoneal incision (T6); surgical manipulation (T7); at the end of operation (T8); and at extubation (T9).

Postoperative recovery analysis

Times to recovery of spontaneous respiration, eye opening, extubation, and orientation were monitored. Pain intensity was assessed using the visual analog score (VAS), on a 0 to 10 scale, in which scores of 0 to 3 were classified as mild pain and 10 was unbearable pain. Moreover, Ramsay sedation score was used to evaluate the depth of sedation, in which 1 = anxious or restless or both; 2 = cooperative, orientated, and tranquil; 3 = responding to commands; 4 = brisk response to stimulus; 5 = sluggish response to stimulus; and, 6 = no response to stimulus. Abnormal sedation was defined as a score = 1 or ≥3. Other emerging adverse effects, such as skin itch, nausea, vomiting, or respiration depression, were recorded in the follow-up period. Morphine or compound aminopyrine phenacetin tablets were applied if patients were in severe postoperative pain.

Statistical analysis

Sample size was based on previous studies.[9] A reduction of 20% in the MAP was thought to be clinically significant. A sample size of 17 patients in each group was calculated to detect this difference with a type I error of 0.05 and type II error of 0.20. Data were analyzed using statistical software (SPSS 11.5, SPSS, Inc, Chicago, Illinois) and were plotted as mean ± SD. Comparison between the 2 groups of subjects was made with one-way analysis of variance (ANOVA), LSD-*t* test, or χ^2 test. A value of $P < 0.05$ was recognized as significantly different.

Results

Patient demographics

As shown in Table 1, the 4 patients groups were matched by age, weight, height, and sex ($P > 0.05$).

Perioperational hemodynamics changes

As shown in Fig. 1, the levels of MAP and HR were dramatically reduced prior to tracheal intubation (T1), compared with baseline values (T0, before induction of anesthesia; $P < 0.05$). These values increased again to baseline values with intubation. However, the levels of these hemodynamic parameters were significantly elevated during surgical manipulation (T7) relative to their baseline levels (T0; $P < 0.05$). Furthermore, hemodynamic parameters were remarkably reduced when a sufentanil infusion of 0.8 (group C) or 1.0 ng/mL (group D) was applied compared with a sufentanil administration of 0.4 (group A) or 0.6 ng/mL (group B; $P < 0.05$), suggesting moderate or high doses of sufentanil treatment (0.8 or 1.0 ng/mL) can maintain stable hemodynamic changes.

Comparison of hemodynamic measurements in patients from different groups

No differences were detected in the incidence of hypotension, hypertension, or tachycardia (Table 2; $P > 0.05$), whereas group D patients exhibited a higher rate of bradycardia following intubation (10 cases, 52.6%) compared with patients in other groups ($P < 0.05$).

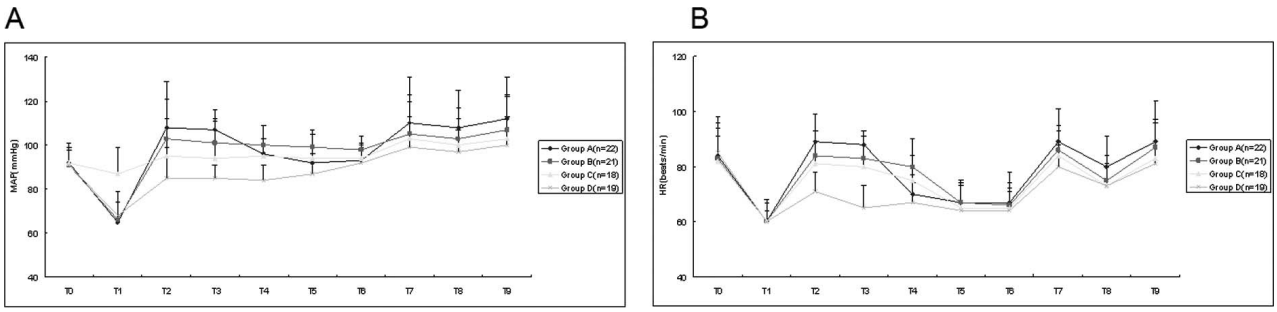

Fig. 1 Hemodynamic changes associated with anesthetic induction and intubation. Patients in groups A, B, C, and D received 0.4, 0.6, 0.8, or 1.0 ng/mL sufentanil, respectively, for anesthesia induction. We recorded MAP (A) and HR (B) at indicated time points as described in "Materials and Methods" section.

Postoperative recovery analyses

All recovery times were significantly increased with the increase in sufentanil dose infused (Table 3). In contrast, no differences were found in pain intensity and sedation depth among the 4 groups. In addition, there were no differences in morphine or aminopyrine phenacetin tablet consumption at 2 or 22 hours following surgery ($P > 0.05$). The incidence of nausea and vomiting was similar, approximately 31.87%, in all 4 groups. Moreover, 4 cases in group D exhibited respiratory depression. Among the 80 patients, no awareness occurred during surgery.

Discussion

A variety of anesthetic agents have been administered during general anesthesia for abdominal surgery. The aim of anesthetic techniques is not only to reduce pain intensity caused by operation, but also to prevent the incidence of postoperative side effects and to improve outcomes following surgery.[10] The present study demonstrated that 0.8 ng/mL sufentanil accompanied with sevoflurane yielded a better hemodynamic stability during anesthesia for abdominal surgery and a favorable postoperative recovery, therefore, providing a valuable strategy for clinical anesthesia for abdominal surgery.

Sevoflurane, a fluorine-containing anesthetic drug, shares similar chemical structures and many physical properties of isoflurane and enflurane.[11] Due to its efficiency in rapid anesthesia induction, maintenance of circulation stability, and few side effects, sevoflurane is believed to be suitable for clinical use. Moreover, sevoflurane has a low blood-gas solubility coefficient and is not irritating to the airways.[12] However, Sloan *et al*[13] reported that patients who received sevoflurane developed one or more complications, such as coughing, shivering, and excessive secretions during emergence from surgery. Sufentanil is an opioid similar to fentanyl, but 8 to 10 times more lipid soluble.[14] The anesthesia start time of sufentanil is 2.8 to 3.2 minutes, and an intravenous injection of sufentanil 1 to 3 minutes prior to intubation can efficiently prevent tracheal intubation responses.[15,16] Emerging lines of research reveal that sufentanil is a potent opioid with a shorter duration of action compared with other opioids, and it preserves hemodynamics in patients.[17,18] Cumulative evidence suggests that the

Table 2 Comparison of the hemodynamic measurements in patients from different groups

		Hypotension, n (%)		Hypertension, n (%)		Tachycardia, n (%)		Bradycardia, n (%)	
Group	n	Before intubation	After intubation	Before intubation	After intubation	Before intubation	After intubation	Before intubation	After intubation
A	22	7 (31.8)	4 (18.2)	3 (13.6)	4 (18.2)	1 (4.55)	3 (13.6)	8 (36.4)	0 (0)
B	21	5 (23.8)	6 (28.6)	1 (4.8)	3 (14.3)	1 (4.8)	4 (19.0)	11 (52.4)	1 (4.8)
C	18	5 (27.8)	4 (22.2)	0 (0)	2 (11.1)	0 (0)	0 (0)	10 (55.6)	1 (5.6)
D	19	12 (63.2)	8 (42.1)	0 (0)	0 (0)	2 (1.1)	2 (1.1)	9 (47.4)	10 (52.6)[a]

Patients in Group A, B, C and D received 0.4, 0.6, 0.8, or 1.0 ng/mL sufentanil, respectively, for anesthesia induction.

[a]$P < 0.05$ compared with groups A through C.

Table 3 Comparison of the mean recovery time periods in patients from different groups

Group	Spontaneous respiration, min	Eye opening, min	Extubation, min	Recovery time of orientation, min
A	3.5 ± 1.3	4.4 ± 2.1	9.4 ± 3.2	12.6 ± 4.4
B	3.8 ± 1.5	4.8 ± 2.3	10.1 ± 3.8	14.8 ± 4.9
C	6.4 ± 2.8	7.7 ± 0.1	17.2 ± 5.1	18.1 ± 6.3
D	7.2 ± 3.4	8.9 ± 0.5	18.8 ± 6.7	20.0 ± 7.2

Patients in groups A, B, C, and D received 0.4, 0.6, 0.8, or 1.0 ng/mL sufentanil, respectively, for anesthesia induction.

use of TCI enables the efficient, safe, and stable administration of sufentanil.[19,20]

Combined administration of inhaled anesthetics and sufentanil has been widely used. Meaudre *et al*[21] found that 0.30 μg/kg sufentanil supplementation of sevoflurane during induction of anesthesia resulted in a better quality of induction without significant cardiovascular depression. Consistent with previous studies, our results show that infusion of sufentanil in combination with sevoflurane did not lead to any complications such as coughing, laryngospasm, and apnea, suggesting that the combined use of sufentanil and sevoflurane provides a stable and efficient anesthesia induction.

Target-controlled infusion adjusted infusion according to pharmacokinetic models via adjusting plasma drug concentrations and manipulation of sedative depth. A sufentanil TCI, together with sevoflurane, may yield a better induction and reduce side effects. We found that the values of MAP, HR, and BIS were significantly reduced prior to tracheal intubation (T1), compared with baseline (Fig. 1), suggesting the combined administration of sufentanil and sevoflurane has the ability to reduce blood pressure and inhibit electrical activity of the brain. These observations are closely related to the pharmacodynamics of these 2 anesthetics, as sevoflurane can decrease blood pressure through vasodilation, suppress brain activity by affecting the hypothalamus, limbic system projections to the cortical regions, and subsequently reduce the BIS value.[22,23]

It has been previously been recommended that the range of plasma target concentration of sufentanil should be in the range of 0.2 to 1 ng/mL.[24] Consistent with these results, we found that the hemodynamic values were remarkably reduced when 0.8 or 1.0 ng/mL of sufentanil infusion was administered compared with 0.4 or 0.6 ng/mL ($P < 0.05$; Fig. 1), revealing 0.8 or 1.0 ng/mL sufentanil can maintain stable hemodynamic changes. However, 1.0 ng/mL resulted in a higher incidence of bradycardia after intubation (Table 2). Additionally, 4 patients who received 1.0 ng/mL sufentanil exhibited respiratory inhibition (Table 2). After IV naloxone (0.2 mg), their breathing became more rhythmic. Notably, 2 of these subjects were aged 63 to 65 years, implying older patients may be more sensitive to higher doses of sufentanil treatment. Furthermore, the postoperative recovery time was extended with increasing the dose of sufentanil infused (Table 3). These observations demonstrate that sufentanil target concentration in the range 0.8 ng/mL is suitable for the maintenance of anesthesia during abdominal surgery and results in a better postoperative recovery.

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