# Medicine®

# Comparison of 2 effect-site concentrations of remifentanil with midazolam during percutaneous transluminal balloon angioplasty under monitored anesthesia care

## A randomized controlled study

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## Abstract

**Background:** Until now, target-controlled infusion of remifentanil with midazolam in percutaneous transluminal balloon angioplasty for dysfunctional hemodialysis fistulas has not been described. Here, we investigate 2 effect-site concentrations of remifentanil with intermittent bolus midazolam for percutaneous transluminal balloon angioplasty under monitored anesthesia care.

**Methods:** A prospective, randomized controlled trial including patients who received a percutaneous transluminal balloon angioplasty between March 2019 and March 2021 was conducted. Group 1 and Group 2 were, respectively, administered an initial effect-site concentration of remifentanil of 1.0 and 2.0 ng/mL by a target-controlled infusion pump with Minto model. In both groups, maintenance of the effect-site concentration of remifentanil was adjusted upward and downward by 0.5 ng/mL with intermittent bolus midazolam to keep the Observer's Assessment of Alertness/Sedation scale between 2 and 4, mean arterial pressure and heart rate at baseline levels ± 30%, and patient comfort (remaining moveless). The primary outcome was to determine the appropriate effect-site concentration of remifentanil for the procedure in terms of patient comfort (remaining moveless), hemodynamic conditions, and adverse events. Secondary endpoints included the total dosage of anesthetics and total times of target-controlled infusion pump adjustments.

**Results:** A total of 40 patients in Group 1 and 40 patients in Group 2 were eligible for analysis. Most parameters were insignificantly different between 2 groups, except Group 1 having higher peripheral oxygen saturation, while local anesthetic injection compared with Group 2. In addition, Group 1 patients had less apnea with desaturation (peripheral oxygen saturation < 90%; 0 vs 6, $P = .034$), less remifentanil consumption (189.65 ± 69.7 vs 243.8 ± 76.1 μg, $P = .001$), but more intraoperative movements affecting the procedure (14 vs 4; $P = .016$), total times of target-controlled infusion pump adjustment [2 (1-4) vs 1 (1–2), $P < .001$] compared with Group 2.

**Conclusion:** In percutaneous transluminal balloon angioplasty for dysfunctional hemodialysis fistulas, target-controlled infusion with remifentanil Minto model target 2.0 ng/mL with 3 to 4 mg midazolam use provided appropriate hemodynamic conditions, sufficient sedation and analgesia, and acceptable apnea with desaturation.

**Abbreviations:** ANI = analgesia nociception index, ASA = American Society of Anesthesiologists, BIS = bispectral index, BPB = brachial plexus block, Ce = effect-site concentration, EtCO$_2$ = end-tidal carbon dioxide pressure, HR = heart rate, IRB = institutional review board, MAC = monitored anesthesia care, MAP = mean arterial pressure, OAA/S = Observer's Assessment of Alertness/Sedation, PONV = postoperative nausea and vomiting, PTA = percutaneous transluminal balloon angioplasty, SD = standard deviation, SpO$_2$ = peripheral oxygen saturation, TCI = target-controlled infusion, TSGH = Tri-Service General Hospital.

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## 1. Introduction

Percutaneous transluminal balloon angioplasty (PTA) is recommended as the first choice to treat dysfunction of hemodialysis fistulas.[1] To facilitate successful procedure and improve patients' discomfort and safety, intravenous sedation and analgesia under monitored anesthesia care (MAC) are frequently used during PTA.[2,3] Besides providing effective sedation and analgesia to reduce pain and anxiety, MAC is necessary to maintain stable hemodynamic and respiratory conditions during diagnostic and therapeutic interventional procedures.[4,5]

For its unique properties, including rapid onset, precise intraoperative control, and a fast recovery profile, remifentanil is preferable to other opioids administration in a target-controlled infusion (TCI) pump.[6,7] Midazolam, a short-acting benzodiazepine, is the most commonly used sedative agent for PTA.[8] Midazolam with remifentanil is widely used due to its quick onset of action and relatively short duration of effect during painful procedures under MAC.[8]

Combination of remifentanil with propofol may improve sedation experience; however, it can increase a risk of respiratory depression.[2] Moreover, propofol and remifentanil are often administered with 2 TCI pumps to, respectively, provide hypnotic and analgesic effects, which together are considered to be an ideal anesthetic technique.[9] In addition to a 2-fold increase in the number of TCI supplies used (including pumps, syringes, and extension tubes, etc), it takes time to set the TCI model for propofol and remifentanil if they are infused separately. Therefore, we conduct TCI of remifentanil with intermittent bolus midazolam to deal with abovementioned problem.

Park et al[3] and Jun et al[8] reported that remifentanil by syringe pump infusion was successfully used in combination with midazolam in PTA under MAC. Until now, there are limited data on the use of TCI of remifentanil with midazolam in PTA under MAC. Thus, this study investigated 2 effect-site concentration (Ce) of remifentanil with midazolam in PTA under MAC for dysfunctional hemodialysis fistulas.

## 2. Methods

### 2.1. Study design and setting

This prospective, randomized controlled trial was conducted at Tri-Service General Hospital (TSGH), Taipei, Taiwan, Republic of China.

### 2.2. Participants and data sources

This study was approved by the Ethics Committee (TSGHIRB No: 2–108–05–010) of Tri-Service General Hospital, Taipei, Taiwan (Chairman, Professor Yu Mu Hsien) on February 20, 2019. All patients provided written informed consent before being enrolled. All methods were performed in accordance with the relevant guidelines and regulations by our IRB.

From March 2019 to March 2021, 80 patients with American Society of Anesthesiologists (ASA) score of I–III in our medical center scheduled to undergo PTA (not just balloon but balloon angioplasty) under MAC were enrolled in this study. The definition of criteria for percutaneous interventions in hemodialysis fistulas was based on reporting standards of Society of Interventional Radiology.[10] Patients were randomized 1:1 into the Group 1 (initial remifentanil Ce of 1.0 ng/mL) or Group 2 (initial remifentanil Ce of 2.0 ng/mL) by using a table of random, computer-generated digits in sealed and numbered envelopes by an anesthesiologist. All MACs were performed by the same anesthesiologist, and medical data were recorded by a nurse anesthetist who was blinded. Participants and the surgeon were blinded after assignment to interventions. Exclusion criteria were as follows: age < 20 years or older than 80 years, ASA score more than III, body mass index > 30 kg/m$^2$, allergy to midazolam, remifentanil, and contrast medium, chronic obstructive pulmonary disease, congestive heart failure, hepatic failure, and chronic use of opioid drugs.

### 2.3. Anesthesia and monitoring

All patients were fasted overnight before the procedure, and no medications were allowed before induction of anesthesia. Standard monitoring, such as noninvasive arterial blood pressure, electrocardiography (lead II), pulse oximetry, end-tidal carbon dioxide pressure (EtCO$_2$) were applied for each patient. Participants were pre-oxygenated and adequately maintained with 100% oxygen at 6 L/min via a facial mask during the entire procedure.

During anesthesia induction, all patients received intravenous midazolam 2.0 to 2.5 mg, then continuous infusion of remifentanil (50 μg/mL) was delivered using Minto model of TCI (Fresenius Orchestra Primea; Fresenius Kabi AG, Bad Homburg, Germany) with the Ce of 1.0 ng/mL in Group 1 and 2.0 ng/mL in Group 2. In both groups, maintenance of the remifentanil Ce of was adjusted upward by 0.5 ng/mL, while patient movements or pain complaints. On the contrary, once apnea without desaturation (SpO$_2 \geq$ 90%) happened, we would perform jaw elevation to keep airway open. When apnea with desatuation (SpO2 < 90%) occurred, positive-pressure mask ventilation (with 100% oxygen at 6 L/min) and reducing remifentanil Ce by by 0.5 ng/mL would be conducted. In addition, intermittent bolus midazolam 1 to 1.5 mg per time (total maximum dose of intravenous midazolam was limited to 5 mg in both groups) to keep the Observer's Assessment of Alertness/Sedation (OAA/S) scale between 2 and 4. The mean arterial pressure (MAP) and heart rate (HR) were kept at baseline levels ± 30%.[11] As soon as the procedure ended, the remifentanil was discontinued. After each patient regained consciousness by name, the patient was sent to the postoperative anesthesia care unit for further care. Patients were monitored for MAP, HR, peripheral oxygen saturation (SpO$_2$), respiratory rate (RR), EtCO$_2$, Ce of remifentanil, and OAA/S scale at the T1: before anesthesia induction, T2: time at the local anesthetic injection, T3: time at the incision, T4: time at the ballooning, T5: 5 min after the ballooning, and T6: time of the end of procedure.

### 2.4. Surgical procedure

All procedures were performed by the same cardiovascular surgeon under MAC. A local anesthetic agent (3–5 mL of 2%

lidocaine) was injected into the incision site before the incision by the cardiovascular surgeon. After the puncture of the fistula with a 21G or 18G needle under ultrasound guidance, a vascular sheath in sizes ranging from 5 to 9F was placed. Flow-limiting stenosis or occlusion was treated with conventional balloon angioplasty. If postangioplasty fistulography revealed persistent stenosis, balloon angioplasty was repeated with a larger balloon. Cutting balloons were used for some tight stenoses that were resistant to conventional balloon angioplasty. Thrombosis was treated using thrombectomy with or without thrombolysis.

### 2.5. Outcomes

The primary outcome was to determine the appropriate Ce of remifentanil of for PTA in terms of hemodynamic conditions (such as MAP, HR, $EtCO_2$, $SpO_2$, and RR) and adverse events [such as patient movements affecting the procedure, hypotension (MAP $< 60$ mm Hg), ephedrine requirements (systolic blood pressure $< 90$ mm Hg), apnea with desaturation ($SpO_2 < 90\%$), postoperative nausea and vomiting (PONV) at post-anesthesia care unit (PACU), and remifentanil-induced hyperalgesia]. Secondary endpoints included total dosage of anesthetics and total times of TCI pump adjustments during the procedure. Each adjustment of TCI pump was recorded, and once the Ce was adjusted, it was counted in the number of adjustments. We also recorded total times of upward or downward adjustment of the TCI pump, respectively. In addition, visual analogue scale (VAS) at PACU, and patient or surgeon satisfaction (0–4) were recorded. Patient or surgeon satisfaction levels were evaluated at discharge on a 0 to 4 point numerical scale: 0 = extremely dissatisfied; 1 = dissatisfied; 2 = neither satisfied nor dissatisfied; 3 = satisfied; 4 = extremely satisfied.

### 2.6. Statistical analysis

The sample size was calculated based on a power of 80% and a 5% type-I error by the incidence of patient movements affecting procedures (from 40% to 12%). A size of 37 patients per group was required at a power of 80% and a type I error of 0.05. Considering loss to follow-up, as this was ambulatory surgery, the sample size was calculated to be 40 patients per group. Data are expressed as means ± standard deviations (SD) or as medians with the range or percentage counts, unless otherwise indicated. Demographic and perioperative variables were compared using Student $t$ tests or Mann–Whitney test if the data were not normally distributed. Categorical variables were compared using Chi-square or Fisher exact test if need. Statistical significance was accepted for 2-tailed $P$ values of $< .05$ and statistics were performed by using SigmaStat version 3.5 for Windows.

### 3. Results

A total of 80 patients with ASA III undergoing PTA under MAC were enrolled, ultimately, 40 patients in Group 1 and 40 patients in Group 2 (Fig. 1). The demographic data and analysis of anesthetic management for the 2 groups are summarized in Table 1. The 2 groups showed similar patient characteristics. There was no significant difference between 2 groups in terms of anesthesia time ($58.7 \pm 18.3$ vs $64.2 \pm 21.0$ minutes, $P = .219$) or procedure time ($48.8 \pm 17.4$ vs $54.3 \pm 19.7$ minutes, $P = .191$). Midazolam consumption during the procedure was $3.63 \pm 0.66$ mg in Group 1 and $3.73 \pm 0.63$ mg in Group 2 ($P = .490$).



Group 1: initial remifentanil Ce of 1.0 ng/mL;

Gropu 2: initial remifentanil Ce of 2.0 ng/mL;

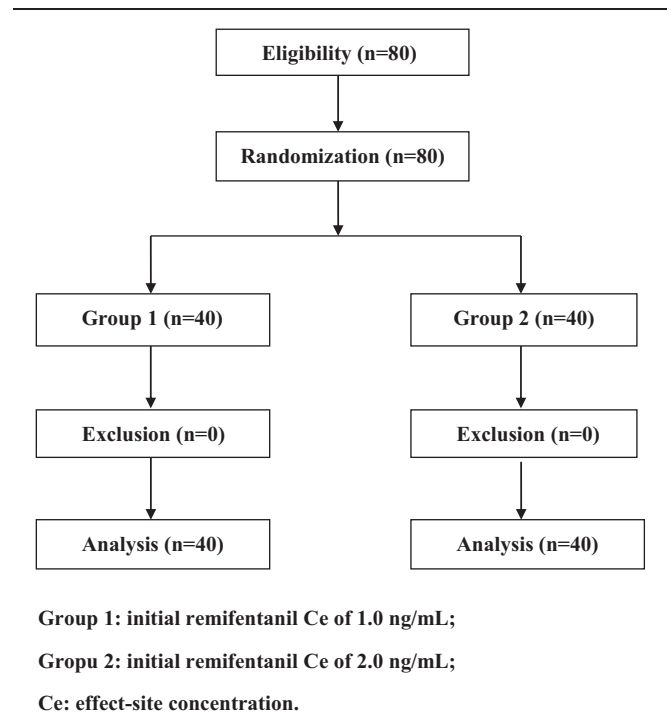Ce: effect-site concentration.

**Figure 1.** Flow diagram showing patient flow according to the study protocol.

Remifentanil consumption during the procedure was less in Group 1 ($189.7 \pm 69.7\,\mu g$) compared with Group 2 ($243.8 \pm 76.1\,\mu g$; $P = .001$). The median of upward adjustments was 1 (0–3) in Group 1 and 0 (0–1) in Group 2 ($P < .001$) and the median of downward adjustments was 1 (1–1) in Group 1 and 1 (1–2) in Group 2, respectively ($P = .013$). The total number of TCI pump adjustments was higher in Group 1 than in Group 2 overall [2 (1–4) vs 1 (1–2), respectively, $P < .001$] (Table 1). In addition, VAS at PACU was $2.90 \pm 0.37$ in Group 1and $2.88 \pm 0.33$ in Group 2 ($P = .780$). Patient satisfaction level (0–4) was

**Table 1**

**Patients' characteristics and analysis of anesthetic management.**

| | Group 1 (n = 40) | Group 2 (n = 40) | P |
|---|---|---|---|
| Sex (male/female) | 19/21 | 21/19 | .823 |
| Age, yr | 67.2 ± 10.1 | 63.9 ± 10.0 | .149 |
| Height, cm | 160.7 ± 6.5 | 160.5 ± 7.5 | .925 |
| Weight, kg | 61.3 ± 10.5 | 62.6 ± 10.4 | .557 |
| Anesthesia time, min | 58.7 ± 18.3 | 64.2 ± 21.0 | .219 |
| Procedure time, min | 48.8 ± 17.4 | 54.3 ± 19.7 | .191 |
| Midazolam consumption, mg | 3.63 ± 0.66 | 3.73 ± 0.63 | .490 |
| Remifentanil consumption, μg | 189.7 ± 69.7 | 243.8 ± 76.1 | .001 |
| Total times of TCI pump adjustment (n) | 2 (1–4) | 1 (1–2) | <.0001 |
| Upward (n) | 1 (0–3) | 0 (0–1) | <.0001 |
| Downward (n) | 1 (1–1) | 1 (1–2) | .013 |
| VAS at PACU | 2.90 ± 0.37 | 2.88 ± 0.33 | .780 |
| Patient satisfaction (0–4) | 3.13 ± 0.33 | 3.15 ± 0.36 | .796 |
| Surgeon satisfaction (0–4) | 3.25 ± 0.43 | 3.68 ± 0.47 | <.0001 |

Data shown as mean ± SD or median (range) or number.
Group 1: initial remifentanil Ce of 1.0 ng/mL; Group 2: initial remifentanil Ce of 2.0 ng/mL.
Ce = effect-site concentration; PACU = postanesthesia care unit; TCI = target-controlled infusion; VAS = visual analogue scale.
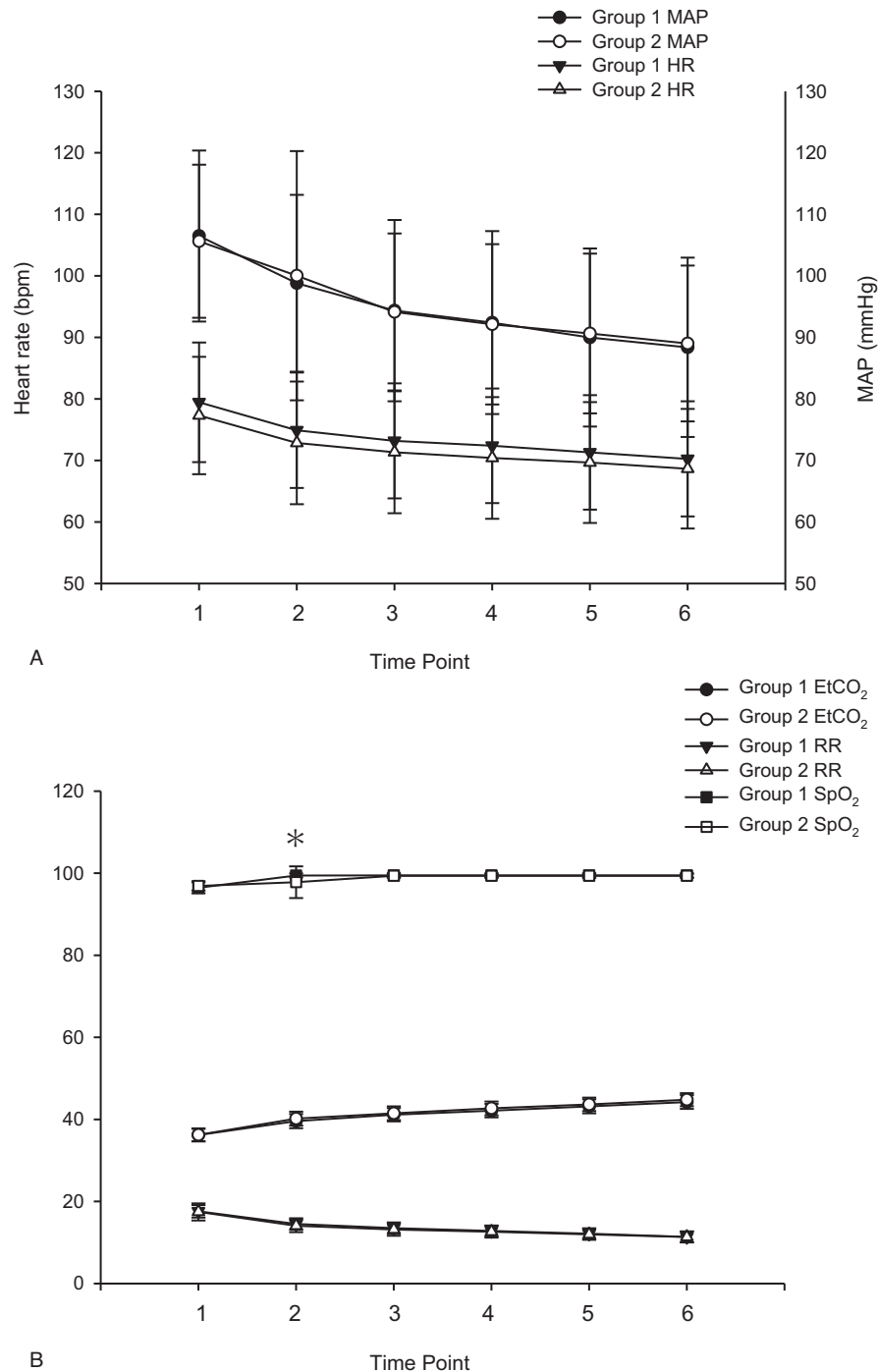
**Figure 2.** Changes of MAP and HR (A); RR [times/min], EtCO$_2$ [mm Hg], and SpO$_2$ [%] (B) during every step of percutaneous transluminal balloon angioplasty. Time point: (1) before anesthesia induction, (2) time at the local anesthetic injection, (3) time at the incision, (4) time at the ballooning, (5) 5 min after the ballooning, and (6) time of the end of procedure. Data were presented as mean ± SD; bpm = beats per minute; EtCO$_2$ = end-tidal carbon dioxide pressure; HR = heart rate; MAP = mean arterial pressure; RR = spontaneous respiratory rate; SpO$_2$ = peripheral oxygen saturation. $^*P < .05$ compared with Group 1 at each time point measurement.

3.13 ± 0.33 in Group 1 and 3.15 ± 0.36 in Group 2 ($P = .796$; Table 1). By contrast, surgeon satisfaction level (0–4) was higher in Group 2 (3.68 ± 0.47) than in Group 1 (3.25 ± 0.43; $P < .001$) (Table 1).

There was no significant difference in MAP or HR between the 2 groups at each time point (Fig. 2A). There was no significant difference in RR or EtCO$_2$ pressure between the two groups at each time point (Fig. 2B). There was also no significant difference in SpO$_2$ between the two groups at each time point (except T2). At T2 (time at the local anesthetic injection), the SpO$_2$ in Group 1 was significantly higher (99.4 ± 0.5%) than that in Group 2 (97.8 ± 3.9%; $P = .001$; Fig. 2B).

**Table 2**

**Adverse events during the procedure.**

| | Group 1 (n=40) | Group 2 (n=40) | *P* |
|---|---|---|---|
| Patient movements affecting the procedure | 14 (35.0%) | 4 (10.0%) | .016 |
| Hypotension (mean arterial pressure < 60 mm Hg) | 0 (0%) | 0 (0%) | 1.000 |
| Patients requiring ephedrine (systolic blood pressure < 90 mm Hg) | 0 (0%) | 0 (0%) | 1.000 |
| Apnea with desaturation (SpO2 < 90%) | 0 (0%) | 6 (15.0%) | .034 |
| Postoperative nausea and vomiting | 0 (0%) | 0 (0%) | 1.000 |
| Remifentanil-induced hyperalgesia | 0 (0%) | 0 (0%) | 1.000 |

Data shown as number (percentage). Group 1: initial remifentanil Ce of 1.0 ng/mL; Group 2: initial remifentanil Ce of 2.0 ng/mL.
Ce = effect-site concentration.

Table 2 indicated adverse events that occurred during the procedure for the 2 groups. Fourteen patients (35.0%) in Group 1 and 4 patients (10.0%) in Group 2 moved and affected the procedure ($P=.016$; Table 2). After judicious adjustment of the Ce, the procedures were completed without any incident. There was occurrence of hypotension (MAP $< 60$ mm Hg) in either group, and there was no patient requiring ephedrine administration due to systolic blood pressure $< 90$ mm Hg in either group. In addition, there was no patient with PONV or remifentanil-induced hyperalgesia at PACU in the 2 groups. No patient (0%) developed apnea with desaturation ($SpO_2 < 90\%$) in Group 1 and 6 patients (15.0%) developed apnea with desaturation ($SpO_2$, 88 - 89%) in Group 2 while local anesthetic injection ($P=.034$; Table 2). The $SpO_2$ returned to normal range immediately after mask ventilation and reducing remifentanil Ce.

Table 3 compared the remifentanil Ce and OAA/S scale during PTA between the groups. There were significant differences in remifentanil Ce between the 2 groups at each time point except T1 (before anesthesia induction). At T2, time at the local anesthetic injection, the remifentanil Ce was $1.39 \pm 0.24$ ng/mL in Group 1 and $1.98 \pm 0.25$ ng/mL in Group 2 ($P < .001$); at T3, time at the incision, the remifentanil Ce was $1.56 \pm 0.41$ ng/mL in Group 1 and $1.98 \pm 0.25$ ng/mL in Group 2 ($P < .001$); at T3, time at the incision, the remifentanil Ce was $1.56 \pm 0.41$ ng/mL in Group 1 and $1.98 \pm 0.25$ ng/mL in Group 2 ($P < .001$); at T4, time at the ballooning, the remifentanil Ce was $1.56 \pm 0.41$ ng/mL in Group 1 and $1.98 \pm 0.25$ ng/mL in Group 2 ($P < .001$); at T5, 5 minutes after the ballooning, the remifentanil Ce was $1.06 \pm 0.41$ ng/mL in Group 1 and $1.48 \pm 0.25$ ng/mL in Group 2 ($P < .001$); at T6, time of the end of procedure, the remifentanil Ce was $1.06 \pm 0.41$ ng/mL in Group 1 and $1.48 \pm 0.25$ ng/mL in Group 2 ($P < .001$; Table 3). There was no significant difference in OAA/S scale between the 2 groups at each time point (Table 3).

## 4. Discussion

In this study, the major findings reveal that remifentanil Ce of $2.0 \mu g/mL$ by TCI pump with 3 to 4 mg midazolam use provide appropriate hemodynamic conditions, sufficient sedation, and analgesia, acceptable adverse events (such as patient movements affecting the procedure or apnea with desaturation), and better surgeon satisfaction in PTA for dysfunctional hemodialysis fistulas under MAC. Remifentanil by syringe pump infusion has been used successfully in combination with midazolam to provide sedoanalgesia during PTA under MAC.[3,8] However, until now, there are limited data on the use of TCI of remifentanil with midazolam in PTA under MAC. In addition, PTA for the dysfunction of hemodialysis fistula is usually performed on an outpatient basis.[12] Medications should be administered to achieve adequate analgesia, sedation, anxiolysis, and amnesia during the procedures, control of unwanted motor behavior that inhibits the performance of procedures, rapid return of the patient to consciousness, and less risk of adverse events.[8] The combination of midazolam and remifentanil used in the present study has been proven to fulfill those criteria.[13]

MAC is the most often technique used by nonanesthesiologists as well by anesthesiologists for various interventional procedures including PTA.[14] Analgesics (fentanyl, remifentanil) with sedative hypnotics (propofol, midazolam) is commonly used as intermittent boluses, continuous infusion, and target-controlled intravenous sedation/analgesia.[14,15] Fentanyl is one of the most commonly used analgesics during MAC with an onset of 3 to 5 minutes and duration of 45 to 60 minutes.[15] Even 25 to 50 μg of fentanyl may cause respiratory depression if co-infused with other sedatives.[15] Remifentanil with 1 minute onset time and duration is 3 to 10 minutes, is an ideal opioid for continuous infusion, and for managing pain related to surgical stimulation.[15] Jarahzadeh et al[16] reported that the recovery from anesthesia was significantly better in the remifentanil-based MAC

**Table 3**

**Ce of remifentanil and observer assessment of alertness/sedation (OAA/S) scale during the procedure.**

| | | T1 | T2 | T3 | T4 | T5 | T6 |
|---|---|---|---|---|---|---|---|
| Ce of remifentanil OAAS score | Group 1 | $0 \pm 0$ | $1.39 \pm 0.24^*$ | $1.56 \pm 0.41^*$ | $1.56 \pm 0.41$ | $1.06 \pm 0.41$ | $1.06 \pm 0.41$ |
| | Group 2 | $0 \pm 0$ | $1.98 \pm 0.25^*$ | $1.98 \pm 0.25^*$ | $1.98 \pm 0.25^*$ | $1.48 \pm 0.25^*$ | $1.48 \pm 0.25^*$ |
| | Group 1 | $5.00 \pm 0$ | $2.93 \pm 0.41$ | $2.93 \pm 0.41$ | $2.93 \pm 0.41$ | $2.93 \pm 0.41$ | $2.93 \pm 0.41$ |
| | Group 2 | $5.00 \pm 0$ | $2.85 \pm 0.36$ | $2.85 \pm 0.36$ | $2.85 \pm 0.36$ | $2.85 \pm 0.36$ | $2.85 \pm 0.36$ |

Data are shown as mean ± SD. Group 1: initial remifentanil Ce of 1.0 ng/mL; Group 2: initial remifentanil Ce of 2.0 ng/mL.
T1: before anesthesia induction; T2: time at the local anesthetic injection; T3: time at the incision; T4: time at the ballooning.
T5: 5 min after the ballooning; T6: time of the end of procedure; Ce: effect-site concentration.
* $P < .05$ compared with Group 1 at each time point measurement.

compared with fentanyl-based MAC. In addition, Ryu et al[17] revealed that patients under remifentanil-based MAC had lower pain scores than patients under fentanyl-based MAC. Moreover, Moerman et al[18] demonstrated that remifentanil administered via TCI resulted in a lower incidence of apnea and respiratory depression, compared with manually controlled administration of remifentanil. Accordingly, remifentanil-based MAC via TCI might be more suitable for interventional procedures compared with MAC by intermittent boluses of fentanyl or manually controlled pump infusion of remifentanil.

Dexmedetomidine is the α-2 agonist that inhibits endogenous catecholamine release in the locus ceruleus, which results in a sedative-analgesic effect without respiratory depression.[15] Although dexmedetomidine reduces opioid requirements, it leads to hypotension and bradycardia due to the inhibition of catecholamine release.[15,19] Therefore, these adverse events should be considered for elderly patients with diabetes or cardiovascular disease such as hemodialysis patients.[2] Ketamine with profound analgesic, sedative, and amnestic characteristics is a particularly valuable during MAC because it does not cause clinically significant respiratory depression or PONV.[15] Low dose ketamine (0.25–0.50 mg/kg) with propofol has been used during ambulatory MAC for plastic surgery.[15] However, the adverse effects include recovery agitation, transient airway complications such as laryngospasm, and emesis.[20] Avoiding ketamine in hemodialysis patients who are predisposed to psychotic behavior such as is suggested.[20,21]

Benzodiazepines provide patient amnesia during the procedure; midazolam is the most commonly used benzodiazepine.[15] Midazolam shows maximal central nervous system effects within 2 to 3 minutes; however, repeated or continuous injection within a relatively short period may lead to heavy sedation.[15] Propofol remains the mainstay drug of MAC because of its favorable pharmacodynamic and pharmacokinetic profile. Propofol causes equivalent sedation and anxiolysis in patients undergoing PTA compared with midazolam.[22] However, in geriatric patients, propofol induces cardiovascular depression, with a greater extent compared with other intravascular sedative agents.[2] In addition, propofol and remifentanil are often administered with two TCI pumps to respectively provide hypnotic and analgesic effects.[9] Under certain circumstances where multiple TCI systems or syringe pumps are unavailable or are time- and cost-consuming. Finally, remifentanil-midazolam provides more stable hemodynamics, more amnesia, moderate sedation duration, and less side effects compared with remifentanil-propofol under MAC.[23]

This study is based on the results of Jun et al,[8] which reported that PTA was successfully conducted under MAC using 1 mg of midazolam and continuous infusion of 0.05 μg/kg/min remifentanil (about Ce 1.0 ng/mL) with or without an intravenous bolus of 0.5 mg/kg ketamine. The authors concluded that a small dose of ketamine as an adjunct sedative to the combination of midazolam and remifentanil in patients undergoing PTA produced a better quality of sedoanalgesia than without ketamine.[8] The results revealing that patients in the control group suffered from more pain discomfort than patients in the study group,[8] were similar with our results showing that Group 1 patients undergoing more pain discomfort than Group 2 patients. In addition, 3 patients (4.7%) under MAC with or without an intravenous bolus of 0.5 mg/kg ketamine suffered from apnea without significant desaturation requiring tactile stimulation.[8] Our results revealed that 6 patients (7.5%) under MAC suffered from apnea with mild desaturation (SpO$_2$ 88–

89%). However, adverse events such as tachycardia and psychosis may limit ketamine use in patients with renal failure.[24] Park et al[3] reported that using intermittent midazolam boluses (0.03–0.05 mg/kg) and continuous infusion of 0.72 μg/kg/h remifentanil (about Ce 2 ng/mL) was associated with higher procedural pain score than administrating dexmedetomidine 0.2 to 0.7 μg/kg/h after a loading dose of 1.0 μg/kg for 10 minutes with continuous infusion of 0.72 μg/kg/h remifentanil for PTA. However, 14.7% patients under dexmedetomidine-remifentanil anesthesia suffered from hypotensive episodes requiring ephedrine administration.[3]

In addition, Gedikoglu et al[12] reported that ultrasound-guided supraclavicular brachial plexus block (BPB) had advantages over the sedoanalgesia during PTA. However, BPB was time-consuming and might cause complications such as injury to blood vessels or a nerve, pneumothorax, and local anesthetic systemic toxicity.[12] Considering an easier and similar way for our daily hospital practice, TCI of remifentanil with intermittent bolus midazolam was used in the present study. Ultimately, in this study, the initial remifentanil Ce of 1.0 or 2.0 ng/mL with midazolam loading dose of 2 to 2.5 mg, which we chose was based on our clinical experience. In addition, to make our findings more clinically feasible, all participant parameters such as MAP and HR were kept at baseline levels ± 30%,[11] an OAA/S scale between 2 and 4, and patient comfort (remaining moveless) by adjusting the Ce of remifentanil and intermittent bolus midazolam during the procedure, allowing adjustment of the anesthetics concentration in an easier way similar to our daily hospital practice.

The total frequency of TCI adjustment in Group 2 was significantly lower than in Group 1. The remifentanil Ce of 2.0 ng/mL might provide adequate analgesia and the increased dose of midazolam might improve sedation with stable hemodynamics, however, increasing the risk of respiratory depression. There were 6 patients in Group 2 who suffered from apnea with desaturation, but no patient in Group 1 experienced apnea with desaturation. Fortunately, 6 patients with apnea with desaturation in Group 2 were all within SpO$_2$ 88% to 89% and improved by jaw thrust and downward adjustment of remifentanil Ce 0.5 ng/mL. Possible adverse effects of remifentanil include respiratory depression, muscle rigidity, bradycardia, and nausea and vomiting.[25] In the present study, there was statistically significant change in SpO$_2$ while local anesthetic injection; however, after downward adjustment of remifentanil Ce 0.5 ng/mL, the procedures were completed without any incident. Previous studies also reported that when midazolam is combined with an opioid, the likelihood of respiratory depression is increased.[26,27] Occurrence of PONV was also a concern of the anesthetists, but none of the patients experienced nausea and vomiting subsequent to discharge during follow-up. Because combination remifentanil and midazolam can potentially cause severe respiratory depression, we suggest that this technique should only be performed by trained anesthesiologists.

Another important issue for discussion is patient and surgeon satisfaction. In our study, although patient satisfaction was similar between 2 groups, the surgeon reported better satisfaction in Group 2 due to less patient movements affecting procedures. Our findings reveal valuable data that maintaining patient comfort (remaining moveless) during MAC provides better surgeon satisfaction.

There were some limitations in this study. First, we did not apply bispectral index (BIS) and analgesia nociception index

(ANI) monitoring as commonly practiced for PTA. The BIS index, which correlates well with hypnotic state and can reduce the incidence of intraoperative awareness by approximately 80%, is certified as a measurement to monitor anesthetic depth by the US Food and Drug Administration.[28,29] However, because the duration of the procedure was short, the economic effect is required for further evaluation. In addition, BIS is correlated with OAA/S scale.[30] Furthermore, Funcke et al[31] reported that ANI is superior in detecting painful stimuli under sedation compared to clinical signs such as HR and MAP. However, to the best of our knowledge, most anesthetists do not use BIS and ANI during minor procedures of this type. Second, the initial remifentanil Ce of 1.0 or 2.0 ng/mL with midazolam loading dose of 2 to 2.5 mg, which we chose was based on our clinical experience, and further investigation is needed to determine optimal initial and maintenance remifentanil Ce.

In conclusion, TCI of remifentanil with Minto model target 2.0 ng/mL in combination with 3 to 4 mg midazolam use provided appropriate hemodynamic conditions, sufficient sedation and analgesia, acceptable adverse events, and better surgeon satisfaction in PTA under MAC.

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