

Continuous intravenous versus intermittent bolus midazolam with remifentanyl during arteriovenous fistula placement with monitored anesthesia care in chronic renal failure patients: a randomized controlled trial

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BACKGROUND: There is limited data on the use of intravenous continuous infusion (CI) versus intravenous intermittent bolus (IB) doses of midazolam for conscious sedation in patients with chronic renal failure. Unexpected adverse events can occur in chronic renal failure patients undergoing short procedures.

OBJECTIVE: Investigate and compare the sedoanalgesic and adverse effects of intravenous continuous infusion (CI) use of midazolam with intravenous intermittent bolus (IB) doses of midazolam while using intravenous remifentanyl as a rescue medication, and assess patient and surgeon satisfaction.

DESIGN: Prospective, randomized, single-blind controlled study.

SETTINGS: Two tertiary care hospitals.

PATIENTS AND METHODS: Study included patients aged 43-81 years with a diagnosis of chronic renal failure who were referred for an arteriovenous fistula procedure with modified anesthesia care between August 2012 and April 2016. The patients were randomized to intravenous CI or IB doses of midazolam. IB doses of remifentanyl were used as a rescue medication.

MAIN OUTCOME MEASURES: Primary outcomes were amounts of midazolam and remifentanyl medications during the operation, the amount of remifentanyl as a rescue medication, and the satisfaction of patient and surgeon.

SAMPLE SIZE: 116 assessed for eligibility; 99 randomized to CI (n=50) or IB doses (n=49 of midazolam).

RESULTS: The total dose of midazolam by CI was greater than with midazolam by IB ($P=.002$). The total dose of remifentanyl was higher with IB doses of midazolam in comparison to CI of midazolam ($P=.001$). The groups were similar in sedation and pain control, duration of procedure, recovery time, patient satisfaction and adverse events; surgeon satisfaction was greater with CI versus IB ($P=.035$).

CONCLUSIONS: Intravenous CI midazolam during MAC provides better surgeon satisfaction than IB midazolam and can be used safely for arteriovenous fistula procedures.

LIMITATIONS: Two different surgeon groups.

CONFLICT OF INTEREST: None.

Midazolam is a short acting, anxiolytic and sedative benzodiazepine used for conscious sedation during invasive outpatient care or surgical procedures under sedation in the operating room.¹ Midazolam interacts with receptors in the central nervous system and spinal cord. Analgesic properties are mediated by the neurotransmitter gamma-aminobutyric acid (GABA). The antinociceptive effect of midazolam may augment the effect of local anesthetics such as lidocaine and opioids such as remifentanyl. Midazolam is widely used alone or in combination with opioids such as remifentanyl due to its quick onset of action and relatively short duration of effect. Benzodiazepines may have adverse effects and these include a possible increased incidence of respiratory depression especially in elderly patients with comorbidities.^{1,3-5} As a result, the recovery period may be prolonged in patients with comorbidities. Remifentanyl is a synthetic opioid with unique pharmacokinetic properties including a short onset time and an ultra-short duration of action. Recently, remifentanyl has been used in various short procedures for conscious sedation and it is administered intravenously either as a continuous infusion or as patient-controlled analgesia where intravenous bolus doses are administered by the patient. However, the use of remifentanyl in small intravenous bolus doses as a rescue medication has not been studied extensively.⁴

Monitored anesthesia care (MAC) is required for day-surgery procedures such as arteriovenous fistula insertion where an adequate level of sedation and analgesia without respiratory depression is desired for comfort of both the patient and the surgeon.^{1,3} For clinical evaluation, the Modified Observer Assessment of Alertness/Sedation scale (MOAA/S) is a well-established instrument for evaluating the level of consciousness in patients sedated with midazolam.³ A score of 3 and 4 on the MOAA/S scale represents a moderate level of sedation-analgesia. A score of three or more is required for MAC sedation. There is limited data on the use of continuous intravenous versus bolus doses of midazolam for conscious sedation.^{1,3}

Our goal was to investigate and compare the sedo-analgesic and adverse effects of intravenous continuous infusion (CI) midazolam to intermittent bolus (IB) doses of midazolam while using remifentanyl as a rescue medication in patients with chronic renal failure undergoing an arteriovenous fistula procedure during MAC sedation with local anesthetic field infiltration.⁶

PATIENTS AND METHODS

This prospective, randomized, single-blind controlled study was approved by the Ethics Committee of the

Kartal Kosuyolu Training and Research Hospital, Kartal, Istanbul, Turkey. (The Ethical Committee Approval date and number: 09/05/2013,538.38792-903/6023). The study had been registered to ClinicalTrials.gov with a registration number of NCT04226443 (<https://clinicaltrials.gov/ct2/show/NCT04226443>).

Eligibility

Patients aged 43-81 years of American Society of Anesthesiologist (ASA) status of 2 to 3 who had a diagnosis of chronic renal failure and were referred for an arteriovenous fistula procedure between August 2012 and April 2016 were included in the study. The exclusion criteria were as follows: obese patients with body mass index greater than 30, severe respiratory insufficiency related lung disorders, severe cardiovascular insufficiency or dysfunction, insulin-dependent diabetes mellitus, severe hepatic diseases, ASA status of 4 and 5, neurologic disorders, a history of chronic pain, a history of allergy to the study drugs.

Sample size and randomization

The sample size was calculated based on a power of 80% and a 5% type-I error. A size of 24 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 30 patients per group.⁷

After generating the random allocation sequence using a computer program, we used sequentially numbered, opaque, sealed envelopes that were numbered in advance. The envelopes were opened sequentially after the participant's name was written on the appropriate envelope. Patients were randomly allocated in a 1:1 ratio into 1 of 2 groups using a sealed envelope to ensure concealment of the allocation sequence. All interventions were performed by less experienced physicians in advanced training. Verbal informed consent was obtained from all patients or their caregivers. This study was single-blinded because the study protocol was administered by anesthesiology residents who were unaware of the technique and the study protocol. The protocol was known by experienced anesthesiologists who were attending the case and collecting the data during the procedure. The preparation of midazolam and remifentanyl solutions and installation of the infusion devices were done by an anaesthesiologist who was blinded for the study groups.

Sedation protocol

In all patients, the use of premedication was not included in the study protocol. Before the start of the pro-

cedure, all patients were informed about the method of sedation including explanation of medication use in continuous form and intermittent form and local anaesthesia. Patients were informed about advantages and disadvantages of sedation. Preoperatively, a physical exam and routine clinical tests were completed. Patients were advised to attend on the day of the operation, having fasted for at least six hours prior to the start of surgery.

All patients received 2 mL/kg per hour of 0.9% NaCl infusion intravenous and 2 litre per minute nasal oxygen during the procedure. The main sedative agent in the study was intravenous midazolam administered either as a continuous infusion or intermittent bolus doses of midazolam (Dormicum, Deva Pharmaceutical, Turkey). The rescue medication during sedation was the opioid agent remifentanyl (Ultiva, Glaxo Smith Kline Pharmaceutical, England), which was administered in intravenous bolus doses. The total maximum dose of intravenous midazolam was limited to 4 mg in patients with chronic renal failure.⁵

The groups were divided according to continuous or intermittent midazolam. Both groups of patients received an intravenous IB dose of midazolam at a dose of 0.015 mg/kg before the start of the surgery. In the CI group (n=50); IV midazolam at a dose of 0.02 to 0.04 mg/kg/h was started in a CI form and adjusted by sedation level while the IB (n=49) patients received intravenous IB doses of 0.015 mg/kg every 10 minutes. The midazolam CI was prepared as 5 mg midazolam in a 20 mL syringe of 5% dextrose water solution (0.25 mg/mL). The rate was adjusted to give a smooth slow infusion until the patient showed a clinical response. A rescue medication of remifentanyl (5 µg/mL) was used every 5 to 10 minutes depending on pain level. Throughout the procedure, the resident anesthesiologist continuously appraised the patient's level of sedation.

During the operation, before incision, the operative field was injected subcutaneously with lidocaine %1 and 1:100000 epinephrine at a dose of 10 mL up to 20 mL depending on the anatomical region. All patients were monitored with continuous ECG, automated non-invasive intermittent blood pressure (BP) measurements, respiratory rate (RR) and SpO₂. Data on vital-signs was collected during the intraoperative and postoperative periods. All patients were monitored noninvasively for systolic blood pressure (SBP), diastolic BP, mean arterial pressure (MAP), heart rate (HR) and rhythm, RR and SpO₂ before the procedure and every five minutes during the procedure. An SpO₂ value of less than 90% for more than 10 seconds was defined as respiratory depression. Hypotension was defined as

an SBP <70 mm Hg, MAP <60 mm Hg or a decrease of 30% of the baseline value. In this case, intravenous fluid infusion in combination with repeated doses of intravenous ephedrine (10 mg) was administered until SBP >70 mm Hg and a MAP of greater than 60 mm Hg was achieved. In both groups of patients, the sedation was interrupted if the anesthesia resident recognizes one of the following parameters and calls for the experienced anesthesiologists to resume the sedation protocol and these parameters include: RR<8 breaths/min for at least 1 min, SpO₂<90%, MAP<60 mm Hg, HR<40 beats/min for at least one minute and excessive sedation recorded as an MOAA/S score of less than 2. Bradycardia was considered when HR was <40 beats per minute. Bradycardia was treated with intravenous atropine at a bolus dose of 0.5 mg. Adverse effects such as respiratory depression, hypotension, nausea, vomiting, chilling and shivering were recorded.

Pain and sedation measures

Throughout the procedure, the resident anesthesiologist continuously appraised the patient's pain and level of sedation: the intensity of pain using a verbal numerical sedation scale (VNRS; 0= no pain, 10=the worst possible pain imaginable) and the sedation level by MOAA/S (range 0-6).^{3,7} Rescue medication of intravenous remifentanyl was used as 1 to 3 mL (5 µg or 15 µg) every 5 minutes if necessary for VNRS pain scores greater than 3 and this was prepared as an infusion prior to use during the study. Remifentanyl infusion was prepared as follows: 0.5 mg remifentanyl was added into 100 mL of 0.9% saline at a concentration of 5 µg/mL. The dose and number of patients that required remifentanyl was recorded. The infusion of drugs was discontinued at the end of the procedure. Modified Steward Recovery Score (MSRS) involves 0 to 3 scores. A MSRS score of ≥6 means that the patient is awake or responds to verbal stimuli, has purposeful motor activity, and coughs on command. A MSRS score of 0 means that the patient is unconscious, has no motor activity, and requires airway assistance. After the discontinuation of the infusion, in the recovery room a MSRS of ≥6 was achieved to provide adequate discharge criteria.⁸

Satisfaction measures

Patient 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. Surgeon satisfaction levels were evaluated at discharge on a five-point numerical scale: 0=extremely poor; 1=poor; 2=fair; 3=good; 4=excellent. Patient satisfaction and surgeon

satisfaction was recorded at the end of each procedure for surgeons and at the end of the recovery room period for all patients. There were two different surgeon groups in this study. However, in both groups, the same surgeon was responsible for answering the questionnaire. Primary outcomes were: 1) comparison of use of midazolam and remifentanyl drugs during operation, 2) evaluation of the satisfaction of patient and surgeon at the end of the operation. Hemodynamical data, adverse events, hospital stay were also recorded.

Statistical analysis

Statistical analyses were performed using SPSS software for Windows version 15.0. Normal distribution was determined using the Shapiro- Wilk test. Continuous variables were expressed as median or mean values and standard deviation. Categorical variables were expressed as number and percentages. Independent samples t test, Mann-Whitney U test, chi-square or Fisher's exact test were used where appropriate.

RESULTS

Of 116 patients assessed for eligibility, 99 patients met inclusion criteria and were randomized to intravenous midazolam as CI or to IB doses of midazolam (Figure

1). There were no differences in demographic and clinical characteristics (Table 1). In the CI group midazolam consumption was statistically significantly greater than in the IB group ($P < .001$) (Figure 2). The use of remifentanyl as a rescue medication was less in the CI than in the IB group ($P = .001$) (Figure 3). MOAA/S and VNRS scores were similar at all time measurement points intraoperatively (Table 2). Operative data (procedure time, recovery times and hospital stay) and satisfaction scores were not significantly different, except that surgeon scores showed greater satisfaction with CI ($P = .035$) (Table 3). Although hypotension and bradycardia was observed more in the IB group there were no statistical significant differences between groups (Table 4).

DISCUSSION

MAC is a type of sedation that provides analgesia along with local anesthesia to a patient during a planned procedure.⁹ During dialysis vascular access procedures, conscious sedation and analgesia using midazolam is able to provide pain relief, tolerability to anxiety and relief of discomfort during the procedure.^{10,11} However, administration of both intravenous use of midazolam either continuously or intermittently along with remifentanyl as a rescue medication has not been investigated

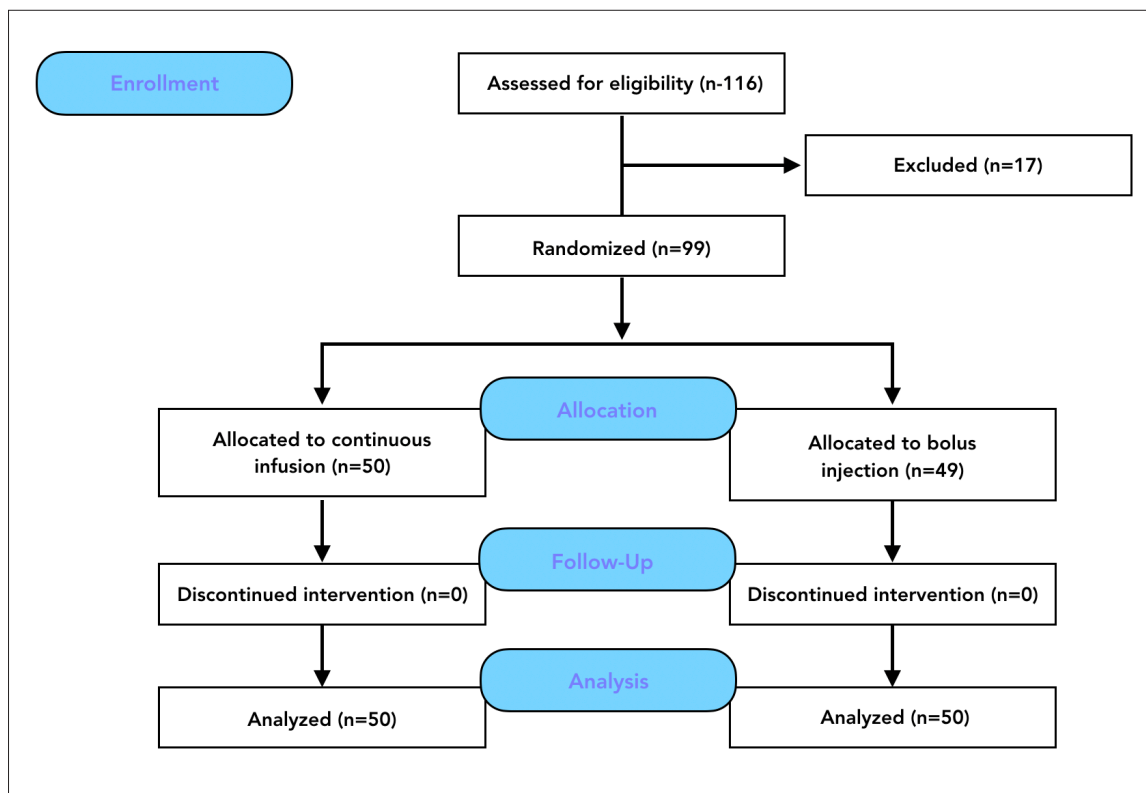


Figure 1. CONSORT 2010 flow diagram.

extensively. For this reason, there is a need for careful investigation of dose requirements of the sedative agents during short procedures in patients with chronic renal failure.^{5,10-12}

In our study, the main outcomes were as follows: 1) The total dose of intravenous midazolam use was higher with continuous use of intravenous midazolam in comparison to intermittent use; 2) The continuous use of intravenous midazolam provided better surgeon satisfaction than intermittent bolus midazolam; and 3) The continuous use of intravenous midazolam was used safely for arteriovenous fistula procedures. These results show us that while using intravenous midazolam in end-stage renal failure, there is a need for careful dose titration, and to prevent adverse events during the procedure, the rescue medication needs to be carefully selected.¹²⁻¹⁶

The total dose of midazolam is restricted in chronic renal failure.^{8,10,14} In several studies the total mean dose of midazolam has been restricted to between 3.4 mg and 7 mg.^{5,13} In a large cohort of study including 12896 hemodialysis patients undergoing dialysis access maintenance procedures with sedation the total mean dose of midazolam when used alone was 3.4 mg.⁵

There are physiological changes that also affect the pharmacokinetics of the drugs in patients with renal disease. Midazolam has the characteristics of a short duration of onset of action, a fast redistribution phase, a clearance rate of 1.7 to 4 hours; metabolism is related to cytochrome-P450 3A4 enzyme.^{1-3,12-14} Factors that affect dosing of midazolam include time of dialysis, volume overload, intravascular volume depletion,

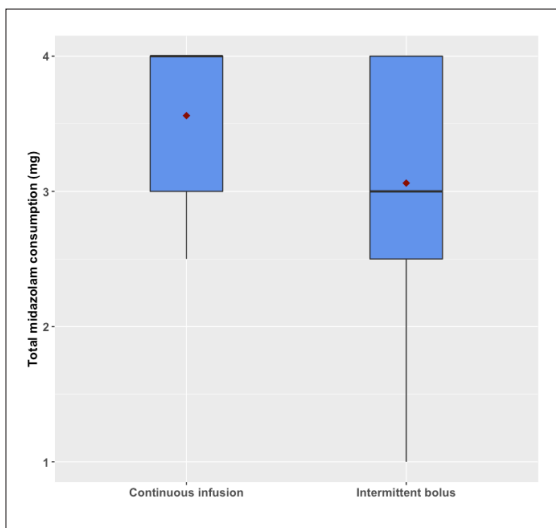


Figure 2. Total midazolam consumption by method of administration (median [IQR]: 4.0, [3, 4] vs 3.0 [2.5, 4], $P < .001$) (red diamond is mean).

Table 1. Demographic and clinical characteristics by treatment groups (n=99).

	Continuous infusion (n=50)	Intermittent bolus (n=49)	P value
Male	19 (38)	23 (47)	.368
Female	31 (62)	26 (53)	
Age (y)	67.4 (14.2)	63.6 (12.2)	.15
Height (cm)	1.7 (0.1)	1.6 (0.1)	.082
Weight (kg)	69.3 (12.4)	66.5 (13.0)	.274
Body mass index (kg/m ²)	24.9 (4.2)	24.7 (4.4)	.825
Preoperative disease			
Hypertension	18 (36)	14 (29)	.429
Coronary artery disease	11 (22)	19 (39)	.069
Diabetes mellitus	34 (68)	27 (55)	.187
Pulmonary disease	5 (10)	3 (6)	.479
Smoking status	16 (32)	12 (25)	.407

Values shown as mean (standard deviation) or number (percentage) unless otherwise noted.

Table 2. The comparison of Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) and Verbal Numerical Rating Scale (VNRS) between treatment groups.

	Continuous infusion (n=50)	Intermittent bolus (n=49)	P value
MOAA/S			
0	2 (4)	None	.157
1	7 (14)	4 (8)	.356
2	24 (48)	19 (39)	.355
3	16 (32)	22 (45)	.187
4	1 (2)	3 (6)	.298
5	None	1 (2)	.31
6	None	None	NS
VNRS			
0	8 (16)	5 (10)	.393
1-2	19 (38)	13 (27)	.222
3-4	22 (44)	28 (57)	.191
5-6	1 (2)	3 (6)	.298
7-8	None	None	
9-10	None	None	

Values shown as number (percentage).

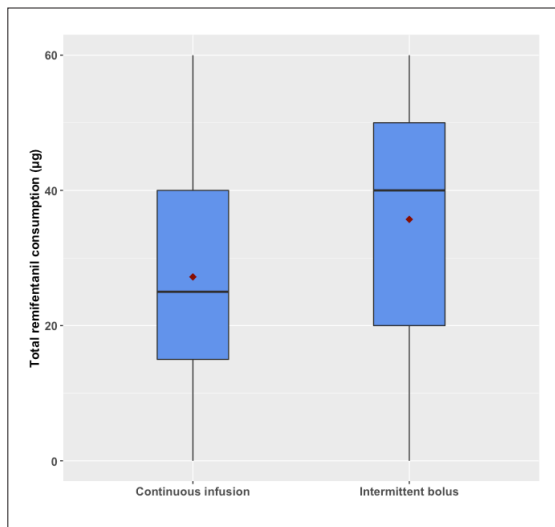


Figure 3. Total remifentanyl consumption by method of administration of midazolam (median [IQR]: 25.0, [15, 40] vs 40.0 [20, 50], $P < .001$) (red diamond is mean).

Table 3. Operative data and satisfaction scores by method of administration.

	Continuous infusion (n=50)	Intermittent bolus (n=49)	P value
Operative data			
Duration of procedure time (min)	62.8 (20.6)	70.5 (26.5)	.124
Recovery time (min)	19.2 (3.7)	17.6 (4.5)	.109
Hospital stay (h)	34.3 (2.8)	33.3 (3.3)	.105
Satisfaction (0-4)			
Patient	3.1 (0.9)	2.8 (0.8)	.056
Surgeon	3.4 (1.1)	2.9 (1.0)	.035
Modified Steward Recovery Score	6.5 (0.5)	6.7 (0.5)	.052

Values are as mean (standard deviation) and median (interquartile range) for drug consumption (statistical comparison using Mann Whitney U test for drug consumption).

presence of chronic metabolic acidosis, and hypoalbuminemia causing high free drug availability.¹⁵ Because of these factors, total midazolam dose should be decreased at a rate of 30-50% in patients with chronic renal disease.^{15,16} In our study, we limited our total dose of intravenous midazolam to 4 mg during arteriovenous fistula procedures, which usually takes place at a duration of one to two hours. Continuous use of midazolam has been used for several in-hospital procedures in previous studies and continuous infusion of midazolam was considered a satisfactory sedation technique without significant adverse events when the dose is adjusted appropriately.^{4,15-17}

The major adverse effects associated with midazolam administration are related to pulmonary and cardiovascular events.^{10-12-16,18} In our study, intravenous midazolam as a continuous infusion did not cause an increase in the reported adverse event rates. In previous studies, remifentanyl use during colonoscopy provided sufficient pain relief with fast recovery without any significant adverse events related to hemodynamic parameters or respiratory depression.^{10-12,18-20} Our findings are similar to the findings in the literature that the incidence of adverse events does not rise with intravenous remifentanyl bolus doses. In a recent study with local anesthetic injection for needle or open breast biopsy, remifentanyl provided excellent analgesia and this finding was similar to our findings.²⁰ Midazolam use as intravenous intermittent bolus doses has been shown to cause more hypotension and bradycardia during sedation related procedures especially in patients with renal failure.^{5,11,12,17} In our study, the incidence of hypotension and bradycardia was observed more in the intermittent bolus patients in comparison to continuous infusion group, but the difference was not statistically significant.¹⁸⁻²⁰ In our study, we were able to make necessary dose adjustments depending on the sedation protocol.

There is also discussion on the analgesic effects of intravenous midazolam and use of lidocaine in the literature. The discussions are not on infiltrative use of lidocaine and midazolam but mainly use of intravenous midazolam in intravenous regional anesthesia along with intravenous use of lidocaine. Studies have demonstrated an enhanced intraoperative analgesia and improved anesthesia quality with the addition of intra-

venous midazolam providing evidence to its analgesic effects for use in clinical studies.²

In previous studies, postoperative hospital stay during short procedures has been discussed and several reports provide data that MAC with sedation provides shorter hospital stay in comparison to general anesthesia. Our findings are similar to the previous studies that hospital stay was not prolonged in neither our study group of patients.^{2,16,21} Another important issue for discussion is patient and surgeon satisfaction.²² In our study, although patient satisfaction was similar between groups, surgeons reported better satisfaction in the continuous infusion study group. Our findings provide valuable data that maintaining a constant steady state of drug concentration during monitored anesthesia care provides better surgeon satisfaction.

The limitation of our study includes the presence of two different surgeon groups who completed the questionnaire for surgeon satisfaction and in these two groups the same surgeon was responsible for completing the questionnaire. Because of this limitation, the study may need to be performed in a larger group of patients. In conclusion, continuous use of intravenous midazolam during MAC provides better surgeon satisfaction than intermittent bolus midazolam and can be used safely for arteriovenous fistula procedures.

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Table 4. The comparison of hemodynamic parameters and adverse events.

	Continuous infusion (n=50)	Intermittent bolus (n=49)	P value
Minimum SBP (mm Hg)	109 (68-149)	96 (64-155)	.104
Minimum HR (bpm)	66 (37-83)	59 (41-79)	.093
Minimum SpO ₂ (%)	98 (93-100)	97 (92-100)	.12
Complications, n (%)			
Hypotension (SBP <70 mm Hg)	7 (14)	13 (27)	.121
Bradycardia (HR <50 bpm)	5 (10)	9 (18)	.232
Desaturation (SpO ₂ ≤94%)	2 (4)	3 (6)	.63
Nausea/Vomiting	2 (4)	4 (8)	.385
Pruritus	1 (2)	2 (4)	.546
Shivering	18 (36)	14 (29)	.429
Use of ephedrine	5 (10)	9 (18)	.232
Use of atropine	4 (8)	7 (14)	.32

Values shown as median (min-max) or number (percentage) unless otherwise noted. SpO₂: peripheral oxygen saturation.

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