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Ventilatory Effect of Midazolam in Propofol Deep Sedation for Hepatic Tumor Patients Undergoing Percutaneous Radiofrequency Ablation Procedure

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Abstract: Objective: The aim of the study was to compare the ventilatory effect between propofol deep sedation technique with and without midazolam in hepatic tumor patients undergoing radiofrequency ablation procedure. Methods: Three hundred and seventy-four patients who underwent radiofrequency ablation procedure in a single year were randomly assigned to the deep sedation without midazolam group (A, n = 187) and deep sedation with midazolam group (B, n = 187). Patients in group A received normal saline, and those in group B received 0.02 mg/kg of midazolam intravenously in equivalent volume. All patients were oxygenated with 100% O_2 via nasal cannula and sedated with intravenous fentanyl and the titration of intravenous propofol. Ventilatory parameters, including oxygen saturation, end tidal carbon dioxide, and respiratory rate every five minutes, during and after the procedure, as well as the duration of sleep and sedation score in the recovery room, were recorded. Results: There were no significant differences in the patients' characteristics, duration of procedure, total dose of propofol, ventilatory parameters including oxygen saturation, end tidal carbon dioxide, and respiratory rate, as well as sedation score at 20, 25, 30, 35, and 40 min after the procedure, between the two groups. However, mean sedation score at 5, 10, and 15 min after the procedure, in group B, was significantly lower than in group A. In addition, the duration of sleep after the procedure, in group B, was significantly greater than in group A. No serious ventilatory adverse effects were observed either group. Conclusion: Propofol deep sedation with and without midazolam for hepatic tumor patients who underwent radiofrequency ablation procedure was safe and effective. A low dose of midazolam in propofol deep-sedation technique did not create serious ventilatory effects.

Keywords: ventilatory effect; midazolam; propofol; deep sedation; radiofrequency ablation; hepatic tumor

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1. Introduction

Radiofrequency ablation (RFA) is an alternative technique for treatment of small hepatic tumors that cannot be managed with surgical treatment, because of its equivalent long-term survival, decreased morbidity, and better preservation of hepatic parenchyma. This technique is defined as direct application of radiofrequency energy therapy to the cancerous tissue, in an attempt to achieve eradication or substantial tumor destruction. The intense heat leads to thermal coagulation that can destroy the tumor [1,2]. RFA is considered to be equally effective as surgical resection in patients with solitary tumor nodules of $\leq$2 cm [3]. RFA provided five-year survival rates of 40–70% and a lower local recurrence rate [2].

Most RFA procedures are done by radiologists, under intravenous sedation. The depth of sedation level and sedative drugs used vary according to the condition of the patient, the site and size of the tumor, the experience of the anesthesiologist, and the

satisfaction of the radiologist. In our center, intravenous sedation (99.3%) was the main anesthetic technique. The mainly used sedoanalgesic drugs were propofol, fentanyl, and midazolam [4,5]. However, midazolam can create hypoventilation or respiratory depression. Furthermore, previous reports demonstrated that the risk for adverse respiratory events increased with an increase in dose and is synergistically worsened by opioids and other anesthetic agents [6,7]. This study was therefore designed to compare the ventilatory effect of midazolam in combination of propofol and fentanyl for deep sedation in patients undergoing percutaneous RFA procedure.

2. Materials and Methods

2.1. Patients

This study was conducted from July 2018 to January 2020, at a radiology unit, outside the operating room, in Siriraj Hospital, Bangkok, Thailand. Hepatic tumor patients who were at least 20 years of age and who presented for percutaneous RFA procedure were eligible for the study. Exclusion criteria included patients with severe cardiorespiratory diseases or end-stage renal disease, any clinical evidence of hepatic encephalopathy, American Society of Anesthesiologists (ASA) physical status of class IV or V, and refusal to participate in the study. A total of 374 consecutive patients were eligible and were randomized for the study. The study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital (Certificate of Approval: Si086/2018) and verified by ClinicalTrials.gov (accessed on 1 March 2021): TCTR20180909002. All patients provided written informed consent for the study and the procedure.

2.2. Study Design

The study was a double-blind, randomized, controlled study. Hepatic tumor patients were randomized into either the normal saline group (A) or the midazolam group (B) by using computer-generated randomization numbers placed in sealed envelopes (Figure 1). The anesthetic personnel and the research assistant were blinded to the randomization procedure. Randomization took place in the pre-procedure room, separate from the procedure room and the recovery room. The blinded research assistant was present in the procedure room and/or recovery room, to collect procedural data and other research data. All RFA procedures were done by the percutaneous technique, using an ultrasound and/or a computerized tomography-guided technique, and were performed by an intervention radiologist. The objective of the study was to compare the ventilatory effect between propofol deep-sedation technique with and without midazolam in hepatic tumor patients undergoing percutaneous RFA procedure.

2.3. Sedation-Related Procedure

Each patient was monitored in the standard manner for blood pressure, heart rate, heart rhythm with single lead electrocardiogram, and oxygen saturation with pulse oximetry, as well as end tidal carbon dioxide ($ETCO_2$). No other pre-medications were administered before the procedure. All patients in both groups were oxygenated with 100% O_2 via nasal cannula (3 L/min). The $ETCO_2$ was measured by using a newly developed nasal cannula with a carbon dioxide–sampling port. Our modified nasal cannula could be invented with a short venous catheter punctured through the nasal prong (Figure 2). Lastly, the nasal cannula could provide oxygen via one nostril and carbon dioxide could be sampled through the present invention one (Figure 3).

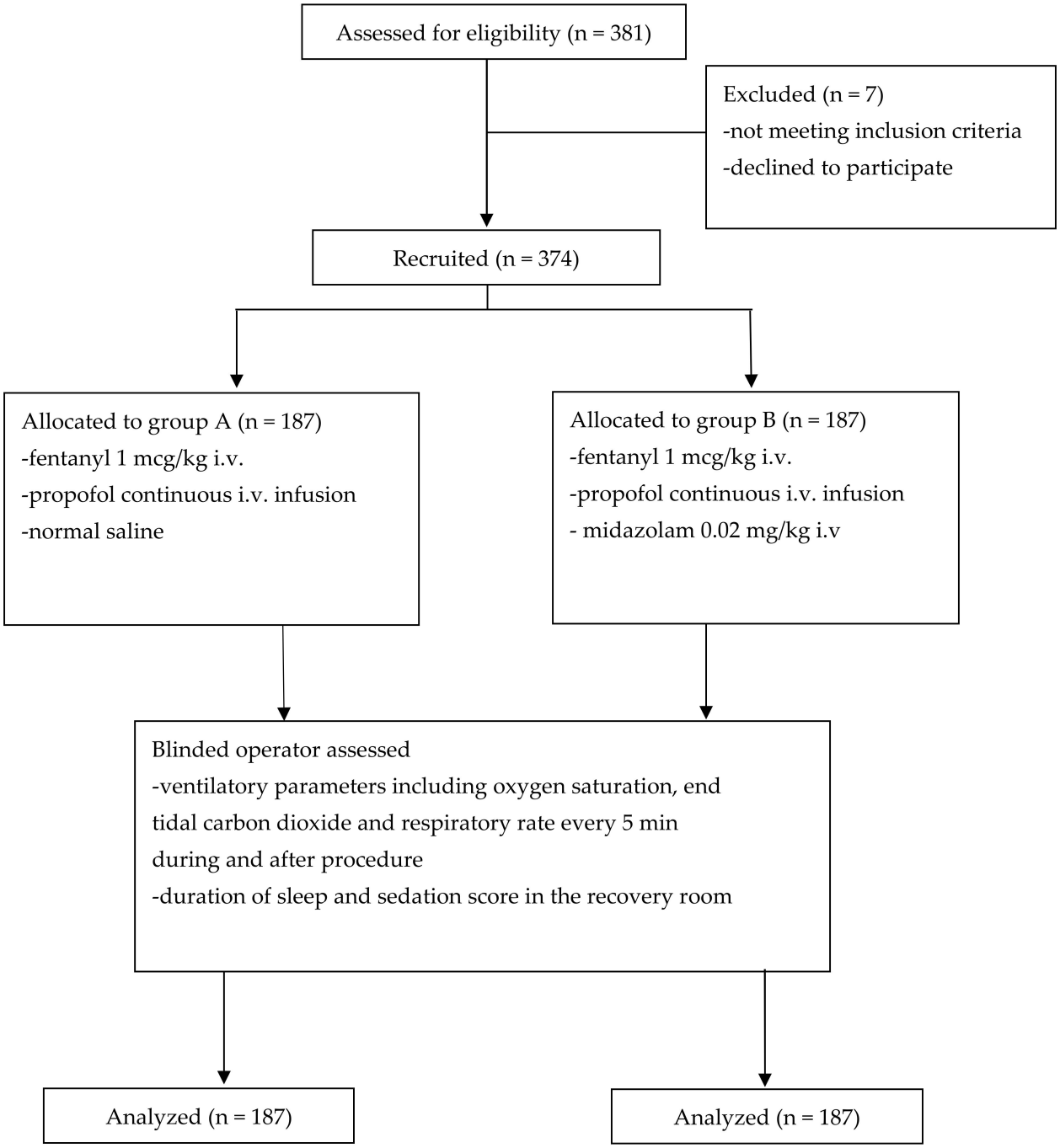

Figure 1. Enrollment and study procedure. Intravenous = i.v.

All procedures were done by using the propofol deep sedation (PDS) technique, and all patients were sedated to a deep-sedation level, according to the guidelines of the American Society of Anesthesiologists [8] and American Gastroenterological Association [9]. All patients were sedated, using clinical assessment, with depth of sedation assessed with the use of the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. The MOAA/S score ranges from 1 to 5 (1 = unresponsive to shaking, 2 = responsive to shaking only, 3 = responsive to loud verbal command, 4 = lethargic but responsive to normal verbal command, and 5 = responsive and alert). The sedation level was targeted and maintained at scale 1 or 2. All patients were sedated with intravenous (i.v.) fentanyl 1 mcg/kg and the titration of i.v. propofol by continuous infusion. Group A received normal saline, and group B received midazolam 0.02 mg/kg i.v., in an equivalent volume. PDS was given by the anesthetic personnel, including residents in the anesthesiology residency program

and anesthetic nurses supervised by a staff anesthesiologist in a radiology unit outside the operating room.

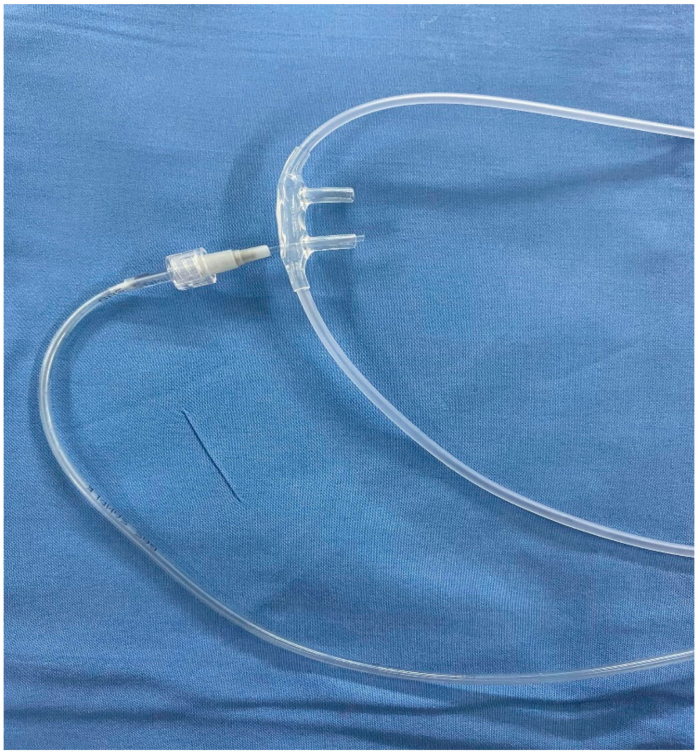

Figure 2. Newly developed nasal cannula.

Figure 3. Nasal cannula with a carbon dioxide–sampling port.

2.4. Sedation-Related Ventilatory Effects

All ventilatory parameters were noted. Ventilatory parameters included oxygen saturation, $ETCO_2$, and respiratory rate. Respiratory depression was defined as the reduction of respiratory rate, oxygen saturation, and increase of $ETCO_2$, as well as other adverse events, such as upper-airway obstruction. These parameters were recorded every 5 min, during and after RFA procedure. Moreover, sedation scores every 5 min after the procedure were evaluated. The sedation score was defined as follows: 0 = awake; 1 = slightly drowsy, easily aroused; 2 = frequently drowsy, arousable, drifts off to sleep during conversation; 3 = somnolence, minimal or no response to verbal or physical stimulation.

2.5. Statistical Analysis

The study was designed to test the null hypothesis that PDS with low-dose midazolam would offer no greater ventilatory adverse effect than PDS without midazolam. In the previous report, respiratory depression was 23% and 16% in with and without midazolam, respectively [10]. The sample size calculation was done from n4 studies. For a non-inferiority trial for binary data: proportion in group A (p1) = 0.160, proportion in group B (p2) = 0.160, non-inferiority or superiority margin (δ) = 0.100, ratio between 2 groups (k) = 1.0, alpha (α) = 0.05, Z (0.950) = 1.644854, and beta (β) = 0.20, Z (0.800) = 0.841621. To detect a 10% difference between each group, the estimated sample size was calculated to range from 167 patients per arm. The power of the test was 0.8. Additionally, α was set to 0.05 for all comparisons. Results were expressed as mean $\pm$ SD or percentage, when appropriate. The statistical software package SPSS for Windows Version 16 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. All statistical comparisons were made at the two-sided 5% level of significance.

3. Results

Three hundred and seventy-four hepatic-tumors patients undergoing percutaneous RFA procedures during the study period were enrolled in the study. After randomization, 187 patients were in each group. Mean age in group A was 63.5 $\pm$ 9.7 years, and mean age in group B was 62.7 $\pm$ 9.2 years. There were no statistically significant differences in age, gender, weight, height, ASA physical status, duration of procedure, and the total dose of propofol between the two groups (Table 1).

Table 1. Characteristics of patients, duration of procedure, and total dose of propofol.

	Group A (n = 187)	**Group B (n = 187)**	***p*-Value**
Age (year)	63.5 (9.7)	62.7 (9.2)	0.638
Gender: Male	126 (67.4)	141 (75.4)	0.086
Female	61 (32.6)	46 (24.6)	
Weight (kg)	65.8 (12.4)	67.6 (11.9)	0.615
Height (cm)	163.1 (8.3)	164.1 (7.7)	0.372
ASA physical status:			
I	0	0	0.489
II	132 (70.6)	138 (73.8)	
III	55 (29.4)	49 (26.2)	
Duration of procedure (min)	50.2 (23.6)	58.1 (28.2)	0.56
Total dose of propofol			
mg	295.4 (139.3)	306.9 (162.8)	0.369
mg/kg	4.6 (2.2)	4.6 (2.5)	0.446
mg/kg/h	5.8 (2.3)	5.1 (2.2)	0.476

The data are presented as mean $\pm$ SD or n (%). Group A = propofol deep sedation (PDS) without midazolam. Group B = PDS with midazolam. ASA = American Society of Anesthesiologists.

Table 2 shows the ventilatory parameters, including oxygen saturation, end tidal carbon dioxide, and respiratory rate during the procedure, in the two groups. All patients in both groups were concluded with successful completion of the procedure. There were

no significant differences in ventilatory parameters, including oxygen saturation, end tidal carbon dioxide, and respiratory rate during procedure, between the two groups.

Table 2. Ventilatory parameters during procedure.

	Group A (n = 187)	**Group B (n = 187)**	***p*-Value**
5 min during procedure			
SpO_2 (%)	98.7 (1.8)	98.6 (1.9)	0.521
$ETCO_2$ (mmHg)	35.4 (4.6)	34.7 (4.2)	0.349
Respiratory rate (breath per minute)	16.1 (3.6)	16.7 (3.9)	0.197
10 min during procedure			
SpO_2 (%)	98.6 (1.9)	98.3 (2.1)	0.636
$ETCO_2$ (mmHg)	35.8 (4.6)	34.8 (4.6)	0.285
Respiratory rate (breath per minute)	16.1 (3.5)	16.8 (3.5)	0.757
15 min during procedure			
SpO_2 (%)	98.6 (1.9)	98.3 (2.0)	0.355
$ETCO_2$ (mmHg)	35.6 (4.9)	34.9 (4.6)	0.585
Respiratory rate (breath per minute)	16.1 (3.4)	17.3 (3.8)	0.288
20 min during procedure			
SpO_2 (%)	98.6 (1.9)	98.4 (1.9)	0.485
$ETCO_2$ (mmHg)	35.5 (4.6)	35.1 (4.6)	0.217
Respiratory rate (breath per minute)	16.2 (3.4)	17.3 (3.5)	0.059
25 min during procedure			
SpO_2 (%)	98.6 (1.8)	98.4 (1.7)	0.116
$ETCO_2$ (mmHg)	35.1 (4.6)	34.7 (4.6)	0.755
Respiratory rate (breath per minute)	16.4 (3.5)	17.5 (3.6)	0.136
30 min during procedure			
SpO_2 (%)	98.4 (2.0)	98.4 (1.7)	0.535
$ETCO_2$ (mmHg)	34.8 (4.6)	34.7 (4.9)	0.327
Respiratory rate (breath per minute)	16.9 (3.5)	17.5 (3.5)	0.375
35 min during procedure			
SpO_2 (%)	98.5 (1.8)	98.3 (1.8)	0.394
$ETCO_2$ (mmHg)	34.5 (4.3)	34.7 (4.7)	0.236
Respiratory rate (breath per minute)	16.9 (3.4)	17.7 (3.6)	0.318
40 min during procedure			
SpO_2 (%)	98.5 (1.7)	98.4 (1.7)	0.475
$ETCO_2$ (mmHg)	34.3 (4.0)	34.3 (4.3)	0.304
Respiratory rate (breath per minute)	17.0 (3.8)	17.9 (3.6)	0.422
45 min during procedure			
SpO_2 (%)	98.5 (1.8)	98.5 (1.6)	0.646
$ETCO_2$ (mmHg)	34.3 (3.8)	34.2 (4.4)	0.691
Respiratory rate (breath per minute)	16.9 (3.2)	18.0 (3.6)	0.105
50 min during procedure			
SpO_2 (%)	98.4 (1.8)	98.3 (1.9)	0.625
$ETCO_2$ (mmHg)	34.1 (4.1)	34.2 (5.0)	0.238
Respiratory rate (breath per minute)	16.9 (3.7)	18.5 (3.5)	0.335
55 min during procedure			
SpO_2 (%)	98.4 (1.8)	98.4 (1.9)	0.67
$ETCO_2$ (mmHg)	33.5 (4.1)	34.4 (4.6)	0.451
Respiratory rate (breath per minute)	17.0 (3.3)	18.2 (3.1)	0.691

Table 2. *Cont.*

	Group A (n = 187)	Group B (n = 187)	*p*-Value
60 min during procedure			
SpO_2 (%)	98.5 (1.7)	98.4 (2.0)	0.265
$ETCO_2$ (mmHg)	33.4 (5.0)	34.7 (4.0)	0.654
Respiratory rate (breath per minute)	17.3 (3.3)	18.2 (3.5)	0.709

The data are presented as mean ± SD. Group A = PDS without midazolam. Group B = PDS with midazolam. SpO_2 = oxygen saturation. $ETCO_2$ = end tidal carbon dioxide.

Table 3 demonstrates the ventilatory parameters, including oxygen saturation, end tidal carbon dioxide, and respiratory rate, as well as the sedation score, and duration of sleep after the procedure. There were no significant differences in ventilatory parameters, including oxygen saturation, end tidal carbon dioxide, and respiratory rate, as well as sedation score at 20, 25, 30, 35, and 40 min after the procedure, between the two groups. Sedation score at 5, 10, and 15 min after the procedure, in group B, was significantly lower than in group A. In addition, the duration of sleep after procedure in group B was significantly greater than in group A. However, all patients in both groups at 50 min after the procedure were wakeful. No serious ventilatory adverse effects were observed in either group.

Table 3. Ventilatory parameters, sedation score, and duration of sleep after procedure.

	Group A (n = 187)	Group B (n = 187)	*p*-Value
5 min after procedure			
SpO_2 (%)	98.7 (1.7)	98.2 (2.0)	0.234
$ETCO_2$ (mmHg)	32.4 (4.3)	32.0 (4.3)	0.079
Respiratory rate (breath per minute)	16.5 (3.3)	17.2 (3.5)	0.636
Sedation score (0–3)	0.8 (0.5)	0.6 (0.6)	0.026 *
10 min after procedure			
SpO_2 (%)	98.9 (1.4)	98.5 (1.8)	0.058
$ETCO_2$ (mmHg)	33.0 (4.3)	32.5 (4.4)	0.79
Respiratory rate (breath per minute)	16.4 (3.3)	17.1 (3.6)	0.328
Sedation score (0–3)	1.2 (0.6)	0.9 (0.6)	<0.001 *
15 min after procedure			
SpO_2 (%)	98.5 (1.7)	98.6 (1.8)	0.321
$ETCO_2$ (mmHg)	33.4 (5.0)	32.9 (4.0)	0.685
Respiratory rate (breath per minute)	17.3 (3.3)	17.0 (3.4)	0.134
Sedation score (0–3)	1.5 (0.6)	1.2 (0.6)	<0.001 *
20 min after procedure			
SpO_2 (%)	99.2 (1.3)	98.9 (1.6)	0.519
$ETCO_2$ (mmHg)	33.7 (3.8)	32.6 (4.1)	0.625
Respiratory rate (breath per minute)	16.3 (3.6)	17.1 (3.2)	0.069
Sedation score (0–3)	1.6 (0.5)	1.5 (0.5)	0.203
25 min after procedure			
SpO_2 (%)	99.4 (1.1)	99.0 (1.4)	0.186
$ETCO_2$ (mmHg)	33.9 (3.4)	32.0 (4.1)	0.51
Respiratory rate (breath per minute)	16.2 (3.7)	16.6 (3.0)	0.075
Sedation score (0–3)	1.5 (0.6)	1.5 (0.6)	0.658
30 min after procedure			
SpO_2 (%)	99.6 (0.8)	99.2 (1.2)	0.397
$ETCO_2$ (mmHg)	33.2 (3.1)	31.8 (3.8)	0.658
Respiratory rate (breath per minute)	15.9 (3.0)	16.6 (3.0)	0.821
Sedation score (0–3)	1.6 (0.6)	1.7 (0.5)	0.454

Table 3. *Cont.*

	Group A (n = 187)	Group B (n = 187)	*p*-Value
35 min after procedure			
SpO_2 (%)	99.6 (0.8)	98.9 (1.5)	0.369
$ETCO_2$ (mmHg)	34.2 (2.5)	32.6 (4.2)	0.822
Respiratory rate (breath per minute)	16.8 (2.8)	16.9 (3.0)	0.449
Sedation score (0-3)	1.6 (0.5)	1.7 (0.5)	0.724
40 min after procedure			
SpO_2 (%)	100.0 (0.0)	99.3 (1.0)	0.399
$ETCO_2$ (mmHg)	34.0 (1.7)	34.3 (3.3)	0.125
Respiratory rate (breath per minute)	18.7 (1.2)	16.6 (3.7)	0.179
Sedation score (0-3)	2.0 (0.0)	1.9 (0.4)	0.49
Duration of sleep after procedure (min)	18.9 (7.4)	22.4 (7.7)	<0.001 *

The data are presented as mean ± SD; * $p < 0.05$ indicated statistically significant. Group A = PDS without midazolam. Group B = PDS with midazolam. SpO_2 = oxygen saturation. $ETCO_2$ = end tidal carbon dioxide.

4. Discussion

In procedural sedation, the most common sedoanalgesic drugs are propofol, narcotics, and shorter-acting benzodiazepines, owing to their relatively rapid onset and rapid offset [7,11]. The use of propofol for deep sedation has been extensively accepted by anesthesiologists. It has anxiolytic, hypnotic, anti-emetic, and anesthetic properties [12,13]. Fentanyl has a short half-life and rapid onset of action. It has been frequently used for this procedure. Generally, deep sedation might be satisfactory for RFA cases. It is commonly achieved by a combination of midazolam and fentanyl [14]. For benzodiazepine drugs, midazolam has the shortest half-life and duration of action, when compared with diazepam, making it an ideal agent when prolonged sedation is not mandatory. It is an ideal agent to provide anxiolysis and anterograde amnesia for RFA procedures. Several reports demonstrated that the presence of hepatocellular damage did not alter the required dosage of midazolam. No effect of midazolam administration was realized on aspartate aminotransferase and alanine aminotransferase, in the patients with liver dysfunction [15,16]. However, midazolam is thought to cause hypotension through peripheral vasodilation, and it also can cause respiratory arrest or apnea. The combination of midazolam and fentanyl can increase the risk of respiratory depression [6,7].

The present study demonstrates that PDS for percutaneous RFA procedure in hepatic-tumor patients, by anesthetic personnel with appropriate monitoring, is relatively safe and effective, even in a radiology unit outside the operating room. All RFA procedures were able to be accomplished. A combination of low-dose midazolam with propofol and fentanyl for deep sedation in these patients does not create serious ventilatory adverse effects. Although, mean sedation score at 5, 10, and 15 min after procedure, as well as mean duration of sleep, was statistically different between the two groups. However, they were not clinically significant. Our report of PDS practice for percutaneous RFA procedure demonstrated that it could be managed safely with or without midazolam. This might be due to the low dose of midazolam utilized in the study. In the present study, the MOAA/S scale was used for clinical assessment of the depth of sedation. In the review of the literature comparing the OAA/S scale with electroencephalography (EEG)-based monitoring, there is good correlation of the corresponding scores with depth of sedation [17]. The correlation was also confirmed by our previous report between the MOAA/S scale and Narcotrend™ monitoring in adult patients who underwent gastrointestinal endoscopic procedures under the PDS technique [18].

The use of continuous pulse oximetry is associated with significant improvement in the detection of oxygen desaturation versus intermittent nursing spot-checks. In the present study, we used a modified nasal cannula with a carbon dioxide-sampling port. Importantly, several previous reports confirmed that the measurement of the $ETCO_2$ through a nasal

cannula with an appropriate sampling port would offer reliable $ETCO_2$ measurements without clinical problems [19]. Capnography provides an early warning of postoperative respiratory depression before oxygen desaturation, especially when supplemental oxygen is administered. The previous study supported the use of continuous pulse oximetry and capnography in postoperative monitoring, to prevent respiratory depression and adverse events [20]. In our previous report, the overall sedation-related complication rate in PDS with and without midazolam for RFA procedure is 24.8% and 26.1%, respectively. There were no significant differences in overall cardiovascular- and respiratory-related complications between the two groups [21]. However, that previous report was a retrospective study. Some limitations might have occurred. We could not accurately assess all ventilatory data. This present study is designed to assess these ventilatory data.

Gonzalez Castro and colleagues evaluated the effects of pre-operative midazolam administration on clinically significant respiratory parameters, including minute ventilation, tidal volume, and respiratory rate, using an impedance-based respiratory volume monitor. The respiratory monitoring data offered the chance for individualized dosing and modification of clinical interventions, which is especially important in elderly patients. With these supplementary respiratory data, clinicians might be able to better classify and quantify respiratory depression, decrease adverse effects, and increase overall patient safety [22]. Clinical implications for the monitoring of ventilation were also confirmed in the endoscopy unit. Respiratory rate alone could lead to both over-management of benign events and under-recognition of potentially hazardous events. Consequently, enhanced ventilation monitoring, as provided by a non-invasive respiratory volume monitor, had the potential to make a significant impact on patient safety during procedural sedation [23].

There are several limitations in our study. First, this study did not assess ventilatory parameters by using impedance-based respiratory volume monitors. Pulse oximetry and end tidal carbon dioxide ($ETCO_2$) monitoring are insufficient to recognize early signs of respiratory compromise in non-intubated patients. Standard patient care with these monitoring methods is a less-than-optimal solution for identifying changes in respiratory status in non-intubated patients. Direct monitoring of minute volume with a non-invasive respiratory volume monitor may be preferable for continuous assessment of adequacy of ventilation in non-intubated patients [24,25]. Second, the study employed sedation score and duration of sleep after the procedure that had not been previously validated. As of these reported scales remained unfair by the use of these scales. Third, this is a single-center study. These results could not be reproducible continuously in other settings. Fourth, the authors did not assess the recovery time. However, the total time to ward in both groups is comparable.

Despite the limitations discussed, we are confident that our findings can be generalized to the practice of percutaneous RFA that uses the PDS technique. For the best result, we believe that several steps in utilizing midazolam in PDS should be followed. First, a low dose of midazolam is used. Second, titration of sedoanalgesic drugs and continuous intravenous infusion of propofol should be utilized in the PDS method. Third, appropriate patient selection and preparation have to be done before the procedure. Fourth, closed monitoring for prevention and early detection of adverse events during and after the procedure need to be performed. We assume that the data are realistic and show daily clinical practice.

5. Conclusions

PDS with low-dose midazolam for hepatic tumor patients who underwent a percutaneous RFA procedure did not show a distinct disadvantage over PDS without midazolam, in terms of ventilatory effect. Additionally, our study suggests that the use of low-dose midazolam in the PDS technique is safe, with rare serious adverse events. All procedures were successfully completed. The duration of sleep in PDS with midazolam is significantly longer than in PDS without midazolam. However, all patients awaked within one hour after the procedure.

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Informed Consent Statement: All patients provided written informed consent for the study and the procedure.

Data Availability Statement: All data generated for this study are included in this article.

Conflicts of Interest: The authors declare no conflict of interest.

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