Original Article

Propofol Deep Sedation with and without Midazolam for Percutaneous Radiofrequency Ablation in Patients with Hepatocellular Carcinoma: A Retrospective Cohort Study

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Objective: The study is aimed to evaluate and compare clinical efficacy of propofol deep sedation [PDS] with and without midazolam for percutaneous radiofrequency ablation [RFA] in adult patients with hepatocellular carcinoma in a radiology unit of a teaching hospital, Thailand.

Materials and Methods: The authors undertook a retrospective review of RFA procedures. Patients were classified into two groups: group P (PDS without midazolam) and group PM (PDS with midazolam). The primary outcome variable of the study was the successful completion of procedure. Secondary outcome variable was sedation-related complication during and immediately after the procedure.

Results: After matching patients' characteristics and duration of procedure, there were 65 patients in group P and 194 patients in group PM. There were no significant differences in characteristics of patients, duration of procedure and preprocedural problems between the two groups. All procedures were successfully completed. There were no significant differences in overall complication rate and hemodynamic parameters including systolic and diastolic blood pressure, heart rate and oxygen saturation between the two groups. However, hypotension and bradycardia in group P was relatively greater than in group PM.

Conclusion: PDS with and without midazolam for RFA in patients with hepatocellular carcinoma with appropriate monitoring is relatively safe and effective. Clinical efficacy of PDS with midazolam for this procedure is not different or greater than in PDS without midazolam. No serious complication is noted.

Keywords: Deep sedation, Propofol, Midazolam, Radiofrequency ablation, Hepatocellular carcinoma

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Radiofrequency ablation [RFA] is a minimally invasive procedure for treatment of small hepatic tumors that cannot be treated with surgical procedure. For early-stage hepatocellular carcinoma, RFA is considered a viable alternative to surgical treatment because of its equivalent long-term survival, decreased morbidity, and better preservation of hepatic parenchyma[1,2]. These tumors are ablated by radiofrequency. Radiofrequency is the heating and destruction of tissues in which a high-frequency alternating current raises the temperature of the tissues beyond 60°C, causing an area of necrosis. This ultrasonic energy is a strong stimulus that requires deep sedation and anesthesia levels during the procedure. RFA is considered to be equally effective as surgical resection in patients with solitary tumor nodules of ≤2 cm[3].

In our center, most RFA procedures are done

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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, experience of the anesthesiologist and satisfaction of the radiologist[4]. Generally, a combination of propofol and sedoanalgesic drug for deep sedation is commonly used for this procedure. Little data is known about the clinical efficacy and safety of propofol deep sedation [PDS] by anesthetic personnel for RFA procedure in the radiology unit outside the operating room. To date, there are several combination techniques for administration of propofol and sedoanalgesic drug[4]. It is believed that the use of sedoanalgesic drug in combination with propofol might influence successful completion of the procedure[5]. However, this combination may produce a high complication rate[5,6]. Additionally, midazolam in combination with propofol and narcotic drug for patients with hepatic dysfunction may increase an adverse effect[7]. The authors conducted a retrospective study to evaluate and compare the clinical efficacy of PDS with and without midazolam for percutaneous RFA procedure in adult patients with hepatocellular carcinoma in a tertiary-care teaching hospital in Thailand. The present study does not focus on the procedure-related complications.

Materials and Methods

Study design

The present study was a retrospective cohort study. The patients were classified into two groups. In group P, the patients were sedated with PDS without midazolam. In group PM, the patients were sedated with PDS with midazolam. The primary outcome of the study was successful completion of the procedure. The successful completion of the procedure was defined as the completion of the procedure as planned without additional general anesthesia once the RFA procedure had started. Failed procedure is defined as the procedure that could not be completed by using the PDS technique in deep sedation level, or having the sedation-related serious complications such as severe hypoxemia (SpO_2 <85% more than 3 minutes and cannot be relieved by airway management), severe cardiorespiratory instability.

The secondary outcome variable was sedation-related complication.

Patients

Patients with hepatocellular carcinoma undergoing RFA procedures in a radiology unit outside the operating room in Siriraj Hospital from January 2011 and January 2013 were enrolled in the present study. Inclusion criteria were adult patients (age ≥18 years) who underwent percutaneous RFA procedure by using PDS technique. The RFA procedures performed in the operating rooms and the procedures performed without PDS, or procedures performed under monitored anesthesia care and general anesthesia were excluded. This present study was approved by the Institutional Review Board of the Faculty of Medicine, Siriraj Hospital (Si 597/2012).

RFA procedure

All RFA procedures were done by the percutaneous method using an ultrasound and/or a computerized tomography-guided technique. The success rate in both groups was recorded. After completion of the procedure, admission into the inpatient hospital service was prepared to observe the post-RFA complications.

Sedation-related complications

All sedation-related complications were recorded. Sedation-related complications were defined as follows: hypertension or hypotension (increase or decrease in blood pressure by 25% from baseline); tachycardia or bradycardia (increase or decrease in heart rate by 25% from baseline); any cardiac arrhythmias; hypoxia (oxygen desaturation, SpO_2 <90%); upper airway obstruction.

Statistical analysis

The authors hypothesized that the rate of successful completion of the procedure in each group was 95%. The non-inferiority margin was 10%.

The type I and II errors were 0.5 and 0.1, respectively. The ratio of Group P and PM was 1: 3. After 15% of drop out population, 65 patients were in Group P, and 194 patients were in Group PM. Results were expressed as mean ± standard deviation or number (percentage), when appropriate. Comparison between group P and PM was analyzed using Chi-square test (for categorical variable), Chi-square test for trend (for ordinal variable), and two-sample independent t-test (for continuous variable). Statistics software SPSS for Window version 18 (SPSS Inc., Chicago, IL) was used to analyze the data. All statistical comparisons were made at two-sided 5% level of significance.

Results

Four hundred and eight patients undergoing

RFA procedures during the study period were enrolled in the study. After matching age, gender, weight, height, ASA physical status and duration of procedure as well as the type of anesthetic technique, 65 patients were in Group P, and 194 patients were in Group PM. Mean age in Group P was 63.0±10.0 years, and mean age in Group PM was 63.2±11.4 years. There were no statistically significant differences in gender, weight, height, ASA physical status, duration of the procedure and preprocedural problems between the two groups (Table 1).

The patients were monitored with non-invasive blood pressure, electrocardiogram and pulse oximetry. End-tidal carbon dioxide monitoring with capnography was not used during sedation. No pre-medication was used before the procedure. All patients in both groups were oxygenated with 100% O_2 via oxygen mask (5 to 6 liters/minute). All procedures were done by using the PDS technique and all patients were sedated in deep sedation level, according to guidelines of the American Society of Anesthesiologists [ASA][8]. The dose of sedative and analgesic agents was evaluated. When the procedure was a failure, general anesthesia was carried out. All 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.

Table 2 showed the success rate and sedative/analgesic agents used in the two groups. All patients in both groups were concluded with successful completion of the procedure. Combination of propofol and fentanyl was used for PDS technique. There was no significant difference in the mean dose of propofol and fentanyl between the two groups.

Table 3 demonstrated sedation-related complications during and immediately after the procedure. Overall, 17 patients (26.1%) in group P and 48 patients (24.8%) in group PM, experienced sedation-related complications. There were no significant differences in overall, respiratory and cardiovascular related-complications between the two groups. However, hypotension and bradycardia in group P were relatively higher than in group PM. In addition, procedure-related complications were none in both groups. All sedation-related complications were under the care of an anesthesiologist. No serious complications were observed.

The hemodynamic parameters including systolic and diastolic blood pressure and heart rate during the procedure were demonstrated in Figure 1 to 3 respectively. Systolic and diastolic blood pressures in both groups reduced during the procedure. Heart rate in both groups decreased in the first 20-minutes,

Table 1. Characteristics of patients, duration of procedure and underlying problems

	Group P (n = 65)	Group PM (n = 194)	*p*-value
Age (yr)	63.0±10.0	63.2±11.4	0.659
Gender: Male	40 (61.5)	141 (72.7)	0.090
Weight (kg)	63.6±11.7	65.1±11.8	0.203
Height (cm)	161.7±9.2	163.7±7.9	0.177
ASA physical status:			
I	1 (1.5)	4 (2.1)	0.691
II	42 (64.7)	135 (69.5)	
III	22 (33.8)	55 (28.4)	
Duration of procedure (min)	83.8±43.1	85.2±44.1	0.377
Underlying problems			
Liver disease	43 (66.2)	107 (55.2)	0.120
Hypertension	29 (44.6)	89 (45.9)	0.860
Hematologic disease	28 (43.1)	74 (38.1)	0.481
Diabetes mellitus	26 (40.0)	70 (36.1)	0.571
Others	37 (56.9)	101 (52.1)	0.497

The data are presented as mean ± standard deviation or n (%)
Group P = Propofol deep sedation [PDS] without midazolam, Group PM = PDS with midazolam, ASA=American Society of Anesthesiologists

Table 2. Success rate and sedative/analgesic agents

	Group P (n = 65)	Group PM (n = 194)	*p*-value
Success rate	65 (100.0)	194 (100.0)	1.000
95% confidence interval	(0.952, 1.000)	(0.983, 1.000)	
Sedative/analgesic agents			
Fentanyl			
Dose/body weight/time (µg/kg/hr)	1.01±0.57	1.01±0.56	0.610
Propofol			
Dose/body weight/time (µg/kg/hr)	3.76±1.53	3.74±1.46	0.641
Midazolam			
Dose/body weight/time (µg/kg/hr)	N/A	0.02±0.01	

The data are presented as mean ± standard deviation or n (%)
Group P = Propofol deep sedation [PDS] without midazolam, Group PM = PDS with midazolam

Table 3. Sedation-related complications during and immediately after the procedure

Complications	Group P (n = 65)	Group PM (n = 194)	*p*-value
Overall	17 (26.1)	48 (24.8)	0.820
Respiratory-related	1 (1.5)	5 (2.6)	0.630
Hypoxemia (SpO_2 <90%)	1 (1.5)	5 (2.6)	0.630
Cardiovascular-related	16 (24.6)	43 (22.2)	0.684
Hypotension	11 (16.9)	34 (17.5)	0.912
Hypertension	0 (0)	5 (2.6)	0.191
Bradycardia	1 (1.5)	1 (0.5)	0.415
Hypotension and bradycardia	4 (6.2)	3 (1.5)	0.047*

The data are presented as n (%). * $p<0.05$ indicates statistical significance.
Group P = Propofol deep sedation [PDS] without midazolam, Group PM = PDS with midazolam

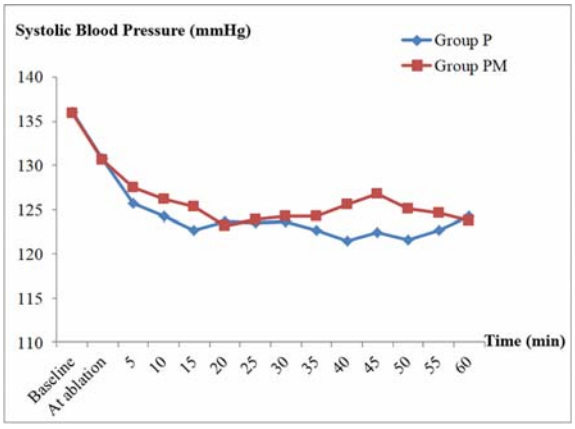

Figure 1. Systolic blood pressure during the procedure. Group P = Propofol deep sedation [PDS] without midazolam, Group PM = PDS with midazolam.

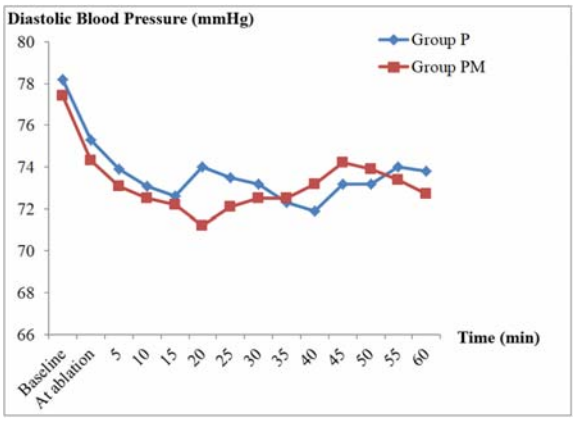

Figure 2. Diastolic blood pressure during the procedure. Group P = Propofol deep sedation [PDS] without midazolam, Group PM = PDS with midazolam.

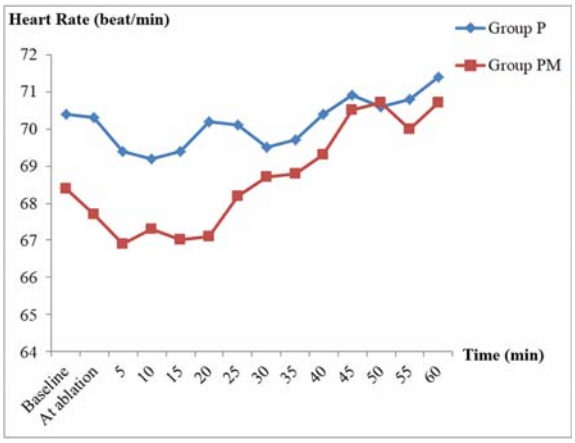

Figure 3. Heart rate during the procedure.
Group Pm = Propofol deep sedation [PDS] without midazolam, Group PM = PDS with midazolam.

after that it increased. Mean oxygen saturation at all time periods in both groups was 99% or 100%. There were no significant differences in mean systolic and diastolic blood pressure, heart rate as well as oxygen saturation between the two groups.

Discussion

The present study demonstrates that PDS for RFA procedure in adult patients by anesthetic personnel with appropriate monitoring is relatively safe and effective, even in a radiology unit outside the operating room. A combination of midazolam with propofol and fentanyl for PDS in RFA patients does not increase the success rate compared with a combination of propofol and fentanyl. All RFA procedures were able to be completed. Our report of PDS practice in adult patients showed that it could be managed safely with or without midazolam. Our study also demonstrates that the rate of complication for this procedure was not significantly different between PDS with and without midazolam. This might be due to low dose of midazolam utilized in the study.

RFA is an alternative technique for treatment of small hepatic tumors that cannot be managed with surgical procedure. It is one of the most common interventional medical procedures. 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[9,10]. The intense heat leads to thermal coagulation that can destroy the tumor. The technology of RFA has been improved over the past 20 years and the methods of anesthesia have been developed as well[4,11]. However, RFA procedure is an invasive and time-consuming procedure, requiring special equipment, training and an experienced radiologist. It is normally denied by the patient because of anxiety and severe discomfort and pain. Patients undergoing RFA procedures usually obtain some forms of anesthesia. In Siriraj Hospital, the anesthesiologists regularly perform deep sedation technique for this procedure[4]. The role of the anesthesiologist for RFA therapy in patients with hepatocellular carcinoma is to facilitate patient's safety and satisfaction as well as to ensure the patient experiencing minimal pain during the procedure. To date, there is evidence that percutaneous RFA procedure can be safely performed with sedation or general anesthesia[4,11,12]. In sedation technique, moderate to deep sedation is required for this procedure. The appropriate administration of sedoanalgesic drugs is needed for successful procedure. The goal of sedation during the procedure is to relieve the procedural pain and the patient's anxiety. In our center, intravenous sedation technique is normally used for various procedures outside the operating room including percutaneous RFA procedure[4,13-16].

Most sedoanalgesic drugs can be used safely in patients with cirrhosis[17]. The use of these drugs for these patients is a challenging task. However, the sedoanalgesic drugs should be individualized depending upon several factors. The commonly used sedoanalgesic drugs are shorter-acting benzodiaze pines and narcotics owing to their relatively rapid onset and rapid offset[18,19]. Midazolam is an anti-anxiety, sedative, amnestic, hypnotic, anti-convulsant and muscle relaxant drug. Several reports demonstrated that the presence of hepatocellular damage did not alter the required dosage of midazolam. No effect of midazolam administration was seen on aspartate aminotransferase and alanine aminotransferase in the patients with liver dysfunction[20,21]. Fentanyl has a short half-life and rapid onset of action. It has been frequently used for this procedure[19]. Generally, deep sedation might be acceptable for RFA cases[4]. It is commonly utilized by a combination of midazolam and fentanyl[22]. This combination technique provides excellent sedation and helps reduce patient's discomfort. Moreover, the use of propofol for deep sedation has been widely adopted by anesthesiologists. It has anxiolytic, hypnotic, anti-emetic and anesthetic properties. Importantly, propofol used in deep sedation technique allows a significant increase in the rate of successful completion of the

procedures as well as patient's and radiologist's satisfaction.

A systematic review reported a major complication rate of 4.1% and mortality rate of 0.15% in this procedure[23]. According to various causes, complications of RFA can be classified into collateral thermal damage, direct mechanical injury and other complications. These complications can arise from the ablative procedure itself, the RFA device and sedation/anesthesia[24]. However, deep sedation is the potential for risks. This study recommends that cardiovascular-related complications might be significantly more common in patients undergoing RFA procedure. The most common complication was hypotension. The incidence rate of sedation-related complications during and after RFA procedure is comparable with other outside operating room procedures[14-16].

The present study used only basic monitoring, including an assessment of non-invasive blood pressure, pulse rate, respiratory rate and pulse oximetry, as well as electrocardiogram. The authors noticed a relatively high overall rate of complications in both groups. This rate is relatively higher than previously reported, and there may be several factors.

There are several limitations of the present study that should be mentioned. First, the present study is retrospective in nature. The main limitation of the study is its reliance on self-reported data. Second, the end-tidal carbon dioxide monitoring was not routinely used during deep sedation for RFA procedure. This may tend toward an underestimation of unpleasant data. 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. Fifth, there are several anesthesiologists and radiologists performing this procedure. A wide variability of experiences could occur. The authors assume that the data are realistic and show daily clinical practice. Finally, because the sample population in our study is small, further randomized controlled studies in larger prospective groups of patients are recommended.

Conclusion

RFA procedure utilized by PDS with and without midazolam for adult patients is relatively effective and safe. Hypotension and bradycardia in the PDS without midazolam group is relatively greater than in the PDS with midazolam group, but this event is transient and easily treated with no adverse sequelae. The combination of propofol and fentanyl for RFA procedure may be beneficial in patients with hepatocellular carcinoma.

What is already known on this topic?

Most RFA procedures are done by radiologists under sedation technique. There are several combination techniques for administration of sedative and analgesic drugs. A combination of propofol and sedoanalgesic drug for deep sedation is commonly used for this procedure. This combination technique may produce a high complication rate.

What this study adds?

PDS with midazolam for RFA procedure in patients with hepatocellular carcinoma with appropriate monitoring is relatively safe and effective. Clinical efficacy of this regimen for this procedure is not different or greater than in PDS without midazolam. An addition of midazolam in PDS technique does not increase a complication rate.

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Potential conflicts of interest

The authors declare no conflict of interest.

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