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Original Research Article

Can liver cirrhosis patients benefit from target controlled infusion of propofol for conscious sedation during endoscopic variceal ligation?

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ABSTRACT

Background: The aim of the present study was to evaluate the feasibility of conscious sedation using target controlled infusion of propofol combined with a single dose of fentanyl during endoscopic variceal ligation in patients with liver cirrhosis.
Methods: Forty-eight patients with liver cirrhosis scheduled for endoscopic variceal ligation were randomly assigned to deep sedation group (DS group) with intravenous bolus of propofol and conscious sedation group (CS group) with target controlled infusion of propofol, 1 μg/kg fentanyl was intravenously injected in each patient before administration of propofol. Cardiorespiratory parameters were monitored, and the side-effects were recorded. The depth of sedation was assessed by both of the sale of observer′s assessment of alertness/sedation (OAA/S) and the bispectral index (BIS). The quality of sedation/analgesia was evaluated by the endoscopist and patients using Visual Analog Scores (VAS). The recovery level was evaluated with the Aldrete scales.
Results: No significant differences were found on demographic data and initial parameters in the two groups. Compared with the CS group, the changes of mean arterial pressure (MAP) and heart rate (HR) and the signs of respiratory depression were significant in the DS group ($p<0.05$). The recovery time in DS group (16.7±2.7 minutes) was much longer than that in the CS group (9.3±3.0 minutes, $p<0.01$). There was no difference in Visual Analogue Scale scores for endoscopist's satisfaction between the two groups (9.2±0.6 versus 9.0±0.6, $p>0.05$), but a higher degree of satisfaction for patient was found in the DS group (9.3±0.6 versus 7.9±0.7, $p<0.01$).
Conclusions: Conscious sedation with target controlled infusion of propofol combined with a single bolus of fentanyl for endoscopic variceal ligation in patients with liver cirrhosis had better hemodynamic stability, less respiratory depression and shorter recovery time.

Keywords: Endoscopic variceal ligation, Propofol, Sedation, Target controlled infusion

INTRODUCTION

Bleeding from esophageal varices is one of the life-threatening complications, and its morbidity is commonly about 30%.[1,2] Since endoscopic variceal ligation (EVL) was initially introduced successfully by Steigmann in 1986, it has become one of the most popular treatments for bleeding esophageal varices.[3]

Although diagnostic gastroscopy can be performed with topical anesthesia without sedation, it often induced discomfort and gagging reactions when endoscope was

inserted and passed through patient's pharynx.[4] Therefore, appropriate sedation/analgesia is preferable.

Patients with liver cirrhosis undergoing endoscopy may face a high risk of complications related to over sedation, such as hypotension, hypoxemia and delayed recovery.[5,6] The choice of sedation program or sedative agents varied in different hospitals and clinicians. Propofol, an ultrashort acting anesthetic agent, has been increasingly used in the field of gastrointestinal endoscopy sedation, and is often intravenously administered alone or combined with opioids or/ and midazolam.[9] However, if inappropriately, propofol may cause undesirable effects, such as hypotension, apnea and oxygen desaturation.[10]

Target controlled infusion (TCI) of propofol can provide an accurate control of the plasma concentration of propofol, thus reduces the incidence of an inadequate depth of anesthesia.[11] Although TCI of propofol has been successfully applied to diagnostic gastroscopy, there is little information about its application in those patients who have liver cirrhosis with anemia and hypoalbuminemia undergoing endoscopic variceal ligation.[12-13]

In this study, we hypothesized that patients with hypoalbuminemia and anemia may have drastic hemodynamic fluctuations and respiratory depression when intravenous bolus of propofol combined with fentanyl for deep sedation were employed.

METHODS

After obtaining approval from local ethics committee in our hospital and informed consent, forty-eight patients diagnosed for hepatic cirrhosis, aged 18-75 years, American Society of Anesthesiologists (ASA) physical status II or III, Modified Child Grade of hepatic function A to C, scheduled for EVL, were randomly assigned to deep sedation group (DS group) or conscious sedation group (CS group) by opening a sealed envelope in which "DS" or "CS" was marked. The exclusion criteria are as follows: severe cardiac and pulmonary disease, psychiatric/emotional disorder and renal dysfunction, history of addiction to opiates or sedatives, allergy to any medication used in the study.

In the gastroscopy room, a brachial intravenous cannula was inserted for administration of drugs. Oxygen was delivered to patient by face mask at a flow rate of 4 L/min. A gas sampling catheter was inserted into the respiratory circuit to measure the end-tidal carbon dioxide ($EtCO_2$) and respiratory rate (RR). Noninvasive blood pressure (NIBP), heart rate (HR), pulse oximetry (SpO_2), were also measured and recorded at 1-minute intervals.

The status of patient′s consciousness was assessed with the scales of the observer′s assessment of alertness/sedation (OAA/S) (Table 1) and the value of bispectral index (BIS).

Table 1: Observer′s assessment of alertness/sedation (OAA/S) score.

Score	Responsiveness
5	Responds readily to name spoken in a normal tone.
4	Lethargic response to name spoken in a normal tone.
3	Responds only after name is spoken loudly or repeatedly, or both.
2	Responds only after mild prodding or shaking.
1	Does not respond to mild prodding or shaking.
0	Does not respond to noxious stimulus.

In the CS group, the criteria of conscious sedation correspond to 3 scores of OAA/S, and a BIS value of 70～80, while in the DS group, the criteria of deep sedation was that each patient was unconscious and unresponsive with 2 scores of OAA/S and a BIS value of 50～60. The sedation level was assessed at 1-minute intervals.

Each patient in the two groups was initially given a single bolus of fentanyl intravenously for 1 μg/kg. In the CS group, patients were sedated by target controlled infusion of propofol 1% with 50 ml syringes (Diprivan, Astra-Zeneca) at a starting plasma concentration of 1.5 μg /ml using a Graessby 3500 pump (Smiths Medical MD. Inc USA). Thereafter, the target propofol concentration was adjusted to a maximum concentration of 3.0 μg/ml by 0.25 μg/ml for each increment to obtain a required sedation level if necessary.

Drug infusion was halted if one of the following "end-points" was observed: apnea last for more than 30 seconds, the partial pressure of $EtCO_2$ was more than 45 mmHg or respiratory rate less than 8 breaths per minute, oxygen saturation less than 90%, and the deterioration of consciousness which made verbal communication with the patient difficult in the CS group. The maneuver of jaw lift was applied to all patients in the two groups if necessary. Additionally, when bradycardia (HR<50bpm) and hypotension (MAP <60mmHg) occurred, 0.3～0.5 mg atropine and 10 mg ephedrine were administered, and all the "end-points" events were noted.

In the DS group, propofol was administered by intermittent intravenous bolus to obtain the desired level of sedation. Especially, we started with a bolus of 0.5mg/kg propofol, followed by bolus doses of 20 mg for each after 30～60 seconds, until the level of deep sedation was achieved. Sedation and monitoring were performed by the same qualified anesthesiologist. Time from the scope insertion to the end of procedure was recorded. All the therapy procedures were performed by the same experienced endoscopist using an Olympus video system (Olympus, Tokyo, Japan). The whole

procedure was divided into three separate phases as follows: 1) diagnostic endoscope insertion to confirm esophageal varicosis; 2) endoscopic variceal ligation; 3) the recovery of patient's consciousness. If somatic response (remarkable movement of head or extremities) and gag reactions appeared, the plasma concentration of propofol was increased by 0.25ug/ml in the CS group and 20 mg propofol or more was intravenously injected in the DS group.

The quality of sedation was assessed by the endoscopist based on easy insertion of endoscope, retching/vomiting, cough, belching or defense reaction. A fully satisfactory Visual Analog Score (VAS) was given 10 points totally. All patients were transported to post anesthesia care unit (PACU) and assessed by a nurse anesthetist blind to randomization. Recovery time, which was defined as from the last time of drug administration to the time of full recovery of consciousness, was recorded based upon the OAA/S and Alderete scores assessments (Table2).

Table 2: Modified Aldrete score.

Category	Description	Score
Consciousness	Fully awake and orientate (name, place, date)	2
	Arousable on calling	1
	Not responding	0
Activity	Moves all 4 extremities voluntarily or on command	2
	Moves 2 extremities	1
	Unable to move extremities	0
Respiration	Breathes deeply and coughs freely	
	Dyspnea, limited breathing, or tachypnea	1
	Apneic or mechanical ventilation	0
Circulation	Blood pressure ±20% of preanesthetic level	2
	Blood pressure ±20%～49% of preanesthetic level	1
	Blood pressure ±50% of preanesthetic level	0
Oxygen saturation	Spo_2 >92% on room air	2
	Supplemental O_2 required to maintain spo_2 >92%	1
	Spo_2 < 92% with O_2 supplementation	0
Maximum score		10

Only when patients became completely conscious with nine points assessed by Alderete system, could they be allowed to send back to wards. Undesired symptoms such as oxygen desaturation, hypotension, nausea/vomit and pain were also documented. Before discharge, patients were asked to describe their satisfactory degree associated with the procedure using a VAS score from 0 to 10.

Data are expressed as mean and standard deviation (SD). The general data such as age, body weight and laboratory test parameters were studied with multivariate analysis of variance (MANOVA); the parameters of gender and ASA grades were compared with Chi-square test. Hemodynamic and respiratory parameters were studied with repeated measures analysis of Variance. The total dose of drugs, VAS scores and procedure time were also analysed by the unpaired Student t test. All the analysis was performed by the SPSS 17.0 soft package (SPSS Inc, Chicago, IL). $P<0.05$ was accepted as statistical significance.

RESULTS

One patient in CS group had to be excluded due to severe movement of limbs and automatic extubation reaction although the target concentration of propofol had exceeded 4μg/ml. Table 3 shows the basic characteristics of study population for the two groups. Between the two groups, and no significant differences were found in age, weight, gender, ASA classification, Child-Pugh classification, total bilirubin (TBIL), prothrombin time (PT), hemoglobin and albumin levels.

Table 3: Baseline characteristics of study population and laboratory tests.

	DS group	CS group	P value
Age (years)	49.9±12.4	48.8±14.9	0.786
Weight (kg)	58.2±9.3	58.2±8.6	0.997
Female/ male	6/18	7/16	0.173
ASA classification II/III	19/5	19/4	0.09
Child classification A/B/C	7/15/2	8/12/3	0.581
Hemoglobin (g/L)	80.3±19.0	78.0±18.4	0.677
Albumin (g/L)	35.2±6.4	33.7±5.2	0.401
TBIL# (umol/L	18.5±5.2	25.3±9.7	0.111
PT§ (second)	13.8±1.6	16.0±5.0	0.059

#means total serum bilirubin; §means protrombin time

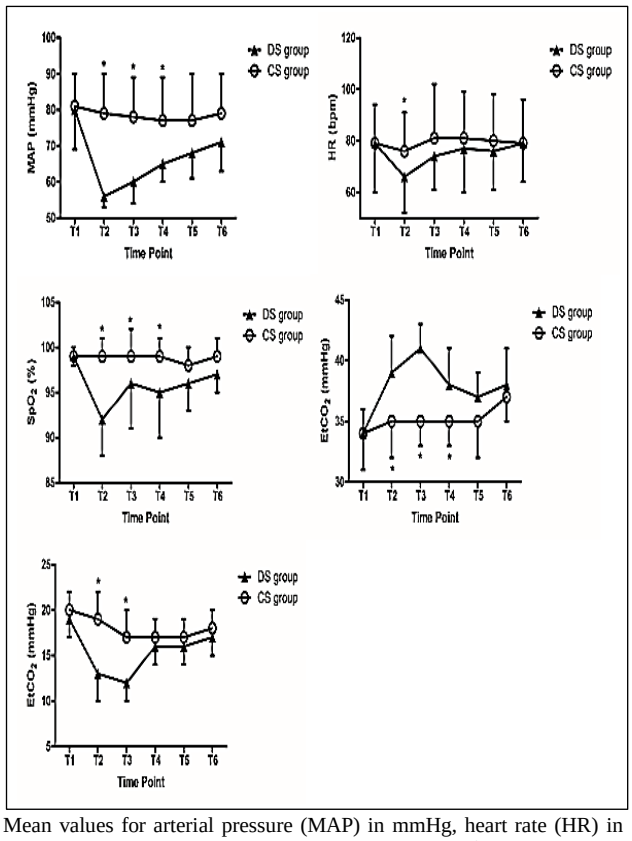
The mean dose of propofol administered in the CS group was 75.9 mg and in the DS group was 85.8 mg. The dose of fentanyl used in the CS group and DS group was 87.3 μg and 85.8 μg respectively ($p>0.05$). When referring to the degree of satisfaction, the VAS of endoscopist was similar in both groups, that is, 9.2±0.6 in the CS group and 9.0±0.6 in the DS group ($p>0.05$), the patient's VAS scores in the DS group (9.3±0.6) were higher than that of in the CS group (7.9±0.7). Compared to the DS group, patients in the CS group had much shorter recovery time ($p<0.01$) (Table 4), as well as much better hemodynamic stability, and less respiratory depression (Figure 1).

Table 4: Dose of drugs, VAS scores and procedure time.

	DS group	CS group	P value
Total dose of drugs			
Propofol (mg)	85.8±17.1	75.9±21.5	0.088
Fentanyl (ug)	85.8±14.0	87.3±12.4	0.694
VAS scores (mean)			
Patient VAS	9.3±0.6	7.9±0.7	0.000*
Endoscopist VAS	9.2±0.6	9.0±0.6	0.078
Procedure time (minutes)			
Endoscopy time	7.3±1.3	7.3±1.0	0.970
Recovery time	16.7±2.7	9.3±3.0	0.000*

*Compared with DS group, P<0.05.

However, there were 11 patients in the DS group need vasoconstrictive medications, and 6 patients need jaw thrust maneuver, but in the CS group only one patient need jaw thrust maneuver. During the procedure, 1 patient had somatic reactions in both groups, but another 3 patients had slight cough in the CS group.



Mean values for arterial pressure (MAP) in mmHg, heart rate (HR) in beats per minute, respiratory rate (RR) in number of respirations per minute, end-tidal carbon dioxide (EtCO2) in mmHg, pulse oximetry (SpO2) as a percentage, determined at different stages of endoscopic procedure: T1, baseline (minimum 3 minutes before administration of the first drug); T2, 1 minute after administration of the last drug; T3, time of insertion of the diagnostic endoscope; T4, time of insertion of the therapeutic scope; T5, time of endoscopic variceal ligation; T6, time of endoscope withdrawn. Solid boxes: DS group, Open boxes: CS group. *Compared with baseline; #Compared with CS group.

Figure 1: Cardiorespiratory parameter changes between CS group and DS group.

DISCUSSION

In the present study, it demonstrated that patients in the CS group who used TCI system had more stable hemodynamics and less respiratory depression than those patients who received a bolus injection of propofol and fentanyl in the DS group. There were three probable reasons as follows: First, our patients had a mild to moderate decrease of plasma albumin (33.7±5.2g/L) and hemoglobin (78.0±18.4g/L), which had a little effect on the pharmacokinetics and pharmacodynamics of propofol achieved by TCI devices. Cavaliere F et al, also reported that hypoalbuminaemia does not impair Diprifusor performance during sedation with propofol.[14] Second, hypovolemia can induce a reduction in the volume of distribution or clearance, and this can result in an increase in the plasma propofol concentration, thereafter, the infusion rates automatically reduced by the TCI system to maintain the selected target plasma concentration.[15-16] Thirdly, we set a low initial target concentration with stepwise increases to reach desired sedation level, which may avoid overshooting of the propofol. Conversely, those patients received bolus of propofol had pronounced fluctuations of hemodynamics and more respiratory depression because overshooting was unavoidable.

Remarkably, one patient with ASA III classification and a deteriorative status in the CS group occurred a severe oxygen desaturation. Fortunately, the patient's SpO2 was returned to 96% after a jaw thrust maneuver. Therefore, attention still should be paid to those patients in case of respiratory depression, even if a low concentration of propofol for TCI was performed.

It is a challenge for anesthesiologist to provide sedation for those patients undergoing EVL. Over sedation may cause catastrophic complications such as severe cardiorespiratory depression, hepatic encephalopathy. What's more, patients who received deep sedation or general anesthesia without endotracheal intubation may face high risk of aspiration. Fortunately, patients in the CS group were responsive and the cough reflex still existed, which may reduce the incidence of aspiration to a large extent once the varices were ruptured and hemorrhagic. Compared with the DS group, it seems more patients had cough reflex in the CS group. However, cough is a protective airway reflex, for these patients with high risk of aspiration, its advantages greatly outweigh its disadvantages.[17] Almost all cough reflexes happened during the insertion of the scope, and it did not affect the subsequent procedure.

The satisfaction degree for patients in the DS group was higher than that in the CS group, but for endoscopists it was similar in the two groups. Previous study showed that the technical skills of endoscopists, the adequacy of sedation, and the degree of anxiety of the patients may affect patients' satisfaction scores.[18-19] However, in the CS group, three patients were encountered with cough when inserted the endoscope, and these patients had low

satisfaction scores. Although propofol produces a good amnesia, most of patients still had part memory during the procedure, and it may affect the patients' satisfaction scores. The quality of conscious sedation may be improved if small dose of midazolam was added. The recovery time in the DS group was significantly longer than that in the CS group, it may due to better hemodynamic and respiratory stability, and a slight depression of consciousness in the CS group.

BIS is extensively used to measure the depth of general anesthesia or sedation, and demonstrates high correlation with target or effect-site concentration of propofol, OAA/S scores are also highly correlated with BIS values but the accuracy of BIS monitor in critically ill patients or cirrhotic patients with hypoalbuminemia and anemia was suspensive, therefore, both the OAA/S scores and BIS monitor were used to assess the sedation level. [20-21]

CONCLUSION

Conscious sedation with TCI of propofol under a low concentration during EVL in patients with liver cirrhosis provides sufficient anxiety relief, better hemodynamic stability and less respiratory depression by comparison with deep sedation by bolus of propofol and fentanyl. This method of analgesia/sedation for EVL provides extremely fast recovery to full psychomotor function. Patients in the CS group are still responsive and cooperative, thus decrease the incidence of aspiration if esophageal varices hemorrhage occurred. However, there are some limitations in the present study. Firstly, the sample size is too small, it need more evidence to verify the superiority achieved by TCI of propofol over deep sedation by bolus of propofol and fentanyl in patients with liver cirrhosis. Secondly, we used two different sedation techniques, so it is difficult to achieve double blinded.

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