Comparison of Dexmedetomidine and Midazolam in Sedation for Percutaneous Drainage of Hepatic Hydatid Cysts

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Objective: Hydatid cyst still continues to be a public health problem. The basic treatment for the disease is surgery, but ultrasound-guided percutaneous drainage has become an important treatment alternative. Agents preferred for sedation during drainage performed under local anaesthesia must also preserve respiration and hemodynamic stability while providing adequate sedation. We compared the sedative properties of midazolam, which has a short duration of action, and a selective α_2 adrenergic receptor agonist, dexmedetomidine, and the intraoperative complications.

Methods: After approval by the clinical trials ethics committee, 40 patients with similar demographic data were randomized into two groups. All patients received 10 mg metoclopramide and 45.5 mg pheniramine before the procedure. Then, midazolam (0.07 mg kg⁻¹ IV bolus followed by 0.01 mg kg⁻¹ h⁻¹ infusion) was administered to Group 1, and dexmedetomidine (1 µg kg⁻¹ loading dose in 10 minutes, followed by 0.2 µg kg⁻¹ h⁻¹ continuous infusion) was administered to Group 2 for sedation. Just before the surgical procedure, all patients received IV propofol in a subhypnotic dose of 0.5 mg kg⁻¹; the dose was repeated if adequate sedation could not be achieved. Observer's assessment of alertness/sedation (OAA/S) scale and Bispectral index (BIS) were used to evaluate the sedation level during the procedure. Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), peripheral oxygen saturation (SpO₂) and end-tidal carbon dioxide pressure (ETCO₂) were monitored before and after induction and every 5 minutes thereafter. Propofol requirement was noted for each group.

Results: Sedation in the dexmedetomidine group was as effective and adequate as that observed in the midazolam group. BIS values were significantly lower in the dexmedetomidine group, especially after 10 minutes and thereafter. RR, SpO₂, and ETCO₂ were similar in both groups, whereas clinically insignificant decreases in HR and MAP were observed in the dexmedetomidine group. Propofol requirements were similar in both groups.

Conclusion: We conclude that dexmedetomidine, providing adequate sedation without respiratory depression, can be considered as an appropriate agent for sedation in surgical procedures performed under local anaesthesia.

Key Words: Dexmedetomidine, midazolam, sedation

Introduction

The hydatid cyst, which is a common parasitic disease in regions where agriculture and animal husbandry is common and the preventive medicine is limited, still remains a health care problem in our country. Although surgery is the conventional approach for treatment of hepatic hydatid cyst, percutaneous treatment, performed in selective cases, stands out as an effective and safe alternative in terms of its satisfactory long term results (1, 2).

Interventional radiology techniques are being utilized for percutaneous treatment of hydatid cyst and the procedures are performed under ultrasound guidance outside the operating rooms. A variety of agents are being used to achieve sedation and to provide analgesia for interventional procedures (3).

It is required to provide sedation and to reduce the anxiety of patients in many interventional procedures, like percutaneous drainage, that are performed under local anaesthesia. However, vital parameters of

the patient, such as blood pressure and respiration rate should be kept close to normal ranges as far as possible throughout the procedure. Although many drugs including phenothiazines, benzodiazepines, barbiturates, opioids and antihistamines may be used for this purpose, benzodiazepines are today the most preferred agents (4).

Midazolam is a benzodiazepine, which has a rapid onset of action and short duration; it has been emphasized as an appropriate sedative drug in many studies (5-9). However, it may cause respiratory depression due to the accumulation of active metabolites, especially with repeated doses.

Dexmedetomidine is a selective alpha-2 receptor agonist (10). Besides the sedative effects, it also has anxiolytic, hypnotic and analgesic properties. Dexmedetomidine has become the preferred agent in intensive care units as it affects the α_2 receptors in central nervous system, peripheral nerves and autonomic ganglia (11). It has been started to be used for sedative purposes in non-intubated patients during surgical procedures or other interventions (12).

In the present study, we used midazolam, a benzodiazepine, and dexmedetomidine, a selective α_2 agonist, for sedation in different treatment groups during percutaneous treatment of hepatic hydatid cyst under local anaesthesia.

Methods

After approval by the local ethics committee (Local Ethics Committee of the Ankara Numune Education and Research Hospital, 19/10/2011, decision number: 2011-255), 40 adult patients (18 years and over) who were admitted to the Department of Interventional Radiology for the purpose of treatment for hepatic hydatid cyst were included in the study. The hydatid cysts of the patients were "active cysts" according to the classification of World Health Organization. The study was designed as a prospective, randomized, double blind study. The patients who had advanced heart, liver, kidney disease, severe bronchial asthma, alcohol addiction or drug abuse and those with a previous history of drug allergy to the drugs that would be used during the study period were excluded. The patients who were recruited for the study were informed about the method and gave consent to take part in the study before the procedure.

The patients were randomly allocated into two treatment groups (Group 1 or Group 2), each containing 20 patients, by drawing a sealed-envelope. Both groups of patients were taken to the intervention room and their demographic data were recorded, before pre-medication. Standard monitoring included electrocardiogram, non-invasive blood pressure (NIBP), end-tidal carbon dioxide pressure (ETCO₂) and peripheral oxygen saturation (SpO₂). End-tidal carbon dioxide pressure was measured by connecting the mainstream capnometer directly to the patient's oxygen mask. BIS analysis was performed by dual channel frequency measurement, with the leads applied to the frontotemporal areas. At the beginning of the intervention, all patients were administered 10 mg of metoclopramide and 45.5 mg of pheniramine and oxygen was given by facemask at 3 l min⁻¹ flow during the intervention. In group 1, the patients were given an intravenous bolus of midazolam at a dose of 0.07 mg kg⁻¹, followed by infusion at a rate of 0.01 mg kg⁻¹ hour⁻¹ until the end of the procedure. In group 2, the patients were given a loading dose of 1 µg kg⁻¹ dexmedetomidine in 10 minutes followed by infusion at a rate of 0.2 µg kg⁻¹ hour⁻¹. At the beginning of the procedure, the patients in both groups received intravenous propofol at a subhypnotic dose (0.5 mg kg⁻¹), and if adequate sedation was not achieved, the dose was repeated and the need for additional doses of propofol infusion was recorded for both groups. The measurements were performed at five minute intervals during and after the procedure. The Bispectral index (BIS, 40-65: general anaesthesia, 65-85: sedation) and the modified observer's assessment of alertness/sedation (Modified OAA/S, 1-12: deep sedation, 13-20 mild sedation) were used to evaluate the depth of sedation in patients. Percutaneous drainage was performed by the same radiology team in all patients.

Statistical analysis

The data were analyzed using SPSS version 15.0. Variables with normal distribution were presented as mean (±SD) and variables with non-normal distribution were presented as median (1st and 3rd quartiles). The Kolmogorov-Smirnov test was used to test the normal distribution of the variables. The Levene test was used to test equality of variances. The normally distributed variables were compared using independent samples t-test whereas non-normally distributed variables were compared using Mann-Whitney U test. Inter-group comparison of categorical variables was performed using Pearson chi-square test. A p value of less than 0.05 was considered to be statistically significant.

Results

There was no difference between the two groups in regard to mean age, weight and height, whereas the total duration of the procedure and the total duration of anaesthesia were significantly different between the two groups (Table 1).

The heart rate (HR) values were not different between the two groups before the induction of anaesthesia. However, HR was significantly lower in Group 2 than that in Group 1 in all measurements performed after the induction of anaesthesia (Figure 1). The mean arterial pressure (MAP) measured before and after anaesthesia induction, and those obtained at each measurement within 25 minutes after induction were similar in both groups. However, the MAP values obtained after the 25th minute were lower in Group 2 (Figure 2). These changes in hemodynamic status were not of clinical importance.

There was no significant difference between groups in regard to the peripheral oxygen saturation values obtained at time points before and after the induction of anaesthesia. While end-tidal carbon dioxide levels measured 1 minute after the induction of anaesthesia were significantly different between the groups, there was no difference regarding the values obtained at the other time points. Although the difference in the 1st minute of induction was statistically significant, it was not of clinical importance. There was no significant difference between the groups in terms of respiratory rate.

The OAA/S values obtained at 15 and 30 minutes of induction and at the other time points after 30 minutes were significantly lower in Group 2 when compared to that in Group 1 (Figure 3).

There were no difference between the two groups in regard to BIS values at the 1st and 5th minutes of induction, whereas BIS values at the 10th minute and at the measurements that were performed afterwards were significantly lower in Group 2 than that in group 1 (Figure 4).

There was no significant difference between the groups in regard to the need for additional doses of propofol whereas the difference between the two groups in surgeon satisfaction was significant (Table 2).

Discussion

In the present study, dexmedetomidine and midazolam were used for sedation during hepatic hydatid cyst drainage and the data were compared in terms of level of sedation and vital parameters. It was observed that dexmedetomidine produced a deeper level of sedation when compared to midazolam. There was no difference between the groups in regard to the need for additional doses of propofol whereas surgeon satisfaction was significantly higher in the dexmedetomidine group.

During interventional procedures such as percutaneous transhepatic drainage, which necessitates a high level of analgesia and sedation,

Table 1. Patient Demographics

	Group 1 mean (SD)	Group 2 mean (SD)	p
Age (years)	48.70±18.59	40.05±13.84	0.103
Height	162.75±8.25	165.75±9.32	0.288
Weight	70.70±17.80	72.75±17.43	0.715
Total duration of intervention	36.75±10.67	44.50±11.23	0.031
Total duration sedation	46.75±10.67	54.50±11.23	0.031

Figure 1. Mean heart rate values of the groups

Figure 2. Mean blood pressure values of the groups

Figure 3. Mean OAA/S values of the groups

Figure 4. Mean BIS values of groups

attempts are made not only to relieve patients' anxiety and pain, but also to keep heart rate, blood pressure and respiratory rate close to the normal limits. A variety of agents including propofol, benzodiazepines and opioids are being used as sedatives during these procedures. However, propofol may cause oversedation and loss of orientation, benzodiazepines may cause confusion and opioid agents may cause respiratory depression and oxygen desaturation. In addition, maintenance of hemodynamic stability and achieving adequate depth of anaesthesia with anaesthetic medication is more challenging in geriatric population (13, 14).

Takimoto et al. (15) compared dexmedetomidine, propofol and midazolam for sedation during endoscopic submucosal dissection of gastric cancers, and using the Ramsay Sedation Scale, they found that the level of sedation was 95% in dexmedetomidine group, 65% in propofol group and 25% in midazolam group.

Similarly, in our study, a deeper level of sedation was achieved in the dexmedetomidine group. In both groups, BIS values, which we used as an objective indicator for depth of sedation, decreased after induction in comparison to the values obtained before induction. However the decrease in BIS values was more pronounced in the dexmedetomidine group. Dexmedetomidine produces a dose-dependent sedation if it is infused within more than 2 minutes. Onset of the effects of midazolam occurs within 3 minutes, whereas the peak effect of dexmedetomidine occurs within 10 minutes of infusion (16). This fact seems to explain the significant decrease observed in BIS values after the 10th minute of induction of anaesthesia.

Huncke et al. (17) reported that dexmedetomidine was effective in terms of providing sedation during vascular surgical operations. They reported that the requirement for intraoperative analgesics was lower in the group who were sedated with dexmedetomidine compared to midazolam and fentanyl in awake carotid endarterectomy under cervical plexus blockade (18). Similarly, the patients who received dexmedetomidine for sedation during aesthetic facial surgery required lower doses of narcotics and midazolam during the operation when compared to those who received conventional sedative drugs (19).

Sedation produced by dexmedetomidine mimics natural sleep. The patients can easily be awakened by verbal stimuli and the sedation produced by dexmedetomidine does not cause a significant respiratory depression (20, 21). Although no significant difference was observed between dexmedetomidine and midazolam in regard to SpO₂, ET CO₂ and respiratory rates, the effects of dexmedetomidine on respiratory system is less prominent than that of other commonly used sedative drugs.

In children and adults, it was observed that arterial oxygen saturation was better protected during sedation induced by dexmedetomidine when compared to propofol (19, 22).

A significant superiority of dexmedetomidine over other commonly used sedative drugs is that it has a broad therapeutic index. Dexmedetomidine does not cause clinically significant respiratory depression even at doses 15 fold higher than the recommended doses (23). However, midazolam, in repeated doses, may cause respiratory depression by inhibiting respiratory response to CO₂ (24). The fact that dexmedetomidine diminishes the need for narcotics during the

Table 2. Need for additional doses of propofol and surgeon satisfaction

	Group 1 (n)	Group 2 (n)	p
Need for additional propofol (yes/no)	8/12	3/17	0.183
Surgeon satisfaction (yes/no)	9/11	18/2	0.014

operation may explain the lower rate of side effects (i.e. respiratory depression) which occur due to the use of narcotics (23). This fact may be suggested as a legitimate reason to prefer dexmedetomidine over midazolam although both drugs have equivalent sedative properties.

Dexmedetomidine use was reported to cause hypotension in 30% and bradycardia in 9% of cases in studies evaluating its effects on hemodynamic parameters (25). Compared to baseline values, we observed some reduction after induction of anaesthesia in both groups; however the reduction in heart rate and MAP values was more evident in the dexmedetomidine group than in the midazolam group. Although these quantitative reductions were of statistical significance, they were not at levels to cause hemodynamic alterations and to require medical therapy.

Compared with midazolam, the amnesic properties of dexmedetomidine are inferior. Anterograde amnesia properties of midazolam may be of importance in relieving patient's anxiety and this fact may justify its use over dexmedetomidine.

Demiraran et al. (26) compared the effects of dexmedetomidine and midazolam for sedation during upper gastrointestinal endoscopy and found that surgeon satisfaction was higher in the dexmedetomidine group. We also found that surgeon satisfaction was significantly higher in the dexmedetomidine group. Given the possible benefits of surgeon satisfaction regarding the postoperative course, dexmedetomidine may be taken as an appropriate drug for sedation.

The hydatid cysts of the patients from both groups were "active cysts" according to the classification of World Health Organization. This category corresponds to the stage 1 and 2 cysts according to the old Gharbi classification (27). As interventional radiology clinics are equipped with advanced anaesthesia equipments, it has become possible to perform more challenging and complicated interventions. By expanding the context, the present study may also be conducted on transitional and inactive hydatid cysts according to the classification of World Health Organization (Stage 3, 4 and 5 according to the Gharbi classification).

Conclusion

We concluded that dexmedetomidine, providing a better sedation with lesser side effects is superior to midazolam and may be preferable for sedation during percutaneous drainage of hepatic hydatid cysts under local anaesthesia.

Conflict of Interest

No conflict of interest was declared by the authors.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Education and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions

Concept - E.A.; Design - E.A., E.N.B.; Supervision - E.A., N.G., D.D.; Funding - R.A., E.N.B.; Materials - E.A., E.N.B.; Data Collection and/or Processing - E.N.B.; Analysis and/or Interpretation - E.N.B., E.A.; Literature Review - E.N.B., E.A., R.A.; Writer - E.N.B., R.A.; Critical Review - E.A., N.G., D.D.; Other - N.G., D.D.

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