Dexmedetomidine in combination with dezocine provides superior analgesia and sedation in trepanation and drainage of chronic subdural hematoma under monitored anesthesia care

Chao-Liang Tang, Fang Kang, Xiang Huang, Xiao-Qing Chai, Tao Hou, Juan Li*

**Background:** Sedation and analgesia are usually required for patients during trepanation and drainage of chronic subdural hematoma under local anesthesia. In the study, we studied and compared two analgesic and sedative combinations for this purpose.

**Methods:** Sixty patients undergoing trepanation and drainage under monitored anesthesia care were randomly allocated to receive either intravenous bolus of dezocine 100 μg/kg with intravenous dexmedetomidine 1 μg/kg over 10 min (Group DD), or intravenous bolus of fentanyl 1 μg/kg with intravenous midazolam 60 μg/kg over 10 minutes (Group MF). Sedation was titrated according to modify observer’s assessment of alertness/sedation/ (MOAA/S) with a target of MOAA/S score ≤ 4. Mean arterial pressure (MAP), heart rate (HR), consumption of rescue analgesic (fentanyl) and sedative (midazolam), adverse events, satisfaction scores of patient and surgeon, and sedation recovery time were also compared between groups.

**Results:** Thirty percentage and 13% of patients from group MF required rescue fentanyl and midazolam respectively, while none from Group DD (all p < 0.05). Intraoperative heart rate and mean arterial pressure in Group DD were lower than that of Group MF (p < 0.05). Respiratory rate, end-tidal carbon dioxide and oxygen saturation were similar between both groups. Satisfaction scores both of the patient and surgeon were significantly better in Group DD (p < 0.05). In addition, sedation recovery time was significantly shorter in Group DD (p<0.05).

**Conclusions:** Use of dexmedetomidine-dezocine in chronic subdural hematoma patients for sedation and analgesia appeared to be safe and surgeon and patient were more satisfied compared to midazolam-fentanyl.

**Keywords:** Dexmedetomidine-dezocine sedation, midazolam-fentanyl sedation, monitored anesthesia care, satisfaction scores, chronic subdural hematoma

( J Perioper Sci 2015, 2:3)

**Introduction**

Chronic subdural hematoma (CSH), one of the most common diseases of daily neurosurgical practice usually performed under monitored anesthesia care (MAC), which can provide adequate sedation and analgesia, patient feeling relaxed and comfortable, and surgical competence during the procedure [1]. The ideal pharmacokinetic characteristics of sedatives during MAC for trepanation and drainage for CSH are rapid effect, short duration, and rapid recovery, because the procedure usually takes a short time.

Generally used medications for MAC are propofol, benzodiazepines and opioids, which are either administered alone or in combination[2]. Midazolam with its quick onset, produces amnesia and improves patient comfort, but a relatively long half-life can cause prolonged sedation after repeated administration[3]. Midazolam in combination with opioids increases the risk for hypoxemia and apnea [4, 5]. However, interactions and synergism between sedatives and opioids might result in respiratory depression, which has been reported to cause patient injuries during MAC [6], and it’s also the major concern regarding sedation during trepanation and drainage for CSH.

Dexmedetomidine is a highly selective α2 receptor agonist with properties of sedation and...
analgesia, cardioprotection, renal protection, and neuroprotection without major respiratory depression [7-9]. It has an analgesic-sparing effect, significantly reducing opioid requirements in both intraoperative and postoperative period [10]. It also has a sympatholytic effect, which can reduce the stress response to surgery and ensure a stable hemodynamic state [11]. Dezocine is a new bridge central amino tetralin, a mixed opioid agonist/antagonist analgesic, a completely κ-receptor agonist, and a partial μ-receptor agonist without classic μ-receptor dependence liability [12, 13]. It is a little bit more potent respiratory depressant than morphine in single analgesic doses[14]. Both dexmedetomidine and dezocine are widely being used as a sedative for MAC for various surgeries [15, 16]. However, no data is available comparing the combination of dexmedetomidine-dezocine and sedation with the combination of midazolam-fentanyl during trepanation and drainage for CSH.

We therefore conducted this prospective, randomized and double blind study to compare the combination of dexmedetomidine-dezocine with a combination of midazolam-fentanyl in patients undergoing trepanation and drainage for CSH under local anesthesia (LA). We assumed that the use of the combination of dexmedetomidine-dezocine would increase perioperative haemodynamic stability without respiratory depression during trepanation and drainage for CSH. We compared the combination of dexmedetomidine-dezocine and the combination of midazolam-fentanyl during MAC for trepanation and drainage for CSH in terms of haemodynamic stability, respiratory depression, patient and surgeon satisfaction and the usage of intraoperative rescue analgesics to keep the patient cooperative.

Methods

This study was carried out as a prospective, randomized, double blind clinical trial and approved by the Ethics Committee of Anhui Provincial Hospital, Anhui Medical University. All the patients were recruited in this university hospital and wrote the written informed consent. We recruited sixty patients of either sex with the American Society Anesthesiologists physical status I–II, aged between 18 and 75 years, undergoing trepanation and drainage for CSH under local anesthesia from the neurosurgery department of our center. We applied the following exclusion criteria: patients with known sensitivity to study drugs, hypotension [baseline systolic arterial pressure (SAP), 100 mm Hg], bradycardia [baseline heart rate (HR), 60 beats/min]; Patients on pain perception modifying drugs and those with history usage of any opioid or sedative medications in the week prior to surgery. The visual analogue scale (VAS) (0, no discomfort and no pain; 10, a high level of discomfort and maximum pain) was explained to the patients during the preoperative visit. The patients were randomized to the two groups by random number table method (n = 30), Group DD (dexmedetomidine-dezocine) and Group MF (midazolam-fentanyl). The anesthesiologist conducting the case, but the patients and the anesthesiologist in the post anesthesia care unit (PACU) were all blinded to group assignment. A blinded observer recorded the data and an anesthesiologist who did not participate in the research prepared the drugs. Two 50ml syringes, labeled dexmedetomidine and midazolam as loading were prepared for each patient. Group DD patients had dezocine 100 μg/kg plus dexmedetomidine 1 μg/kg and Group MF had fentanyl 1 μg/kg plus midazolam 60 μg/kg in their respective loading syringes diluted up to 50 ml with normal saline.

Standard monitoring consisted of five-lead electrocardiography (ECG), oxygen saturation (SpO2), respiratory rate (RR), end-tidal carbon dioxide (ETCO2) and non-invasive blood pressure. Then an infusion of hydroxyethyl starch 130/0.4 (Voluven) 8~10 ml/kg was given. No sedative premedication was used. All patients received supplemental oxygen (4 liter/min) via a CO2 oral/nasal cannula with O2 delivery (Spacelabs 704-0020-00, America). Group DD received I.V. dezocine 100 μg/kg plus I.V. dexmedetomidine 1 μg/kg over 10 min using an infusion pump (ALARIS MK III, Switzerland). Group MF received I.V. fentanyl 1 μg/kg plus I.V. midazolam 60 μg/kg over 10 min. During this period the patients were assessed every three minutes using Modified observer’s assessment of alertness/sedation (MOAA/S) score (0 (asleep) = Does not respond to painful trapezius squeeze; 1 = Responds only after painful trapezius squeeze; 2 = Responds only after mild prodding or shaking; 3 = Responds only after name is called loudly, repeatedly, or both; 4 = Lethargic response to name spoken in normal tone; 5 (alert) = Respond readily to name spoken in normal tone)[17]. The target end point was a patient
having MOAA/S ≤4. The infusion must be stopped and noted, once the target end point was reached whether the loading infusion completed or not. After the loading drug infusion, any patient in either of the groups having a score > 4 received I.V. midazolam 10 μg/kg, repeated until MOAA/S ≤4. After the loading infusion of the drugs was completed and MOAA/S of 4 was achieved, the blinded neurosurgeon (with a minimum of five years of experience) administered local anaesthesia using 2% lignocaine with adrenaline (2-3 ml) (1:2, 00,000) at the surgical site, and then commenced the surgery after confirming adequate analgesia. MAP, HR, RR and SPO2 were recorded at five time points (T0, baseline; T1, the start of surgery; T2, the time of drilling; T3, the time of suturing; T4, the end of surgery). We assessed the sedation level (MOAA/S) every 5 min. When MOAA/S > 4, we administered I.V. midazolam 10 μg/kg as a common rescue sedative in both groups. We evaluated intraoperative pain intensity by the VAS. If the VAS >3, gave rescue I.V. fentanyl in the dose of 1μg/kg. The number of rescue doses of midazolam and fentanyl was noted.

Adverse events like hypotension (drop in systolic blood pressure >20% of baseline or MAP <60 mmHg), treated with fluid replacement and if needed, with I.V. ephedrine hydrochloride 5 mg. Bradycardia (HR <45 bpm) was treated with I.V. atropine sulphate 0.01mg/kg. An additional bolus dose of the rescue drug was administered when hypertension (blood pressure >140/90 mmHg or increases more than 20% value) and tachycardia (HR>100 beats/min or an increase of >30 beats/min from baseline). Bradypnea (RR <8 breaths/min), patients were woken up and asked to take deep breaths. Desaturation (SpO2 <90%), treated by increasing O2 flow up to 6 liters and if needed, using nasopharyngeal airway.

After the procedure we transferred patients to the PACU and monitored hemodynamic parameters, degree of analgesia and adverse events, if any for 1 h. Also we evaluated MOAA/S immediately on arrival in the PACU and every 15min thenceforth until transfer to surgical ward. Sedation recovery time (patients with MOAA/S≥4) was documented. Surgeons (immediately after the surgery) and patients (at least 6 h after the surgery to exclude the amnesic effect of midazolam) were asked to evaluate their overall satisfaction with the procedure by numerical rating scale (NRS; 0, being least satisfied; 10, being most satisfied).

### Statistical Analysis

The statistical analyses were performed using SPSS Statistics 13.0 software. Hemodynamic and respiratory data were evaluated using unpaired t test for between-group and paired t test for within group comparisons. Data not normally distributed was compared using Mann Whitney U test. The χ2 test was used to analyze categorical variables. Data are presented as mean (SEM) or as count (%). P value less than 0.05 was considered as significant.

### Results

Sixty patients were randomized from May 2013 to April 2014. No assigned patients withdrew from the study. All patients underwent their planned surgical procedure and received their allotted study drug. Table 1 shows the patient and procedural characteristics of both groups, respectively. No differences were found about MAP and HR at baseline between the two groups, but Group DD had significant fall in heart rate (15-20%) from the start of surgery till the end (P < 0.001). On the contrary, there were no significant changes from baseline till the end of surgery in Group MF (P > 0.05). MAP in both groups had significant reduction from the baseline values; however on analyzing the magnitude of decrease, patients in Group DD had a greater fall (10-18%) in contrast with Group MF (5-10%) over time during the procedure [Figure 1]. Between-group comparison of MAP at the same time period, Group DD had a lower MAP till the end of surgery (P < 0.05). Two patients in Group DD developed hypotension and bradycardia after completing the loading infusion that was successfully treated with I.V. ephedrine 6 mg and I.V. atropine 0.6 mg. There was no episode of hypertension in either group. SpO2, RR and ETCO2 were comparable and within normal limits in both groups (P > 0.05). No patient had any episode of desaturation in either group [Figure 2].

After loading dose infusion, all the patients reached MOAA/S ≤4 in both groups, and no additional supplementation was required. During surgery, four (13%) patients in Group MF required rescue sedation with midazolam when MOAA/S >4 in comparison to none in Group DD (P < 0.01), three of them happened at the second time of
trepanation. In Group MF, significantly more number of patients required rescue fentanyl. In contrast, none in Group DD (P < 0.01). The MOAA/S score not only during the surgery but also 30 min after the patients in PACU was significantly different between the study groups (P =0.026; P =0.039). Patients in Group DD had less sedation recovery time (P =0.016). Two patients were in deep anesthesia in Group MF, and they needed to use nasopharyngeal airway. However, no patient was in deep anesthesia in Group DD [Table 2].

### TABLE 1. Subject and operative characteristics. Values are given as Mean (SD) or number of patients (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DD group (n=30)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.4 (13.6)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>19 (63)/11 (37)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.5 (15.8)</td>
</tr>
<tr>
<td>ASA class (I/II) (%)</td>
<td>24 (80)/6 (20)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>45.2 (10.8)</td>
</tr>
<tr>
<td>Type of surgery (single / double) (%)</td>
<td>22 (73)/8 (27)</td>
</tr>
</tbody>
</table>

![Figure 1](https://www.perioperative-science.com/content/02/03/FIGURE%201.png)

**FIGURE 1. Changes in mean arterial pressure and heart rate during operation. Data expressed as mean (SEM)*P < 0.05.** T0, baseline; T1, the start of surgery; T2, the time of drilling; T3, the time of suturing; T4, the end of surgery.

Patients NRS scores for sedation and analgesia were significantly higher in Group DD than Group MF (P < 0.01) [Table 3]. Similarly, surgeons NRS scores for patients’ sedation and surgical conditions were higher in Group DD than in Group MF (P < 0.01). In the postoperative period two patients in Group MF had nausea and vomiting which was symptomatically treated. Two had shivering in Group MF in contrast to one in Group DD. No serious adverse events were observed in our study. Subjects in both groups were generally satisfied with the procedure without serious discomfort, and none of them had to be converted to an alternative sedative or anesthetic therapy.

*Journal of Perioperative Science*
FIGURE 2. Changes in oxygen saturation, respiratory rate and end-tidal carbon dioxide during operation. Data expressed as mean (SEM). T0, baseline; T1, the start of surgery; T2, the time of drilling; T3, the time of suturing; T4, the end of surgery.

TABLE 2. Rescue sedatives and analgesics during the procedure, MOAA/S score, Sedation recovery time and Using nasopharyngeal airway. Values are given as number of subjects (%) or mean (SD). DD group, dexmedetomidine-dezocine group; MF group, midazolam-fentanyl group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment groups</th>
<th></th>
<th></th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>DD group (n=30)</td>
<td>MF group (n=30)</td>
<td></td>
<td></td>
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<tr>
<td>Rescue midazolam</td>
<td>0/30</td>
<td>4/26(13)</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>Rescue fentanyl</td>
<td>0/30</td>
<td>9/21(30)</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>MOAA/S score</td>
<td>0/4/22/4/0/2/0/0</td>
<td>4/12/12/2/0/0/2/0</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>During the surgery: 5 (alert)/9 (asleep)</td>
<td>4/3/2/1/0/0/0/0/0</td>
<td>6/16/8/0/0/0/0/0</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>30 min after the patients in PACU:</td>
<td>16/12/2/0/0/0/0/0</td>
<td>6/16/8/0/0/0/0</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>5 (alert)/4/3/2/1/0 (asleep)</td>
<td>24.5 (8.5)</td>
<td>37.6 (17.9)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Sedation recovery time (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using nasopharyngeal airway</td>
<td>0/30</td>
<td>2/28(15)</td>
<td></td>
<td>0.00</td>
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</table>

Discussion
This randomized, double-blinded, comparative study was undertaken to compare dexmedetomidine-dezocine and midazolam-fentanyl in terms of haemodynamic stability, respiratory depression, satisfaction of the patient and surgeon, sedation recovery time, and adverse events. Our principal findings are that dexmedetomidine-dezocine administration during trepanation and drainage of chronic subdural hematoma can be used safely and improve the satisfaction of patient and surgeon with no increase in side effect and delay in recovery compared to midazolam-fentanyl combination.

CSH is one of the most common clinical diseases of daily neurosurgical practice[18]. However, local anesthesia for surgical treatment of CSH is not consistently comfortable for patient in relation to pain, neck position, and noise in the room. The movements of anxious patient cause increased bleeding and disturbed the final procedure of the surgery that may even lead to graft failure. MAC can provide adequate sedation and analgesia; facilitate patient comfort and surgical competence.
during the procedure. Guzel et al.[19] first reported the combination use of midazolam and fentanyl in 24 surgical treatment of CSH under MAC. However, this combination could cause intraoperative respiratory depression[5]. In contrast, previous researches have shown that both dexmedetomidine and dezocine provides proper sedation and analgesia under MAC for various surgical procedures. There wasn’t any previous comparative study on dexmedetomidine-dezocine compared with another sedative regimen during trepanation and drainage of CSH after searched the PubMed.

TABLE 3. Patient and surgeon satisfaction scores. Values are given as median (IQR [range]). DD group, dexmedetomidine-dezocine group; MF group, midazolam-fentanyl group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment groups</th>
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<tbody>
<tr>
<td></td>
<td>DD group (n=30)</td>
<td>MF group (n=30)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>Surgeon satisfaction</td>
<td>9 (2)</td>
<td>8 (3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>9 (1)</td>
<td>8 (2.5)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

The doses of dezocine and dexmedetomidine in the current study were based on previous literature and researches. When dexmedetomidine is administered with low or moderate doses and slow rates of infusion, $\alpha_2$ agonist effects will be observed but not $\alpha_1$ effect. The sedative effect of the dosage of 1 $\mu$g/kg of dexmedetomidine can continue to 30 minutes based on a recent study by Eren et al.[20]. Taking it into account, in the present study, we used it in a dosage of 1 $\mu$g/kg; so as to avoid side effects associated with high infusion rates. In view of the operation time was not long and the surgery was essentially done under local anesthesia and dezocine was also combined, we did not use the maintenance dose. Gal et al.[12] demonstrates that dezocine is an effective analgesic with morphine-like effects in human subjects in usual clinical doses of 150 $\mu$g/kg. At this dosage level, dezocine appears to be slightly more potent than morphine in both its respiratory depressant and analgesic effects. In view of using dexmedetomidine as the primary sedative permits significantly reduced requirements for analgesic, the dose of dezocine we chose was 100 $\mu$g/kg. According to the study of Eren, we chose the dose of midazolam 60 $\mu$g/kg which is comparable to dexmedetomidine 1 $\mu$g/kg in terms of sedation[20]. To keep the rescue drugs consistent, midazolam and fentanyl were used respectively if additional sedatives and analgesics required in both the groups. We chose the equivalent doses of both the drugs so as to avoid any bias in our results. Moreover, drugs in both groups were targeted to a predefined end point (MOAA/S score $\leq$ 4). As midazolam has no analgesic properties, we combined fentanyl with it and this combination is conventionally used for trepanation and drainage of CSH under MAC. Although dexmedetomidine has both sedative and analgesic properties and has been used as a single agent in many painful procedures, the analgesic potential, however, does not approximate the potency of opioids[21]. Many patients who received dexmedetomidine required supplemental analgesia and according to our observation, in the implementation of local anesthetic to the patient, pain was also existent, especially with bilateral trepanation and drainage, so we combined with dezocine.

Haemodynamic variables, such as HR and MAP, over time in dexmedetomidine-dezocine group were lower compared to the midazolam-fentanyl group and it could be explained by the markedly decreased sympathetic activity. [22, 23]. These findings suggest that dexmedetomidine-dezocine has clinical advantage over midazolam-fentanyl in providing a better operative field for trepanation and drainage of CSH under local anesthesia. Hemodynamic parameters must be closely monitored, though only two patients in dexmedetomidine-dezocine group developed hypotension and bradycardia after
performing the loading infusion that was successfully treated.

The major safety concerns with sedation during trepanation and drainage of chronic subdural hematoma are apnoea, oxygen desaturation and carbon dioxide accumulation [24]. As we all know carbon dioxide accumulation may lead to intracranial pressure increased, and can lead to intracranial hemorrhage amount increased [25]. In the present study, in addition to comparable respiratory rates and end-tidal carbon dioxide there was no evidence of bradypnea and carbon dioxide accumulation in either of the groups. However, the respiratory mechanics tended to be better in Group DD, although the differences did not reach statistical significance. Dexmedetomidine is unique in that it does not cause respiratory depression even used with opioids [22]. These findings are similar to our study. However, many studies have demonstrated midazolam-fentanyl could cause intraoperative respiratory depression and this was also found in our study that two patients were in deep anesthesia and had respiratory depression. As we made a comprehensive monitoring of respiratory mechanics, both of them can keep SpO2 > 95% after using nasopharyngeal airway.

It was interesting that surgeons rather than patients in both groups reported high scores for satisfaction. This means that surgeons in both groups were generally satisfied with the procedure without interrupted by patient movement. However, satisfaction scores by patient and surgeon were significantly higher in the dexmedetomidine-dezocine group. Due to the lower HR and MAP in the group, it had a better surgical field, which may attribute to better surgeon satisfaction. Also, surgeons are satisfied with no patient movement during surgery. Eren and colleagues had reported the efficacy of 1μg/kg dexmedetomidine persisted in the 30th minute, the sedative effect of 60μg/kg midazolam decreased[20]. The decrease was suggested to be due to shorter half-life of midazolam. Also, dexmedetomidine combined with dezocine, the sedation effect did not stack but analgesic action greatly enhanced. This may be proved in our study that no patient receiving dxemnedetomidine-dezocine demanded rescue sedation and analgesics as compared to the midazolam-fentanyl group (13% and 30%).

Trepanation and drainage of CSH is usually performed as an ambulatory procedure. In the present study, sedation recovery time was longer in the midazolam fentanyl group.

The current study has certain limitations. One possible limitation could be that the effects of the drugs were seen only in ASA I/II patients. Another limitation could be that 2 different combinations with 4 different drugs were compared in our study, and it might not correctly represent the sedative and analgesic properties of dexmedetomidine. What we want to see is dexmedetomidine-dezocine combination would be superior to midazolam-fentanyl combination in trepanation and drainage of chronic subdural hematoma under monitored anesthesia care.

Conclusions

Dexmedetomidine in combination with dezocine in patients undergoing trepanation and drainage of chronic subdural hematoma for sedation and analgesia appeared to be safe. No increase in side effect and delay in recovery were found compared to midazolam-fentanyl combination. Patients and surgeons were more satisfied with its use.

Competing Interests

All the authors deny any competing interests.

Acknowledgements

The authors thank Prof. Chaoshi Niu, M.D., Ph.D. and Wanhai Ding, M.D., Department of Neurosurgery, for consultative advice in designing and conducting the study. We are grateful for the enthusiastic support of the nurses of the PACU at Southern District of Anhui Provincial Hospital.

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Huo et al. J Perioperative Science 2015, 2:3
http://www.perioperative-science.com/content/02/03


