Sedative, haemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results


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Background. We evaluated the sedative, haemodynamic and respiratory effects of dexmedetomidine and compared them with those of midazolam in children undergoing magnetic resonance imaging (MRI) procedures.

Methods. Eighty children aged between 1 and 7 yr were randomly allocated to receive sedation with either dexmedetomidine (group D, n=40) or midazolam (group M, n=40). The loading dose of the study drugs was administered for 10 min (dexmedetomidine 1 µg kg⁻¹ or midazolam 0.2 mg kg⁻¹) followed by continuous infusion (dexmedetomidine 0.5 µg kg⁻¹ h⁻¹ or midazolam 6 µg kg⁻¹ min⁻¹). Inadequate sedation was defined as difficulty in completing the procedure because of the child's movement during MRI. The children who were inadequately sedated were given a single dose of rescue midazolam and/or propofol intravenously. Mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (S̄pO₂) and ventilatory frequency (VF) were monitored and recorded during the study.

Results. The quality of MRI was significantly better and the rate of adequate sedation was higher in group D than in group M (P<0.001). In group D, the requirement for rescue drugs was lower and the onset of sedation time was shorter than in group M (P<0.001). MAP, HR and VF decreased from baseline during sedation in both groups (P<0.001).

Conclusions. Dexmedetomidine provided adequate sedation in most of the children aged 1–7 yr without haemodynamic or respiratory effects during MRI procedures.

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Children may be frightened by being in the magnetic resonance imaging (MRI) tunnel or duct and the loud noise generated during the imaging process. Thus sedation is required for children aged between 1 and 7 yr. MRI examination is very sensitive to motion artifacts. If any movement occurs during the imaging process for one sequence, the entire sequence must be repeated. Consequently, a deep level of sedation is required during MRI. Deep sedation is defined as 'a medically induced state of central nervous system depression in which the patient is essentially unconscious, and so does not respond to verbal command'. The potential complications of deep sedation include hypventilation, apnoea, airway obstruction, aspiration, hypotension, bradycardia, and increased intracranial pressure. If any complications occur during an MRI examination, the nature of the set-up precludes easy access to the patient.

There has been debate over the appropriate drugs and dosage regimes for MRI sedation in children. Dexmedetomidine is a potent highly selective α₂-adrenoreceptor agonist with a distribution half-life of approximately 8 min and a terminal half-life of 3.5 h. Dexmedetomidine, as a sedative agent, can provide easily controllable analgesia and sedation without respiratory depression and has been widely used in the intensive care unit (ICU) for sedation and postoperative analgesia. Its use for sedation in children in situations outside the operating theatre or ICU has not been studied, other than in a few case reports.

In this preliminary study, the aim was to improve sedation and develop a regimen based on dexmedetomidine, and to evaluate the sedative, haemodynamic and respiratory effects of dexmedetomidine compared with midazolam in children undergoing MRI examination.
Methods
After local institutional ethics committee approval and written parental consent, 80 ASA I–II children aged 1–7 yr undergoing MRI were included in this randomized prospective study. Patients with heart, lung or neurological disease, central nervous system or extremity trauma, or contraindication or allergy to any of the drugs studied, or who had received any study drug in the last 30 days were excluded. All children were allowed to take clear liquids up to 2 h before sedation but food (including milk) intake was withheld for at least 8 h in children >36 months, and for 6 h in children aged 12–36 months. To facilitate i.v. cannulation, EMLA cream was applied on the dorsum of both hands 1 h before transfer to the preparation room. Presedation behaviour was assessed on a four-point scale (1=calm, cooperative; 2=anxious but reassurable; 3=anxious and not reassurable; 4=crying or resisting) by a team member blinded to the drug allocation (anaesthetist 1). Categories 1 and 2 were classed as undistressed and categories 3 and 4 as distressed. Baseline values were recorded upon arrival in the preparation room. A 22G or 24G venous cannula was inserted in the dorsum of the hand. Children were allocated according to a random number table to either the study group receiving dexmedetomidine (group D, n=40) or the control group receiving midazolam (group M, n=40). Dexmedetomidine (Precedex®; Abbott Laboratories, North Chicago, IL, USA) and midazolam (Dormicum®; Roche, Basel, Switzerland) were prepared by a team member not involved in data recording (anaesthetist 2). One millilitre of dexmedetomidine 100 µg ml\(^{-1}\) was diluted with 49 ml normal saline to a concentration of 2 µg ml\(^{-1}\). Two millilitres of midazolam 5 mg ml\(^{-1}\) were diluted with 48 ml normal saline to a concentration of 200 µg ml\(^{-1}\). A loading dose (dexmedetomidine 1 µg kg\(^{-1}\) or midazolam 0.2 mg kg\(^{-1}\)) was given over 10 min followed by continuous infusion (dexmedetomidine 0.5 µg kg\(^{-1}\) h\(^{-1}\) or midazolam 6 µg kg\(^{-1}\) min\(^{-1}\)).

The sedation level was measured every 10 min using the Ramsay sedation scale\(^{13}\) by evaluating response to sound, verbal commands or tactile stimulation by anaesthetist 1. The Ramsay scale assigns a score of 1–6 based on the clinical assessment of the level of sedation (1=awake; 2=distressed; 3=responds to verbal commands only). Scores 4–6 apply to sleeping patients and are graded according to the response to sound (4=no response; 5=minor movement; 6=major movement necessitating another scan). The onset of sedation time was defined as the time from starting drug infusion to achieving a Ramsay score of 6. Recovery time was the time between discontinuation of drug infusion and reaching a Ramsay score of 2. Discharge time was the time between discontinuation of drug infusion and discharge of the child from the unit. Discharge criteria were the return of vital signs and level of consciousness to baseline, and the ability to maintain a patent airway.

Statistical analyses were made using SPSS\(^{9}\) 10.0 (SPSS Inc., Chicago, IL, USA). Analysis of variance for repeated measures was performed on haemodynamic and respiratory parameters, with compensation for post hoc comparisons using the Bonferroni correction. Intergroup statistical analyses were performed using the t-test, and non-parametric data were analysed using the χ\(^2\)-test. Statistical significance was assumed at P<0.05. Results are presented as mean (SD) or their 95% confidence interval (CI). Because of the lack of a primary outcome, the power of the study was calculated based on the onset of sedation time. Setting a significance level of P=0.05, it was calculated that a group size of 40 patients allowed detection of a difference between groups with a power of 100%.

Results
The patient characteristics, presedation behaviour scores and duration and type of MRI procedure were not statistically different between groups. The quality of MRI was significantly better in group D than in group M (P<0.001) (Table 1). MRI examination was successfully completed in all patients and no complications were observed during or after sedation in either group.

Adequate sedation was obtained in 32 children from group D (80%, 95% CI, 0.64–0.91) and in eight children from group M (20%, 95% CI, 0.09–0.36) (P<0.001). After infusion of the study drug for 30 min, the median Ramsay score was 5 in eight children from group D and 4 in 34 children from group M. In these children, a Ramsay score of 6 was obtained with the rescue dose of midazolam and/or propofol before MRI examination. Inadequate sedation was
Table 1 Patient characteristics, duration, types, quality, and details of MRI procedures. Values are mean (range) for age and mean (SD) for weight and duration of MRI, or number of children. *Significant difference between groups (P < 0.001)

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=40)</th>
<th>Group M (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>4 (1–7)</td>
<td>4 (1–7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14 (4.1)</td>
<td>14 (5.1)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>26/14</td>
<td>25/15</td>
</tr>
<tr>
<td>Presedation behaviour score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undistressed (score 1 and 2)</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Distressed (score 3 and 4)</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Duration of MRI (min)</td>
<td>23 (8.1)</td>
<td>20 (6.1)</td>
</tr>
<tr>
<td>Cranial MRI</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Extremity MRI</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Cranial and extremity MRI</td>
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<td>0</td>
</tr>
</tbody>
</table>

Table 2 Results of sedation and duration of study drug infusion. Values are mean (SD) or number of children. *Significant difference between groups (P < 0.001)

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=40)</th>
<th>Group M (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate sedation (n)</td>
<td>8*</td>
<td>32</td>
</tr>
<tr>
<td>Onset of sedation (min)</td>
<td>19 (8.2)*</td>
<td>35 (11.0)</td>
</tr>
<tr>
<td>Duration of study drug infusion (min)</td>
<td>45 (11.7)</td>
<td>55 (10.0)</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>24 (17.6)</td>
<td>25 (13.2)</td>
</tr>
<tr>
<td>Discharge time (min)</td>
<td>32 (20.1)</td>
<td>39 (13.3)</td>
</tr>
</tbody>
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observed in eight children from group D and in 32 children from group M during MRI. The eight children in group D who were inadequately sedated received a rescue dose of midazolam which was sufficient for adequate sedation during MRI. The 32 children in group M who had already received midazolam as a rescue drug also required propofol as an additional rescue drug during MRI. The requirement of rescue drugs was significantly lower in group D than in group M (P < 0.001). MRI examination was successfully completed in all these children. In group D, the onset of sedation was significantly shorter than in group M [19 (8.2) min vs 35 (11) min, P < 0.001]. The duration of drug infusion, recovery and discharge times were not different between groups (P > 0.05) (Table 2).

MAP and HR were not statistically different between groups before and during sedation. They decreased significantly from baseline during sedation in both groups (P < 0.001). MAP in groups D and M was 82 (7.8) mm Hg and 83 (11.0) mm Hg, respectively, before sedation, and 72 (8.1) mm Hg and 71 (7.5) mm Hg, respectively, during sedation. HR in groups D and M was 109 (12.3) beats min$^{-1}$ and 113 (8.6) beats min$^{-1}$, respectively, before sedation, and 96 (12.2) beats min$^{-1}$ and 104 (10.5) beats min$^{-1}$, respectively, during sedation. No children experienced bradycardia or hypotension during sedation. The maximum decrease in MAP during sedation in groups D and M was 16% and 17%, respectively, and the maximum decrease in HR during sedation was 15% and 10%, respectively.

VF was decreased significantly from baseline in both groups during sedation (P < 0.001) but was not significantly different between groups before or during sedation. Mean VF in groups D and M was 27 (3.6) bpm and 28 (5.2) bpm, respectively, before sedation, and 25 (3.2) bpm and 24 (4.8) bpm, respectively, during sedation. The maximum decreases in VF during sedation in groups D and M were 8% and 14%, respectively. $\Delta$PO$_2$ did not fall below 93% in any children in group D during the study, but VF<93% was observed in three children in group M (P > 0.05) before MRI examination. These three children had been given rescue propofol because of a Ramsay score <6 before MRI examination. In these children, the decrease in $\Delta$PO$_2$ was easily treated with oxygen supplementation via a facemask.

Discussion

Sedation of children for MRI can be associated with difficulty in obtaining deep sedation while maintaining haemodynamic and respiratory stability remotely. Inadequate sedation during MRI occurred in 5–15% of cases, causing failure in 3.7%, and the incidence was higher in hyperactive, uncooperative and older children. Previous studies indicate that infusion of dexmedetomidine 0.1–0.7 $\mu$g kg$^{-1}$ h$^{-1}$ provides effective sedation. A sedation score between 2 and 4 was obtained with 0.5 $\mu$g kg$^{-1}$ loading and 0.25–0.5 $\mu$g kg$^{-1}$ h$^{-1}$ infusion dose of dexmedetomidine. In our study, a dexmedetomidine loading dose of 1 $\mu$g kg$^{-1}$ and infusion of 0.5–0.7 $\mu$g kg$^{-1}$ h$^{-1}$ was used. Effective sedation with midazolam has been reported with loading doses of 0.2–0.5 mg kg$^{-1}$ and infusion of 1–8 $\mu$g kg$^{-1}$ min$^{-1}$ in children. These doses are similar to our midazolam doses. Midazolam, as a sole sedative agent, has been associated with a higher incidence of failed sedation during MRI procedures, which is consistent with our results. It is known that midazolam has a quick onset of action and a short recovery room stay when it is administered intravenously over 2–5 min. However, in our study the midazolam loading dose was administered over 10 min to parallel that of the dexmedetomidine. The rate of administration of the midazolam loading dose may explain the low rate of adequate sedation rate. There were also more distressed patients before sedation in group M. Adequate sedation was obtained with dexmedetomidine in most of the children and the others were effectively sedated with rescue midazolam.

Arian and colleagues reported a sedation induction time of 25 min and a recovery time of 34 min with dexmedetomidine in adults. The onset of sedation time and the recovery time was shorter in our study. This could be explained by the fact that the subjects were children and that the duration of infusion was shorter.
Although the most important disadvantage of dexmedetomidine is adverse haemodynamic effects, there are conflicting reports on these.\textsuperscript{5,6,9,15,20,21} Hypotension and bradycardia have been reported, particularly with high-bolus dosing regimens, in patients with pre-existing cardiac problems and a loading dose infusion given over <10 min.\textsuperscript{4,22} Midazolam is said to have more haemodynamic stability,\textsuperscript{17} but in our study MAP and HR decreased significantly after both drugs. These decreases could be because of high baseline values which, in turn, could have occurred because the children were not premedicated. On the other hand, the decreases in MAP and HR were <20% from baseline and were considered to be clinically insignificant.

Respiratory events make up a large proportion (5.5%) of the complications of the sedation in children.\textsuperscript{3} Some authors have reported that dexmedetomidine had no respiratory effects,\textsuperscript{7,23} but others have described respiratory complications with large and rapid loading doses.\textsuperscript{4,21,24} A loading dose of dexmedetomidine given over 2 min caused irregular respiration, apnoea, slight hypoxaemia and hypercapnia.\textsuperscript{20} Respiratory depression and apnoea were not observed in any of the children who received dexmedetomidine during our study. The desaturation observed in three children who received midazolam may have been caused by rescue propofol.

Propofol, chloral hydrate, and midazolam have been used as sedative agents for children,\textsuperscript{1,18} and a complication rate of 20% in sedation performed for diagnostic procedures in children has been reported.\textsuperscript{3} Chloral hydrate may cause desaturation and may be associated with restlessness and prolonged imbalance.\textsuperscript{3,18} Propofol can cause respiratory depression, loss of protective airway reflexes and bradycardia in appropriate doses.\textsuperscript{25,26} Midazolam may cause paradoxical excitation and agitation with higher doses.\textsuperscript{18} In our study, no complications were seen in any child who received dexmedetomidine.

In conclusion, dexmedetomidine provided adequate sedation at 1 μg kg\textsuperscript{-1} loading and 0.5–0.7 μg kg\textsuperscript{-1} h\textsuperscript{-1} infusion doses in most of the children (aged between 1–7 yr) without affecting haemodynamics and respiration. Thus dexmedetomidine may be a suitable agent for MRI sedation in children.

References