Preanesthetic Medication of Children with Midazolam Using the Biojector Jet Injector

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Background: A rapid, dependable, and economical technique toatraumatically sedate children before anesthesia when does not prolong postanesthesia care unit time remains elusive. The Biojector jet injection system uses carbon dioxide rather than a needle to deliver an intramuscular injection. The dose-response relationship when midazolam is administered was studied using this jet injector.

Methods: Forty children (2.3 to 13.5 yr old) undergoing elective myringotomy and tube placement were randomly assigned to receive 0.05, 0.1, 0.15, 0.2, or 0.3 mg/kg of midazolam injected intramuscularly using the Biojector disposable syringe (0.06-cc 22-gauge needle). Assessment of each child before, during, and 10 min after injection, on application of the anesthesia face mask, and every 15 min for 1 h after arrival to the postanesthesia care unit was made by an observer blinded to drug dosage.

Results: Face mask tolerance using doses ≥ 0.1 mg/kg of midazolam was acceptable and statistically different from 0.05 mg/kg. Crying on injection tended to increase with increasing dose. All children were awake and arousable, meeting discharge criteria, at 30 min from arrival in the postanesthesia care unit.

Conclusions: Midazolam (0.1-0.15 mg/kg) administered using jet injection effectively and rapidly produces sedation, in a manner acceptable to parents, without delaying postanesthesia care unit discharge. (Key words: Anesthesia; Jet injectors; Intramuscular injection. Equipment: jet injection. Hypnotics: midazolam.)

FEAR of painful and unpleasant procedures, separation from parents, and an unwillingness to breathe through an anesthesia face mask may produce levels of anxiety that are unacceptable in unpremedicated children. About 30-60% of young unpremedicated children have been reported to resist application of the face mask or become uncooperative during inhalational induction.

Because of this, preanesthetic sedation has become an integral part of pediatric anesthesia practice.

Methods and Materials

After approval by the institutional review board, a convenient cohort of 40 children (11 female: 29 male; age range: 11 months to 12 yr) was enrolled. All children were premedicated with oral midazolam (0.5 mg/kg), and naso and/or rectal administration was achieved in conjunction with the 0.06 cc 22-gauge needle. Children were studied in the postanesthesia care unit to determine whether or not the scale dose would provide acceptable levels of sedation, and to determine whether additional doses could be used with the same safety and efficacy. The Biojector jet injection system is a hand-held device that makes use of a carbon dioxide propellant to generate the compression energy to inject a preformed dose of propo- nent mixture into the subcutaneous or intramuscular layers of the skin and deposits the medication bypassing the upper and middle layers of the skin.

We hypothesized that administration of predose prior to the Biojector would provide acceptable sedation, and that additional doses could be used if the scale dose did not provide adequate sedation.

After Midazolam Administration, Children Become Relaxed and Cooperative. Thus Easing the Induction of Anesthesia. Furthermore, the hypnotic and respiratory effects of midazolam may be antagonized by fentanyl, thereby enhancing its safety.

MIDAZOLAM IS WELL ABSORBED AFTER RECTAL INFUSION. INTRAMUSCULARLY. INTRANASALLY, AND ORALLY. Rectal administration avoids the pain of intramuscular needle injection but requires larger doses and slower onset times and may delay emergence. The pain and anxiety associated with intramuscular injection generally has precluded its routine use in children. Nasal administration is complicated by a significant incidence of burning and discomfort as well.

An alternative to an intramuscular needle injection is jet injection, a technique that uses compressed gas rather than a needle to inject medication into muscle. It reduces the pain of injection and eliminates the risk of contaminated needle-stick injury. It is primarily used for immunizations and insulin administration. The Biojector injection system is a hand-held device that makes use of a carbon dioxide propellant to generate the compression energy to inject a preformed dose of medication into the subcutaneous or intramuscular layers of the skin. This ejection creates a stream of liquid that deposits the medication bypassing the upper and middle layers of the skin.

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device that makes use of a carbon dioxide cartridge to generate the compression energy to displace a plunger and force medication from a syringe through a fine oriifice. This ejection creates a stream that penetrates the skin and deposits the medication in the subcutaneous and intramuscular layers.

We hypothesized that administration of midazolam using the Biojector would produce adequate preoperative sedation in children, as defined as acceptance of the anesthesia face mask for inhalational induction of anesthesia. In addition, we sought to determine whether an optimal dose existed that would allow rapid recovery from general anesthesia and timely discharge from the postanesthesia care unit (PACU).

Methods and Materials

After approval by the institution’s Committee on Clinical Investigation and obtaining informed parental consent, 40 children (11 female), 9 months of age or older, ASA physical status 1 or 2, undergoing elective placement of myringotomy tubes, were studied. Patients were randomly assigned to receive 0.05 (n = 4), 0.1 (n = 9), 0.15 (n = 9), 0.2 (n = 9), or 0.3 (n = 9) mg/kg midazolam (5 mg/ml, multidose vial, Roche Laboratories, Nutley, NJ) into jet injection (Biojector 2000, Bioject, Portland, OR) into the left anterolateral thigh using the 0.086-inch-orifice disposable syringe.§ Nine children were to be studied at each dose; if a dose of midazolam failed to provide adequate sedation in more than three patients on application of face mask (as happened in the 0.05 mg/kg-dose group), that dose was eliminated from further study.

Heart rate, blood pressure, respiratory rate, and oxyhemoglobin saturation (SpO₂; Tramsope 12, Marquette Electronics, Milwaukee, WI) were recorded before the dose was administered and immediately after the induction of anesthesia. An attending anesthesiologist unaware of the dosage of drug being administered assessed the child’s mood (calm or agitated) and attempted to separate the child from his/her parent(s) immediately before and 10 min after midazolam administration. This blinded observer also determined the child’s cooperation (acceptance of an anesthesia face mask and absence of physical and verbal resistance at the induction of anesthesia), as well as airway complications at the induction and emergence from anesthesia. Sedation was assessed using the scoring system: crying, awake/alert, awake/calm, asleep/arousable, and needs airway support in the induction area.

Anesthesia was induced and maintained using spontaneous ventilation of oxygen (30%), nitrous oxide, and halothane (1–3%) administered by a resident physician. Emergence and recovery was evaluated every 15 min for 1 h after arrival to the PACU by a nurse unaware of the dose of midazolam administered using an emergence scoring system: crying, awake/alert, awake/calm, asleep/arousable, and needs airway support in the PACU. Tolerance of jet injection was scored using crying as a marker of pain. Bleeding and/or erythema at the injection site were noted.

Statistical analysis was performed using the chi-square analysis and a significance level of 0.05. Data are presented as the mean ± SD. The changes in mean values of blood pressure, heart rate, respiratory rate, and SpO₂, before and after jet injection, were compared using a regression model to determine trends or changes that were significantly different from zero. This analysis model accounts for the paired nature of the before and after measurements taken on the same patient in a way directly analogous to the paired t test (table 2).

Results

There were no differences in weight, age (table 1), heart rate, blood pressure, and SpO₂ before treatment in any of the five treatment groups (table 2). Respiratory rate increased after jet injection in all patients and was unrelated to the administered dose. Systolic blood pressure increased with increasing midazolam dose but by clinically insignificant amounts.

The smallest midazolam dose, 0.05 mg·kg⁻¹, was ineffective: It neither improved the child’s separation

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<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>No. of Patients</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>4</td>
<td>11.6 ± 2.4</td>
<td>2.1 ± 1.2</td>
</tr>
<tr>
<td>0.1</td>
<td>9</td>
<td>12.4 ± 4.1</td>
<td>2.5 ± 1.9</td>
</tr>
<tr>
<td>0.15</td>
<td>9</td>
<td>14.0 ± 2.3</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td>0.2</td>
<td>9</td>
<td>13.3 ± 2.8</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>0.3</td>
<td>9</td>
<td>11.9 ± 2.5</td>
<td>1.8 ± 0.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Table 2. Physiologic Parameters

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>BP (mmHg)</th>
<th>HR (beats/min)</th>
<th>RR (breaths/min)</th>
<th>SPO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>ΔBP</td>
<td>Pre</td>
</tr>
<tr>
<td>0.05</td>
<td>92 ± 6</td>
<td>89 ± 6</td>
<td>2.7</td>
<td>115 ± 19</td>
</tr>
<tr>
<td>0.1</td>
<td>95 ± 10</td>
<td>93 ± 8</td>
<td>2.5</td>
<td>112 ± 24</td>
</tr>
<tr>
<td>0.15</td>
<td>91 ± 11</td>
<td>89 ± 8</td>
<td>1.7</td>
<td>107 ± 18</td>
</tr>
<tr>
<td>0.2</td>
<td>88 ± 11</td>
<td>93 ± 8</td>
<td>4.5</td>
<td>110 ± 16</td>
</tr>
<tr>
<td>0.3</td>
<td>85 ± 6</td>
<td>95 ± 9</td>
<td>9.6</td>
<td>109 ± 16</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Pre = before midazolam was administered; Post = immediately after inhalational induction of general anesthesia; ΔBP = blood pressure; ΔHR = heart rate; ΔRR = respiratory rate; ΔSPO2 = oxyhemoglobin saturation; Δ = the average of differences (Post − Pre value) for all patients in each group.

* Changes that were significantly different from zero (P < 0.05) using a regression model.

from his/her parents nor produced acceptance of the face mask for inhalational induction of general anesthesia. All other doses were effective at producing sedation and acceptance of the face mask for inhalational induction while not prolonging emergence in the PACU.

Assessment of initial sedation of children revealed 90% (36 of 40) were not crying in the preinduction area and was similar in all groups. Although the 0.05-mg·kg⁻¹ dose was not effective in improving sedation, separation was improved in groups receiving doses greater than or equal to 0.1 mg·kg⁻¹ (fig. 1). Although larger doses (greater than or equal to 0.1 mg·kg⁻¹) improved separation scores in all but one child, and four children at these larger doses did not reach a score of “awake/calm,” there were no significant differences among these doses.

Crying on injection tended to increase with increasing dose. To compare small versus large doses and crying (given the small sample sizes in each group), data from patients receiving 0.05, 0.1, and 0.15 mg·kg⁻¹ were grouped and compared to data from patients receiving the two largest doses, 0.2 and 0.3 mg·kg⁻¹, as a group. Eight of 22 patients (36%) given the smaller doses cried in response to the injection, whereas 12 of 18 patients (67%) given the larger doses cried (P = 0.057).

The 0.05-mg·kg⁻¹ dose was ineffective at inducing tolerance of the anesthesia face mask. All other doses were essentially equivalent at increasing acceptance of the face mask (decreasing resistance) for anesthetic induction (table 3).

Although there is an apparent (though not statistically significant) trend of increasing calming effect with increasing dose, overall acceptance of face mask for doses 0.1–0.3 mg·kg⁻¹ was 69%. All children were awake or asleep and arousable after 30 min in the recovery room. This was not related to dose of midazolam received and corresponded to 64 ± 18 min of recovery of the dose of midazolam. Side effects noted at the injection site were “reddened,” and one case was “pale” (15% total incidence).

Discussion

Jet injection of midazolam, in mg·kg⁻¹, is a clinically useful technique for anesthetic management of children. This dose of midazolam, in a manner similar to that reported in other studies, produces a smooth, struggle-free induction of anesthesia. Additionally, this dose of midazolam did not affect duration of emergence from anesthesia.

Fig. 1. Effect of midazolam jet injection on calm separation. White bars = before midazolam was administered; black bars = 10 min after midazolam was administered.

Table 3. Face Mask Acceptance on Induction of Anesthesia

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Acceptance</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0 (0)</td>
<td>4</td>
</tr>
<tr>
<td>0.1</td>
<td>7 (78)</td>
<td>9</td>
</tr>
<tr>
<td>0.15</td>
<td>4 (44)</td>
<td>9</td>
</tr>
<tr>
<td>0.2</td>
<td>7 (78)</td>
<td>9</td>
</tr>
<tr>
<td>0.3</td>
<td>7 (78)</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>25 (63)</td>
<td>40</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
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Discussion

Jet injection of midazolam, in doses of 0.1–0.15 mg·kg⁻¹, is a clinically useful new tool in the preanesthetic management of children. As a premedication technique, this dose of midazolam reliably improves separation of a child from his/her parent(s) and facilitates a smooth, struggle-free inhalational induction of anesthesia. Additionally, this dose of midazolam neither delayed emergence from general anesthesia nor prolonged the possible discharge time from the PACU. Doses of midazolam greater than 0.15 mg·kg⁻¹ did not improve this technique’s effectiveness and were more frequently associated with crying on injection. There was no clinically significant effect of jet injection of midazolam on heart rate, arterial blood pressure, or $\text{SpO}_2$, at any dose of midazolam studied. Tachypnea, noted in all groups after induction of anesthesia, probably was related to inhalation of halothane rather than midazolam administration. Finally, in this small study, airway complications, such as coughing, laryngospasm, or vomiting, were not seen.

Use of jet injection for preanesthetic medication in children has not been reported in the literature. This technique offers several advantages to the anesthesiologist and patient: It is rapidly effective with a predictable onset and duration of action and is cost-effective. Furthermore, jet injection does not require patient cooperation and avoids the complications of needle injection.

Current anesthesia practice requires efficient and rapid management of patients—especially for procedures such as placement of myringotomy tubes. Unanticipated changes in the operating room schedule may result in children either entering the operating room before sedation has taken effect or after it has abated. Preanesthetic medication using the Biojector jet injection system is rapid (10 min) and allows the anesthesiologist (or nurse) to administer sedative drugs when they are needed, immediately before the induction of anesthesia, rather than “on call” to the operating room. Thus, sedation may be achieved more safely be-

cause a trained observer with readily available resuscitation equipment is always available.

In this study, the 0.05 mg/kg dose effectivly was the control group. Unfortunately, these children received the painful stimulus of the injection with an ineffective dose of midazolam. This was considered to be better than using a group given saline placebo or no injection at all. We chose to use a dose which, owing to the small delivery volume, may have hurt less and still have been effective for our purposes. In contrast, a control group that received no injection would have subjected the child to a different situation (i.e., no sound or feeling/sensation of injection). Considering this low-dose group as our control is an inherent but unavoidable weakness in study design, and although we believe that the dose comparisons presented are valid, interpretation of this data and subsequent generalization to all children receiving preanesthetic medication must be made cautiously. Likewise, because all of the children in this study received a jet injection, we are unable to extricate the inherent effect and potential bias of jet injection itself, including the sound and pain of injection, as well as the unavoidable sense and anxiety of “imminent injection” during skin preparation with alcohol, for example. Comparison of jet injection technique (using what is determined to be an effective dose) with other techniques (oral, rectal, behavioral) would seem reasonable and is being pursued.

The lack of sedative effect of the 0.15 mg/kg-dose group in this study seemed to be an aberration when viewed among the 0.1, 0.2, and 0.3 mg/kg-dose groups. This may reflect the small sample sizes used.
Administration of midazolam by jet injection must be distinguished from an intramuscular injection using a needle and syringe. The mere sight of a syringe and needle may produce terror in many children, thereby increasing the midazolam requirement necessary to create sedation. Although the present use of the Biojector is not painless, it is less painful than a needle and syringe and eliminates the visual impact of a needle to the child. Additionally, the characteristics of the jet injection may increase the efficiency of medication absorption. Instead of a bolus deposit of drug in a contained space in the muscle, the spray dispersion effect of jet injection is more likely to spread the injected drug into a larger volume of tissue. 16-20 This may increase the surface area of potential drug absorption and increase the rate of rise of serum drug concentrations. 16,17 Complications associated with the use of this device, including redness, swelling, and discoloration at the site of injection, have been compared to needle injections and may be more related to the medication administered rather than the injection technique. 21 Finally, the Biojector jet injector avoids the user complications of needle injection: There is no possibility of a contaminated needle injury when properly using this device.

The Biojector jet injector also eliminates the need for patient cooperation. Patients do not have to drink and/or retain their sedative. Thus, the possibility of a child refusing, spitting up (oral), or expelling (rectal) the midazolam dose or a portion of the dose is eliminated. Furthermore, the amount of midazolam required to premedicate a child is significantly less with the jet injector compared to the oral or rectal routes of drug administration. 3,5 In an effort to determine whether the Biojector could be cost-effective as a method of preinjection sedation, an assessment and comparison of costs expected to be encountered using jet injection, nasal, oral, and rectal administration, were made. Costs per injection were compared, based on material and medication costs in our hospital for a hypothetical 10-kg child.

The Biojector Jet Injector 2000 costs $600; amortizing this cost over 2,500 injections yields $0.24 per injection. Biojector syringes cost $0.60 each. The carbon dioxide cartridge (ten injections) costs $50 ($0.50 per injection). Midazolam costs $2.00 per milligram in our pharmacy. A standard 10-ml syringe and needle costs $0.11, a suction catheter (used for rectal injection) costs $0.76, and 10 ml of flavored juice costs $0.01.

Addition of material and medication costs for jet injection (amortization of jet injector, syringe, carbon dioxide cartridge, midazolam) yields $3.89 per jet injection. Similar calculation for nasal, oral, and rectal administration yields $4.11, $10.12, and $10.87, respectively (Table 4).

The major disadvantage of this method of drug delivery is that it is not completely painless. The usefulness of this technique and its ability to decrease preoperative anxiety, will be enhanced if it could be made painless. Little information is available regarding the cause of pain in intramuscular injection using jet injection. Whether pain is related to a characteristic of the injection (pressure, speed of injection) or volume, temperature, pH, or osmolality of injectate is unclear. Further investigation, using EMLA cream to minimize the pain associated with the jet injection, may increase the usefulness of this technique and is being studied.

In any study of effectiveness of a technique, one must balance the required effect or benefit with possible side effects or risks. The clinician must decide which evil is less unacceptable: pain on injection of midazolam (using jet injection), the burning discomfort of nasal

<table>
<thead>
<tr>
<th>Dose</th>
<th>Jet Injection (0.15 mg/kg)</th>
<th>Nasal (0.2 mg/kg)</th>
<th>Oral (0.5 mg/kg)</th>
<th>Rectal (0.5 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam Syringe</td>
<td>3.00</td>
<td>4.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Injector (amortization) + CO2 cartridge Juice</td>
<td>0.60</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Catheter</td>
<td>0.29</td>
<td>0.01</td>
<td>0.76</td>
<td>10.87</td>
</tr>
<tr>
<td>Total</td>
<td>3.89</td>
<td>4.11</td>
<td>10.12</td>
<td>10.87</td>
</tr>
</tbody>
</table>

† This conservatively assumes five injections per day, 250 operating days a year, amortized over a device life-span of 2 yr.
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administration, or the higher dose (and potential prolonged emergence and cost) using oral or rectal administration. A rate of resistance to face mask inhalational induction of 22% compares favorably with other techniques designed to offer simple, dependable onset and predictable, prompt emergence.

Finally, each parent was asked whether jet injection seemed an acceptable technique for sedating their child and whether they would accept having their child sedated using this technique again. Jet injection was uniformly accepted (even among those parents whose children resisted the face mask), and all would allow their child to have sedation using this device again.

In conclusion, we have shown that 0.1–0.15 mg·kg⁻¹ midazolam administered by the Biojector jet injection system effectively and rapidly produces sedation, in a manner acceptable to parents, without delaying PACU discharge or increasing costs.

The authors thank the nurses of The Johns Hopkins Outpatient Center, for their help in performing these studies.

References