Effect of a small priming dose on myoclonic movements after intravenous anaesthesia induction with Etomidate-Lipuro in children

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Background. In children, the incidence of injection pain at i.v. anaesthetic induction with Etomidate-Lipuro is low when compared with propofol mixed with lidocaine (5%). However, the incidence of involuntary myoclonic movements (MM) after induction of anaesthesia is higher compared with propofol (85% vs 15%). In adults, the incidence of MM is reported to be significantly reduced if a small priming dose is administered immediately before the main injection of etomidate. The aim of this prospective, randomized, double-blind, placebo-controlled clinical trial was to investigate if a small priming dose of etomidate effectively can reduce the incidence of MM also in children.

Methods. Eighty ASA I–II children (1–15 yr) were randomized to receive either a small priming dose of etomidate (0.03 mg kg⁻¹) or a lipid emulsion placebo. A standardized induction dose of etomidate (0.3 mg kg⁻¹) was administered 60 s after the priming dose. The occurrence and severity (observational score 0–3) of MM was defined as the primary endpoint of the study and was recorded during a 2 min period after induction of anaesthesia. A post hoc analysis was performed regarding the incidence of MM with respect to age.

Results. No difference in the occurrence or severity of MM was found between the two study groups, the total incidence of MM being 73.8% (95% confidence interval: 62.7–83.0%). The incidence of MM (score 0) was found to be statistically higher in the age group 5–10 yr compared with children aged <5 yr and >10 yr (P=0.0008 and 0.01730, respectively). The MM scores were highest in patients aged 5–10 yr (P=0.0021).

Conclusions. Children in the age range of 5–10 yr appear to be especially prone to react with involuntary MM after i.v. induction of anaesthesia with etomidate. The use of a small, non-sedative, priming dose did not influence the incidence of involuntary MM after i.v. induction of anaesthesia with etomidate in children 1–15 yr of age.

Keywords: anaesthetics i.v.; etomidate; children; complications; myoclonia

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Despite numerous manipulations, i.v. induction of anaesthesia with propofol in children is typically associated with injection pain in 30–80% of cases, although occasional studies report somewhat lower incidence figures.

Even with the most widely used method, where lidocaine is co-administered with propofol, injection pain is reported in 30–50% of paediatric patients. Although the dilution of propofol to a 5% solution significantly reduces the pain compared with a 10% solution, the incidence of injection pain is still as high as 23%.

In a previous randomized clinical trial, we found that the use of the alternative hypnotic agent Etomidate-Lipuro was associated with minimal injection pain when compared with the use of propofol with added lidocaine (5% vs 47.5%) and, thus, appears as a very attractive solution to the problem of propofol-induced injection pain in children. One of the few drawbacks associated with the use of Etomidate-Lipuro is that it increases the incidence of myoclonic movements (MM) soon after the induction of anaesthesia (etomidate 85% vs propofol 15%). Although the occurrence of MM does not cause any known problems to the child, it...
would still be desirable to reduce this high incidence of MM if it could be accomplished through simple and safe means.

In adults, the use of a small, non-sedating, priming dose of etomidate given immediately before the administration of the larger induction dose has been reported to reduce the incidence of MM from 75% to only 25%. The aim of the current prospective, randomized, double-blind, placebo-controlled clinical trial was to investigate whether the use of a small priming dose of etomidate can reduce the incidence of MM after i.v. induction of anaesthesia also in children.

Methods

After Ethics Committee approval and written parental informed consent 80 children 1–15 yr of age undergoing outpatient surgical procedures were enrolled in the study. Exclusion criteria were ASA class ≥ III and/or a known allergy to lipid emulsions or etomidate.

By means of computer-generated random numbers, the patients were randomized to one of two study groups. Children were either allocated to receive an active priming dose of 0.03 mg kg⁻¹ of Etomidate-Lipuro 2 mg ml⁻¹ (B. Braun, Melsungen, Germany) (Group E) or an equal priming volume of placebo (Intralipid 200 mg ml⁻¹, Fresenius Kabi, Uppsala, Sweden) (Group P). To achieve proper blinding, the randomization was performed at the Hospital Pharmacy.

After arrival at the out-patient unit and adequate application of an EMLA cream patch (AstraZeneca, Macclesfield, UK), a 22 G i.v. cannula (B. Braun) was inserted at the dorsum of the hand. Thereafter, all patients received i.v. premedication with midazolam 0.05 mg kg⁻¹ (maximum dose restricted to 2 mg) and were subsequently transferred to the operating theatre. All patients were accompanied by a parent until induction of anaesthesia was accomplished.

After the attachment of standard non-invasive anaesthesia monitoring, patients were given the i.v. priming dose from the pre-filled study syringe. Sixty seconds later, anaesthesia was induced by the i.v. injection of 0.3 mg kg⁻¹ of Etomidate-Lipuro.

After induction of anaesthesia was accomplished, the airway was handled by a regular facemask and ventilation was assisted if needed. No further anaesthetic agents were administered during the subsequent assessment period.

The occurrence of MM after the injection of the induction dose of etomidate was recorded during a 2 min period. MM were classified according to a 0–3-point scale, as previously described (0, no; 1, minor; 2, moderate; 3, major movements). All myoclonic assessments were made by one of the authors (K.H.), who also had made all myoclonia assessments in our previous study.

After the myoclonia assessment period was completed, the study was terminated and the anaesthetic continued according to the preference of the attending anaesthetist.

Post hoc the patients were divided into subgroups according to age (≤5, 5–10, >10 yr) and also according to individual MM score.

Statistics

A power calculation was performed based on data from our previously published study and adult data reported by Doniwick and colleagues. The primary goal of the study was to decrease the incidence of MM from 80% to 40% with α- and β-values set at 0.05 and 90%, respectively. On the basis of these parameters, a total study size of 80 patients (40 patients per group) was suggested.

Non-parametric statistical procedures were used in all the analyses. The 95% confidence intervals (95% CIs) for proportions were calculated as given in Ott and Mendenhall. Classified data from two independent populations were compared by Fisher’s exact test. Classified data from several independent populations were compared by the χ² test for independence. The Wilcoxon matched-pairs signed-ranks test was used for comparison of two independent data sets. Several independent data sets were evaluated by the Kruskal–Wallis test with Dunn’s post-test. Correlations were assessed by the Spearman rank correlation test. The tests were two-tailed and P-values of <0.05 are described as statistically significant.

Results

Of the 80 patients included in the study, 40 were randomized to Group E and 40 patients to Group P. No patients were excluded from the final analysis. Patient characteristics are shown in Table 1.

Neither the total incidence nor the degree of MM was found to differ between the two study groups (Fig. 1). Incidences of MM (score >0) were observed in 75.0% and 72.5% of the patients in the etomidate and placebo groups, respectively, the total incidence of myoclonic movements being 73.8% (95% CI: 62.7–83.0%).

The incidence of MM (score >0) differed significantly between the age groups (P = 0.0014) and was found to be significantly higher in the age group 5–10 yr (90.2%; 95% CI: 76.8–97.3%) compared with both younger (<5 yr, 47.1%; 95% CI: 23.0–72.2%; P = 0.0008) and older children (>10 yr, 63.6%; 95% CI: 40.7–82.8%; P = 0.01730) (Fig. 2). The MM scores were significantly higher in patients aged 5–10 yr when compared with younger and older patients (P = 0.0021).

Discussion

The main finding of this prospective, randomized, double-blind, placebo-controlled clinical trial was that the use of a small, non-sedative, priming dose of etomidate did not influence the incidence of involuntary MM after i.v. induction of anaesthesia with etomidate in children. A secondary finding was that children in the age range of 5–10 yr appear to be especially prone to the side-effect of etomidate.

Etomidate, when used as an induction agent, produce a very similar onset–offset of action compared with propofol and can from this point of view be seen as interchangeable.
A negligible incidence of injection pain when administered as a lipid-based solution, the administration of etomidate is also associated with exceptionally stable haemodynamics, even if used in trauma victims or in patients with already compromised circulation (e.g. cardiac failure). However, if used as an i.v. infusion in the setting of intensive care unit sedation or as the hypnotic agent for total i.v. anaesthesia (TIVA) etomidate will cause interference with corticosteroid synthesis in the adrenal cortex, resulting in reduced cortisol levels and the potential for corticosteroid deficiency or even overt Addison crisis. This is in contrast to propofol infusions that do not interfere with adrenocortical steroid synthesis in any clinically relevant manner. However, no adverse effects related to the effect on corticosteroid synthesis have been demonstrated after the use of a single regular induction dose of etomidate in healthy adults. In children, a 2 h period of etomidate-based TIVA has been found to result in a transient reduction in serum cortisol, which returned to normal levels within 12 h. The effect in children of a single induction dose of etomidate on serum cortisol levels has so far to our knowledge not been reported but is currently under investigation by our group.

One of the few other side-effects associated with i.v. induction with etomidate is the relatively high incidence of MM that can appear shortly after the induction of anaesthesia. The occurrence of MM appear harmless to the patient since it occurs after the patient already is put in a hypnotic state, but may interfere with the clinical evaluation of depth of anaesthesia. In paediatric patients, the occurrence of MM may also look disturbing to an accompanying parent that has not already left the operating theatre by the time the movements become visible. Thus, it would be desirable to reduce the incidence of MM by some simple and safe means since the incidence of MM in children after administration of etomidate can be as high as 85%. However, propofol is also associated with this side-effect, albeit at a lower frequency (15%).

The use of a small, non-sedating, priming dose of etomidate represents a simple and safe potential alternative to reduce the occurrence of MM and has been found to result in a significant reduction of MM in adult patients. However, in the present study, we were unable to show any benefit of this method when compared with a lipid placebo (Fig. 1). It should be noted that the lipid emulsion used in the Etomidate preparation (mixture of long- and medium-chain triglycerides) differs slightly from the lipid placebo used (only long-chain triglycerides). However, to the authors’ knowledge, this difference in lipid emulsions used is unlikely to have influenced the incidence of MM.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group E (etomidate + etomidate)</th>
<th>Group P (placebo + etomidate)</th>
</tr>
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<tr>
<td>Age (yr)</td>
<td>7.49 (1.68–14.7)</td>
<td>7.47 (1.35–14.5)</td>
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<td>Gender M/F (n)</td>
<td>30/10</td>
<td>32/8</td>
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<tr>
<td>Weight (kg)</td>
<td>24.5 (14–67)</td>
<td>22 (10–66)</td>
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<tr>
<td>Height (cm)</td>
<td>130 (84–176)</td>
<td>125 (80–175)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>16.4 (13.1–23.2)</td>
<td>16.5 (11.0–24.0)</td>
</tr>
<tr>
<td>n</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

**Fig 1** Distribution of MM score in the etomidate and placebo groups. The total incidence of MM was 73.8% (95% CI: 62.7–83.0%).

**Fig 2** Distribution of MM score in the three age groups of patients. The incidence of MM score (score >0) was significantly higher in the age group 5–10 yr (90.2%; 95% CI: 76.8–97.3%) when compared with both younger (<5 yr, 47.1%; 95% CI: 23.0–72.2%; P=0.0008) and older children (>10 yr, 63.6%; 95% CI: 40.7–82.8%; P=0.0173). The MM scores were highest in patients aged 5–10 yr (P=0.0021). Data from all patients in the etomidate and placebo groups are included in the figure. Median values are given by the horizontal lines.
One possible explanation for this negative finding may be that the priming dose used was too small to be effective. However, our priming dose was based on a dose that has successfully been used in adults (~10% of the calculated induction dose of 0.3 mg kg⁻¹). Furthermore, pilot testing of higher priming doses resulted in a degree of sedation that would have made it impossible to use a double-blind design.

A second explanation for our negative result is associated with the age range studied (1–15 yr of age) and the effects that this may have had on the study power calculation. A post hoc analysis of our results did identify children in the age range of 5–10 yr as being particularly prone to react with MM (Fig. 2) and may therefore be seen as a high-risk population. Thus, it may be possible that the results would have been different if only patients in the 5–10 yr age span had been studied.

The underlying reason for the higher incidence of MM in the age group 5–10 yr is currently unknown. However, a pharmacokinetic explanation can be speculated since Sfez and colleagues previously have reported a 30% higher bolus dose requirement in children within approximately the same age span (7–12 yr). Thus, despite using the same per kilogram dose in all study patients, this standardized dose may have produced a lighter plane of anaesthesia in the 5–10 yr age group, potentially resulting in a higher likelihood of MM.

The above should have consequences for the design of further priming dose studies in children. First, only children in the 5–10 yr age bracket should be studied. Secondly, the use of a higher priming dose should be investigated. This will most likely produce slight preinduction sedation that will make use of the double-blind design impossible. However, a possible alternative to minimize this problem would be to use an observer-blinded design where the observer is only allowed to see the patient after the predetermined induction dose has been administered.

In conclusion, the use of a small, non-sedating, priming dose of etomidate did not reduce the incidence of involuntary MM after i.v. anaesthesia induction in children. Children in the age group 5–10 appear particularly prone to react with MM and should, thus, be the focus group in further studies investigating MM after etomidate administration in children.

Conflict of interest

None declared.

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