APA national audit of pediatric opioid infusions

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Summary

Introduction: A prospective audit of neonates, infants, and children receiving opioid infusion techniques managed by pediatric acute pain teams from across the United Kingdom and Eire was undertaken over a period of 17 months. The aim was to determine the incidence, nature, and severity of serious clinical incidents (SCIs) associated with the techniques of continuous opioid infusion, patient-controlled analgesia, and nurse-controlled analgesia in patients aged 0–18.

Methods: The audit was funded by the Association of Paediatric Anaesthetists (APA) and performed by the acute pain services of 18 centers throughout the United Kingdom. Data were submitted weekly via a web-based return form designed by the Document Capture Company that documented data on all patients receiving opioid infusions and any SCIs. Eight categories of SCI were identified in advance, and the reported SCIs were graded in terms of severity (Grade 1 (death/permanent harm); Grade 2 (harm but full recovery and resulting in termination of the technique or needing significant intervention); Grade 3 (potential but no actual harm). Data were collected over a period of 17 months (25/06/07–25/11/08) and stored on a secure server for analysis.

Results: Forty-six SCIs were reported in 10 726 opioid infusion techniques. One Grade 1 incident (1 : 10 726) of cardiac arrest occurred and was associated with aspiration pneumonitis and the underlying neurological condition, neurocutaneous melanosis. Twenty-eight Grade 2 incidents (1 : 383) were reported, of which half were respiratory depression. The seventeen Grade 3 incidents (1 : 631) were all drug errors because of programming or prescribing errors and were all reported by one center.

Conclusions: The overall incidence of 1 : 10 000 of serious harm with opioid infusion techniques in children is comparable to the risks with pediatric epidural infusions and central blocks identified by two recent UK national audits (1,2). Avoidable factors were identified including prescription and pump programming errors, use of concurrent sedatives or opioids by different routes and overgenerous dosing in infants. Early respiratory depression in patients with specific risk factors, such as young age, neurodevelopmental, respiratory, or cardiac comorbidities,
who are receiving nurse-controlled analgesia or continuous opioid infusion suggests that closer monitoring for at least 2 h is needed for these cases. As a result of this audit, we can provide parents with better information on relative risks to help the process of informed consent.

Keywords: analgesia; pediatric; opioids; patient-controlled analgesia; nurse-controlled analgesia

Methods

Eighteen acute pediatric pain teams in the United Kingdom and Eire volunteered to participate in the audit. Each center had a specialist pain nurse who collected and submitted data electronically on a weekly basis. The target denominator dataset was 10 000 patients aged 0–18 managed by the pediatric acute pain teams and receiving opioid infusion analgesia by continuous infusion (CI), patient-controlled analgesia (PCA), or nurse-controlled analgesia (NCA). It was estimated that the prospective data collection would take 12–18 months. The Document Capture Company was commissioned to design a web-based data reporting form for denominator data and a detailed serious clinical incident (SCI) reporting form. Patient data were anonymous, but each center had an identifier number to assist feedback of results and further investigation into SCI reports if needed. Centers were asked to report their weekly activity in four age bands (<1 month, 1 month < 1 year, 1–8 year, and >8 year), by opioid infusion technique (CI, PCA, NCA) and by broad clinical indication (surgical, nonsurgical, or palliative care). Data were stored on a secure server, and reports were generated monthly in Excel format. Data were summarized after 6 months, and each center was asked to validate their dataset. The data entered on the master database was checked by each center against copies of their locally held weekly data entries to insure accuracy of the overall data. This validation exercise was repeated at the end of the data collection period. Feedback was given to centers after 6 months and at the end of the audit.

Eight categories of SCI were identified in advance by an expert panel (Table 1) and were graded by severity (Table 2). This was similar to the methodology of the UK National Epidural Audit (1).

Reports on all SCIs were sent to the expert panel for review. A committee meeting was held to categorize each SCI in terms of severity and relation to the opioid infusion technique. If any further information on an individual incident was required, the center involved was contacted for a more detailed report.

Results

Denominator data

Data on 10 726 children were collected from 18 centers from June 2007 to November 2008. The age distribution of patients and the opioid infusion techniques used in different age groups are detailed in Table 3.

There are small errors in the dataset with PCA listed as the mode of infusion in 16 patients under 1 year, but it has not been possible to definitively reallocate these cases. This slight inaccuracy does not affect the overall analysis significantly. The broad indications for each opioid infusion technique are listed in Table 4.
Serious clinical incidents

Fifty-one SCIs were reported from ten of the eighteen hospitals. Five patients were excluded namely a patient with postoperative hypothermia, a patient with pump malfunction where the child received no morphine, two patients with whom the error was simply the use of the wrong type of infusion pump, and one with blank data entry. The final number of SCIs was therefore 46 (Table 5). The final overall risk levels are given in Table 6. The overall risks compare favorably with epidural infusion techniques (Table 7).

Details of serious clinical incidents

Cardiac arrest (n = 1).
The patient was a 2.5-kg, full-term neonate who had a giant melanocytic naevus covering 70% of his...
body. A curettage of 10% of this lesion was performed during which analgesia was provided by fentanyl, 2 \( \mu g \cdot kg^{-1} \) and morphine, 0.1 \( \mu g \cdot kg^{-1} \). Postoperative analgesia was with NCA (morphine 10 \( \mu g \cdot kg^{-1} \) per hour, bolus 20 \( \mu g \cdot kg^{-1} \), and lockout interval 30 min). After some 37 h and an average dose of morphine of 15 \( \mu g \cdot kg^{-1} \) per hour, the baby had two major desaturations during a 2-h period and had been noted to be irritable. The baby had a cardiorespiratory arrest and aspirated, requiring full advanced life support measures including cardiac massage, adrenaline administration, intubation, and ventilatory support. The baby required intensive care for a period of 2 weeks during which seizures were noted and MRI and CT scans revealed changes in neurocutaneous melanosis. Subsequent follow-up at 1 year confirmed developmental delay, but the relative contribution of the cardiac arrest episode to the child’s neurological state is not clear.

Respiratory depression (n = 14) (see Table 8)
There were 14 reports of respiratory depression, eight of whom received naloxone. Ten patients were with NCA, two with CI, and two with PCA. All children were monitored at the time of the incident with oxygen saturations and regular pains and sedation scores. We did not collect data on the pain or sedation scores. Local guidelines and protocols for management of opioid infusions were in place and followed in all instances. All participating hospitals had acute pain services managing the children. Of particular note were three cases where opioids or sedatives were given concurrently with the opioid infusion technique, namely clonidine, fentanyl, or codeine. One child was found to be profoundly anemic with Hb 4.0 g dl\(^{-1}\). All these patients made a full recovery. Seven of the cases of respiratory depression occurred within 1 h of starting the technique, and all were either very young or had significant neurodevelopmental, respiratory, or cardiac comorbidities.

Less serious adverse effects (n = 14).
There were five reports of emesis, five of pruritis, and four of urinary retention requiring intervention and/or termination of the technique. There were 12 of 14 adverse events observed in children receiving PCA. Interventions included antiemetics, naloxone, or urinary catheterization as appropriate. All children made a full recovery.

Drug errors (n = 17).
All the drug error reports were from a single center which resulted in skewing of the overall dataset. None of the incidents resulted in harm, and all were identified early in the postoperative period by routine cross-checks. Some incidents however had the potential to become serious incidents. There were 12 of 17 programming errors and five of 17 prescribing errors. Out of the 17, 9 would have resulted in over-administration of opioid, in one case by a factor of 80, and two of the 17 would have resulted in under-delivery of opioid with resultant inadequate analgesia. Of the 17, 6 were very minor errors, which would in fact have resulted in the correct dose of opioid being administered.

Additional information on SCI reporting.
There were no reports of myoclonic jerking requiring termination of a technique and no reports of pump malfunction.

Discussion
The purpose of this prospective audit was to determine the incidence, nature, and severity of serious clinical events occurring with opioid infusions to give parents more accurate information during the consent process. The large denominator as well as the complexity of the cases included in this audit provides a wide range of data for analysis. The incidence of 1:10 000 of Grade 1 incidents with opioid infusion techniques compares favorably with the figure of 1:2000 in the national pediatric epidural audit (1). The Grade 2 incidents were more common in opioid infusions (1:383 vs 1:1100) and Grade 3 incidents more prevalent in epidurals (1:233 vs 1:631). The overall risk of 1:10 000 of permanent harm is equivalent to the overall risk in both recent epidural audits (1,2).

There have been a number of studies evaluating the safety and the side effects of different opioid infusion techniques in children (3–7), but few have quantified the risks in terms of severity. In a recent retrospective study of 302 opioid naïve children receiving PCA by proxy (PCA-P) vs PCA, clinically significant adverse effects occurred in 22% and 24%
Table 8  
Details of cases of respiratory depression

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Comorbidity</th>
<th>Surgery type</th>
<th>Infusion mode</th>
<th>Time of incident (hours after start of technique)</th>
<th>Concurrent sedative</th>
<th>Location of event</th>
<th>Trigger for intervention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 year</td>
<td>19</td>
<td>VATER syndrome</td>
<td>Ligation of Tracheal oesophageal fistula</td>
<td>Nurse-controlled analgesia (NCA)</td>
<td>10</td>
<td>No</td>
<td>ICU</td>
<td>RR</td>
<td>O₂, IS</td>
</tr>
<tr>
<td>15 year</td>
<td>57</td>
<td>Developmental delay</td>
<td>Ligation of Tracheal oesophageal fistula</td>
<td>NCA</td>
<td>&lt;1</td>
<td>Epidural with 2 mcg ml⁻¹ Fentanyl</td>
<td>HDU</td>
<td>RR</td>
<td>N₂x2, IS, Epidural fentanyl stopped. High dependency unit</td>
</tr>
<tr>
<td>15 year</td>
<td>37</td>
<td>APML</td>
<td>Laparotomy-bleeding ulcer</td>
<td>Patient-controlled analgesia (PCA)</td>
<td>41</td>
<td>No</td>
<td>Ward</td>
<td>RR</td>
<td>O₂, Nₓ1</td>
</tr>
<tr>
<td>4 month</td>
<td>5.9</td>
<td>No</td>
<td>Nephrectomy</td>
<td>NCA</td>
<td>&lt;1</td>
<td>Fentanyl</td>
<td>Ward</td>
<td>RR</td>
<td>O₂, Nₓ1</td>
</tr>
<tr>
<td>1 year</td>
<td>10 month</td>
<td>13.4</td>
<td>No</td>
<td>NCA</td>
<td>&lt;1</td>
<td>No</td>
<td>Ward</td>
<td>Sats</td>
<td>O₂, IS</td>
</tr>
<tr>
<td>4 month</td>
<td>5.7</td>
<td>Ex prem (31/40) prev LADD’s procedure</td>
<td>reversal of ileostomy</td>
<td>NCA</td>
<td>31</td>
<td>No</td>
<td>Ward</td>
<td>Ap</td>
<td>O₂, PITU transfer – Hb = 4 g dl⁻¹ Transfusion and MR</td>
</tr>
<tr>
<td>3 month</td>
<td>2.5</td>
<td>Ex prem (27/40) Bowel obstruction, ventilated postnatally</td>
<td>Laparotomy-closure of stoma</td>
<td>NCA</td>
<td>&lt;1</td>
<td>No</td>
<td>Transfer to ward</td>
<td>Sats</td>
<td>O₂, IS for 2 h MR</td>
</tr>
<tr>
<td>13 year</td>
<td>46</td>
<td>No</td>
<td>Laparoscopic appendicectomy</td>
<td>PCA</td>
<td>5</td>
<td>No</td>
<td>Ward</td>
<td>RR</td>
<td>Nil</td>
</tr>
<tr>
<td>3 month</td>
<td>5.4</td>
<td>Bronchiolitis</td>
<td>Medical-mucositis</td>
<td>NCA</td>
<td>Fentanyl</td>
<td>Changed from Morphine NCA</td>
<td>Ward</td>
<td>Ap</td>
<td>O₂, BMV Nₓ1</td>
</tr>
<tr>
<td>1 year</td>
<td>6.8</td>
<td>Cardiac</td>
<td>VSD and RVOTO repair</td>
<td>NCA</td>
<td>&lt;1</td>
<td>Codeine</td>
<td>Ward</td>
<td>Ap</td>
<td>Nₓ2</td>
</tr>
<tr>
<td>12 year</td>
<td>25.5</td>
<td>Neurological disorder</td>
<td>Femoral osteotomy</td>
<td>NCA</td>
<td>&lt;1</td>
<td>Caudal clonidine</td>
<td>Ward</td>
<td>RR</td>
<td>Nₓ2</td>
</tr>
<tr>
<td>7 year</td>
<td>15</td>
<td>Cerebral Palsy, Asthma GORD</td>
<td>Fundoplication</td>
<td>Continuous infusion</td>
<td>&lt;1</td>
<td>Codeine charted – not given</td>
<td>Ward</td>
<td>RR</td>
<td>O₂, IS, Nₓ2</td>
</tr>
<tr>
<td>2 month</td>
<td>2</td>
<td>No</td>
<td>Closure of colostomy</td>
<td>NCA</td>
<td>6</td>
<td>No Caudal</td>
<td>Ward</td>
<td>Sats</td>
<td>O₂, BMV IS</td>
</tr>
<tr>
<td>1 day</td>
<td>3</td>
<td>Respiratory disease</td>
<td>Laparotomy and LADD’s procedure</td>
<td>NCA</td>
<td>14</td>
<td>No</td>
<td>HDU</td>
<td>Sats</td>
<td>O₂, BMV</td>
</tr>
</tbody>
</table>

Ap, Apnoea; O₂, Oxygen; BMV, Bag mask ventilation; N, Naloxone; IS, Infusion Stopped; MR, Morphine recommenced.
of PCA-P and PCA groups respectively. More children in the PCA group had minor or ‘threshold events,’ and more children in the PCA-P group had ‘rescue events’ (opioid reversal or escalation of level of care) (3). Members of the Society of Pediatric Anesthesia completed an online national survey in 2007 (4). Respondents recalled 154 patients during the year as having received naloxone for cardiopulmonary side effects of opioids (denominator unknown). In addition, over a 5-year period, at least 18 deaths were considered to be secondary to opioid administration.

One Grade 1 incident in a child with an underlying neurological condition was reported in this audit. It is difficult to determine the extent the morphine infusion contributed to the poor outcome in this case. Underlying comorbidities clearly contribute to the occurrence of Grade 1 and 2 SCIs. This increased risk has also been reported in previous studies (3,5,6).

Twenty-eight Grade 2 SCIs (0.26%) were reported. Half of these were classified as respiratory depression giving an incidence of 0.13%. This figure is considerably lower than the incidence reported in a smaller study were 25% of patients required supplemental O₂ and 1.7% received naloxone for respiratory depression (5). Ten of the fourteen children had associated comorbidities (cerebral palsy, respiratory, cardiac and hematological disease). Only eight of the 14 children required naloxone. This is also a lower naloxone requirement than previously reported by Monitto (4.2%) (5) and Malviya (2.3%) (6). A recent study of 46 patients suggested that low-dose infusion of naloxone could decrease the incidence and severity of opioid-induced side effects with PCA (8). The lower incidence of respiratory depression in our audit may be explained by the fact that all hospitals involved had guidelines in place for the management of opioid infusions in children, all had acute pain services managing the children, and we were only looking for cases of SCIs requiring intervention, therefore minor respiratory depression was not reported.

The association of sedation and respiratory depression with the concurrent use of other sedative drugs has also been documented (5,6,9). Clonidine, fentanyl, and codeine were used in three of the 14 cases of respiratory depression. A limitation of the audit is that the amount of opioid given intraoperatively was not accounted for, and half of the respiratory events are recorded as having happened in the immediate postoperative period. Most of these cases had risk factors for respiratory depression including young age, neurodevelopmental, respiratory or cardiac comorbidities. This suggests that some of these cases were being transferred away from high dependency care too early and that a period of closer monitoring for at least 2 h in such cases is needed. To keep data collection simple, we did not collect data on pain or sedation scores during the opioid infusions. We are therefore not able to relate the events to the pain or sedation scores.

Eleven of the respiratory events were with NCAs, two with CIs, and one with a PCA. The safety of PCA-P (nurse or care giver controlled) has been debated in the literature with studies supporting and questioning their safety (5,7,10). Although the incidents were higher in the NCA group, the overall incidence is still very low. The NCA is generally used in children with a higher prevalence of underlying medical conditions.

In a recent systematic review of morphine treatment in children, the most common side effects were nausea and vomiting, sedation, and pruritis (11). Of the remaining 14 Grade 2 SCIs, five were classified as nausea and vomiting, five as pruritis, and four as urinary retention. The incidence of nausea and vomiting varies from 30% to 46% and pruritis from 8% to 26% (5,12,13), but this audit shows that the incidence of serious clinical events requiring termination of technique is low (approx 0.05% for each). Naloxone was administered in only five cases.

All the Grade 3 incidents (n = 17) were drug errors reported by a single center. This clearly results in skewing of the data. The drug errors were all avoidable by following the recommended institute guidelines for checking prescriptions and pump programs. The Acute Pain Service identified most of the errors in the early postoperative period. This supports the literature regarding improved safety with such a service (14).

Age distribution of the incidences was 0.29% for 1 month < 1 year, 0.41% for 1–8 year, 0.47% for >8 year, and 0.59% for those <1 month. Literature suggests that neonates are not more receptive to respiratory depression with opioids than older children despite pharmacokinetic variability with
age (15,16). Increased half life and decreased clearance in premature and young neonates (15,16) may result in relative cumulative overdosage with infusion techniques.

In conclusion, the audit shows that the incidence of Grade 1 SCIs with opioid infusion techniques in infants and children is low (1 : 10 000). Safety can be improved by the avoidance of concurrent sedatives or opioids by other routes, by being aware of the extra risks posed by comorbidities and by careful dosing and heightened monitoring in infants. Following guidelines for checking opioid prescriptions and programming opioid infusion pumps can minimize drug errors. As a result of this audit, parents can be provided with better information on relative risks to help the informed consent process.

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Expert panel

Dr Peter Crean, Consultant Pediatric Anesthetist, Royal Belfast Hospital for Sick Children; Dr Mary Cunliffe, Consultant Pediatric Anesthetist, Royal Liverpool Children’s Hospital; Dr Ursula Dickson, Consultant Pediatric Anesthetist, Birmingham Children’s Hospital; Sister Noelle Llewellyn, Clinical Nurse Specialist, Birmingham Children’s Hospital; Dr Richard Howard, Consultant Pediatric Anesthetist, Great Ormond Street Hospital; Dr Neil Morton, Consultant Pediatric Anesthetist, Royal Hospital for Sick Children, Glasgow; Dr Peter Stoddart, Consultant Pediatric Anesthetist, Bristol Royal Hospital for Sick Children; Sister Sarah Parry, Clinical Nurse Specialist, Bristol Royal Hospital for Sick Children.

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