Sedation and analgesia in children submitted to mechanical ventilation could be overestimated?

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Abstract

Objective: to describe the pattern of analgesic and sedative infusions in children submitted to mechanical ventilation in a regional pediatric intensive care unit during a 12-month period. To compare the use of these drugs among clinical and surgical patients, as well evaluate the influence of the length of use on the average daily doses and on the incidence of abstinence syndrome.

Methods: this cohort study was performed from April 2001 to March 2002, involving children (1 month old to 15 years old) submitted to the mechanical ventilation through a tracheal tube for a period longer than 12 hours and who were successfully extubated (dead patients and those who required reintubation were excluded from the study). A team of professionals not involved with the patient’s assistance performed a daily collection of all data up to the 28th day under mechanical ventilation (maximum length of follow up for those who remain longer under mechanical ventilation). The main outcome was the infusion doses of morphine, fentanyl, ketamine and midazolam administered at 12 AM (considering this dose as the average dose for that day). The diagnosis of abstinence syndrome was based on the chart revision (recorded diagnosis or based on the specific antagonist treatment used) and in an interview with the assistant physician on the following days after the extubation. This study was approved by the Ethics and Scientific Committee of the HSL-PUCRS.

Results: 127 children were eligible for this study, but only 124 patients were analyzed (16.0 ± 29.5 months old; 58% male; 92 defined as clinical patients and 32 as surgical patients). An average of 1.7 sedative-analgesic infusion per patient a day was used in the whole group (without difference between clinical and surgical groups). Morphine and fentanyl were the most common drugs infused in both groups (fentanyl was preferred for the clinical group and morphine for the surgical group). The mean length of infusion was different (p < 0.01) between clinical and surgical patients (6.8 and 3.9 days, respectively). After the 7th day, there was a significant increase in the fentanyl and midazolam doses (p < 0.01), as well as a higher incidence of abstinence syndrome in the clinical group (p < 0.01).

Conclusions: this study evaluated the daily practice in a regional PICU, and it demonstrated that analgesic and sedative infusions in children submitted to mechanical ventilation are used according to an uncontrolled pattern (average 1.7 drugs/patient/day) and those classified as clinical patients used these drugs for longer periods, what could explain the higher prevalence of abstinence syndrome in this group.

Introduction

During recent years sedation and pain relief have become priorities in the care of critically ill patients. In addition to blocking nociceptive perception, the aim is to satisfy the anxiolytic, hypnotic and amnestic needs of patients in Pediatric Intensive Care Units (PICU). Failure to satisfy these requirements has disastrous effects since untreated pain induces persistent catabolism, activates the sympathetic nervous system, alters cardiovascular demand, and may even trigger intense anxiety and delirium.

The sedative requirements of each patient change constantly, depending on the nature and the course of the disease and on interaction with other treatments. The majority of sedative agents have variable anxiolytic, hypnotic and amnestic actions, but poor analgesic effects. Similar plasma concentration levels of a given sedative can produce distinctly different effects in different patients as a result of factors linked to pharmacodynamics and pharmacokinetics.

Sedatives and analgesics have come to be administered, preferably by means of continuous infusion, to critically ill patients. Among those most often used in PICU are benzodiazepines (midazolam), morphine derivatives (morphine and fentanyl), barbiturates (thiopental) and ketamine.

In general, agents which are employed continuously and for prolonged periods induce tolerance, defined as the need for larger doses in order to achieve the same sedative or analgesic effect. Similarly, patients who are exposed to sedative treatments, whether with opioids or not, may develop neuroadaptation or physiological dependence. Thus, the rapid suspension of these agents can cause withdrawal symptoms which include the dilation of pupils, perspiration, lacrimation, rhinorrhea, piloerection, tachycardia, vomiting, diarrhea, hypertension, fever, tachypnea, psychomotor agitation and anxiety.

There is not yet any consensus on the best sedatives and painkillers to be used in the many different situations which involve critical patients. Studies evaluating the profile of sedative and analgesic use in pediatric ICUs have revealed that the choice varies in accordance with the type of patient to be treated and their pharmacokinetics and pharmacodynamics, previous experience, economic factors, and also local tendencies based on either subjective or undefined criteria. Obviously, as a result of this wide variation, there is also a large divergence between abstinence syndrome incidences at different centers.

The current study was performed with the intention of describing the profile of sedative and pain killer usage with children on mechanical ventilation, interned in a leading pediatric ICU in the South of Brazil, aiming at evaluating the influence that the length of time for which these drugs are used has on the occurrence of abstinence syndrome.

Materials and methods

All children admitted to the pediatric ICU of the Hospital São Lucas at PUCRS (HSL-PUCRS) between 01 April 2001 and 31 March 2002 who underwent mechanical ventilation for more than 12 hours were included in this prospective cohort study. The study was submitted to, and approved by, the Committee for Ethics and Research of HSL-PUCRS.

The inclusion criteria were: (a) age, between 30 days and 15 years; (b) on mechanical ventilation for more than 12hrs; (c) ventilation by means of endotracheal intubation (tracheostomy patients or those on non-invasive ventilation were excluded); (d) successfully extubated from mechanical ventilation (patients who died while on MV or who required re-intubation because of upper airway obstruction or failed extubation were not considered in this study).

A team of four medical students not involved with treatment was specially trained to perform daily, uninterrupted, data collection from all included patients, over a twelve-month period. The following data were collected: (i) identification data; (ii) diagnoses of cause of PICU internment and indications for mechanical ventilation (defined by surgical or clinical complaint); (iii) the dosage being infused at midday of morphine, fentanyl, ketamine and midazolam (this dose being taken as the average for that day of each of these drugs). The continuous infusion dose was recorded as units (mg or µg) per kilogram of weight by time (minutes or hours), in accordance with the reference standards for each medication; (iv) after extubation or the twenty-eighth day of mechanical ventilation, data were only recorded on the date of discharge from the PICU, the date of hospital discharge, clinical status at discharge and the presence or absence of abstinence syndrome. A diagnosis of abstinence syndrome was made based on medical records (a record of this diagnosis or of the administration of therapy for such, for example the prescription of methadone, clonidine and/or benzodiazepines post-extubation, etc.) and on an interview with the each patient’s treating doctor, which was always conducted during the days following extubation. In situations in which there was doubt about abstinence syndrome diagnosis, the case was discussed with the research supervisors (JPP and PCRG) at which point a decision was made.

Any patient who had been successfully extubated, been discharged home and for whatever reason required readmission to the PICU and further mechanical ventilation and sedation was considered, for the purposes of this study to be a new case. Conversely, in the event that any patient who had been extubated and transferred to another unit, but had not been discharged from hospital later returned to the PICU and was submitted to mechanical ventilation, the readmission was not considered in this study.

Once data collection was complete for each patient, the information was entered onto an Excel for Windows spreadsheet (Microsoft Office) which had been specially
programmed for the study. Quantitative data was compared using the Student *t* test, while categorical data was compared with the Chi-squared test and by association tests (Relative Risk), with “p” values less than 5% being designated as of significance.

**Results**

During the twelve-month study period 303 patients were admitted to the PICU at HSL-PUCRS. In 164 cases (54.1%) it was necessary to employ mechanical ventilation for a period of more than 12 hours. Of these, 37 did not meet the pre-defined inclusion criteria (27 because of death while on mechanical ventilation, five because tracheostomy was performed before extubation, three because of upper respiratory obstruction and two due to accidental extubation), leaving, therefore, 127 patients. Data was analyzed from 124 patients (97.6% of those eligible), because in three cases medical records were incomplete or insufficient (2.4% loss).

The average age of the 124 patients was 16.0 ± 29.5 months, with 73 children (58.8%) being male. Mechanical ventilation was indicated in consequence of clinical indication in 92 cases (74.2%) and secondary to surgical procedures in 32 patients (25.8%). Sixty-seven children required ventilation because of pulmonary system dysfunction (asthma, bronchiolitis, pneumonia, etc); 10 because of neurological disturbances (epilepsy, encephalitis, etc); eight because of sepsis or septic shock; and the remaining seven cases were ventilated for a variety of reasons (cardiogenic shock, apnea, upper airway obstruction). Within the group of patients that required mechanical ventilation for surgical reasons, cardiac surgery post-op was the predominant cause (20 cases), followed by general pediatric surgery post-op (nine cases) and neurosurgery post-op (three cases).

During the period in which they were mechanically ventilated, these 124 patients received an average of 1.72 sedative and/or analgesic drugs in continuous daily infusion; without statistical significance (p = 0.2) in the average number of infused drugs between the clinical and surgical groups (1.95 as against 1.28; respectively). It was further observed that 80.4% of the clinical patients and 78.1% of the surgical patients were administered an opioid by continuous infusion (morphine or fentanyl) during the mechanical ventilation period, with morphine being used significantly more frequently in the surgical patients while fentanyl was preferred for the clinical patients (p < 0.01) (Table 1). It is noteworthy that a continuous infusion of midazolam was used in 90% of the clinical cases compared with only 50% of the surgical ones (p < 0.01).

**Table 1 - Pattern of sedatives and analgesics use among clinical and surgical patients who needed mechanical ventilation for longer than 12 hours**

<table>
<thead>
<tr>
<th></th>
<th>Clinical (n = 92)</th>
<th>Surgical (n = 32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (%)</td>
<td>84 (91.3)</td>
<td>16 (50.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fentanyl (%)</td>
<td>70 (76.1)</td>
<td>14 (43.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Morphine (%)</td>
<td>4 (4.3)</td>
<td>11 (34.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ketamine (%)</td>
<td>21 (22.8)</td>
<td>0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The average period over which the drugs were administered was significantly longer (p = 0.002) among the clinical patients (6.8 ± 5.0 days), than among the surgical patients (3.9 ± 3.3 days). However the average doses of sedatives and opioids used in both clinical and surgical patients did not differ significantly (Table 2).

**Table 2 - Comparison of mean doses used in clinical and surgical patients submitted to mechanical ventilation for longer than 12 hours**

<table>
<thead>
<tr>
<th></th>
<th>Clinical patients</th>
<th>Surgical patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose ± SD</td>
<td>Mean dose ± SD</td>
<td></td>
</tr>
<tr>
<td>Midazolam (mg/kg/hora)</td>
<td>0.546 ± 0.3</td>
<td>0.424 ± 0.3</td>
<td>0.172</td>
</tr>
<tr>
<td>Fentanyl (µg/kg/hora)</td>
<td>5.5 ± 3.8</td>
<td>4.87 ± 3.3</td>
<td>0.597</td>
</tr>
<tr>
<td>Morphine (µg/kg/hora)</td>
<td>22.2 ± 17.0</td>
<td>12.86 ± 5.3</td>
<td>0.325</td>
</tr>
<tr>
<td>Ketamine (µg/kg/min)</td>
<td>33.8 ± 9.6</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>
Abstinence syndrome was diagnosed in 46 of the 124 (34.1%) patients studied, with a wide range and varied intensity of symptoms. Otherwise, abstinence syndrome was diagnosed in 45 (49%) of the 92 clinical patients, whose average period of usage was 6.8 ± 5.0 days in contrast to the 32 surgical patients who had used the drugs for an average period of 3.9 ± 3.3 days and only one of whom was diagnosed (p < 0.001). This represents a relative risk of 15.65 (95% CI: 2.25 - 108.96).

When we analyzed the average daily dose of the intravenous sedatives and analgesics as continuously infused, classified into groups banded by duration of usage (up to 3 days, from 3 to 7 days and more than 7 days) we observed that the average doses of midazolam and fentanyl employed after a week’s usage were significantly greater (p < 0.01) than those used during the first seven days (Table 3).

**Discussion**

This study, which evaluates over a one-year period the daily practices involved in the use of intravenous sedative and analgesic continuous infusion in children on mechanical ventilation in an Brazilian University affiliated to a referral ICU we observed that: (a) these drugs are prescribed in a most liberal manner (an average of 1.7 drugs per patient per day); (b) morphine derivatives are used in 80% of these patients, with morphine being preferred for surgical patients while fentanyl is more common for clinical patients; (c) the average sedative and analgesic dosage does not differ between surgical and clinical patients, although clinical patients were administered these drugs for significantly longer periods (6.8 days compared with 3.9 days) and presented a higher incidence of abstinence syndrome (49% as against 3%), which appears to be related more to the period than the condition; (d) after seven days of use, both midazolam and fentanyl required significantly increased infusion dosages.

When this study was conceived and planned, we decided to assess a population made up of patients who required short-term mechanical ventilation with a tracheal tube. We decided to exclude patients ventilated through a tracheostomy because such patients generally present chronic problems and, with a few exceptions, received very low quantities of sedatives which could result in a bias. Similarly, patients requiring reintubation in consequence of failed extubation or accidental extubation have their period of ventilation prolonged with additional quantities of sedatives that would result in a distortion of the data (bias).

One possible criticism of this study is connected to the fact that the doses of other sedatives, such as Chloral hydrate were not recorded. Attack dosages of midazolam, diazepam, thionembutal, morphine, and others were also left unrecorded. It is probable that such additional administrations occurred, which would demonstrate inadequate sedation. However, at our unit, as it occurs in other centers, when frequent intermittent infusions are added for better sedating the patients the infusion dosage is adjusted and increased on the next day. For this reason we decided to measure the midday dose as the reference for the day which made data collection easier and more homogenous.

**Table 3** - Relation between duration of usage of sedatives and analgesics and the mean dose used in patients submitted to mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>&lt; 3 days (A)</th>
<th>3 - 7 days (B)</th>
<th>&gt; 7 days (C)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Midazolam (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td>AxB= 0.355</td>
</tr>
<tr>
<td>Mean + SD (mg/kg/h)</td>
<td>(26)</td>
<td>(40)</td>
<td>(34)</td>
<td>AxC= 0.0004</td>
</tr>
<tr>
<td></td>
<td>0.394 ± 0.288</td>
<td>0.460 ± 0.266</td>
<td>0.707 ± 0.351</td>
<td>BxC= 0.001</td>
</tr>
<tr>
<td><strong>Fentanyl (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td>AxB= 0.528</td>
</tr>
<tr>
<td>Mean + SD (µg/kg/h)</td>
<td>(21)</td>
<td>(34)</td>
<td>(29)</td>
<td>AxC= 0.002</td>
</tr>
<tr>
<td></td>
<td>4.00 ± 2.93</td>
<td>4.51 ± 2.82</td>
<td>7.31 ± 4.25</td>
<td>BxC= 0.004</td>
</tr>
<tr>
<td><strong>Morphine (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td>AxB= 0.466</td>
</tr>
<tr>
<td>Mean + SD (µg/kg/h)</td>
<td>(8)</td>
<td>(4)</td>
<td>(3)</td>
<td>AxC= 0.409</td>
</tr>
<tr>
<td></td>
<td>12.18 ± 3.96</td>
<td>15.50 ± 7.31</td>
<td>23.65 ± 19.15</td>
<td>BxC= 0.544</td>
</tr>
<tr>
<td><strong>Ketamine (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td>AxB= 0.934</td>
</tr>
<tr>
<td>Mean + SD (µg/kg/min)</td>
<td>(3)</td>
<td>(5)</td>
<td>(12)</td>
<td>AxC= 0.666</td>
</tr>
<tr>
<td></td>
<td>36.31 ± 15.01</td>
<td>37.21 ± 12.41</td>
<td>31.89 ± 7.19</td>
<td>BxC= 0.409</td>
</tr>
</tbody>
</table>
Even considering that the drugs and the doses used are in accordance with recommendations proposed in the literature, it is not possible to extrapolate or to consider these findings as representative of all pediatric ICUs in our environment. Obviously, these results reflect the reality at one specific unit and should be analyzed as such. Nevertheless, as there is no standardized practice in the use of these medications, it can be considered that the data presented here may well reflect the practice in a considerable number of units.

In this sample it was observed that fentanyl was the opioid of choice for clinical and surgical patients (76% and 43.8%, respectively), with morphine used in many fewer cases (4% e 34%, respectively). It is known that morphine presents certain disadvantages when compared to fentanyl, such as promoting a greater liberation of histamine (induces bronchospasm) and a higher incidence of hypotension. In contrast, fentanyl appears to induce abstinence syndrome with greater frequency and has a significantly higher cost. Our findings oblige us to question whether opting more often for fentanyl is really due to the clinical limitations and contra-indications of morphine or whether this is merely an expression of treatment practices which are defined randomly or are based on reasons particular to each doctor with no adequately founded motive.

No significant differences were observed between the clinical and surgical patients in terms of average midazolam, opioid and ketamine doses. One fact which attracts attention is that the average doses of infused fentanyl and morphine can be considered light doses; while the average midazolam and ketamine doses are towards the upper limits of recommended dosages. We believe that in our analysis these results merely express a highly consistent preference in the choices made at our unit, but which cannot be analyzed in terms of efficacy or safety.

It appears that there is evidence of a changed level of importance attributed to sedation and pain relief nowadays in comparison with recent times. It appears that their use is now much more liberal, as is demonstrated by this study in which children on mechanical ventilation were given an average of 1.7 analgesic sedatives per day. Despite the obvious advantages (provides pain relief and comfort), of the use of these medications in this situation, there is also a flip side to the coin: its morbid potential. Prolonged and excessive use of these medications can trigger cardiovascular (hypotension and bradycardia), gastrointestinal (ileum), hepatic, neurological and renal alterations. In parallel, certain studies demonstrate that, with adults, the use of sedatives in continuous infusion increases the total time of artificial ventilation, the period of ICU internment and the total hospital stay when compared with patients who are not sedated or who are dosed with bolus.

It has been sufficiently demonstrated that, in addition to these consequences, the liberal and prolonged use of analgesics and sedatives can induce tolerance and abstinence syndrome. Tolerance is the necessity to increase the dose in order to achieve the same clinical effect (loss of sensitivity or receptor exhaustion, induction of increased metabolism and elimination of the pharmaceuticals). Abstinence syndrome refers to a constellation of behavioral autonomic and motor manifestations, (constant crying, perspiration, agitation, tremors, hallucinations, irritability, lacrimation, salivation, masticatory movements, etc) in response to the suspension or reduction of the infusion. Abstinence syndrome has a direct relationship with the total cumulative dose received and, in the majority of cases, requires therapeutic intervention to combat these manifestations.

In the current study it was shown that there was a significant increase in average daily doses of opioids and midazolam after a week’s use. This leads us to assume that the adjustments to the dosage were in response to developed tolerance. This assumption is strengthened when the elevated rates of abstinence syndrome (49%) found among the clinical patients are observed. These patients were administered sedatives by continuous infusion for longer periods (6.8 ± 5.0 days).

In the face of this data it is correct that we ask ourselves if we are not going from one extreme to the other: excessively sedating these children who are undergoing mechanical ventilation? Do we consider our system for evaluating sedation and pain relief to be safe efficient in such cases? There is consensus that the tables currently in vigor for assessing sedation and pain relief are far from a standard which could be considered ideal. As no trustworthy test or marker exists which can reflect the “optimum level” this assessment ends up being based on subjective interpretations made by the medical teams. Therefore, with the instrumentation which we have available to monitor the use of these drugs, the possible risk of “hypertreatment” should not be ruled out.

One further factor to be taken into account relates to the necessity for new pharmaceuticals to be added to the currently available arsenal, with fewer adverse effects, and, primarily, ones which are safe and effective for prolonged use because existing medication, despite being effective over the short term, leaves a lot to be desired in terms of adverse effects when used for longer periods.

For a long time morphine and diazepam were used in this situation, not only because they were the only drugs available, but also because of their low cost. Nevertheless, this situation has been changing: (a) morphine is being progressively substituted by fentanyl, which is an opioid that is one hundred times more potent and that liberates less histamine than morphine; (b) diazepam is being substituted by midazolam, which is a rapid action diazepine with excellent distribution and with greater amnestic power. Allied to these beneficial effects, these medications are much more expensive and induce rapid tolerance (requiring rapid adjustment of dosage and, as a consequence, even greater costs). The option for more expensive derivatives is observed both in this study.
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and in other reports in the literature. References


References

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