Intravenous Magnesium Sulfate for Vaso-occlusive Episodes in Sickle Cell Disease

WHAT’S KNOWN ON THIS SUBJECT: Vaso-occlusive episodes (VOEs) are a common complication of sickle cell disease, resulting in morbidity. Magnesium is a vasodilator and has been shown to improve red blood cell hydration. Previous small studies have suggested that treatment with magnesium may decrease VOEs.

WHAT THIS STUDY ADDS: Intravenous magnesium sulfate is well tolerated in relatively high doses but had no effect on the length of stay in hospital, pain scores, or cumulative analgesia used in children admitted with painful VOEs in sickle cell disease.

abstract

BACKGROUND AND OBJECTIVE: Vaso-occlusive episodes (VOEs) are the most common complication of sickle cell disease in children. Treatment with magnesium seems to improve cellular hydration and may result in reduced vaso-occlusion. This study aimed to determine if intravenous (IV) magnesium sulfate (MgSO4) reduces length of stay (LOS) in hospital, pain scores, and cumulative analgesia when compared with placebo.

METHODS: Randomized, double-blind, placebo-controlled trial in children aged 4 to 18 years requiring admission to hospital with a sickle cell disease VOE requiring IV analgesia. Participating children received IV MgSO4 (100 mg/kg) every 8 hours or placebo in addition to standard therapy. We used a t test or Mann-Whitney test (continuous variables), Fisher’s exact test, or chi-squared test (frequencies). P values were considered significant if <.05, and 95% confidence intervals were calculated for the difference between groups.

RESULTS: One hundred six children were randomly assigned to the study, and 104 were included. Fifty-one (49%) received MgSO4. Children’s mean age was 12.4 years (range: 4–18 years; SD: 3.8 years), and 56 (54%) were females. There was no significant difference in the primary outcome measure, LOS in hospital, with a mean of 132.6 and 117.7 hours in the MgSO4 and placebo groups, respectively (P = .41). There was no significant difference between groups for the secondary outcomes of mean pain scores (4.9 ± 2.6 vs 4.8 ± 2.6, respectively; P = .92) or analgesic requirements (continuous morphine infusion [P = .928], boluses of IV morphine [P = .82], acetaminophen [P = .34], ibuprofen [P = .15], naproxen [P = .10]). Only minor adverse events were recorded in both groups. Pain at the infusion site was more common in the MgSO4 group.

CONCLUSIONS: IV MgSO4 was well tolerated but had no effect on the LOS in hospital, pain scores, or cumulative analgesia use in admitted children with a VOE. Pediatrics 2013;132:e1634–e1641

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KEY WORDS: magnesium, sickle cell disease, vaso-occlusive episode, pain, children, admission

ABBREVIATIONS
ED—emergency department
IV—intravenous
LOS—length of stay
MCHC—mean corpuscular hemoglobin concentration
MgSO4—magnesium sulfate
PCA—patient-controlled analgesia
SCD—sickle cell disease
VOE—vaso-occlusive episode

Dr Goldman conceptualized and designed the study, carried out the initial analyses, designed the data collection instruments, supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Mounstephen and Kirby-Allen participated in study planning and protocol preparation and reviewed and revised the manuscript. Dr Friedman conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Sickle cell disease (SCD) is the most prevalent inherited hematologic disease, with frequent, recurrent episodes of intense pain caused by vaso-occlusion. Vaso-occlusive episodes (VOEs) account for 80% to 90% of emergency department (ED) visits and 60% to 70% of hospitalizations in patients with SCD and result in significant morbidity, chronic organ damage, and an economic burden. Timely analgesia is critical, and despite existence of guidelines advocating aggressive pain management, pain control with opiate analgesics is frequently inadequate and may result in complications such as acute chest crisis. New agents have been tested in the setting of acute VOE without much success.

Magnesium may contribute to vasodilation by an endothelium-dependent release of nitric oxide, and inhibition of calcium in smooth muscle. Magnesium may also decrease vaso-occlusion by slowing clotting time. Finally, magnesium has been shown to improve red blood cell hydration.

A distinguishing feature of SCD is the presence of dense, dehydrated erythrocytes. Red cell dehydration results in increased sickle cell hemoglobin, sickling, and possible VOE. By increasing magnesium, the KCl cotransporter is blocked, thereby inhibiting efflux of potassium and loss of water from the cell. Studies in transgenic sickle mice show that magnesium supplementation results in decreased red blood cell density, mean corpuscular hemoglobin concentration (MCHC), and reticulocyte count.

Among 17 of 20 adult patients with SCD treated in an open-label, unblinded follow-up study, 6 months of oral magnesium pidolate administration resulted in a significant increase in red blood cell potassium and magnesium and a significant decrease \((P < .0025)\) in erythrocyte MCHC, hemoglobin distribution width, and reticulocyte mean cell volume. The median number of painful days in a 6-month period decreased from 15 (range: 0–60 days) in the year before the trial to 1 (range: 0–18 days; \(P < .0005)\) during therapy.

In 1964, a small case series revealed intravenous (IV) magnesium to reduce pain in adults with SCD. More recently, in a single-arm, unblinded study, 19 children admitted with a painful VOE due to SCD received 40 mg/kg IV magnesium sulfate (MgSO\(_4\)), along with IV fluids, opioids, and nonsteroidal anti-inflammatory drugs. A shorter length of stay (LOS) was found: a median LOS of 3 days compared with 5 and 4 days for the previous 2 admissions \((P = .006)\). The only adverse event was asymptomatic hypotension in 1 patient.

Our objective was to determine if IV MgSO\(_4\) treatment when compared with placebo reduces the LOS in the hospital, reduces perceived pain as reported by children, and reduces the total amount of analgesia provided to children with acute VOE.

**METHODS**

Our trial design was a 2-armed randomized, double-blind, placebo-controlled trial. Children arriving at the pediatric ED at The Hospital for Sick Children, Toronto, Canada, with known SCD and symptoms compatible with VOE were managed according to the hospital's clinical practice guidelines (Appendix), including continuous morphine infusion with bolus for breakthrough pain, nonsteroidal antiinflammatory drugs (ketorolac uncommonly), acetaminophen, and patient-controlled analgesia (PCA).

An acute painful VOE was defined as occurrence of pain in the extremities, back, abdomen, or chest that could not be explained except by SCD. Those children aged between 4 and 18 years who required IV therapy and admission were recruited (for inclusion and exclusion criteria, see Table 1). Children were excluded if there was a contraindication to receiving magnesium or if they returned to the ED within 30 days of their last admission.

Families providing consent were randomly assigned by the research pharmacy to receive IV MgSO\(_4\) (100 mg/kg, maximum of 2 g/dose) 8 times hourly or IV placebo (normal saline in a volume equivalent to MgSO\(_4\)) 8 times hourly (Fig 1). We chose 100 mg/kg as the highest safe dose.

The study was approved by the hospital's institutional review board. Consent from families and assent from developmentally appropriate children were provided. A data safety monitoring board, which included 2 physicians at arm's length, reviewed the study after recruitment of 40 patients and at study completion and had no concerns.

**Primary Outcome Measure**

The primary outcome measure was LOS in hospital, measured as number of hospitalization days in a 30-day period decreased from 15 (range: 0–60 days) in the year before the trial to 1 (range: 0–18 days; \(P < .0005)\) during therapy.

**Inclusion and Exclusion Criteria for the MAST Study**

**Inclusion criteria**
- Known SCD (documented on hospital files)
- Previous painful VOE resulting in an ED visit
- Current visit with a chief complaint of pain
- Age 4–18 years
- Attending ED staff decision to admit to the hospital
- Attending ED staff decision to start an IV line

**Exclusion criteria**
- Fever (>38.5°C) during the 24 hours before ED visit
- Transfusion within 90 days of study entry
- Known renal disease
- Known heart block or myocardial damage
- Any regular magnesium supplementation or calcium channel blocker
- Anesthetics, cardiac glycosides, and neuromuscular blockers during the acute illness in the past 24 hours
- Unable to communicate in English
- Known pregnancy
- Known allergy to magnesium
- Admission to the ICU

**Enrollment in the study in the past 30 days**

**TABLE 1**

**Inclusion and Exclusion Criteria for the MAST Study**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>Known allergy to magnesium</td>
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<tr>
<td></td>
<td>Admission to the ICU</td>
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</tbody>
</table>

**MAST**: Magnesium for Sickle Cell Acute Crisis in Children.
hours from the first study dose until the physician’s decision to discharge. This time correlates most closely with the termination of IV analgesia. Physical or administrative discharge time may include bias due to barriers to leaving the hospital, such as lack of transportation.

**Secondary Outcome Measures**

Secondary outcome measures were as follows:

1. mean daily pain intensity, self-reported by using the Faces Pain Scale–Revised, which has been validated for children 4 to 18 years of age, and by visual analog pain scales (0 indicating “no pain” and 10 indicating “very much pain”);
2. cumulative analgesic dose required during admission, measured as milligrams or micrograms per kilogram of body weight per hour while enrolled in the study; and
3. adverse events, such as changes in vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation), appearance of a rash, allergic reactions, diarrhea, fever, nausea, vomiting, and pain at the infusion site.

**Monitoring**

Cardiorespiratory, oximeter, and blood pressure monitors were used. During study drug administration, vital signs were monitored every 15 minutes by a pediatric nurse. The infusion was required to be stopped immediately with any blood pressure change $\geq 20$ mm Hg or in the presence of a rash or an
 Secondary outcomes were as follows:

Secondary Outcomes

Secondary outcomes were as follows:

1. Pain score: median pain scores were calculated on the basis of all pain measurements for each child over the course of hospitalization. Student’s t test was used to compare mean and median pain scores between groups.

2. Cumulative drug use: the cumulative dose of each analgesic drug was calculated as the total number of milligrams or micrograms. We report the number of milligrams or micrograms per kilogram of body weight per hour of stay. A 2-sample, 2-sided t test was used to compare the mean between the 2 treatment groups.

3. Adverse events. We report the incidence of all anticipated and unanticipated adverse events.

RESULTS

Baseline Characteristics

A total of 159 children were approached for the study, 106 (67%) of whom consented. Two children (2%) withdrew from the study because of withdrawal of consent. A total of 88 unique patients who had 104 episodes in which they were recruited to the study: 51 (49%) in the MgSO₄ group and 53 in the placebo group.

Population demographic characteristics are shown in Table 2. Patients’ mean age was 12.4 years (median: 12.9 years; range: 4–18 years; SD: 3.8 years) and was similar in both groups (P = .80). Fifty-six (54%) patients were male. Sixty-one (58.6%) had homozygous sickle cell anemia, 33 (31.7%) had sickle hemoglobin C disease, and 10 (9.6%) had sickle β thalassemia.

Pain started a median of 24 hours before arrival (range: 4–240 hours; SD: 72.8 hours). Elapsed time from the last visit to the ED until study admission was a mean of 7.3 and 8.7 months in the MgSO₄ and placebo groups, respectively (P = .477).

The most frequent sites involved were the back (n = 42; 40%), lower limbs (n = 41; 39%), chest (n = 32; 31%), and upper limbs (n = 31; 30%). There was no significant difference between the groups.

Table 3 shows the mean and median LOS for each child over the course of hospitalization. Student’s t test was used to compare mean and median LOS from 5 to 4 days.

Data Analyses

Primary Outcome: LOS

A 2-sided Fisher’s exact test was used to compare the 2 treatment groups with respect to the proportion achieving the primary outcome of reduction in LOS.

Sample Size

The sample size was calculated on the basis of the primary outcome of LOS in the hospital. A group of experienced pediatric emergency medicine specialists, pediatric hospitalists, and hematologists agreed that a 1-day reduction in the LOS would justify the use of MgSO₄, even in the case of some non-life-threatening side effects. Based on a review of 50 charts, the mean LOS for a VOE was 5 days (SD: 2 days). A sample size of 63 patients per arm was determined to provide 80% probability of achieving statistical significance at the 0.05 level (2-sided). If IV MgSO₄ reduced LOS from 5 to 4 days.

Blinding and Randomization

Investigators, physicians, nurses, parents, and patients were blinded to the treatment arm. Study drug and placebo looked exactly the same (volume and appearance). Randomization and dispensing were conducted by the research pharmacy using a preset randomization table (blocks of 4).

Outcomes

LOS in hospital, which was the primary outcome measure, was a mean of 125 hours (SD: 90.8 hours; range: 6–536 hours) (Table 3). There was no significant difference between MgSO₄ and placebo groups: 132.6 ± 106.6 hours and 117.9 ± 72.8 hours, respectively (P = .41).

Secondary outcome measures included the following:

1. Pain score: median pain scores were similar between groups (5.4 ± 2.5 and 5.3 ± 2.3 respectively; P = .80).

2. Cumulative drug dose: with regard to analgesia provided to all patients,
children in the control group, respectively \(P = .03\).

The study cohort received acetaminophen at a mean 1.2 mg/kg per hour. The mean cumulative dose was 1.4 \(\pm\) 1.3 versus 1.1 \(\pm\) 1.0 mg/kg per hour for their LOS \(P = .34\). The study cohort was provided with a mean of 0.8 mg/kg of ibuprofen per hour. The mean cumulative dose was 0.9 \(\pm\) 1.1 versus 0.6 \(\pm\) 0.5 mg/kg per hour for their LOS \(P = .15\). The study cohort received a mean of 0.3 mg/kg of naproxen per hour. The mean cumulative dose was 0.5 \(\pm\) 0.3 versus 0.2 \(\pm\) 0.1 mg/kg per hour for their LOS \(P = .10\).

The most common adverse event was pain at the infusion site (9 patients \(8.6\%\): 7 in the MgSO4 group \(14\%\) and 2 in the placebo group \(4\%\)). Nausea and vomiting were recorded in 4 (3.8\%) patients and transient hypotension in 2 (2\%) patients, with an equal number in each group. Pruritus, tachycardia, and drowsiness were reported in 1 patient each (see Table 4).

### DISCUSSION

This is the first randomized clinical trial, to our knowledge, to evaluate the use of IV MgSO4 for acute VOE in children with SCD. We found no significant difference between MgSO4 and placebo in LOS in hospital, self-reported pain scores, or in cumulative total analgesia given (with the exception of hydromorphone, which was used in a small subset of the cohort). Although well tolerated, IV MgSO4 did not seem to reduce pain more than placebo.

The cohort in our study is representative of the population of children with SCD in our center and was similar at baseline in both groups. Most of them came to the ED after \(\sim\)1 day of pain at home, and the majority visited our hospital at least once in the year before the visit during which they were recruited. Only 6 patients were recruited twice, and in these patients more than a month had passed between visits. Pain was reported in different body parts without any significant difference between the groups.

Our finding of an average LOS of \(\sim\)5 days (125 hours) is comparable to the LOS for this patient group in our facility before the study commenced, similar to a previous report by our group.25 It is just slightly longer than the average LOS for this condition in a large US database using data from 2500 hospitals in the Healthcare Cost and Utilization Project (4.4 days).26

Analgesia is the mainstay of treatment of children with painful VOEs. We found that the average dose of continuous morphine infusion was \(\sim\)28 \(\mu\)g/kg per hour while in hospital in both groups.

### TABLE 3 Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>MgSO4</th>
<th>Placebo</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome measure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LOS in the hospital, mean (\pm) SD, h</td>
<td>51 (132.8 \pm 106.6)</td>
<td>55 (117.9 \pm 72.8)</td>
<td>(-20.85) to 50.11</td>
</tr>
<tr>
<td>Secondary outcome measure: pain, mean (\pm) SD score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pain throughout admission</td>
<td>51 (5.4 \pm 2.5)</td>
<td>53 (5.5 \pm 2.3)</td>
<td>(-0.88) to 1.02</td>
</tr>
<tr>
<td>Median pain throughout admission</td>
<td>51 (4.5 \pm 3.1)</td>
<td>53 (4.6 \pm 3.2)</td>
<td>(-)</td>
</tr>
<tr>
<td>Secondary outcome measure: analgesia, mean (\pm) SD, (\mu)g/kg per hour of stay</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Morphine infusion (N = 88)</td>
<td>47 (28.2 \pm 10.9)</td>
<td>51 (28.4 \pm 8.8)</td>
<td>(-4.13) to 3.77</td>
</tr>
<tr>
<td>Morphine boluses (N = 88)</td>
<td>43 (1.6 \pm 1.3)</td>
<td>45 (1.6 \pm 1.3)</td>
<td>(-0.63) to 0.50</td>
</tr>
<tr>
<td>IV hydromorphone (N = 17)</td>
<td>7 (1.4 \pm 0.7)</td>
<td>10 (6.6 \pm 6.3)</td>
<td>(-9.69) to (-0.69)</td>
</tr>
<tr>
<td>Acetaminophen (N = 83)</td>
<td>41 (1.4 \pm 1.3)</td>
<td>42 (1.1 \pm 1.0)</td>
<td>(-0.26) to 0.74</td>
</tr>
<tr>
<td>Ibuprofen (N = 77)</td>
<td>43 (0.9 \pm 1.1)</td>
<td>34 (0.6 \pm 0.5)</td>
<td>(-0.10) to 0.66</td>
</tr>
<tr>
<td>Naproxen (N = 11)</td>
<td>5 (0.5 \pm 0.3)</td>
<td>6 (0.2 \pm 0.1)</td>
<td>(-0.02) to 0.59</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>11 (22)</td>
<td>—</td>
<td>7 (13)</td>
</tr>
</tbody>
</table>
This is a relatively low dose compared with the current recommended dose in our hospital (10–100 μg/kg per hour). This finding may be due to prolonged periods of titration of analgesia (during initiation and gradual titration upward, or tapering of morphine infusion before discontinuation of the drug) or may reflect underdosing of analgesia for this patient population. Reasons for underdosing are not clear from this particular study, but this finding concurs with other published work from our hospital, which concluded that pain may not be adequately treated at this time. Furthermore, during the study period, there was relatively little use of medications such as ketorolac or analgesia administration using PCA devices. This finding reflects the practice at our particular institution.

Our results regarding the lack of effect of IV MgSO4 versus placebo differ from those of Brousseau et al, which may be due to the different study design. Brousseau et al conducted an open-arm, unblinded study and compared LOS with a historic cohort of admissions for the same patient. It is possible that differences in patient population and previous admissions for more severe VAE may have been the basis for their reduced LOS findings. In addition, there may have been additional confounding factors that changed over time.

There could be several further hypotheses as to why we did not see an effect with the use of IV MgSO4. It is possible that the identified in vitro effect of magnesium on red blood cell hydration did not occur in vivo during a VAE. We postulate that during a VAE it may be “too late” for magnesium to improve hydration. Brousseau et al found similar MCHC and cellular adhesion in children with VAE despite treatment with magnesium and interpreted these findings to suggest that the action of magnesium may not be simply related to hydration of red blood cells. Studies assessing prophylactic treatment with oral magnesium supplementation found promising results in adult patients with reduced frequency of VAE and with minimal toxicity. It is unclear if the same positive results would be found if magnesium was used prophylactically or earlier in the course of the evolving VAE in children.

It is possible that LOS may not be the best primary outcome measure. We measured LOS to reflect the time from starting the study drug until the child had recovered to the point at which the responsible physician elected to discontinue the IV analgesia in the hope of minimizing confounding psychosocial factors involved with the actual discharge process. Nevertheless, the decision to decrease IV analgesia is at least partly determined by factors that are harder to capture, such as social and environmental issues. One randomized controlled trial revealed that inhaled nitric oxide in patients with VAE did not reduce the LOS of hospitalization.

It is possible that magnesium will still be effective for a subset of children with VAE. In the past, 2 studies have revealed decreased magnesium levels in the plasma and erythrocytes of SCD patients. In the first, a negative correlation (r = −0.2661, P < .02) was documented between erythrocyte magnesium and plasma magnesium in adults with SCD but not in healthy individuals or those with sickle cell trait. In the second, adults had significantly lower levels of plasma magnesium compared with healthy African Americans and whites. It may be that specific groups of children with SCD may benefit from magnesium more than others, and magnesium levels should be assessed in future research in this area.

An important finding that should be of interest to a wide range of individuals studying the role of therapeutic IV magnesium for various childhood conditions is that the relatively high dose of IV MgSO4 (100 mg/kg every 8 hours) that we used was well tolerated. Only 18 adverse events were recorded, all minor in nature, and only 1 patient in the study group had hypotension that resolved after 10 minutes of withholding the infusion. As expected, pain at the IV site was more frequent in the study group compared with the control group (14% vs 4%, respectively). The limited adverse event findings are reassuring, and future use of this dose could be considered both clinically and in studies looking at the use of IV MgSO4 for various clinical applications in children in this age group. Monitoring of patients receiving IV magnesium is still strongly recommended because this study was not powered to determine safety.

Our study has several strengths. This is the first randomized controlled trial looking at administration of IV magnesium for VAEs in children with SCD. We ensured a robust methodology and used multiple outcomes to explore the potential benefits of magnesium. We feel that the administered dose of magnesium should have been adequate to show benefit, because we used a higher dose than that generally used in previous studies and for other indications such as asthma.

Future research may be needed to determine if there is any effect of magnesium delivered orally in a more prophylactic manner or IV MgSO4 potentially being tested in more specific subpopulations of children with SCD.

Our study has several limitations. It was conducted in only 1 center. However, this allowed us to ensure close adherence to our SCD management protocol and reduce bias between study groups. Also, our a priori sample size called for a total of 126 patients, and we eventually closed the study for recruitment with only 104 children having completed the study because the principal investigator
moved to another hospital, making it logistically difficult to continue further recruitment. Thus, we may have been underpowered to find small differences in LOS, although given the similar results in the 2 groups, it seems unlikely that an additional 22 patients would have led to substantial changes in our findings.

We also did not account for the use of analgesia at home before admission nor for the use of hydroxyurea because these data were not collected, although use of these medications should have applied to both groups equally.

**CONCLUSIONS**

IV MgSO₄ was well tolerated but had no effect on the LOS in hospital, pain scores, or total cumulative analgesia used in admitted children with SCD and painful VOEs.

**APPENDIX**

Following is an abbreviated version of routine protocol for management of acute painful VOEs in SCD patients at The Hospital for Sick Children at the time of the study (note: oral codeine was replaced by oral morphine shortly after study completion).

**In the ED**

Start an IV if the child is febrile, dehydrated, or in moderate or severe pain.

Encourage the patient to drink.

Mild to moderate pain:
- Acetaminophen (15 mg/kg) with codeine (1 mg/kg), every 4 hours
- Ibuprofen (5–10 mg/kg), every 6 to 8 hours

Moderate to severe pain:
- IV bolus morphine (0.1–0.15 mg/kg), can repeat in 1 hour

Severe pain:
- Morphine continuous IV infusion (40 μg/kg per hour)
- Additional boluses of morphine (0.05 mg/kg) can be given every 1 to 2 hours

In all patients with moderate or severe pain: IV fluids with bolus (10 mL/kg) of 0.9 NaCl and then 1.5 times the calculated maintenance fluids, using fluid solution of Dextrose 5% with 0.45 NaCl.

**Inpatient Management**

Continuous cardiac and oxygen saturation monitoring, vital signs every 4 hours, monitor fluid intake and output and daily weight.

Assess comfort level every 4 hours with a consistent pain tool.

Continue IV/oral fluids for a total fluid volume of 1.5 times maintenance requirements.

**Medications:**
- IV morphine continuous infusion at 40 μg/kg per hour
- Titrate the dose by 10 to 20 μg/kg per hour every 8 hours to a maximum of 100 μg/kg per hour
- IV bolus morphine (0.05 mg/kg) every 1 to 2 hours as required for breakthrough pain
- Consider use of a PCA pump in children >6 years old
- An equivalent dose of long-acting oral morphine may be used as an alternative to continuous IV morphine when stable
- Step-down therapy: when patient is comfortable, start reducing morphine infusion gradually and switch to oral analgesia when dose is down to 10 μg/kg per hour
- Acetaminophen (15 mg/kg) with codeine (1 mg/kg) every 4 hours; ibuprofen may also be helpful

**ACKNOWLEDGMENTS**

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