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Efficacy and safety of inhaled low-dose methoxyflurane for acute paediatric pain: A systematic review

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Abstract

Introduction: Undertreatment of acute, moderate-to-severe pain in children is common, due in part to barriers to the use of opioids. Low-dose methoxyflurane is an inhaled, non-opioid analgesic widely used in Australia and recently approved in Europe for the emergency relief of acute moderate-to-severe trauma pain in adults.

Methods: Using an integrative review framework, we conducted a literature analysis to examine the potential utility of methoxyflurane in children with acute pain. EMBASE®, MEDLINE® and PubMed were searched (criteria included 'methoxyflurane' 'child*' or 'adolescent' or 'pediatr*' or 'paediatr*') from January 2000 to October 2017, along with internet-based sources to identify relevant grey literature (no predefined search criteria). A series of investigative questions were developed regarding the safety and efficacy of methoxyflurane in this setting and addressed using evidence collated from the identified studies.

Results: Of 366 results from the literature searches, 6 clinical trials and observational studies were identified which explored the safety and/or efficacy of inhaled methoxyflurane in individuals < 18 years in either a clinical trial or observational study. All six studies concluded that methoxyflurane provides effective and rapid analgesia for paediatric acute moderate-to-severe pain. Methoxyflurane was well tolerated and associated with good levels of patient/healthcare provider satisfaction in this setting.

Conclusions: While large-scale studies are needed to better inform treatment approaches for paediatric use, inhaled methoxyflurane has potential to provide easy to administer, needle-free analgesia with a rapid onset and good safety profile.

Keywords

Acute pain, analgesia, adolescents, children, methoxyflurane, paediatric

Introduction

Despite pain being a key research priority in paediatric emergency care,[1,2] oligoanalgesia is frequently reported. Studies of children with severe trauma-related pain reveal that fewer than half receive analgesia from paramedics,[3–5] or within 1 h of arriving at the emergency department (ED).[6] Many children undergoing painful hospital procedures receive no analgesia, and younger children receive disproportionately less analgesia than school-age counterparts.[3–6] Undertreatment of paediatric pain can have long-term detrimental sequelae including emotional trauma, and alterations to sensory and pain processing pathways, which can diminish the effects of future analgesia.[7–9] Healthcare providers face numerous barriers when addressing acute moderate-to-severe pain in children, including difficulties in accurate pain assessment, treatment knowledge gaps, time constraints and perceived low priority for analgesia.[10–12] Insufficient data and limited

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pain guidelines further complicate effective pain management.[13–15] Opioids provide effective, rapid relief of severe acute pain; however, fewer than 18% of eligible children receive prehospital opioid-based analgesia.[3,16] This may reflect concerns regarding opioid-related side effects as well as the challenges of administering intravenous (IV) medication to distressed children.[10,11] Inhaled or intranasal (IN) analgesics can provide timely relief of pain without the discomfort of IV placement or delay while local anaesthetic creams take effect.

Methoxyflurane is a non-opioid, volatile fluorinated hydrocarbon, initially used for general anaesthesia. Its use was discontinued due to reports of renal toxicity associated with high anaesthetic doses;[17,18] however, administration of methoxyflurane for short periods at sub-anaesthetic concentrations provides rapid analgesia and is not associated with nephrotoxicity.[18–20] Low-dose methoxyflurane has been licensed for over 40 years in Australia to provide short-term relief of acute pain in adults and children and was recently approved in Europe for emergency relief of moderate-to-severe trauma-associated pain in conscious adults.[21–23] Methoxyflurane is self-administered via a hand-held, whistle-like inhaler; patients can titrate the minimum effective dose to relieve their pain, up to a maximum dose of two 3 mL vials (maximum weekly dose of 15 mL).[23]

Given the unmet analgesic needs for some children with acute pain, the aim of this review was to examine the potential utility of inhaled methoxyflurane in this setting. We conducted a qualitative analysis of published clinical trials and observational studies investigating the efficacy and safety of methoxyflurane in children and adolescents with moderate-to-severe acute pain.

Methods

Prior to conducting this systematic review, the authors agreed the objectives of the literature analysis, information sources and search criteria, as well as the eligibility criteria for selected studies (the review protocol was not formally registered). A search of English language publications from January 2000 to October 10 2017 was conducted in EMBASE® and MEDLINE®. Search criteria were 'methoxyflurane' AND ('child*' or 'adolescent' or 'pediatr*' or 'paediatr*'). PubMed was also searched using these terms to capture publications that may not be indexed in EMBASE® and MEDLINE®.

An additional search of internet-based sources was conducted (January 2000 to October 10 2017) to identify relevant grey literature, using the following databases without predefined search criteria: Grey Literature Report (http://www.greylit.org/home), National Research Council Canada (http://cat.cisticicist.nrc-cnrc.gc.ca/search/X), NLM Gateway (https://gateway.nlm.nih.gov/), Open Grey (http://www.opengrey.eu/), ProQuest 'Dissertations and Theses Professional' and 'Newsstand Professional' (http://www.proquest.com/). The authors also requested congress abstracts reporting methoxyflurane in paediatric patients from Mundipharma, which has the product rights for methoxyflurane in France and Belgium.

An integrative review framework was used to allow evaluation of heterogeneous studies.[24] To warrant inclusion in this analysis, the papers had to report the safety (adverse events) and/or efficacy (change in pain scores, rate of analgesic failure, use of rescue medication, and/or patient/healthcare provider satisfaction with treatment) of inhaled methoxyflurane in individuals <18 years in either a clinical trial or observational study (single-agent and comparator studies were permitted). Studies investigating methoxyflurane in adult-only populations were excluded. The exclusion/selection process for the studies identified in the literature searches is detailed in Figure 1. Publication titles and abstracts were tabulated and screened; all authors reviewed the selection of the screened papers and were involved in their appraisal. Reported data were assessed qualitatively. A series of investigative questions were developed and addressed using evidence collated from the identified studies.

Results

Of the 366 results from the literature searches, 6 studies met the inclusion criteria for this analysis. Study design, key outcomes and authors' conclusions for the selected studies are summarized in Table 1. Evidence is presented in terms of the study questions investigated.

Is inhaled methoxyflurane effective in children with moderate-to-severe acute pain?

All included studies concluded that methoxyflurane was efficacious for paediatric acute pain (Table 1). A pilot randomised controlled trial (RCT) of 41 children >5 years with upper limb fracture reported a clinically significant 2.7-point greater reduction in pain (0–10 point scale) at 10 min with methoxyflurane versus placebo ($p<0.05$).[28] An observational case series study of 105 children (median age of 11 years) receiving methoxyflurane during ambulance transfer showed the mean (95% CI) pain score (7.9 (7.5–8.3)) falling to 3.2 (2.8–3.7) after 10 min.[26] A second, smaller observational ED case series study showed methoxyflurane to be useful as a self-titrated analgesic in 14 children (6 to 13 years) undergoing brief, painful procedures.[25] Two ED studies included both adults

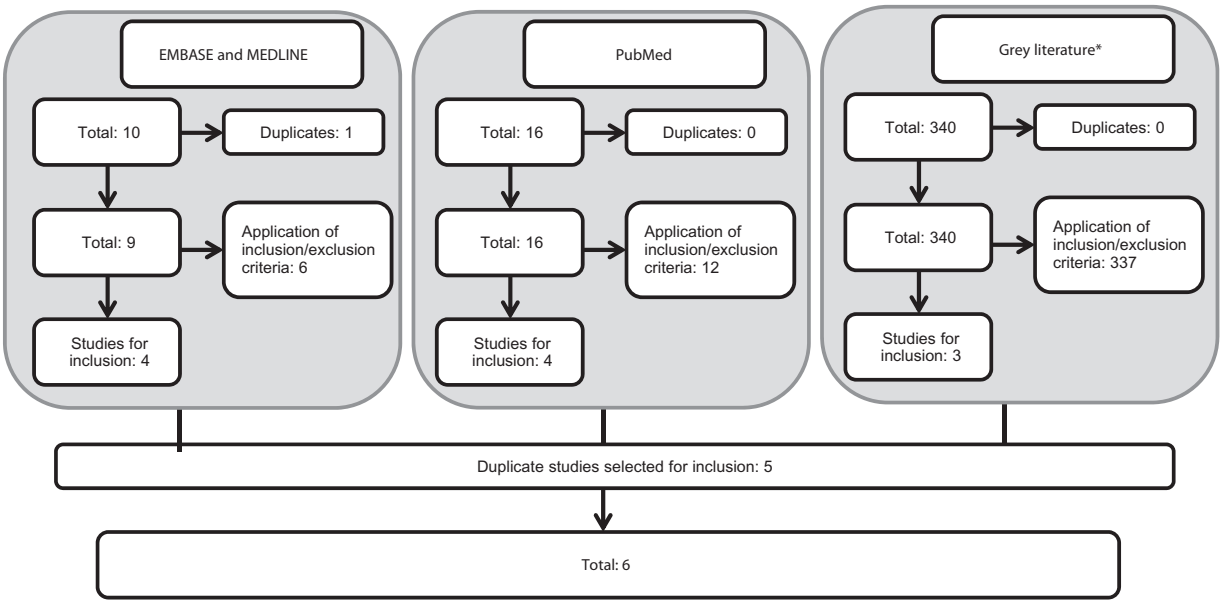

Figure 1. Flowchart of the literature searches and selection criteria. *Search of internet-based sources: Grey literature report (http://www.greylit.org/home), National Research Council Canada (http://cat.cisti-icist.nrc-cnrc.gc.ca/search/X), NLM Gateway (https://gateway.nlm.nih.gov/), Open Grey (http://www.opengrey.eu/), ProQuest 'Dissertations and Theses Professional' and 'Newsstand Professional' (http://www.proquest.com/). Congress abstracts reporting methoxyflurane in paediatric patients were requested from Mundipharma.

and children/adolescents with trauma pain:[29,30] an RCT including 90 adolescents (12 to 17 years) among the 300 participants reported significantly greater improvements in pain with methoxyflurane versus placebo at time points from 5 to 20 min ($p < 0.0001$),[29] and in an observational case series of 59 adults and children (>3 years), pain scores also improved after 15 and 30 min.[30]

What is the time of onset of inhaled methoxyflurane in children with moderate-to-severe acute pain, and how common is treatment failure?

Most studies reported clinically significant improvement in pain scores at the first assessment time point, which ranged from 2–5 min to 15 min.[25,26,28–30] In the RCT of adults and adolescents, median onset of pain relief was 4 min with methoxyflurane compared with 10 min with placebo,[29] while in a paediatric case series, the onset was anecdotally reported to be less than 30 s.[25]

The rate of analgesic failure with methoxyflurane for paediatric acute pain is acceptable; in the observational case study of 14 children described above, analgesia was considered adequate in 71%,[25] while in the adults and adolescents placebo-controlled study, 87% of patients receiving methoxyflurane experienced pain relief.[29] Effective analgesia (≥30% reduction in baseline pain) was also reported in 78% of children >3 years with acute pain treated with methoxyflurane by paramedics ($n = 2093$).[27]

The use of rescue medication may also provide some indication of treatment failure rates. In the observational prehospital case series of 105 children, 9.5% received IV morphine in addition to methoxyflurane.[26] However, in an RCT of adults and adolescents, only 1% treated with methoxyflurane received rescue analgesic medication compared with 17% who received placebo.[29]

How satisfied are patients and healthcare providers with methoxyflurane as a treatment for moderate-to-severe acute paediatric pain?

Available evidence suggests that patients and healthcare providers are satisfied with inhaled methoxyflurane as a treatment for acute pain in children (Table 1). In the case series of 105 children receiving methoxyflurane during ambulance transfer, 89% of paramedics and 87% of patients were satisfied or very satisfied with the analgesia received, and 97% of parents and older patients indicated they would use methoxyflurane again (Table 1).[26] In a case series of 14 children requiring procedural or bridging analgesia at hospital, 93% said they would use methoxyflurane again, with the greatest treatment satisfaction reported in individuals with highest initial pain scores.[25] Of the two studies which included both children and adults with trauma

Table 1. Summary of clinical trials and observational studies investigating methoxyflurane for acute paediatric pain.

Authors	Study population	Trial design and methoxyflurane dose	Key efficacy outcomes	Key safety outcomes	Authors' conclusions
Babl et al.[25]	14 children (6–13 years) requiring procedural or bridging analgesia (upper extremity fracture 71%)	Observational case series 1 × 3 mL inhaled dose (0.4–3.1 g per patient)	Onset of analgesia: 2–5 min (anecdotally <30 s) Adequate analgesia in 71% 93% would use methoxyflurane again All five patients with high initial pain scores (≥6) reported large drops in pain[a] These patients, HCPs and parents were satisfied/very satisfied with analgesia Patients with low initial pain scores were less satisfied with analgesia	No SAEs No patients were deeply sedated Mild, self-resolving AEs: cough (n = 2), agitation, euphoria, blurred vision, dizziness (n = 1, each)	Methoxyflurane appears to be efficacious and have a good AE profile Coaching for inhaler use is important
Babl et al.[26]	105 children (15 months to 17 years; median age 11 years) treated by paramedics (extremity injury: 82%)	Observational case series 1 × 3 mL inhaled dose: 91% 2 × 3 mL inhaled dose: 9%	Mean (95% CI) baseline pain score 7.9 (7.5–8.3) fell to 4.5 (3.9–5.0) at 2–5 min and 3.2 (2.8–3.7) at 10 min[b] 'Satisfied' or 'very satisfied' with analgesia: 89% of paramedics, 87% of patients, 92% of parents 97% of patients would use methoxyflurane again	No SAEs No patients required interventions Common minor AEs: drowsiness (26%), hallucinations/disinhibitions (7%) Deep sedation: patients <5 years, 33%; patients ≥5 years, 8%	Methoxyflurane appears to be efficacious and have a good AE profile May lead to deep sedation in young children
Bendall et al.[27]	3312 children (5–15 years) with moderate-to-severe acute pain treated by paramedics	Retrospective, comparative study of IV morphine, IN fentanyl and methoxyflurane Methoxyflurane: 3 mL inhaled dose (morphine and, fentanyl dosed according to body weight and age, respectively)	Methoxyflurane provided effective analgesia[c] for 78.3% (morphine 87.5%; fentanyl 89.5%) Methoxyflurane was less effective than morphine (OR (95% CI) 0.5 (0.4–0.7)) and fentanyl (0.4 (0.3–0.6)), $p < 0.0001$ No clinical or statistical difference in efficacy between morphine and fentanyl Therapy with >1 agent did not provide better analgesia than morphine or fentanyl alone	NR	Methoxyflurane is an effective analgesic for most children (less effective than morphine or fentanyl)
Chin et al.[28]	41 children (>5 years) with upper limb fracture	Pilot randomized, double-blind placebo-controlled trial Inhaled dose NR	2.7 point (4.0 vs. 1.3) greater reduction in pain score at 10 min with methoxyflurane vs. placebo ($p<0.05$)[d]	NR	Methoxyflurane is effective for acute pain relief in children with upper limb fractures

(continued)

Table 1. Continued.

Authors	Study population	Trial design and methoxyflurane dose	Key efficacy outcomes	Key safety outcomes	Authors' conclusions
Coffey et al.[29]	300 patients, including 90 adolescents (12–17 years) with trauma pain treated at a hospital ED	Double-blind, randomized, placebo-controlled trial 3 mL inhaled dose (second dose if requested)	Methoxyflurane vs. placebo: Greater reduction in baseline pain[e] at 5, 10, 15 and 20 min ($p<0.0001$) Median time to onset of pain relief: 4 vs. 10 min Pain relief in 1–10 inhalations: 85% vs. 51% Rescue medication use: 17% vs. 1% $p=0.0002$ Greatest treatment effect observed at 15 min Patients, physicians and nurses rated global medical performance with methoxyflurane better than placebo ($p<0.0001$)	TEAEs (59% vs. 41%) and drug-related AEs (36% vs. 13%) were more frequent with methoxyflurane vs. placebo One SAE reported with methoxyflurane (lower respiratory tract infection) was not considered treatment related	Methoxyflurane is an effective, safe and rapidly acting analgesic While AEs were more common with methoxyflurane, they were mild and transient
Gilis et al.[30]	59 adults and children (>3 years) with trauma pain presenting at hospital ED	Observational case series Inhaled dose NR	Baseline pain (7.6 ± 1.7) significantly improved after 15 min (5.3 ± 2.1) and 30 min (4.3 ± 2.3) Average appreciation score was 2.5 ± 1.1[f]	Most frequent AEs were funny/high feeling (15%), cough (7%) and bad taste/smell (3%)	Methoxyflurane, as an in-hospital analgesic, significantly reduced pain No significant AEs Most patients and nurses were satisfied and would use methoxyflurane again

AE: adverse event; CI: confidence interval; ED: emergency department; IN: intranasal; IV: intravenous; NR: not reported; OR: odds ratio; TEAE: treatment-emergent adverse event; SAE: serious adverse event.

[a]Pain assessed using a visual analogue scale or Bieri Faces Pain Scale (0 (no pain) – 10 (worst pain)).

[b]Paramedic-assessed pain scale (0 (no pain) to 10 (worst pain)).

[c]Reduction in pain score ≥30%, assessed on an 11-point verbal numerical rating scale.

[d]Pain assessed using Faces Pain Scale (0 (no pain) to 10 (worst pain)).

[e]Pain assessed using a visual analogue scale.

[f]1 = negative to 4 = excellent.

pain, an average appreciation score of 2.5 (4-point scale; 2 = neutral, 3 = good) was reported in the case series that included children >3 years, and in the RCT including adolescents, methoxyflurane provided better global medication performance than placebo ($p < 0.0001$).[29,30]

What is the side effect profile of methoxyflurane in the paediatric setting, and is nephrotoxicity an issue?

Methoxyflurane appears to be well tolerated by children (Table 1). Within the identified safety studies, only one serious adverse event was recorded (lower respiratory tract infection requiring hospital admission) and this was not considered related to methoxyflurane.[29] Adverse events were more common with methoxyflurane than placebo (59% vs. 41%), but were generally mild and transient, including cough and CNS effects such as dizziness, drowsiness, euphoria, disinhibition or hallucinations.[25,26,30] In most children (88%), the lowest sedation score ranged from 'anxious, agitated or in pain' to 'drowsy but easily aroused to consciousness with verbal stimuli'.[26] Deeper sedation was more common in children <5 years (33%) compared with individuals >5 years (8%), and all deeply sedated patients regained full consciousness without intervention within minutes of ceasing methoxyflurane use.[26] There were no reports of requirement for intervention, including airway support, and no episodes of hypoxia.[25,26] It is also noteworthy that there were no reported signs of liver or renal toxicity with low-dose methoxyflurane.

Discussion

Non-opioid analgesics, which are easy to administer and have a rapid onset, may help to improve the management of acute moderate-to-severe pain in children. Our literature search identified six studies specifically investigating methoxyflurane analgesia in children/adolescents. Methoxyflurane provided effective pain relief, and most patients and their healthcare providers expressed a high level of treatment satisfaction.[25–30] Based on the design of the studies, it was not possible to ascertain the exact time of onset of analgesia; however, where reported, pain relief occurred from the first assessment time point (2 to 15 min after inhalation).[25,26,28–30] This timing is consistent with a rapid onset of action occurring after 6–10 inhalations,[23] reflecting findings from studies conducted in adults with moderate-to-severe acute trauma or procedural pain.[22,31]

Deep sedation was observed in some children receiving methoxyflurane but was brief and self-limiting.[26] The side effects reported were all non-serious and reflect known cautions in the product label, including cough and CNS-type reactions such as drowsiness and euphoria resolving soon after cessation of therapy.[23]

Nephrotoxicity has been reported with substantially higher doses of methoxyflurane previously used for anaesthesia.[17] Release of fluoride ions has been linked with renal tubular damage when methoxyflurane is inhaled for >5 h at minimum alveolar concentration (MAC), resulting in serum fluoride concentrations exceeding 90 µmol/L, although fluoride toxicity alone is considered not the be a single cause.[32,33] The absence of renal toxicity with analgesic use of methoxyflurane is likely to reflect the low dose and short duration of inhalation: following a 3 mL dose of inhaled methoxyflurane serum levels of fluoride do not exceed 10 µmol/L.[23] This level of exposure is well under the threshold fluoride concentration of 40 µmol/L (following inhalation of methoxyflurane at MAC for ≤ 2.0 h) below which no biochemical evidence of renal damage has been observed.[32] Based on these findings, the safety margin of inhaled methoxyflurane has been calculated to be 2.7-fold to 8.0-fold.[18] Nevertheless, low-dose methoxyflurane analgesia is contraindicated in patients with renal impairment, and caution should be exercised in patients with known renal or hepatic disease, and with medications which alter hepatic metabolism.[23]

No prospective studies comparing methoxyflurane with other analgesics for acute paediatric moderate-to-severe pain were identified. One large-scale retrospective comparative study suggested that methoxyflurane is less effective than IV morphine and IN fentanyl, based on the proportion of patients with ≥30% reduction in baseline pain.[27] Similar findings were reported in a retrospective, comparative study of adults with moderate-to-severe pain treated by paramedics; methoxyflurane provided effective analgesia (≥30% reduction in baseline pain) for 60% of adults, but higher rates were also observed with morphine (82%) and fentanyl (80%).[34] In a retrospective, observational study of 862 patients, prehospital methoxyflurane provided greater pain relief after 5 min for adults with visceral pain, while IN fentanyl was associated with greater pain reduction at hospital arrival ($p = 0.007$).[35] In contrast, a prospective, randomized study of 251 adults undergoing colonoscopy found methoxyflurane provided similar pain control and procedural success rate to IV fentanyl and midazolam and was associated with a shorter time to being ready for discharge.[36] A prospective cohort study of 40 adults with ankle injuries reported lower pain intensity after 5 min in patients receiving methoxyflurane versus tramadol ($p = 0.001$), and similar low pain intensities with both treatments from 15 to 60 min.[37] These varied findings may reflect sub-optimal use of the methoxyflurane inhaler in some studies.[22]

While methoxyflurane is the analgesic most commonly used by Australian paramedics to treat children, a variety of treatment approaches are used across Europe.[4] For example, oral analgesics (non-steroidal anti-inflammatories and acetaminophen) are commonly used as a first-line approach for mild-to-moderate acute paediatric pain, adding opiates if additional analgesia is required.[3,38,39] Of these opiates, IN diamorphine is widely used in some countries, including the UK.[40,41] IN diamorphine was found to cause less distress, and was as effective as intramuscular (IM) morphine in an RCT of 404 children with acute fracture-related pain, with decreased pain scores observed 5 min after treatment.[42] IN fentanyl has also been shown to provide comparable analgesia to IV or IM morphine for paediatric acute pain.[43] While a pharmacovigilance study of IN diamorphine in 226 children indicated no serious adverse events, a recent systematic review concluded that opioids carry the greatest risk of CNS adverse events, with drowsiness observed in over one-third of children, and dermatological and gastrointestinal effects also being common.[44,45] Such side effects are cited as a barrier to use of opioid analgesics in children and may contribute to documented oligoanalgesia.[11] Inhaled nitrous oxide (50%)/oxygen (50%) is also commonly used for children with moderate-to-severe acute pain in some countries including France and can provide effective analgesia with an acceptable safety profile.[3,38,46,47] Low doses of IN ketamine can also provide effective control of trauma and procedural pain in children and is associated with acceptable levels of patient satisfaction.[48–50] In two small RCTs, IN ketamine was associated with similar or less pain reduction than IN fentanyl and a greater incidence of mild adverse events, including drowsiness, dizziness, bad taste and nausea/vomiting.[48,50]

Due to the small number of comparative trials investigating analgesia for acute paediatric pain, recent systematic reviews conclude that data are too limited to inform optimal approaches in children.[13,14] More RCTs are required to provide insight into relative effectiveness, ease of use and side effect profiles of analgesics for paediatric acute pain. A placebo-controlled trial investigating methoxyflurane for acute, trauma-related pain in 220 children is ongoing in the UK, which will provide further insight into efficacy and safety (registered at ClinicalTrials.gov, NCT03215056).

Our analysis has some limitations; in addition to scarce published data on methoxyflurane use in children, no large-scale RCTs were identified which specifically investigated this setting. Most data were derived from observational case series,[25,26,30] and interpretation of the placebo-controlled trial by Coffey et al., and the observational case series reported by Gillis et al., is limited by data not being reported separately for children and adults.[29,30] Furthermore, evidence collated from the three observational case series reports and one retrospective comparative study was not evaluated differently from the two RCTs. While non-randomised studies can provide real-world insight into treatment outcomes, they are likely to be associated with a greater potential for bias versus the RCTs. The findings from this integrative review emphasize that research is needed to improve the management of paediatric acute pain, which may help to inform future treatment in this vulnerable group of patients.

Conclusions

Inhaled low-dose methoxyflurane is approved for paediatric acute moderate-to-severe pain in Australia and, based on limited available data, is well tolerated and provides rapid and effective analgesia. There is no evidence that efficacy, onset of action or safety profile of methoxyflurane in children differs from that reported in adults. Methoxyflurane may offer intrinsic advantages; patients can self-titrate the minimum effective dose, distressed children are likely to find inhalers more acceptable than needles, and methoxyflurane has the potential for a rapid onset of action without waiting for prior local anaesthetic effect. Analgesics not subject to the barriers associated with opioids, and with the potential to reduce overall opioid usage, will be likely to provide a useful addition to management of acute moderate-to-severe pain in children. Further clinical trials are required to inform optimal treatment approaches in this setting.

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Ethical approval

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Informed consent

None.

Guarantor

SH.

Contributorship

SH and PMM participated in the conception of this article, were involved in the appraisal of the selected papers, edited the manuscript and approved the final version of the manuscript.

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