

Use of methoxyflurane for paediatric patients in a regional burn service outpatient clinic

SL Wall,  DL Clarke,  MTD Smith,  NL Allorto 

Pietermaritzburg Metropolitan Department of Surgery, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa
Corresponding author, email: shelley_wall@hotmail.com

Background: Procedural analgesia is essential for burn-injured patients. Ketamine is the cornerstone of many procedural analgesia protocols for children as it is safe and effective. However, it requires monitoring and the child may remain sedated for a number of hours. We sought an alternative analgesic option. Methoxyflurane is an inhalational analgesic with rapid onset of action for short term analgesia. There is little literature on the use of this drug in children in South Africa, particularly in burns patients. This paper describes our introduction of methoxyflurane into our procedural analgesia protocols for pain associated with dressing changes for paediatric burns.

Methods: We performed a retrospective review of data from the burns database for a two-month period after the addition of methoxyflurane to the paediatric burn outpatient procedural analgesia protocol as the first line analgesia option.

Results: Ninety-five children were reviewed in the clinic over the two-month period. Thirty patients did not require analgesia for their dressing changes. Methoxyflurane provided effective analgesia in 49/65 (75%) patients.

Conclusion: This study has shown that methoxyflurane is a viable option for analgesia for burns dressing changes in a busy outpatient setting. It is an effective and safe alternative to ketamine. Further research is required into the use of methoxyflurane in other burns settings to clarify predictors of failure, ease of use and possible side effect profiles.

Keywords: paediatrics, burns, analgesia, methoxyflurane, pain

Introduction

Procedural analgesia is an essential component of care for burn-injured patients in both inpatient and outpatient settings. Ketamine is regarded as safe and effective for procedural analgesia during burns dressings with minimal side effects.¹⁻³ While ketamine is the mainstay of our current protocol, it is limited by requirements for monitoring and prolonged recovery in a busy outpatient clinic.⁴⁻⁶ We sought an alternative analgesic option. The aim of this study was to determine if methoxyflurane was a viable alternative to ketamine in this setting.

Methoxyflurane is an inhalational analgesic with rapid onset of action for short term analgesia. It belongs to the fluorinated hydrocarbon group of anaesthetic agents. The analgesic potency is high in low concentrations compared with other volatile anaesthetic agents and methoxyflurane was previously used as part of general anaesthesia.⁷ Pain relief begins after 6–8 breaths and continues for several minutes after inhalation has ceased.⁸ Methoxyflurane has been described for the management of acute trauma pain, particularly in the pre-hospital and emergency department setting.⁹ It has also been used for short procedures such as dentistry and dressing changes.⁸

Setting

Edendale Hospital is a regional level hospital serving a population of three million. The burn service consists of a dedicated team, six high care beds and 24 beds in the general surgical wards. The outpatient clinic runs once weekly. This clinic consists of four rooms and between 20 and 50 patients are reviewed per clinic. Patients may be referred from the emergency department, local clinics and referral hospitals, or they will have been admitted to

our burn facility and are now treated as outpatients. The doctor seeing the patient administers the analgesia, either ketamine or methoxyflurane, and does the dressing in one of the four consulting rooms. No monitoring equipment is available in these rooms. Once the dressing has been done by the doctor, the child is then returned to the caregiver and they proceed to the pharmacy queue to fill their analgesia prescription.

Methods

Data during dressing changes are routinely recorded as part of the burns registry. This has class approval granted by the Biomedical Research and Ethics Committee, University of KwaZulu-Natal (BCA106/14), which is renewed annually. Information recorded includes patient demographics, details of the burn injury, wound and medication administered. Pain scores were recorded using the face, legs, activity, cry, consolability (FLACC) scale (Table I).⁷ One of two consultants supervises and records this data. The registry computer is located in a secure area and is password protected.

We reviewed this data retrospectively for a two-month period, January to February 2019, after the addition of methoxyflurane to the paediatric burn outpatient analgesia protocol as the first line analgesic option. All children (age < 12 years) presenting to the burn outpatient clinic were included in the study. The protocol used 1 ml of methoxyflurane (Penthrop®) for all dressing changes, administered with a soft silicone mask (Figure 1). Methoxyflurane was administered without the dilutor hole in the inhaler covered, thus delivering a concentration of 0.2–0.4%. After 5 minutes, clinical assessment is made as to the adequacy of the analgesia.

Table I: Face, legs, activity, cry, consolability (FLACC) scale

Behaviour	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams, sobs, frequent complaints
Consolability	Content, relaxed	Reassured by touching, hugging or being talked to, distractible	Difficult to console or comfort
Assessment of score:			
0 =	Relaxed and comfortable		
1–3 =	Mild discomfort		
4–6 =	Moderate pain		
7–10 =	Severe discomfort/pain		

Table II: Burn characteristics

	Methoxyflurane group	Ketamine group (Methoxyflurane failure)	No analgesia group	Total	Statistical significant impact on methoxyflurane success*
Number in sample	49	16	30	95	
Age					$p = 0.04$
Mean age in years \pm SD (standard deviation)	2.87 ± 2.3	1.90 ± 1.45	4.21 ± 3.05	3.13 ± 2.57	
Gender					
Male	23 (47%)	9 (56%)	15 (50%)	47 (49%)	
Female	26 (53%)	7 (44%)	15 (50%)	48 (52%)	
Day post burn					$p = 0.31$
Minimum days	1	3	7	1	
Maximum days	306	44	97	306	
Mean days \pm SD	27.7 ± 46.0	21.7 ± 14.67	27.3 ± 21.79	26.6 ± 35.59	
Burn depth					$p = 0.003$
Superficial partial burn	19 (39%)	2 (13%)	20 (66%)	41 (43%)	
Mid-dermal burn	10 (20%)	5 (31%)	2 (7%)	17 (18%)	
Mixed depth burn	12 (25%)	6 (37%)	2 (7%)	20 (21%)	
Deep burn	8 (16%)	3 (19%)	6 (20%)	17 (18%)	
Mechanism					$p = 0.12$
Hot water scald	34 (69%)	14 (88%)	22 (73%)	69 (73%)	
Flame	6 (12%)	2 (12%)	1 (3%)	9 (9%)	
Other	9 (19%)	0 (0%)	7 (24%)	17 (18%)	
Total body surface area (TBSA) in %					$p = 0.88$
Initial BSA (mean) in % \pm SD	5.8 ± 6.4	6.9 ± 8.4	4.8 ± 5.3	5.7 ± 6.4	
Residual TBSA (mean) in % \pm SD	2.3 ± 2.6	3.1 ± 3.8	2.1 ± 3.5	2.4 ± 3.1	
Skin grafting	11	2	6	19	$p = 0.05$

* A logistic regression model was run to determine possible impact of specific variables on the success of methoxyflurane. While this study was under powered to predict factors resulting in failure of methoxyflurane, this may guide future research into predictors of failure of methoxyflurane.

Ketamine was used (5 milligrams per kilogram intramuscularly) if:

1. The child refused the face mask and, therefore, the methoxyflurane was not able to be administered.
2. The methoxyflurane was not achieving adequate analgesia (FLACC scale score of 3 or more).

No monitoring equipment is available in the consulting rooms and as a result no monitoring was conducted for either the methoxyflurane or the ketamine administration.

Statistical analysis was conducted by the authors using R studio version 1.1463.⁸ Descriptive statistics were used to describe the variables age, gender, day post burn, burn depth, mechanism of



Figure 1



burn and total body surface area of the burn. A binary logistic regression model was run to assess possible impact of certain variables on methoxyflurane success. This model compares the methoxyflurane success group to the methoxyflurane failure group. A p -value of < 0.05 was considered significant.

Results

Ninety-five children were reviewed in the clinic over the two-month period and one-hundred and twenty dressing changes were performed. Twenty-five of these children were seen more than once in the burns clinic for dressing changes. In all cases where methoxyflurane had been successful for the first dressing change, it was successful again at subsequent dressing changes. The children reviewed consisted of 47 males and 48 females. The mean age of the whole sample was 3.13 ± 2.57 years. The methoxyflurane group had a mean age of 2.87 ± 2.3 years and the ketamine group a mean age of 1.9 ± 1.45 years.

On average, the patients were seen on day 27 post-burn with a median of 17 days and a range of 1–306 days. The child who presented at 306 days had completely healed burns but had a contracture that had torn during mobilisation and had re-presented as a result of this. Burn characteristics are summarised

in Table II. A comparison of characteristics between the methoxyflurane group (i.e. success group) and the ketamine group (i.e. the methoxyflurane failure group) are also shown in Table II.

In terms of distribution of burns, 72% (68/95) of the patients had burn wounds at a single anatomical location. The burns were distributed as follows: 12% had head/facial burns, 25% upper limb burns (not including hands), 9% hand burns, 18% torso burns, 21% lower limb burns (not involving the feet), 12% feet burns and 3% perineal burns.

Forty-nine patients received methoxyflurane alone. Sixteen received intramuscular ketamine: six received ketamine alone as they refused to accept the mask and we were unable to administer the methoxyflurane, and ten received salvage intramuscular ketamine following methoxyflurane. Methoxyflurane provided effective analgesia in 49/65 (75%) patients. Thirty patients did not require any analgesia for their dressing changes.

Discussion

Dressing changes are an essential component of burns care. These dressings can be exceptionally traumatic for children, parents and staff members if done when the child has inadequate

pain control.^{9,10} Ketamine has been the mainstay of our analgesia protocol. Despite being an excellent analgesic, it has limitations in a busy outpatient department. Although ketamine can be administered orally, in this setting, the analgesic needs to have a rapid onset of action and is therefore administered as an intramuscular injection, which is painful. The safe administration of ketamine requires monitoring and an extended recovery period, which is challenging in a busy outpatient department.¹¹ This was our motivation for introduction of an alternative analgesic, methoxyflurane, to provide non-invasive analgesia with a rapid onset of action and short duration of action without the need for monitoring.

In South Africa, methoxyflurane is supplied as a 3 ml vial which is poured onto the wick of a hand-held inhaler. Once the wick is saturated with methoxyflurane, the patient then inhales the methoxyflurane via the mouth-piece.⁵ It can be administered at two different concentrations, depending on whether the dilutor hole, which entrails air during inhalation, is occluded or not. When the dilutor hole is covered with a finger, methoxyflurane is delivered at a concentration of 0.5–0.7%. A concentration of 0.2–0.4% is delivered when the dilutor hole is not covered.⁵ It costs R400 per vial and hand-held inhaler. It is available in private practice and can be made available in state with motivation. This is particularly pertinent in light of the global/national ketamine shortage where finding alternative solutions for procedural analgesia is necessary. It is simple to use, with no training required, which our experience confirmed.

The prolonged recovery period following ketamine sedation is problematic in a busy outpatient setting. Firstly, adequate monitoring is difficult to achieve. Secondly, caregivers are required to fulfil their pharmacy prescription where there are often long delays. This is not achievable with a sedated child. Methoxyflurane is exceptionally useful in our setting as the child recovers from the methoxyflurane and is able to ambulate within minutes of the dressing change, negating the caregiver having to care for the child.^{4,5} We used the lower concentration of 0.2–0.4% given that monitoring facilities are absent. Once further investigation has been done into cases at risk of failure, these patients could potentially receive the higher concentration of 0.5–0.7% in a monitored setting.

Methoxyflurane is not a new agent. The first report of clinical evaluation of methoxyflurane was published in 1960.¹² The use of methoxyflurane for burns dressings in children dates back to the 1970s.^{5,13,14} Various authors found methoxyflurane to be an efficacious analgesic agent in this population.^{6,13-16} Despite its analgesic properties, numerous other advantages of methoxyflurane were noted in these studies, including mood-modifying effects, retrograde amnesia, minimal sedation, lack of the need for starvation prior to administration and avoidance of painful intramuscular or intravenous administration.^{6,13-16} There was growing concern about potential renal toxicity of methoxyflurane in the mid-1960s.¹⁷ In the late 1970s, methoxyflurane was withdrawn from North American clinical practice and over the subsequent 10 years, as newer volatile

agents gained popularity, methoxyflurane gradually fell into disuse.⁵ No evidence of methoxyflurane-induced renal toxicity, either clinical or biochemical, was ever found when it was used for procedural analgesia in the short term at low doses.¹⁸⁻²⁰ Renal tubular dysfunction was observed after high cumulative doses of methoxyflurane from long duration inhalation anaesthesia in a retrospective setting only.^{18,21} Numerous studies have shown no adverse effects to multiple exposures of methoxyflurane.¹³⁻¹⁶ Finn's study exposed children to methoxyflurane between one and thirteen times with no complications. In fact, they reported that after poor effect at first administration, further uses always yielded improved response.¹⁴

The use of methoxyflurane is discouraged by the manufacturers in patients with renal impairment to a history of malignant hyperthermia. While our patients were not specifically tested for these conditions, none of the patients had a history of either condition. It is also discouraged on consecutive days. Our patients received methoxyflurane at most once a week at their clinic follow-up.

Available literature indicates that methoxyflurane is an efficacious analgesic in the paediatric population, although not for all patients.¹²⁻¹⁶ Our findings were consistent with this. In the majority of patients (75%) presenting for review or dressing change who required analgesia for their dressing changes, methoxyflurane was an effective analgesic. Despite the fact that life-threatening adverse events with ketamine are exceedingly rare, ketamine is not without side effects.²² Vomiting, agitation, hypoxia and apnoea are well described side-effects of ketamine.²² The use of methoxyflurane for burns dressings in the outpatient clinic results in the avoidance of ketamine and the risk of these side effects in 60% of these patients.

Burn pain is complex and hyperalgesia, allodynia, neuropathy, anxiety and "windup" are common components of the overall syndrome. This is particularly the case if the child has experienced inadequate analgesia at a previous dressing change.²³ These other components of the pain syndrome may contribute to the failure of methoxyflurane in some patients as it does not address these components of pain. Other possible factors relating to methoxyflurane failure relate to genetically determined metabolism of methoxyflurane. It was our clinical impression that methoxyflurane is not effective in the anxious child. This, however, is subjective, and data was not collected.

In our study, sixteen patients had failure of methoxyflurane, either due to not accepting the mask resulting in us being unable to administer the methoxyflurane or due to the methoxyflurane not being effective. Literature suggests that burns patients demonstrate an altered pharmacodynamic and pharmacokinetic response to numerous drugs.²⁴ This may be a possible explanation for the failure of the methoxyflurane in the patients who required salvage intramuscular ketamine following the administration of methoxyflurane. Our data also suggests that methoxyflurane is less likely to be successful in groups of patients with deep burns and in those who have undergone skin grafting. Unfortunately,

our study was underpowered to conclude this definitively and further research into this is required.

Despite the package insert for Penthrop® stating that children 1–11 years can be given up to 3 ml of methoxyflurane, only 1 ml was administered. The dose of methoxyflurane is dependant on time and tidal volume of the patient. In adults, 3 ml lasts 25–30 minutes with continuous use and one hour with intermittent use.²⁰ We felt that a volume of 1 ml should be adequate in children as did not require such a long duration of action.

Recommendation for future research includes investigation into predictors of failure of methoxyflurane which will guide the choice of analgesia in the outpatient setting pragmatically.

The limitations to this study include the small number of patients and the retrospective analysis, especially as it pertains to a lack of data on previous dressing changes and evaluation of anxiety. However, our findings show that the effective use of methoxyflurane can be achieved in resource-limited settings.

Conclusion

Our study suggests that methoxyflurane is a viable analgesic alternative for burns dressing changes in a busy outpatient setting. This is due to its rapid onset of action and short duration of action. Further investigation into the predictors of failure of methoxyflurane and the role of anxiety in its failure is needed, but methoxyflurane should still be considered a useful adjunct in the analgesia armamentarium of the burn doctor.

Conflict of interest

The authors declare no conflict of interest.

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ORCID

SL Wall  <https://orcid.org/0000-0001-6466-8163>

DL Clarke  <http://orcid.org/0000-0002-6954-153X>

MTD Smith  <http://orcid.org/0000-0003-1491-0534>

NL Allorto  <https://orcid.org/0000-0001-9339-4640>

References

- Gündüz M, Sakalli S, Güneş Y, et al. Comparison of effects of ketamine, ketamine-dexmedetomidine and ketamine-midazolam on dressing changes of burn patients. *J Anaesthesiol Clin Pharmacol*. 2011 Apr;27(2):220-4. <https://doi.org/10.4103/0970-9185.81823>.

- O'Hara D, Ganeshalingam K, Gerrish H, Richardson P. A 2-year experience of nurse led conscious sedation in paediatric burns. *Burns*. 2014 Feb;40(1):48-53. <https://doi.org/10.1016/j.burns.2013.08.021>.
- Owens VF, Palmieri TL, Comroe CM, Conroy JM, Scavone JA, Greenhalgh DG. Ketamine: a safe and effective agent for painful procedures in the paediatric burn patient. *J Burn Care Res*. 2006 Mar-Apr;27(2):211-6; discussion 217. <https://doi.org/10.1097/01.BCR.0000204310.67594.A1>.
- Tomi K, Mashimo T, Tashiro C, et al. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth*. 1993;70(6):684-6. <https://doi.org/10.1093/bja/70.6.684>.
- Jephcott C, Grummet J, Nguyen N, Spruyt O. A review of the safety and efficacy of inhaled methoxyflurane as an analgesic for outpatient procedures. *Br J Anaesth*. 2018 May;120(5):1040-8. <https://doi.org/10.1016/j.bja.2018.01.011>.
- Babl FE, Jamison SR, Spicer M, Bernard S. Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas*. 2006 Aug;18(4):404-10. <https://doi.org/10.1111/j.1742-6723.2006.00874.x>.
- Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997 May;23(3):293-7.
- R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: <http://www.R-project.org/>.
- Upton D, Andrews A. The impact of stress at dressing change in patients with burns: a review of the literature on pain and itching. *Wounds*. 2014;26(3):77-82.
- McGarry S, Elliott C, McDonald A, et al. "This is not just a little accident": a qualitative understanding of paediatric burns from the perspective of parents. *Disability and Rehabilitation*. 2015;37(1):41-50. <https://doi.org/10.3109/09638288.2014.892640>.
- Gales A, Maxwell S. Ketamine: recent evidence and current uses. *World federation of societies of Anaesthesiologists. Anaesthesia Tutorial of the week*. 12 June 2018.
- Artusio JF, Van Poznak A, Hunt RE, Tiers RM, Alexander M. A clinical evaluation of methoxyflurane in man. *Anesthesiology*. 1960 Sep-Oct;21:512-7. <https://doi.org/10.1097/0000542-196009000-00009>.
- Packer KJ. Methoxyflurane analgesia for burns dressings. *Postgrad Med J*. 1972 Mar;48(557):128-32. <https://doi.org/10.1136/pgmj.48.557.128>.
- Firn S. Methoxyflurane analgesia for burns dressings and other painful ward procedures in children. *Br J Anaesth*. 1972 May;44(5):517-22. <https://doi.org/10.1093/bja/44.5.517>.
- Packer KJ, Titel JH. Methoxyflurane analgesia for burns dressings: Experience with the analgizer. *Br J Anaesth*. 1969 Dec;41(12):1080-5. <https://doi.org/10.1093/bja/41.12.1080>.
- Aleksandrin G, Baidurashvili AG, Pakhomova EA. Use of subnarcotic concentrations of methoxyflurane in children with burns. *Vestn Khir Im I I Gek*. 1976 May;116(5):99-101.
- Mazze RI. Methoxyflurane revisited. Tale of an anesthetic from cradle to grave. *Anesthesiology*. 2006 Oct;105(4):843-6. <https://doi.org/10.1097/0000542-200610000-00031>.
- Hetrick WD, Wolfs B, Garcia DA, Siker ES. Renal responses to 'light' methoxyflurane anaesthesia. *Anesthesiology*. 1973 Jan;38(1):30-7. <https://doi.org/10.1097/0000542-197301000-00009>.
- Laird SM, Chrystal KMR. The effect of methoxyflurane analgesia on renal function in burned patients: an investigation. *Postgrad Med J*. 1972 Mar;48(557):133-7. <https://doi.org/10.1136/pgmj.48.557.133>.
- Coffey F, Dissmann P, Mirza K, Lomax M. Methoxyflurane analgesia in adult patients in the emergency department: a subgroup analysis of a randomised, double-blind, placebo-controlled study (STOP!). *Adv Ther*. 2016 Nov;33(11):2012-31. <https://doi.org/10.1007/s12325-016-0405-7>.
- Robertson GS, Hamilton WFD. Methoxyflurane and renal function. *Br J Anaesth*. 1973;45(1):55-62. <https://doi.org/10.1093/bja/45.1.55>.
- Bellolio MF, Puls HA, Anderson JL, et al. Incidence of adverse events in paediatric procedural sedation in the emergency department: a systematic review and meta-analysis. *BMJ Open* 2016;6:e011384. <https://doi.org/10.1136/bmjopen-2016011384>.
- Norman AT, Judkins KC. Pain in the patient with burns. *BJA Educ*. 1 April 2004;4(2):57-61. <https://doi.org/10.1093/bjaceaccp/mkh016>.
- Bittner EA, Shank E, Woodson L, Martyn JAJ. Acute and perioperative care of the burn-injured patient. *Anesthesiology*. 2015 Feb;122(2):448-64. <https://doi.org/10.1097/ALN.0000000000000559>.