Low dose methoxyflurane vs alternative fast acting strong analgesics in the pre-hospital setting: a literature review

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Background

Pain is one of the most common complaints in the emergency and pre-hospital setting. However, oligoanalgaesia and delay in analgesia remains a significant problem (1). Recently, the usefulness of inhaled low dose methoxyflurane as a more practical analgesic in pre-hospital and remote environments has attracted significant attention.

Methoxyflurane is a volatile halogenated ether that is self-administered at sub-anaesthetic doses through a hand-held inhaler. It has shown to be a safe and effective analgesic in large scale clinical trials and systematic reviews. Thus, in 2015 it was approved in Europe for the emergency relief of moderate to severe trauma pain in conscious adult patients (2). However, there are no systematic reviews comparing inhaled methoxyflurane with alternative fast acting analgesics suitable in the pre-hospital setting.

The aim of this review is to assess the evidence for the effectiveness & safety of MXF in the pre-hospital setting versus alternative options: intravenous morphine (**IVM**), intranasal fentanyl (**INF**), intramuscular tramadol (**IMT**) & inhaled nitrous oxide (**Entonox**).

Methods

Studies were identified via search terms. As there are few RCTs, all study designs were eligible for inclusion. The primary outcome was reduction in pain, and secondary outcomes included speed of analgesia onset, speed to administration and adverse effects.

CENTRAL, MEDLINE & Embase were searched up to 01/05/2024. A manual search was performed in the reference lists of all full text articles that were assessed for eligibility. Google Scholar was searched to retrieve grey literature.

All titles & abstracts identified in the searches were screened. Eligible abstracts proceeded to full text review. Articles that met the eligibility criteria at full text screening were included. Data was extracted using a standardized data form.

The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the included observational studies. The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to evaluate randomised control trials.

Results

7 publications were found to be suitable & included in the literature review. The search process is shown in Figure 1.

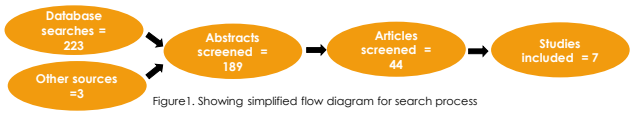


Figure1. Showing simplified flow diagram for search process

Characteristics: 1 randomised control trial (RCT), 1 mixed prospective & retrospective cohort study & 5 retrospective cohort studies. 3 studies have adult only populations, 2 paediatric only, and 2 all ages. 3 specify any type of pain, 2 trauma pain,1 visceral pain, and 1 any pain sustained mountain biking or hiking. 4 studies compare MXF with **IVM**, 4 with **INF**, 1 with **IMT** and 1 with **Entonox**. 3 studies include data on adverse effects and 4 do not.

Bias: All cohort studies had a medium or low risk of bias. However, a limitation of NOS is that it does not consider sample size. RCT had 'some concern'.

Results: Table 1 shows the characteristics and results of the studies. Methoxyflurane was found to be to be more effective and with a faster speed of onset than tramadol and Entonox. Three of four studies observed intranasal fentanyl was more effective, only one compared speed of onset and found methoxyflurane was faster. The results for intravenous morphine were mixed. There were no serious adverse effects recorded and only minimal side effects.

Study	Study Design	Alternative analgesic options	Population	Primary outcome measure(s)	Results
Bendall et al., 2011 (3)	Retrospective cohort Review of electronic care record (ECR) of New South Wales ambulance service over 2-year period Original handwritten notes manually entered into ECR prior to study	IVM INF	Aged 5-15 years with moderate to severe pain (pain score ≥5) Total = 2705 MXF: total = 2093, F = 56.3%, median age 13 IVM: total = 306, F = 42.8%, median age 13 INF: total = 306, F = 51.7%, median age 13	Effective analgesia, defined as a reduction in pain severity of ≥30% of initial pain score Final pain score on arrival at hospital	Achievement of effective analgesia (% of patients): IVM = 87.5 INF = 89.5 MXF = 78.3 AORs of effective analgesia vs IVM (confounders = age & gender) IVM (reference) = 1.00 INF = 1.22 (0.74-2.01) MXF = 0.52 (0.36 - 0.74)
Braybrook et al., 2023 (4)	Retrospective cohort study Review of electronic notes of patients of Western Australian ambulance service over 6-year period (2015–2021)	INF	Any age, treated by ambulance while mountain biking or hiking on a trail Total = 296 MXF: total = 284 INF: total = 12	Clinically meaningful pain reduction, defined as a reduction in pain score of ≥25 % Final pain score on arrival at hospital	Achievement of meaningful pain reduction (% patients) MXF: 67% INF: 50%
Jennings et al., 2015 (5)	Retrospective cohort Review of electronic patient notes of Victoria ambulance service over 4-year period	IVM	Aged < 14 years with pain score ≥3 Total =11479, F = 39.3%, median age = 11 MXF: total = 10483 IVM: total = 996	Clinically important pain reduction, defined as a reduction in pain score of ≥2 Final pain score on arrival at hospital	AORs of clinically important pain reduction vs no analgesia (confounders = sex, case nature, case year & initial pain score) MXF: 5.3 (4.8-5.9), p<0.001 IVM: 2.8 (2.2-3.6), p< 0.001
Johnston et al., 2011 (6)	Retrospective cohort study Review of electronic patient notes of Western Australia ambulance service over 2-year period (2004-2006)	INF	Any age patient with visceral pain (cardiac, renal or abdominal aetiology.) MXF: total = 465, F = 48.6% INF: total = 397, F = 41.2%	Reduction in pain score at 5 mins and at arrival to hospital	Reduction in pain score MXF: 5 mins: 2.0 (1.7-2.2) Hospital: 2.5 (2.1-2.9) INF: 5 mins: 1.6 (1.4-1.8) Hospital: 3.2 (2.9-3.5) MTX produced the greatest initial pain score reduction (p=0.452), and INF provided greater pain reduction by hospital arrival (p=0.007)
Lim et al., 2021 (7)	Prospective, phased, cluster-randomised crossover study 30 Singapore ambulances randomised to carry methoxyflurane or IM tramadol, 6-month crossover	IMT	Aged ≥ 16 years with acute pain (score ≥ 3) arising from MSK trauma (upper and lower limbs, back) Total = 343 MXF: total = 167, F = 40.1%, median age 35 IMT: total = 176, F = 36.9%, median age 39	(a) Reduction in pain score at 5, 10, 15, 20 mins after treatment (b) Time taken to administration (c) Time taken for effective analgesia (≥ 3-point reduction in NRS)	(a) Median reduction in pain score 5 mins: MXF 2 vs IMT 1 (p = 0.001) 10 mins: MXF 3 vs IMT 1 (p = 0.001) 15 mins : MXF 3 vs IMT 1(p = 0.001) 20 mins: MXF 4 vs IMT 1 (p = 0.028) (b) Median time to administration(mins) MXF 9 vs IMT 11 (p < 0.001) (c) Time of onset of effective analgesia (% of patients) 0-5 mins: MXF 38.3% vs IMT 19.4% 5-10 mins: MXF 12.0% vs IMT 5.1%
Middleton et al., 2010 (8)	Retrospective cohort Review of electronic care record (ECR) of New South Wales ambulance service over 2-year period Original handwritten notes manually entered into ECR prior to study	IVM INF	Aged 16-100 with pain score ≥5 Total = 35968 MXF: total = 19235, F = 56.3%, median age = 49 IVM: total = 12955, F = 42.8%, median age = 57 INF: total = 3778, F = 51.7, median age = 55	Effective analgesia, defined as a reduction in pain severity of ≥30% of initial pain score Final pain score on arrival at hospital	Achievement of effective analgesia (% of patients): MXF = 59.1 IVM = 81.8 INF = 80.0 AORs of effective analgesia vs IVM (confounders = age, gender & main condition) IVM (reference) = 1.00 INF = 0.86 (0.78-0.94) MXF = 0.31(0.29-0.33)
Smith et al., 2022 (9)	Mixed prospective/ retrospective cohort East Midland Ambulance Service (EMAS) evaluation of MXF over an 12-month period vs control patients from EMAS database records in similar patients for the same period	IVM Entonox	Aged ≥18 years patients with moderate to severe (pain score ≥ 4) traumatic pain Total= 1984 MXF: total = 429, F = 64.8%, average age = 63.1 IVM: total = 802, F = 58.6%, average age = 61.4 Entonox: total = 753, F = 55.9%, average age = 55.9	(a) Reduction in pain score at 5 mins & 30 mins or on arrival at ED, whichever was sooner. (b) Duration to trough pain	(a) Mean total reduction in pain score MXF: 4.2 IVM: 3.3 Entonox: 2.2 (b) Duration to trough pain (mins) MXF: 26.5 IVM: 41.8 Entonox: 44

Table 1. Characteristics and results of studies investigating inhaled methoxyflurane vs alternative analgesics. Notes: F = female, MXF = inhaled methoxyflurane, IVM = intravenous morphine, INF = intranasal fentanyl, IMT = intramuscular tramadol,, AORs = adjusted odds ratios.

Conclusion

Results suggest that, due to being fast to administer and to act, methoxyflurane may be the preferred first line analgesic in certain cases in the pre-hospital setting. Future research is warranted. There are limitations in quantity, quality and scope of evidence. Future studies would ideally take the form of large scales RCTs using validated pain scores with double blinding. This is if course a challenge in pre-hospital analgesia, but it is achievable. Patients could receive both an inhaled drug and an intravenous, intranasal or intramuscular one, with one being active drug and one being placebo. Larger studies would also enable population analysis, for example whether the effects of inhaled methoxyflurane changes with age, sex, ethnicity or type of pain.

References

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