Global medication performance and safety of methoxyflurane analgesia in patients with severe acute trauma pain treated in the emergency department: a sub-analysis of a randomised, double-blind, placebo-controlled UK study

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BACKGROUND AND GOAL OF STUDY

- Low-dose methoxyflurane administered via a handheld inhaler (Pentrox®) has been used for over 40 years in Australia and New Zealand for short-term pain relief in emergency medicine.
- Previous studies indicate that low-dose methoxyflurane is likely to be an efficacious analgesic in the ED with high patient satisfaction¹.
- The STOP! study^{2,3} was a randomised, double-blind, placebo-controlled UK study that investigated the efficacy and safety of methoxyflurane analgesia (Pentrox®, 3 mL dose) for the treatment of acute pain in adult and adolescent patients presenting to the Emergency Department (ED) with minor trauma and moderate to severe pain (score of 4–7 on the Numeric Rating Scale [NRS]).
- We present a post hoc analysis of satisfaction with study treatment (Global Medication Performance [GMP]) and treatment-emergent adverse events (TEAEs) in a subgroup of patients with severe pain (NRS=7) at baseline.

MATERIAL AND METHODS

- At triage, patients (N=300) were randomised in a 1:1 ratio to receive methoxyflurane (up to 2 x 3 mL) or placebo (normal saline), both self-administered as required via a Pentrox® inhaler.
- To maintain the blind, a drop of methoxyflurane was placed on the outside of the primed inhalers so that the smell between active and placebo treatments was indistinguishable.
- Rescue medication (paracetamol/opioids) was available immediately upon request.
- Prior to ED discharge, the patient, treating physician and research nurse each completed an assessment of GMP using a 5-point Likert scale (“Poor”, “Fair”, “Good”, “Very Good”, or “Excellent”).
- A post hoc subgroup analysis of GMP assessments was performed for patients with severe pain at baseline. The treatment groups were compared using ordinal logistic regression with proportional odds assumption, adjusting for baseline visual analogue scale pain intensity score.
- Adverse events (not related to the trauma presentation) were recorded from enrolment until discharge, and at safety follow up (Day 14±2). TEAEs were summarised for the severe pain subgroup.

RESULTS

Patient Characteristics

- The severe pain subgroup included:
 - 62 methoxyflurane-treated patients, 65% male:35% female, mean age 29 years
 - 71 placebo-treated patients, 52% male:48% female, mean age 30 years
- Injury details are presented in [Table 1](#). The most common injury types were “other” (49%, mostly sprains, soft tissue injury and muscular pain), contusions (23%) and fractures (19%).

Table 1. Injury Details (Severe Pain Subgroup)

NUMBER (%) OF PATIENTS		METHOXYFLURANE (N=62)	PLACEBO (N=71)	TOTAL (N=133)
Injury site	Back	2 (3.2)	3 (4.2)	5 (3.8)
	Chest	3 (4.8)	0	3 (2.3)
	Face	1 (1.6)	0	1 (0.8)
	Left lower limb	12 (19.4)	19 (26.8)	31 (23.3)
	Left upper limb	9 (14.5)	8 (11.3)	17 (12.8)
	Other	6 (9.7)	1 (1.4)	7 (5.3)
	Right lower limb	15 (24.2)	25 (35.2)	40 (30.1)
	Right upper limb	14 (22.6)	15 (21.1)	29 (21.8)
Injury type*	Burn	0	3 (4.2)	3 (2.3)
	Contusion	16 (25.8)	15 (21.1)	31 (23.3)
	Dislocation	0	2 (2.8)	2 (1.5)
	Fracture	15 (24.2)	10 (14.1)	25 (18.8)
	Injury due to foreign body	2 (3.2)	0	2 (1.5)
	Laceration	2 (3.2)	3 (4.2)	5 (3.8)
	Other [†]	27 (43.5)	38 (53.5)	65 (48.9)

Seven patients had more than one injury. Second injuries included contusions (3 Placebo patients, 1 Methoxyflurane patient) and “other” (2 Placebo patients, 1 Methoxyflurane patient). Third injuries included contusion (1 Placebo patient) and “other” (1 Methoxyflurane patient).

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Global Medication Performance

- The GMP ratings by the patient, treating physician and research nurse at ED discharge were each significantly better in the methoxyflurane group compared with the placebo group (p<0.0001 for patient and nurse ratings and p=0.0004 for physician rating).
- 81% of patients, 85% of treating physicians and 77% of research nurses rated methoxyflurane treatment as “Good”, “Very good” or “Excellent”, compared with 41%, 51% and 35% in the placebo group ([Figure 1](#)).

Figure 1. Global Medication Performance (Severe Pain Subgroup)

Safety

- TEAE rates for the severe pain subgroup are presented in [Table 2](#). TEAEs were reported by 31 patients (50%) in the methoxyflurane group and 30 patients (42%) in the placebo group and were mainly mild and transient in nature.

Table 2 Adverse Events (Severe Pain Subgroup)

NUMBER (%) OF PATIENTS	METHOXYFLURANE (N=62)	PLACEBO (N=71)
TEAEs	31 (50.0)	30 (42.3)
Severe TEAEs	2 (3.2)	2 (2.8)
Treatment-related TEAEs	21 (33.9)	9 (12.7)
Serious TEAEs	0	0
TEAEs leading to withdrawal	0	2 (2.8)
TEAEs reported by ≥5% patients in either treatment group		
Dizziness	18 (29.0)	5 (7.0)
Headache	9 (14.5)	12 (16.9)
Somnolence	4 (6.5)	1 (1.4)
Nausea	1 (1.6)	5 (7.0)
Vomiting	0	4 (5.6)
Hypotension	0	4 (5.6)

TEAE = treatment-emergent adverse event.

- TEAEs reported by ≥5% of patients were:
 - Methoxyflurane group: dizziness (29%), headache (15%) and somnolence (6%)
 - Placebo group: headache (17%), dizziness (7%), nausea (7%), vomiting (6%) and hypotension (6%)
- No serious TEAEs were reported.
- Two patients (3%) in the placebo group withdrew due to TEAEs (one patient due to feeling light headed and nausea, and one patient due to vomiting).
- No patients in the methoxyflurane group withdrew due to TEAEs.

CONCLUSIONS

- Patient and treating physician/nurse satisfaction with low-dose methoxyflurane treatment administered via the Pentrox® inhaler was high (≥77%) for this subgroup of patients presenting to the ED with severe trauma pain (NRS=7 at baseline).
- These results support the previously observed high patient and healthcare provider satisfaction with low-dose methoxyflurane analgesia.

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