Short-term efficacy of low-dose methoxyflurane analgesia in adolescent patients presenting to the emergency department with acute trauma pain: a sub-analysis of a randomised, double-blind, placebo controlled UK study

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1717

BACKGROUND AND GOAL OF STUDY

- Although methoxyflurane has been used for pain relief in sub-anaesthetic doses (administered via the Pentrox[®] inhaler, 3mL dose) for over 40 years, there are limited data from the Emergency Department (ED) setting, or outside Australia and New Zealand.
- A previously reported randomised, double-blind, placebo-controlled study (STOP!1²) evaluated the short-term efficacy and safety of methoxyflurane at low analgesic doses for the treatment of adult and adolescent patients presenting to UK EDs with moderate to severe trauma pain (score of 4 to 7 on the 11-point Numeric Rating Scale [NRS]).
- We present a post hoc subgroup analysis of two pain endpoints and rescue medication use in adolescent patients aged 12 to 17 years (N=95) from the STOP! study.

MATERIALS AND METHODS

- A total of 300 patients aged ≥12 years were randomised 1:1 at triage to receive methoxyflurane (up to 2 x 3 mL) or placebo (normal saline), both inhaled as required from 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 of the patient at any time.
- Visual analogue scale (VAS) pain intensity was measured using the Painlog[™] 100 mm VAS (Schlenker Enterprises, Ltd., Lombard, IL., USA) at baseline and 5, 10, 15, 20 and 30 minutes after the start of inhalation of study medication, and every 30 minutes thereafter until rescue medication was administered or discharge from the ED, whichever was sooner.
- The primary efficacy endpoint was the change in VAS pain intensity score from baseline over the first 20 minutes after the start of study medication inhalation, analysed for the adolescent subgroup using repeated measures ANCOVA adjusted for baseline VAS pain score.
- The time from the start of treatment to first pain relief and first request for rescue medication in the adolescent subgroup were each compared between the treatment groups using a Cox proportional hazards model adjusted for baseline VAS pain score. Time was censored at the soonest of: 2 hours from the start of treatment, physician-initiated rescue medication, start of treatment for the injury, or early withdrawal. Kaplan-Meier estimates of time to first pain relief and time to first request for rescue medication were provided.

RESULTS AND DISCUSSION

Patient Characteristics

- The methoxyflurane subgroup (N=47) included 32 males and 15 females with a mean age of 14.4 years.
- The placebo subgroup (N=48) included 35 males and 13 females with a mean age of 13.5 years.
- A summary of injury type and site is presented in [Table 1](#). Most patients had injuries involving the limbs and categorised as “other” (predominantly sprains, soft tissue injury and muscular pain).

Table 1. Injury Details (Adolescent Subgroup)

NUMBER (%) OF PATIENTS		METHOXYFLURANE (N=47)	PLACEBO (N=48)	TOTAL (N=95)
Injury site	Back	1 (2.1)	1 (2.1)	2 (2.1)
	Face	2 (4.3)	1 (2.1)	3 (3.2)
	Left lower limb	5 (10.6)	9 (18.8)	14 (14.7)
	Left upper limb	13 (27.7)	8 (16.7)	21 (22.1)
	Other	7 (14.9)	4 (8.3)	11 (11.6)
	Right lower limb	6 (12.8)	11 (22.9)	17 (17.9)
	Right upper limb	13 (27.7)	14 (29.2)	27 (28.4)
	Contusion	9 (19.1)	6 (12.5)	15 (15.8)
	Dislocation	1 (2.1)	1 (2.1)	2 (2.1)
	Fracture	11 (23.4)	11 (22.9)	22 (23.2)
	Injury due to foreign body	1 (2.1)	-	1 (1.1)
	Laceration	1 (2.1)	1 (2.1)	2 (2.1)
	Other*	24 (51.1)	29 (60.4)	53 (55.8)

* “Other” injury types were predominantly sprains, soft tissue injury and muscular pain.

Note: First injury details are presented. Only one patient had more than one injury.

- Baseline pain severity is presented in [Table 2](#). Almost half of the patients (46%) in the adolescent subgroup had severe pain (NRS score of 7) at baseline. All remaining patients had moderate pain at baseline (NRS score of 4 to 6).

Table 2 Numeric Rating Scale (NRS) Pain Score at Baseline (Adolescent Subgroup)

BASELINE NRS PAIN SCORE	METHOXYFLURANE (N=47) N (%)	PLACEBO (N=48) N (%)	TOTAL (N=95) N (%)
4	4 (8.5)	4 (8.3)	8 (8.4)
5	7 (14.9)	14 (29.2)	21 (22.1)
6	15 (31.9)	7 (14.6)	22 (23.2)
7	21 (44.7)	23 (47.9)	44 (46.3)

Note: A score of 4 to 7 (on the 11-point NRS) was required for study eligibility.

VAS Pain Scores

- Mean (±standard deviation) VAS pain scores at baseline were 61.7 ±16.56 mm in the methoxyflurane group and 61.0 ±13.33 mm in the placebo group.
- Mean change in VAS pain intensity from baseline to 5, 10, 15 and 20 minutes was greater for methoxyflurane (-24.5, -28.1, -31.6 and -31.7 mm, respectively) than placebo (-14.6, -18.8, -19.2 and -23.7 mm, respectively) ([Figure 1](#)).
- Overall, there was a significant treatment difference in the adjusted mean change from baseline in VAS pain over the first 20 minutes (-9.9 mm; 95% confidence interval [CI]: -17.4, -2.4; p=0.0104).

Figure 1. Adjusted Mean Change from Baseline in Visual Analogue Scale Pain Intensity Score (mm) (Adolescent Subgroup)

Time to First Pain Relief

- Time to first pain relief was significantly shorter with methoxyflurane than placebo with a median of 1 minute vs. 3 minutes (hazard ratio: 2.35; 95% confidence interval [CI]: 1.48, 3.76; p=0.0003) ([Figure 2](#)).
- One patient (2.1%) in the methoxyflurane group and 9 patients (18.8%) in the placebo group were censored in the analysis of time to first pain relief.

Figure 2. Median Time to First Pain Relief (Adolescent Subgroup)

Rescue Medication Use

- Only 2 patients (4.3%) in the methoxyflurane group and 3 patients (6.3%) in the placebo group requested rescue medication.
- There was no significant difference in time to request for rescue medication between the treatment groups, reflecting the low number of patients requesting rescue medication (hazard ratio: 0.31; 95% CI: 0.03, 2.97; p=0.3085).
- The proportion of patients requesting rescue medication at any time (prior to censoring) did not reach a level where the median time to request could be estimated.

CONCLUSION

- The results of this study show that low-dose methoxyflurane administered via the Pentrox[®] inhaler is a rapid-acting and effective analgesic in adolescent patients presenting with acute trauma pain.

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