ORIGINAL RESEARCH

Penthrox® (Methoxyflurane) as an Analgesic for Removal of Circular External Fixators and Minor Procedures during the COVID-19 Pandemic

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Abstract

Introduction: Methoxyflurane has excellent analgesic properties and is approved for use in the United Kingdom and Ireland since 2015. It is currently used in emergency departments for analgesia during fracture reductions. During the COVID-19 pandemic, with theatre access severely restricted, Penthrox® had the potential to provide adequate pain relief to aid frame and wire removal in the clinic setting.

Materials and methods: Patients presenting to the limb reconstruction service elective clinic and requiring frame removal or minor procedures were included in the study. Patients with renal, cardiac or hepatic disease, a history of sensitivity to fluorinated anaesthetic agents and those on any nephrotoxic or enzyme-inducing drugs were excluded. All procedures were performed in an appropriate isolated room in the clinic. Patient demographics, procedure details, visual analogue score, Richmond Agitation Scale and patient satisfaction were recorded.

Results: A total of 39 patients were included in the study of which 17 had Ilizarov frames removed, 10 had hexapod removals, nine had heel rings removed and three had an external fixator removed. Eleven patients received additional pain relief in the form of oral analgesia. All patients were satisfied or very satisfied with the experience. One patient required a general anaesthetic for the removal of a wire that could not be removed in the clinic due to bony overgrowth.

Conclusion: Patient satisfaction was very high (>95%), and it was possible to perform frame removals and minor procedures in the clinic environment during the COVID-19 pandemic. We see potential for regular use of Penthrox® in the future for the removal of external fixation outside of the operating theatre.

Clinical significance: Penthrox as an analgesic for frame adjustments and removals is safe and has the potential for significant financial savings for the National Health Service (NHS).

Keywords: Circular frame, COVID-19, External fixator, Methoxyflurane, Removal, Penthrox®.

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Introduction

A large number of limb reconstruction surgery patients are managed with ring fixators and other external fixation devices. They require timely adjustments and removal of the external fixation once treatment is complete. Usually, these procedures are performed under a general anaesthetic in the operating theatre but there is also an increasing trend for alternative modalities in the clinic, including the use of nitrous oxide (Entonox®) as well as regional nerve blocks.[1] The cost of a three-session theatre list is more than £3000 in our trust and removal of external fixation represents a significant use of theatre time. This has become an ever more valuable commodity especially in the post-pandemic era as the National Health Service (NHS) deals with waiting lists following the COVID-19 pandemic.

Methoxyflurane, a fluorinated hydrocarbon, came into use as an inhaled anaesthetic in the 1960s but was discontinued due to the risk of nephrotoxicity from fluoride ions at high doses.[2–4] There have been no reports of nephrotoxicity or hepatotoxicity in clinical studies of analgesic methoxyflurane, and no clinically significant effect on systolic blood pressure, pulse rate, respiratory rate or consciousness level has been observed.[5,6] Methoxyflurane was granted a product license by the Medicines and Healthcare Regulatory Agency and approved for use in the United Kingdom and Ireland in 2015. It is currently being used in emergency departments for short-term analgesia in patients with moderate-to-severe trauma, including during fracture reduction and

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manipulation. Clinical studies to date have proven that at low analgesic doses, methoxyflurane is safe and effective without any significant adverse events including higher risk patients.[7]

Penthrox® comes as a portable, single-use disposable inhaler with an analgesic dose of 3 mL methoxyflurane. Its effects are quickly reversed after inhalation stops and the device can be safely used as an adjunct to other analgesics.[6] There are no special precautions required for storage. Once added to the inhaler, the methoxyflurane liquid is absorbed by a polypropylene wick, vaporised and inhaled by the patient through the mouthpiece. The inhaler includes an activated charcoal chamber, which adsorbs exhaled methoxyflurane when the patient exhales into the mouthpiece, preventing occupational exposure. A standard 3 mL dose of methoxyflurane can provide up to 30 minutes of analgesia when used continuously or up to 60 minutes when used intermittently. The further analgesic effect can be achieved through the use of a further 3 mL of methoxyflurane if required.

During the COVID-19 pandemic, with theatre access severely restricted and the use of shared inhaled nitrous oxide equipment questionable, we identified Penthrox® as a potential candidate for adequate pain relief to aid frame removals and other minor procedures in the clinic setting. The Penthrox® device is single-use and disposable, minimising the risk of infectious diseases between patients. It can be safely stored in the clinic environment and easily transported. Furthermore, there is no requirement for formal monitoring of the patient's vital signs during or following its use. Administration of the drug via the use of the inhaler is straightforward and is usually self-managed by the patient once the process is explained to them.

The aim of this study was to determine the safety and efficacy of Penthrox® in the limb reconstruction clinic setting for patients requiring minor procedures such as removal and adjustment of frames and to further evaluate its economic impact on the Trust.

Materials and Methods

We performed a prospective single-arm cohort study of patients attending a limb reconstruction service elective clinic for removal and adjustment of frames at a tertiary care centre in the North-West of England from March 2020 to October 2020. Approval for the study was obtained from the local hospital ethics committee and audit department, as well as the pharmacy department.

We simultaneously collected retrospective data regarding the removal of frame procedures performed under general anaesthetic in the period between March 2019 to October 2020.

Study data collected included the type of frame, procedure performed, patient demographics, time taken for removal, complications and site of the frame being removed. Patients were excluded if they had a history of renal, cardiac or hepatic disease, a history of sensitivity to fluorinated anaesthetic agents and those taking any nephrotoxic or enzyme-inducing drugs. Patients were enrolled in the study after discussing the risks and benefits of the procedure, explaining the procedure would take place in a clinic and obtaining consent. Patients were shown how to use the Penthrox® inhaler and instructed to inhale the lowest effective dose to achieve adequate analgesia during the procedure.

To assess the effectiveness of methoxyflurane at analgesic doses, patients were asked to complete a visual analogue scale (VAS) score. Richmond Agitation Sedation Scale (RASS) score and patient satisfaction score were documented by the clinician performing the frame removal procedure.

Table 1: Results of Penthrox® use in the elective clinic setting

Number of patients	39
Mean age (years)	44 (19–73)
Sex	24 M:15 F
Mean procedure time (min), $n = 27$	55
Mean VAS score	3.9
Mean RASS score	0.2
Satisfaction rating:	
Very satisfied	29
Satisfied	10
Neither satisfied or unsatisfied or unsatisfied or very unsatisfied	0
Complications	1
Additional analgesia	11
Procedures abandoned	0

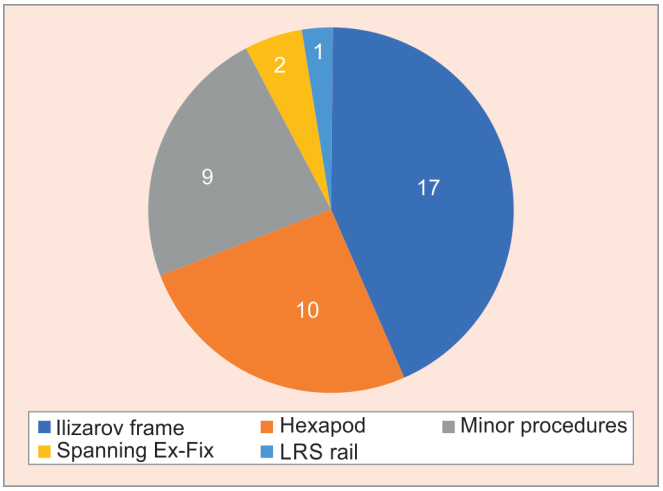

Fig. 1: Procedures performed in the clinic setting

For assessing circular external frame removals in theatre, a retrospective analysis of theatre lists at our Trust was performed. Theatre lists in the time period of March 2019 to October 2020 were included, and any patients having removal of frames were identified. Patients having frame removals combined with other procedures were excluded from the analysis.

To assess the cost savings of our measures, we consulted with the finance department to determine the cost of standard two-session and three-session theatre lists. Coupled with operating time data, this information was used to calculate the costs of frame removals in theatre across the period and the potential cost savings of performing the same procedures in a clinic setting under the use of Penthrox®.

Results

A total of 39 patients were found who fulfilled the inclusion criteria for the prospective arm of this study. The details of these patients are shown in Table 1.

Among the 39 patients with a mean age of 44 years (ranging 19–73 years), five procedure types were performed: removal of Ilizarov frames, hexapod removal, spanning external-fixator removal, rail fixator removals and minor procedures (single wire or heel ring removals). The breakdown of the different procedure types is shown in Figure 1.

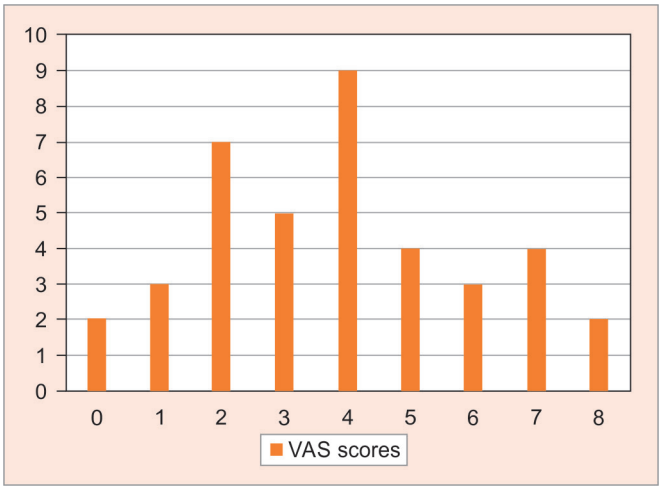

Fig. 2: Visual analogue scale

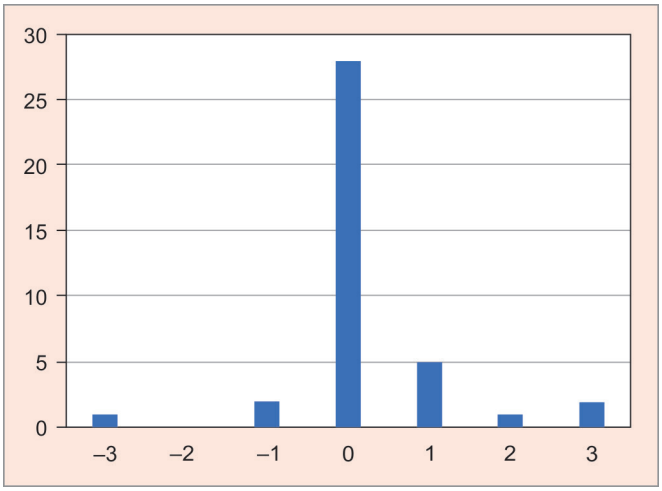

Fig. 3: Richmond Agitation Sedation scores

A total of 37 patients had at least one olive or smooth wire removed, with a maximum of 12 wires removed in one patient (who reported a VAS score of 3 and was very satisfied with the procedure). We also had three cases in which nine wires were removed (two patients were very satisfied with the procedure and one was satisfied). Sixteen patients also had half the pins removed as part of their procedure (13 of these were hydroxyapatite-coated). In this cohort, the mean VAS was only slightly higher at 4.3 and 11 patients were very satisfied, suggesting removal of half-pins was also well tolerated when using Penthrox®.

Further data analysis revealed two patients (5%) who would not have removal using Penthrox® repeated again when compared with the option of having a frame removal under general anaesthetic. There was no particular difference in the technical aspects of their procedure when compared with other patients.

Visual analogue scale results (Fig. 2) suggest the procedure was well tolerated in the majority of patients with a mean score of 3.9. Two patients scored 8 on the VAS, but one of these patients was still very satisfied with the procedure overall. Patient satisfaction was noted to be very high (>95%), and the RASS (Fig. 3) also suggests the same (Table 2).

A total of 89 patients were identified in the retrospective analysis, with a mean age of 52 years (ranging from 19 to 85 years).

Table 2: Patient demographics for removal of frames in the theatre setting

Number of patients, *n*	89
Mean age (years)	52
Male gender	62 (70%)
Mean procedure time (min), *n* = 74	32.8
Mean theatre time (min)	58.7

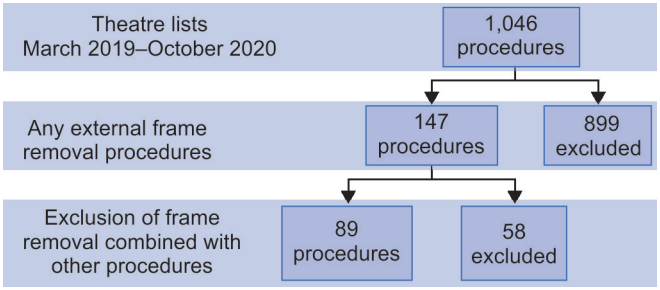

Fig. 4: Data analysis of theatre lists from March 2019 to October 2020

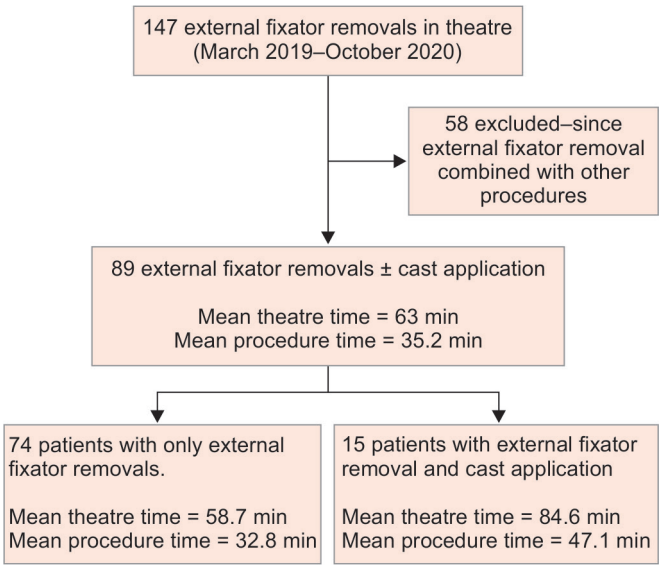

Fig. 5: Only external fixator removal cases in the period March 2019–October 2020 used to compare costs to those done under Penthrox®

There were 147 external fixator removals in the period March 2019 to October 2020; however, 58 of these were excluded as this occurred combined with another procedure. Of the 89 procedures identified, 74 were used to calculate the mean theatre time required for external frame removal. Fifteen cases also had plaster cast application as part of the procedure, making procedure time longer. This is shown in Figures 4 and 5.

A cost comparison between frame removal in the clinic setting and frame removal in the theatre was performed. The average total theatre time taken for frame removal was found to be 63 minutes (58.7 minutes without plaster application and 84.6 minutes with plaster cast application). The mean cost of a two-session theatre list in our trust is approximately £2266, and £3331 for a three-session list as reported by our hospital administration team. This equated to an hourly cost of £283.25.

As a two-session list is normally 8 hours and the average time for frame removal being 63 minutes in theatre, the cost incurred is

approximately £297 per frame removal. One single-use Penthrox® pack costs approximately £24 to our trust with the difference being £273 pounds per frame removal. Considering at least 80 frames are removed every year in our trust, the annual saving over a 12-month period is approximately £22,000.

Discussion

Patients who have completed treatment in an external fixator or circular frame in our unit would usually have the frames removed in the operating theatre under a general anaesthetic. During the COVID-19 pandemic, this was not possible as access to operating theatres was significantly reduced for long periods.

In response, Penthrox®, already used in the prehospital environment and emergency departments as an analgesic for procedures such as fracture reduction and plaster application, was trialled following local institutional approval. Of the 39 patients who received Penthrox®, 11 patients accepted an offer for additional analgesia (including paracetamol, codeine, tramadol, diazepam and Entonox). Baseline vitals were noted at the start and the finish of the procedure including heart rate, blood pressure, respiratory rate and oxygen saturation.

Even though the use of Penthrox® seems to be well-tolerated with minimal side effects, Yeung and Adcock[8] in their systematic review reported that it may not be as effective as intravenous morphine or fentanyl. They found no cost-effectiveness studies and suggested more research into comparing its effectiveness to the more routine intravenous options. Although our study evaluated the outcomes with Penthrox® use, it was not compared with standard options like intravenous morphine or nitrous oxide (Entonox®). We note, however, that the use of nitrous oxide in the clinic setting for such procedures is increasingly prevalent.

The methoxyflurane analgesia for paediatric injuries trial is a multicentre randomised controlled trial (RCT) registered in 2017 to assess the safety and efficacy in managing moderate-to-severe pain in children between 6 and 17 years of age.[9] The study also uses the VAS score as the primary outcome measure, as in our study. Having similarly used the VAS scores for our study, we found high satisfaction rates with over 90% of patients willing to have the procedure under Penthrox® again if needed.

Forrest et al. reported on the use of Penthrox® in a pre-hospital setting in their case series of 14 patients and found significant improvement in pain scores following its administration.[10] They also found that the speed at which the relief was obtained allowed for quicker initiation of assessment and management. This also extends to the use in frame removal as the administration may be timed just before de-tensioning of the frame and removal of the wires and pins thereby limiting the dose and duration needed. This was done for all patients in our study and helped reduce the total dosage administered.

Another advantage of Penthrox® is its safety profile for the administrators as reported in a safety profile study done by Frangos et al.[11] They found the occupational exposure estimates were well below the proposed maximum exposure limit and that the odour was also detectable well below it. This makes it safe for administrators who might have repeated and prolonged exposure to it. None of the administrators in our study had any symptoms of exposure at any point during the administration of Penthrox®.

Penthrox® may provide enough additional benefit over the alternative methods to justify a change in normal practice.[12] Rahman and Quinn in their study found two studies, which found no benefit of methoxyflurane versus standard care.[13] Eager et al. have registered a systematic review and meta-analysis of RCTs comparing Penthrox® to either placebo or standard care.[14] The results of this study may add evidence on whether Penthrox® should be considered for wider use and change standard practice.

We experienced one complication due to an internal screw preventing wire removal in the outpatient setting and requiring a procedure under general anaesthetic for removal. It is imperative to counsel patients before the procedure that this is a risk associated with the removal of external fixation in the clinic environment. Two patients stated they would prefer frame removal under general anaesthetic rather than Penthrox® if they were able to make their choice again. It is possible that supplementing methoxyflurane with oral analgesia may have provided a better patient experience for these individuals. Further research is required to compare the patient experience with additional analgesia and directly against Entonox®.

Besides the direct savings from performing the frame removals outside of the theatre, it furthermore frees up approximately 5000 minutes/80 hours of available theatre time. This time is truly crucial, especially in the current scenario as hospitals try to cope with long waiting lists as a fallout from the pandemic. The authors believe that this dual advantage, if applied nationally, can alleviate some of the clinical challenges faced by the NHS.

The use of Penthrox® for external fixator adjustment and removal in the clinic setting represents a safe, well-tolerated and inexpensive alternative to fixator removal under a general anaesthetic, allowing time in the operating theatre to be used for procedures that cannot be performed in the clinic.

Limitations

This particular study did not compare the use of Penthrox® against Entonox® in the clinic setting. As such, we are unable to comment on direct differences including those of a fiscal nature. There is, however, evidence to suggest that Penthrox® is superior as an analgesic agent.[15] Although this study provides robust evidence against units who conventionally remove frames in theatre, we cannot provide any conclusive evidence against the increasing use of Entonox®. We recommend further research directly comparing these two analgesics in the future to determine the cost implications and resource logistics involved.

Conclusion

Although some studies debate the efficacy of methoxyflurane in comparison to intravenous anaesthetics, we found it to be safe, well tolerated and straightforward to administer. Cost comparison with fixator adjustments or removals done under a general anaesthetic was favourable, providing a significant saving while making theatre time available for other cases.

Further research is required to compare the use of methoxyflurane for fixator removal with nitrous oxide (Entonox®), as well as with additional oral analgesia in different regimes.

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Manufacturer Name

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