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How effective and what is the cost of inhaled methoxyflurane compared to usual analgesia for prehospital injury and trauma?

Prof Niroshan Siriwardena MBBS, MMedSci, PhD

Community and Health Research Unit (CaHRU), University of Lincoln
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@nsiriwardena

Acknowledgements and disclosures

- CaHRU: Dr Murray Smith, Senior Research Fellow in Health Economics and Econometrics; Dr Elise Rowan, Clinical Database Manager EMAS Robert Spaight
- Patients and staff at East Midlands Ambulance Service NHS Trust.
- Funding: Galen Ltd had no role in the study design, conduct and reporting. The views are those of the authors and not necessarily those of the funder.

Background

- Acute pain present in >70% of those attended by EMS for traumatic injury and is often inadequately treated
- Barriers to adequate pain relief include obstacles to accurate pain assessment, contra-indications to administration of effective drugs such as morphine, limited choice of analgesia and delivery routes
- Potential solutions include expanding the range of analgesics available

Methoxyflurane

- Methoxyflurane (Penthrox[®]; Galen Ltd) is a volatile fluorinated hydrocarbon anaesthetic with analgesic properties in sub-anaesthetic doses
- Widely used as an inhalational analgesic in adults and children for over 40 years in Australia and New Zealand
- Easy to administer, with good safety profile
- European licence for emergency relief of moderate to severe pain in conscious adults with trauma pain
- Limited evidence of clinical and cost effectiveness in the prehospital setting

Previous studies

- Recent open-label RCTs in EDs (InMEDIATE, MEDITA, PenASAP, RAMPED) methoxyflurane relieved pain more quickly or more effectively or both compared with usual analgesia Fabbri A et al J Pain Res 2020; 13: 1547-55
- Systematic review indirectly comparing prehospital methoxyflurane with Entonox reported superior (but non-significant) pain relief at 15 minutes for methoxyflurane Porter K et al J Pain Res 2018; 11: 11-21.
- Previous observational study suggested that methoxyflurane was inferior to morphine when used prehospitally. Middleton PM et al Prehosp Emerg Care 2010; 14(4): 439-47



Aims

- To investigate clinical effectiveness and costs of inhaled methoxyflurane delivered by ambulance staff for patients with trauma and associated pain

- Research question:

Does adding inhaled methoxyflurane to usual analgesic practice (UAP) improve prehospital pain relief for patients with traumatic injury and does it offer good value to the NHS?

Method

- Implementation of methoxyflurane and observational comparison versus Entonox[®] or parenteral analgesics
- Verbal numerical pain scores (VNPS) over time in adults with moderate to severe trauma pain attended by ambulance staff trained in administering and supplied with methoxyflurane
- Comparator VNPS from database records of UAP in similar patients over the same time period Dec 2018 – Nov 2019
- Clinical efficacy tested using Ordered Probit panel regression model of pain intensity linked by observational rules to VNPS
- Scenario analyses were used to compare durations under analgesia spent in severe pain, and costs

Training

96 clinicians trained to deliver methoxyflurane as part of the evaluation:

- 45 paramedics
- 1 student paramedic
- 50 EMTs

PENTHROX[®]▼ (methoxyflurane) Checklist for administration

IMPORTANT RISK MINIMISATION INFORMATION FOR HEALTHCARE PROFESSIONALS

This checklist is essential to ensure the safe and effective use of methoxyflurane and appropriate management of important selected risks.

Before using methoxyflurane ...**please CHECK ALL.**

The patient is not known to have:

- C Cardiovascular instability
- H Hypersensitivity to methoxyflurane (or any fluorinated anaesthetic)
- E Elevated temperature from an anaesthetic (malignant hyperthermia)
- C Consciousness reduced (including due to alcohol)
- K Kidney impairment
- A Age below 18 years
- L Lung or respiratory impairment
- L Liver impairment
- L Last administration of methoxyflurane

If patient has any of the conditions listed here or is taking any of the drugs listed on the reverse **DO NOT administer** methoxyflurane.

Instruct patient on the correct administration of methoxyflurane.

Reminder: Please read SmPC before administering and give patient PIL and Alert Card. Ensure lowest required dose is administered and maximum dose of 6ml (2 vials) is not exceeded.

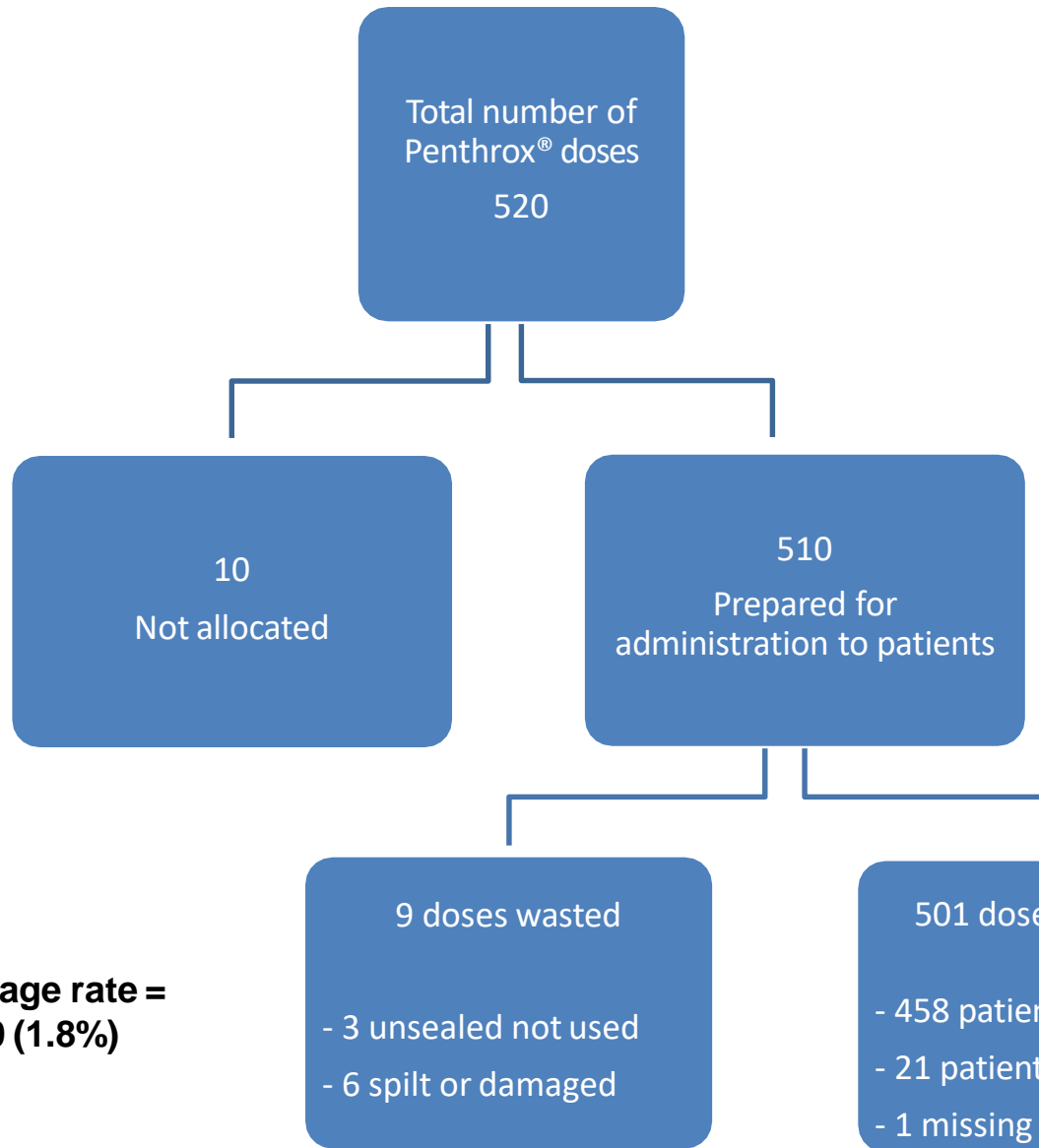
Patient is not taking:

CYP-450 enzyme inducers (e.g. alcohol, isoniazid, phenobarbital or rifampicin).
Antibiotics with known nephrotoxic effect (e.g. tetracycline, gentamicin, colistin, polymyxin B or amphotericin B).

Concomitant use of methoxyflurane with CNS depressants may produce additive depressant effects and patients should be observed closely.

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to the MHRA via the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard. Any suspected adverse reactions should also be reported to Galen Limited on 028 3833 4974 and select the customer services option, or e-mail customer.services@galen-pharma.com.

PMR-APR-2015-0070. Date of preparation: August 2015



**Wastage rate =
9/510 (1.8%)**

**217/479 (45.3%) given
methoxyflurane as the
sole analgesic**

**Double dose rate =
21/479 (4.4%)**



Timing of methoxyflurane administration

- First-line treatment for 89 patients
- Last in sequence for 142 patients.
- Clinicians prepared and administered most doses at the scene of the incident
- 26 doses were prepared for administration during patient conveyance to hospital
- 10 doses were initiated after arrival at hospital but before patient handover.

Control data

- 460,000 patient episodes Dec 2018 - Nov 2019
- 14,000 episodes matched both the patient indication for treatment with methoxyflurane and inclusion/exclusion criteria.
- 1,833 episodes in which the only analgesic used was: Entonox[®] (753 patients), morphine IV (802 patients), paracetamol IV (278 patients).



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Patient treatment characteristics

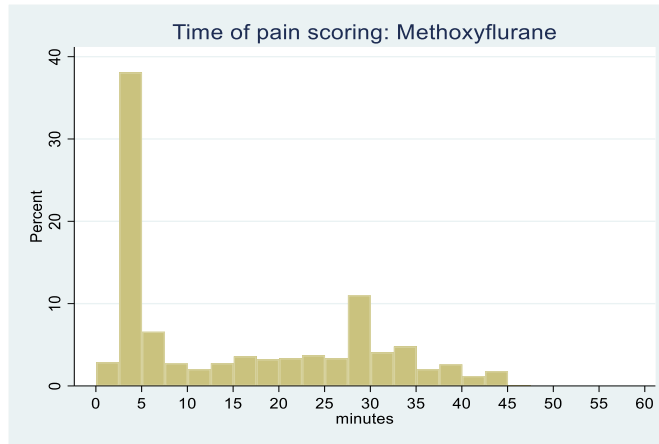
		Comparison groups			
		Methoxyflurane (n=479)	Entonox® (n=753)	Morphine IV (n=802)	Paracetamol IV (n=278)
Sex	Female	313 (64.8%)	421 (55.9%)	470 (58.6%)	160 (57.5%)
	Male	141 (35.2%)	332 (44.1%)	332 (41.4%)	118 (42.5%)
Age (yrs)		63.1 (22.9; 16-98)	55.9 (22.1; 18-96)	66.6 (20.3; 18-100)	66.6 (20.3; 18-100)
Pain score	Pre-administration	8.7 (1.6; 3-10)	7.8 (1.8; 4-10)	8.3 (1.6; 4-10)	7.2 (1.8; 4-10)
	Severe (7-10)	89.7%	74.2%	69.0%	64.0%
	Moderate (4-6)	11.2%	25.8%	31.0%	51.8%
	Final	4.5 (2.5; 0-10)	5.6 (2.5; 0-10)	5.0 (2.6; 0-10)	4.8 (2.3; 0-10)

Mean (Standard deviation; sample range)

Trauma categories for patients given methoxyflurane

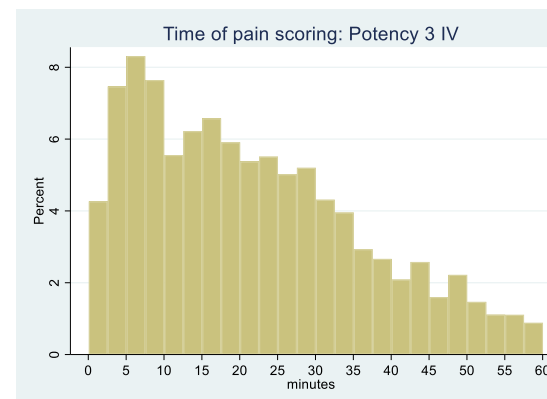
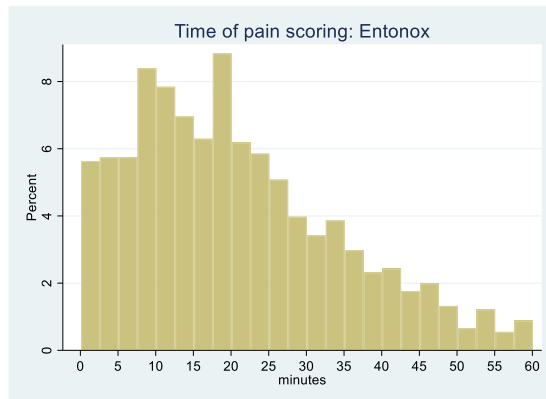
Trauma category	Count
Limb injury or fall +/- soft tissue injury	221
Suspected neck of femur (trauma) or hip injury +/- limb or soft tissue injury	108
Head, neck or back injury +/- soft tissue injury	83
Multisystem or multiple trauma, assault, stab wound, gunshot injury, penetrating trauma	31
Abdominal or chest injury +/- soft tissue injury	15
Soft tissue or thermal injury	15
Other (unclassified non-trauma)	10

Pain score timings



#Scores	Freq
2	432
3	330 (76.4%)
4	59 (13.7%)
5	10 (2.3%)
6	3 (0.7%)
7	1 (0.2%)

#Scores	Freq
2	788
3	125 (15.9%)
4	18 (2.3%)
5	3 (0.4%)



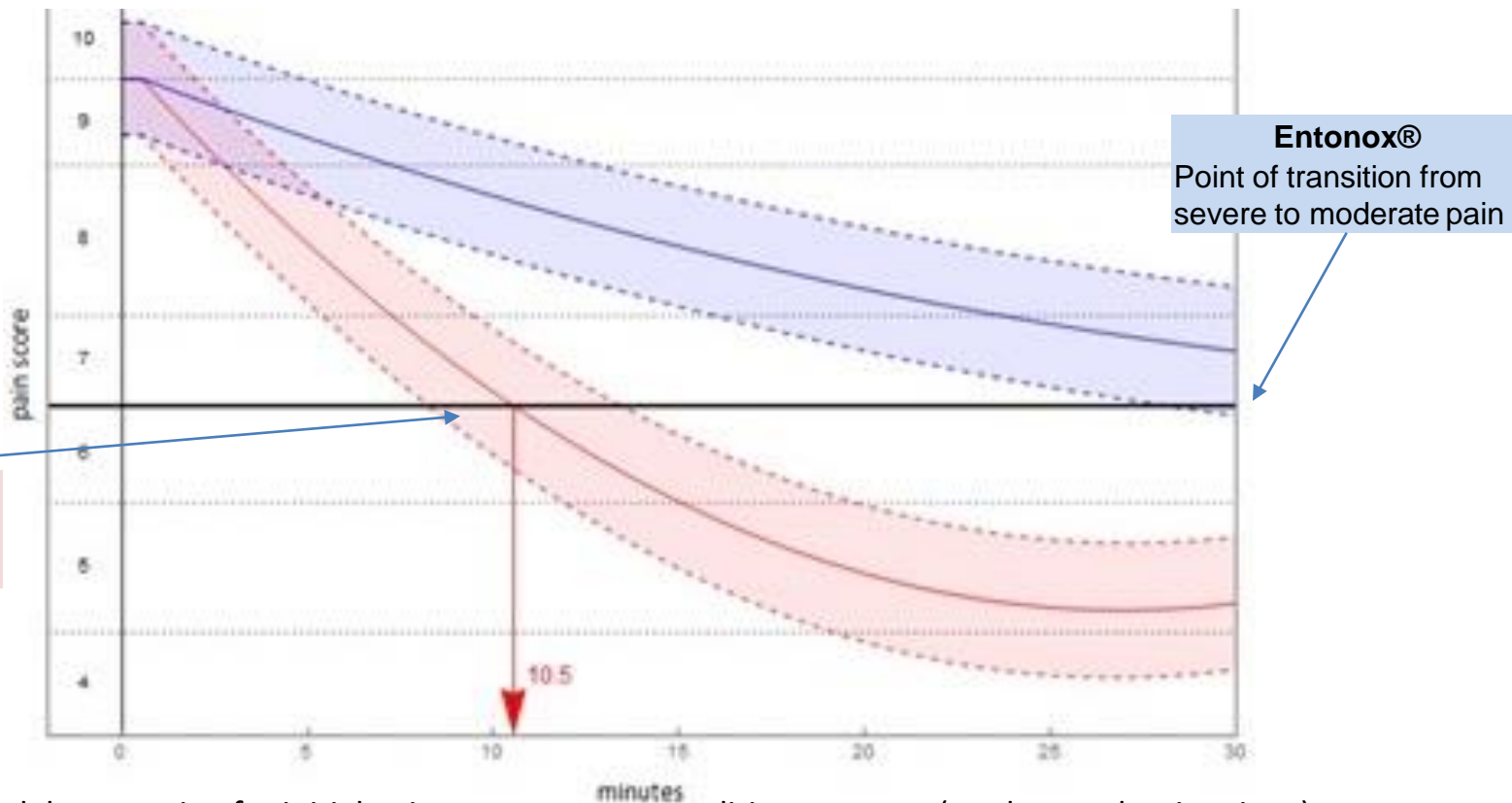
#Scores	Freq
2	1522
3	584 (38.4%)
4	160 (10.5%)
5	43 (2.8%)
6	9 (0.6%)
7	1 (0.1%)

Pain score influence

Analgesic	Route	Effect begins	Effect ends
Methoxyflurane	inhaled	+30 secs after administration	+5 mins after stopping or +45 mins after administration (intermittent use)
Entonox [®]	inhaled	+30 secs after administration	+5 mins after stopping or +45 mins after administration (intermittent use)
Potency 1	oral	+30 mins after administration	+6 hrs after administration
Potency 2	oral	+30 mins after administration	+6 hrs after administration
Potency 3	oral	+30 mins after administration	+6 hrs after administration
Potency 3	IV	+1 min after administration	+4 hrs after administration
Paracetamol	IV	+5 mins after administration	+6 hrs after administration

- We assumed methoxyflurane and Entonox[®] not used at same time, even intermittently
- Potency (mild) 1: oral paracetamol or ibuprofen
- Potency (moderate) 2: oral paracetamol/mild opiate combination
- Potency (high) 3: oral opiate or tramadol, parenteral opiate or paracetamol

Scenario: Predicted pain pathways (with 95% CI)



*Model accounting for initial pain score, trauma condition, age, sex (+ other analgesics given)

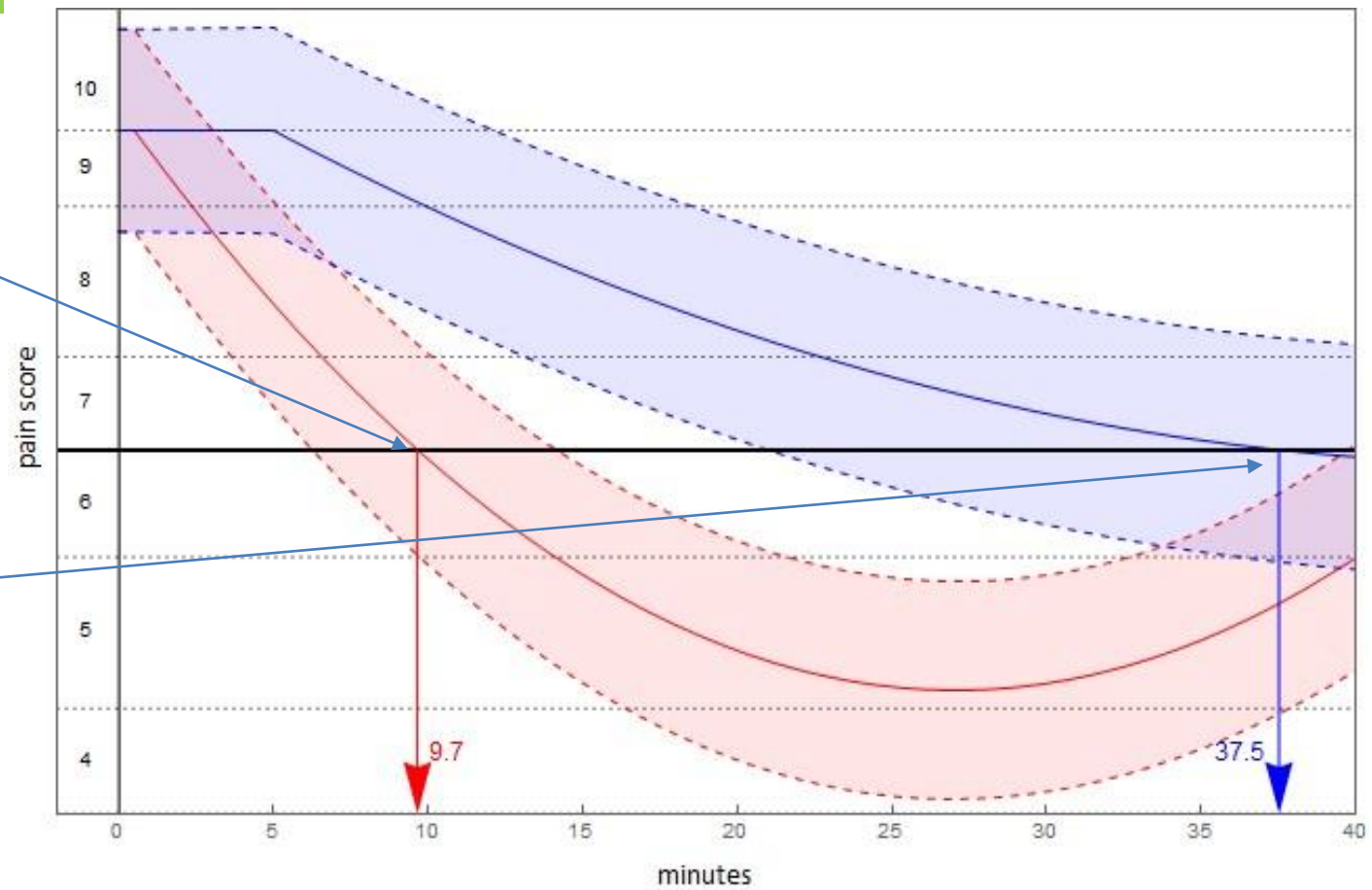
Comparison	Duration in severe pain	Time to least pain	Level of least pain
Methoxyflurane	10.5	26.9***	-1.97***
Entonox	-	45.0	-0.82

Versus Paracetamol IV

Scenario: Predicted pain pathways (with 95% CI)

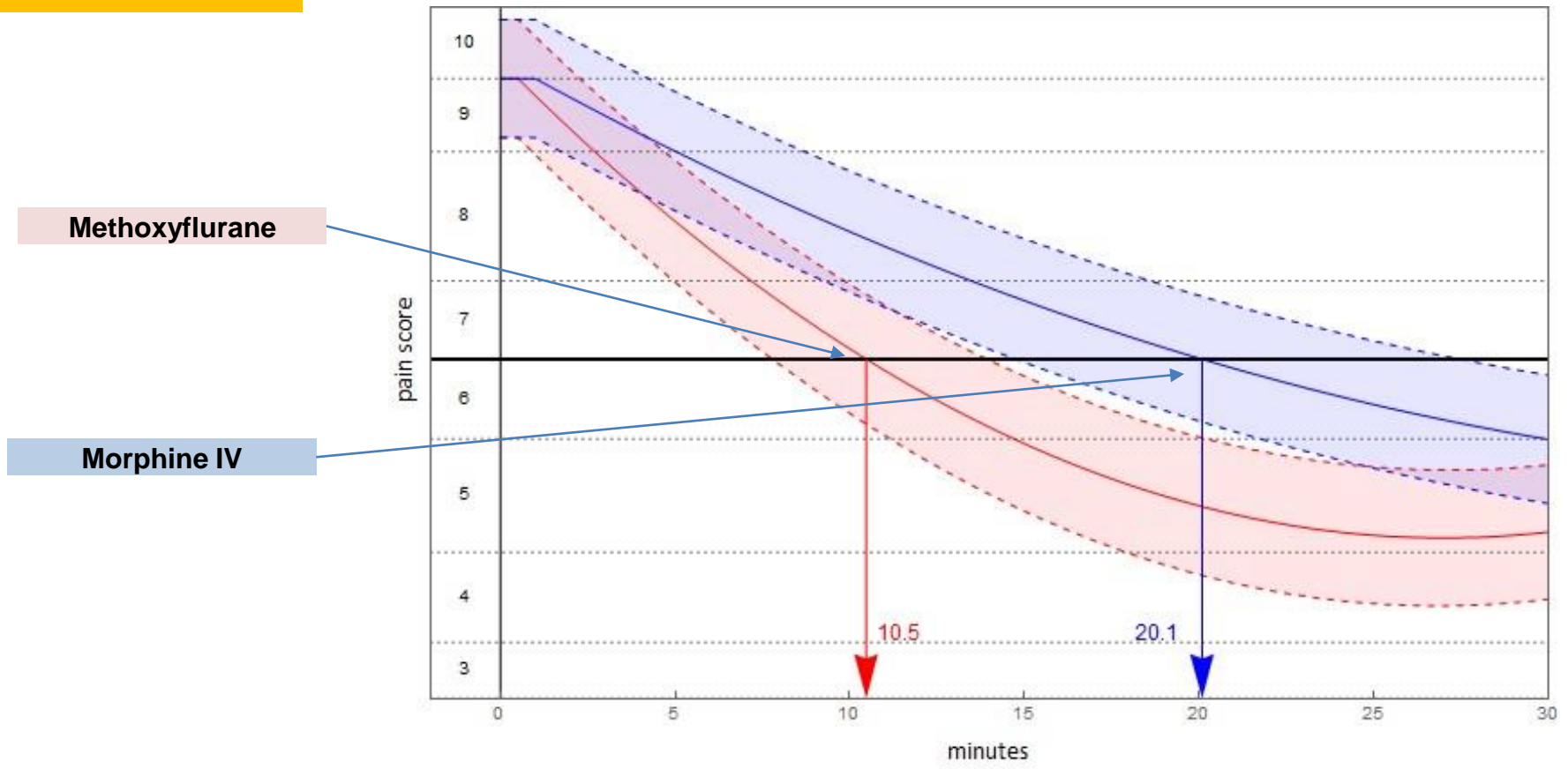
Methoxyflurane

Paracetamol IV



Comparison	Duration in severe pain	Time to least pain	Level of least pain
Methoxyflurane	9.7***	27.1***	-1.89***
Paracetamol	37.5	45.8	-0.76

Scenario: Predicted pain pathways (with 95% CI)



Comparison	Duration in severe pain	Time to least pain	Level of least pain
Methoxyflurane	10.5***	27.0***	-2.16*
Morphine	20.1	42.8	-1.81

Clinician reported side-effects

36 side-effects reported by 32 patients (32/479=6.7%)

19 patients discontinued due to side effects (19/479=4%)

13 patients (10 aged over 75 years) did not comply with inhaler instructions

Side effect	Patient discontinued	Patient continued	Total
<i>Common or very common</i>			
Cough	6	4	10
Taste altered	7	2	9
Nausea	4	1	5
Feeling abnormal	2	2	4
Dizziness	1		1
Drowsiness		1	1
Dry mouth	1		1
Headache		1	1
Mood altered		1	1
<i>Uncommon</i>			
Anxiety	1		1
Oral discomfort	1		1
Paraesthesia		1	1
Total	23	13	36

Costs

- Methoxyflurane £18.89 per patient, based on the overall usage rate observed in the evaluation (510 doses used for 483 patients).
- Entonox[®], added to breathing filter and mouthpiece we apportioned half, per assumption, the monthly bottle refill and rental charge to estimate the per patient cost as £6.60 ($=£0.71+(\pounds4.84+\pounds6.93)/2$) i.e. +£12.29



Costs

- Morphine IV: £7.70 per patient including single use tourniquet, cannula and cannula pack, syringe, drawing up needle, 3 ampoules of sodium chloride and one ampoule of morphine sulfate; paramedic backup of £4.19 as per assumption (£209.38/50) i.e. -£11.19
- Paracetamol IV: £7.87 i.e. -£11.02
- Morphine IV + paracetamol IV combined: £9.98 i.e. -£8.91
- Parenteral weighted casemix we estimated per patient cost to be £8.65, i.e. - £10.24

Conclusions

- Methoxyflurane acted >4 x more quickly vs Entonox to reduce pain from severe to moderate
- Methoxyflurane acted >3 x more quickly vs IV paracetamol
- Methoxyflurane acted 2 x more quickly vs IV morphine
- Both paramedics and EMTs were able to implement the use of methoxyflurane
- Limitations related to observational data and methods

Conclusions (cont.)

- Clinician reported adverse effects minor and infrequent (6.7%) leading to cessation of use in 3/5 of those with side effects or failure to work
- Benefits achieved at higher cost ~£9-11 compared with usual analgesics



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Thank you

Contact: nsiriwardena@lincoln.ac.uk



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