Severe **S**ickle Cell Pai**N** **I**ntranasal **F**entanyl (SSNIF) versus Intravenous Morphine - A Placebo-Controlled, Triple-Blind, Double-Dummy Non-Inferiority Randomized Controlled Trial

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Setting

- Tertiary care teaching hospital
- Paediatric ED
- Annual ED census 35,000
- > 200 sickle cell (SCD) ED attendances/year

The Evidence Gap

- Initial analgesic management of acute pain is devoid of quality studies[1]
- Identified as a research area of high need by national and international organisations[1] (NIH, USA & NICE,UK)

Source of Evidence

1. NIH & NICE Reviews

The Evidence

- INF clinically efficacious (3 RCTs and Cochrane)[1]
- Removes the immediate necessity of IV access for acute pain management[2]
- Mean (SD) time, from triage, to INF administration 23.7 (2.8) minutes[2]
- Empowers nursing staff to safely administer strong opioid analgesia

Source of Evidence

1. *Cochrane Library* Murphy A et al 2014
2. *Emergency Medicine Australasia* Borland M et al 2008

RCT Design

- P= Consecutive consented participants (1-21 years old) with pain due to SCD were randomized after identification at ED triage
- I= INF 1.5mcg/kg and IV placebo (0.9% saline)

- C= IV Morphine 0.1mg/kg and IN placebo (0.9% saline)
- O= Pain severity 10 minutes

Statistical Design

- Non-inferiority RCT
- Clinical meaningful difference in pain score 1.3cm[1,2]
- Non-inferiority margin (Δ) of 0.6 cm
- A sample size of 30 patients (15 per group) provided at least 80% power with a level of significance of 0.05

Source of Evidence
1. *Academic Emergency Medicine* Kelly AM 1998
2. *Annals of Emergency Medicine* Todd KH 1996

RCT Design

- Computer-generated non-stratified 5-per-block randomization
- The allocation codes to sequential sealed trial packs (made up by an independent pharmacist) in sequential numbered opaque sealed envelopes
- Blinding: Patients, Clinical Staff, Pharmacist, Research Assistant/data collector

Inclusion criteria

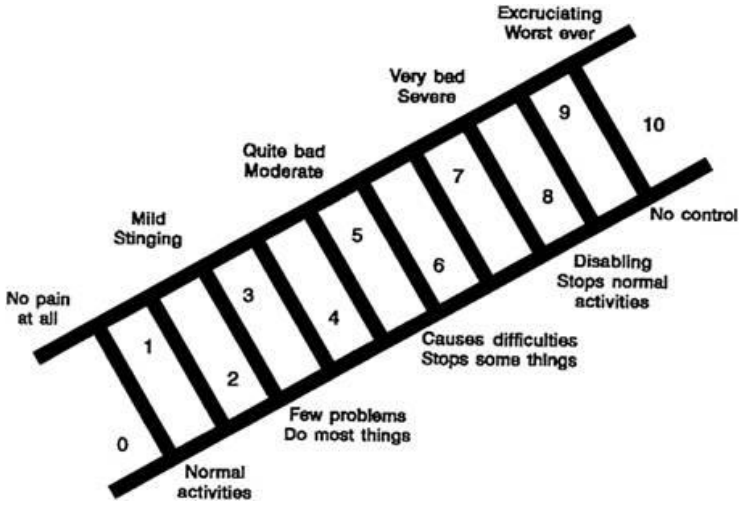
- Weight ≥10 kg and ≤70 kg
- Known SCD presenting with severe pain
- Written informed consent and assent obtained prior to painful crisis
- Verbal consent and assent obtained at the time of ED presentation
- Hospital admission required for painful SCD crisis

Exclusion Criteria

- Previously enrolled in this trial
- Parenteral narcotic within 4 hours of ED presentation
- Oxygen sats below 95% on initial assessment
- Altered conscious state as defined by GCS < 15
- Contraindications to fentanyl/morphine usage
- Inability to secure IV access
- Enrolment in another clinical trial within 4 weeks
- Patients with any condition that would make him/her unsuitable
- Injured or blocked nose

Pain Assessment Tools[1,2]

Manchester Pain Ruler



FLACC Scale			
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort

- **Severe pain:** The occurrence of pain due to SCD in the extremities, back, abdomen or chest that is rated 7 or greater on a Manchester pain ruler or FLACC scale.

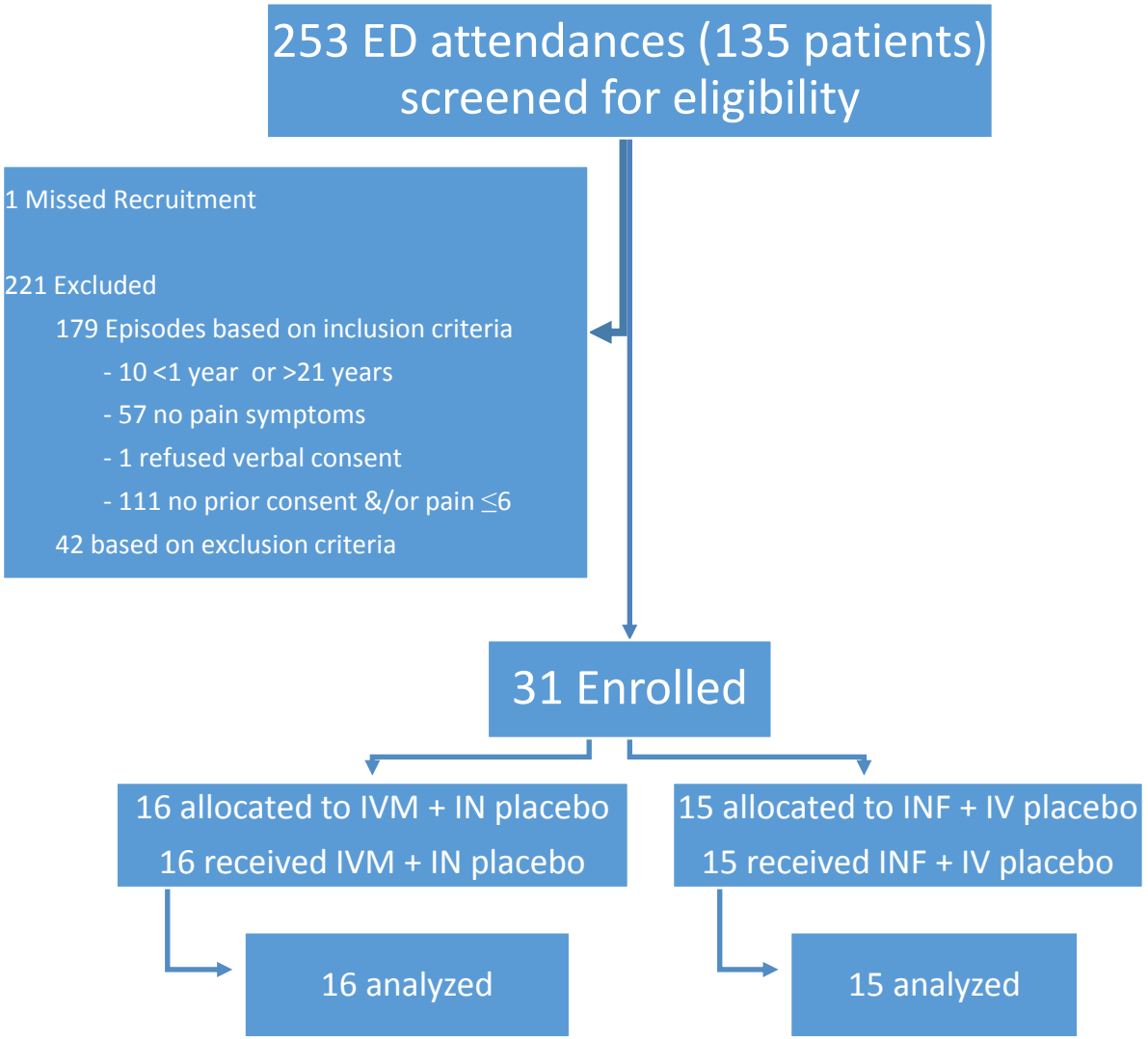
Source of Evidence

1. *The American Journal of Nursing* Merkel S et al 2002
2. *Emergency Nurse* Lyon F et al 2005

Consent

- In the outpatient setting all patients with SCD were approached
- Written pre-consent was attained in 170 of the 397 screened Haematology outpatients
- Occurred in parallel with commencement of RCT
- Verbal re-consent in the PED

Results


253 ED attendances (135 patients) screened for eligibility
1 Missed Recruitment
221 Excluded
179 Episodes based on inclusion criteria
- 10 <1 year or >21 years
- 57 no pain symptoms
- 1 refused verbal consent
- 111 no prior consent &/or pain ≤6
42 based on exclusion criteria
31 Enrolled
16 allocated to IVM + IN placebo
16 received IVM + IN placebo
15 allocated to INF + IV placebo
15 received INF + IV placebo
16 analyzed
15 analyzed

Demographic and Clinical Characteristics

Variable	IV morphine (n=16)			IN fentanyl (n=15)		
Age (years)	11.0 (SD 5.1)			10.3 (SD 5.6)		
Gender Ratio	M:F 10:6			M:F 8:7		
Weight (Kg)	40.3 (SD 19.9)			36.2 (SD 16.9)		
Time Zero Pain Score	8.3 (SD 0.9)			8.3 (SD 1.2)		
Pain Assessment tool	3 FLACC : 13 Manchester Pain Tool			3 FLACC : 12 Manchester Pain Tool		
Administered pre-hospital analgesia	15/16			14/15		
Previous Pain Episodes with Analgesia History						
History of painful episodes	16/16			15/15		
History of IVM administration	Yes=10	No=2	Uncertain=4	Yes=10	No=2	Uncertain=3
Average annual ED attendance	1.4 attendances			1.8 attendances		

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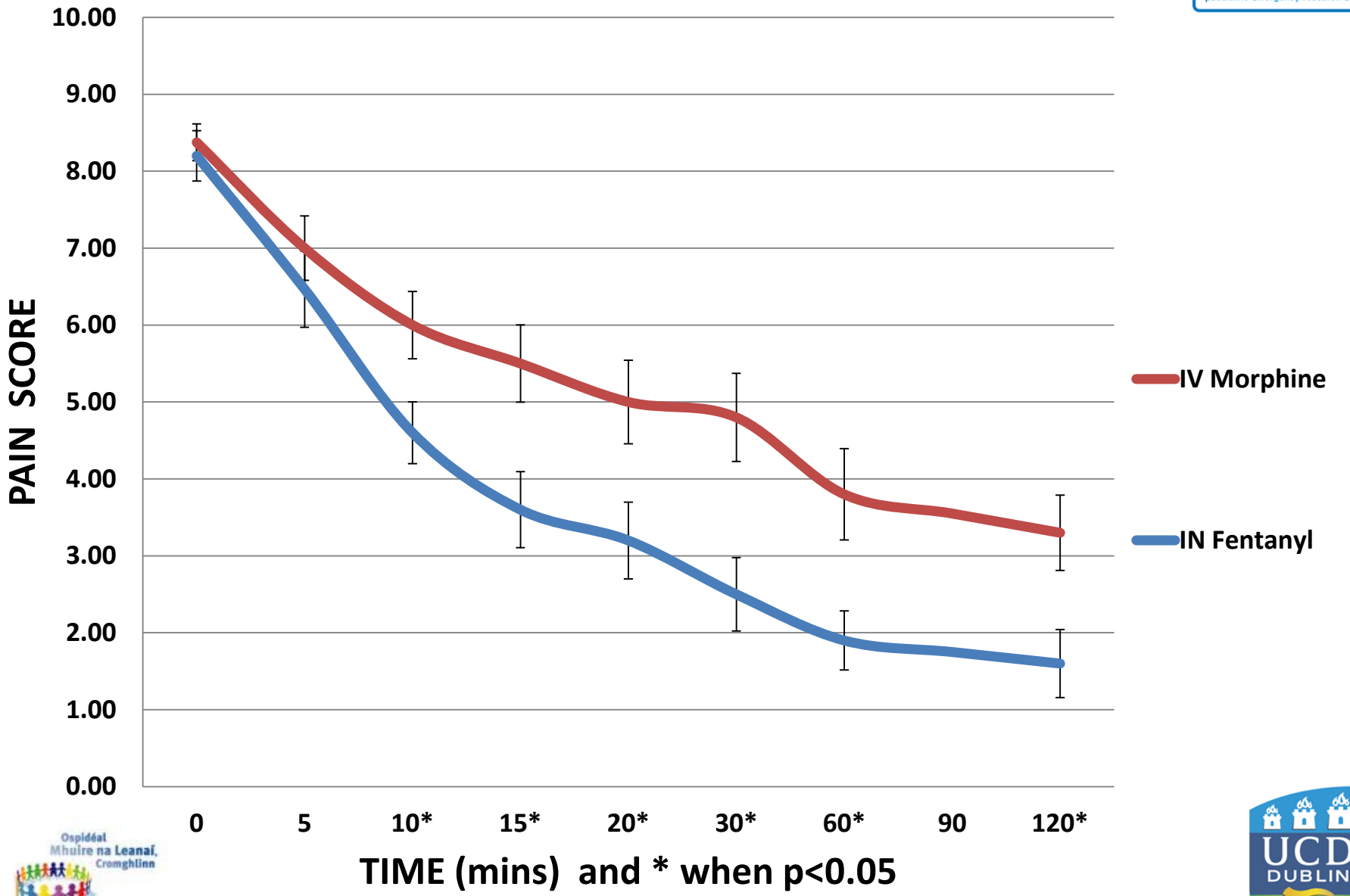
Mean (SEM) Pain Scores at Consecutive Time Points



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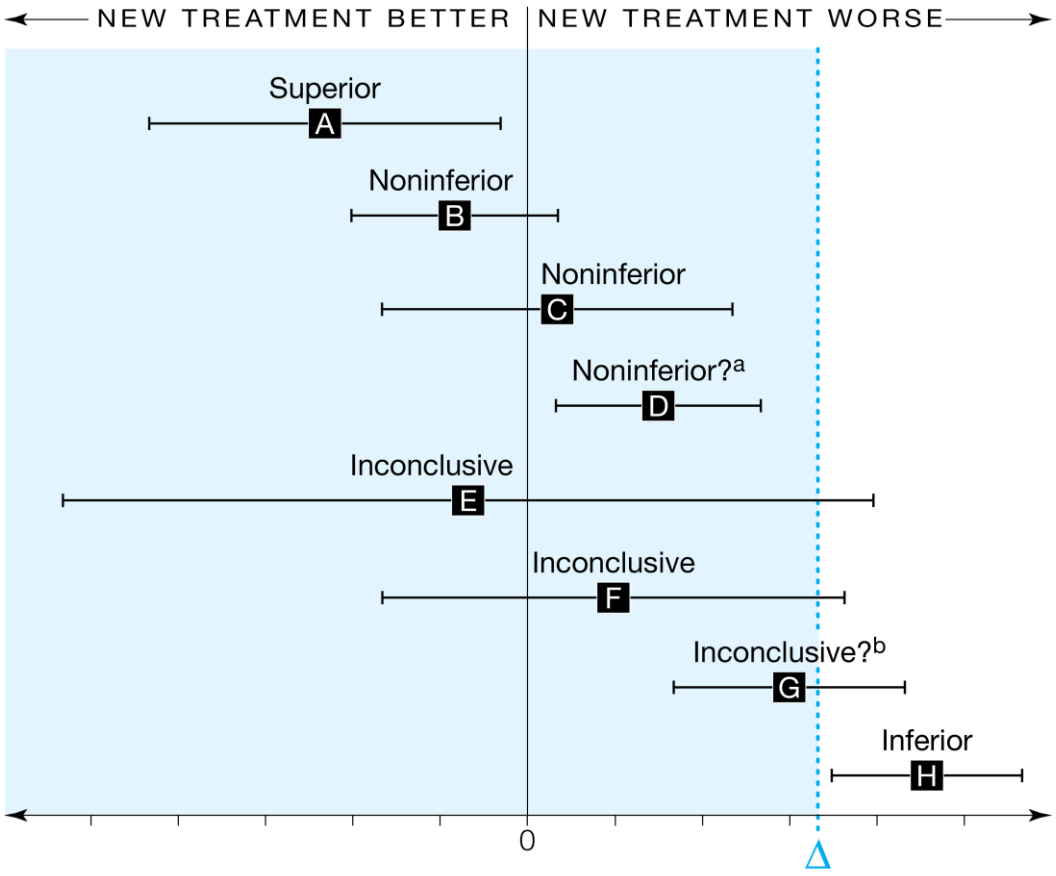

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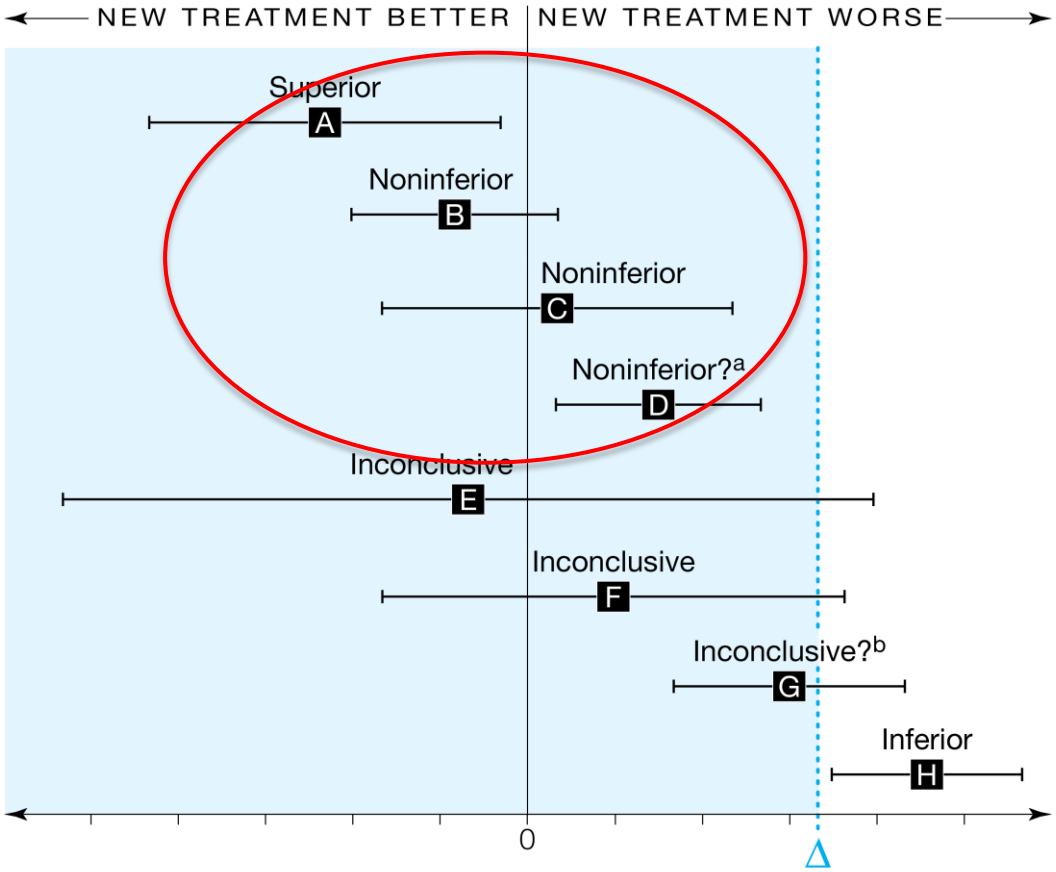
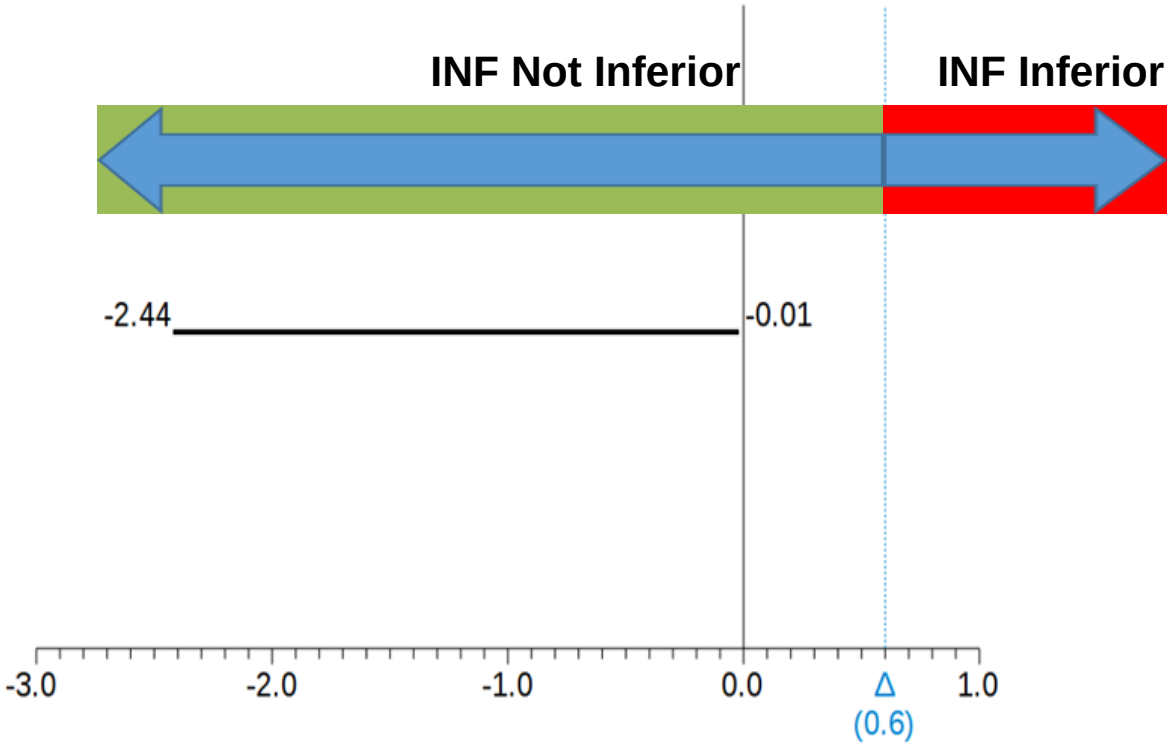


95% Confidence Interval for Difference in Mean Pain Improvement between Fentanyl and Morphine



Adapted from Piaggio et al[1] JAMA 2012

Additional Analgesia and Lowest Sedation Score

Variable	IV morphine	IN fentanyl
IV morphine	2	0
Oral Medications	7	1
Lowest level of Sedation (UMSS)	Level 1 = 7 Level 2 = 7 Level 3 = 2	Level 1 = 12 Level 2 = 3 Level 3 = 0

UMSS = University of Michigan Sedation Scale

Discussion

- We demonstrate the non-inferiority of INF compared to IVM without significant differences in terms of further analgesia, adverse events and sedation scores

- A significant difference of pain scores between groups persisted at time points beyond the primary outcome up to 120 minutes

Discussion

- First RCT comparing INF vs IVM in the initial management of pain in SCD and in non-trauma related pain

- First RCT to *a priori* study acute **severe** pain in a cohort of paediatric patients with SCD

Limitations

- Single centre trial
- Written consent process slowed ED recruitment
- Designed to establish the non-inferiority of INF by the usage of pain scores alone and not for secondary outcomes
- Pain is subjective as is it's measurement but pain scores remain the best method of assessment

Conclusion

- INF is non-inferior to IVM
- IN is a faster route of drug administration than IV route in an emergency setting
- We potentially define the new gold standard for the initial treatment of acute severe pain due to SCD in the ED

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- Clinical Emergency and Haematology Staff

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