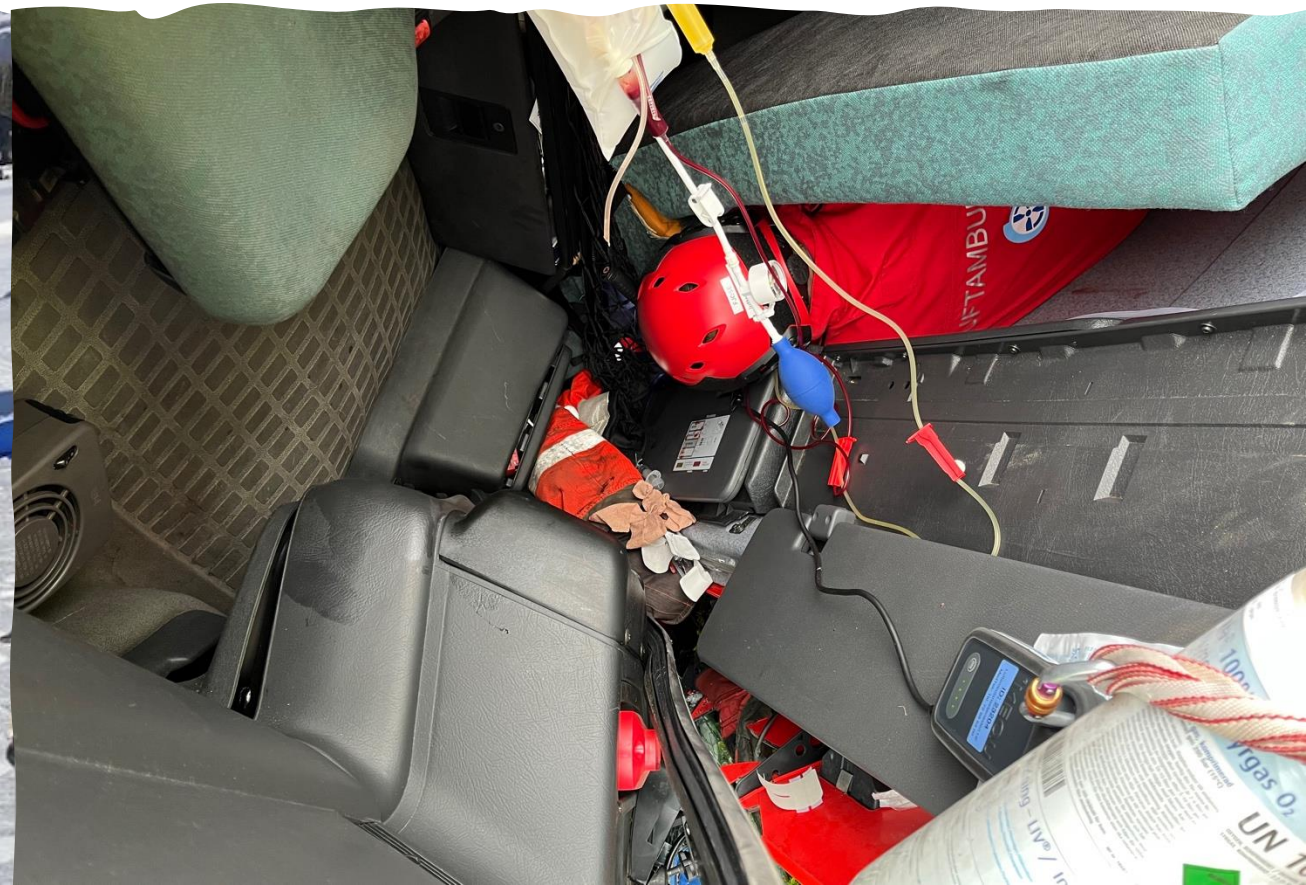
Prehospital non-invasive pain management

Lars Olav Fjose
MD
Sykehuset Innlandet
Hospital trust



Disclosure

Title page

A randomized controlled, open-label, non-inferiority, three arm clinical study to assess the effectiveness and safety of a regimen with inhalation of low-dose Methoxyflurane compared with a regimen of intranasal Fentanyl and a regimen of intravenous Morphine for the treatment of acute pain with NRS $\geq$ 4 in patients from 18 years of age carried out by ambulance workers in pre-hospital setting.

Compound: Inhalational Methoxyflurane versus intranasal Fentanyl versus intravenous Morphine.

Brief Title: A comparison of three regimens with inhalational methoxyflurane versus intranasal fentanyl versus intravenous morphine in pre-hospital acute pain management.

Phase: 3
Inhalation of methoxyflurane and intranasal fentanyl will be used outside approved indication. The study intension is to obtain additional information about the efficacy of the investigational products. The PreMeFen is hence a phase 3 study.

Short name: PreMeFen

Sponsor Name: Oslo University Hospital

Compairing three regimens of analgestic drugs in patients with acute pain, repeated dosing allowed

	Primary Objectives	Number	Primary Endpoints	Assessment
1a	To determine if a regimen of inhalation of 3 ml methoxyflurane is non-inferior to a regimen of intranasal 50 µ (>70) or 100 ug (>18, <70 years) fentanyl in reduction of moderate to severe pain (NRS ≥ 4) after 10 min in patients >18 years of age. (Repeated dosing allowed)	1.1	Changes in pain score from t0 to t10min	ΔNRS t0-t10
1b	To determine if a regimen of inhalation of 3 ml methoxyflurane is non-inferior to a regimen of morphine IV 0.1 mg/kg (0.05 mg/kg from >70 years or fragile patients) in reduction of moderate to severe pain (NRS ≥ 4) after 10 min, in patients >18 years of age. (Repeated dosing allowed)	1.2		
1c	To determine if a regimen of intranasal 50 µ(>70 years) or 100 ug (>18, <70 years) fentanyl is non-inferior to a regimen of morphine IV 0.1 mg/kg (or 0.05 mg/kg >70 years old or fragile patients) in reduction of moderate to severe pain (NRS ≥ 4) after 10 min, in patients >18 years of age. (Repeated dosing allowed)	1.3		
	Secondary Objectives		**Secondary endpoint**	**Assessment**
2	To assess the reduction in NRS from baseline at 5, 20, 30 minutes and/or to emergency department (ED) arrival	2.1	Change in pain score from t0-t5	ΔNRS t0-t5
		2.2	Change in pain score from t0-t20	ΔNRS t0-t20
		2.3	Change in pain score from t0-t30	ΔNRS t0-t30Δ
		2.4	Change in pain score from t0-tED-arrival	ΔNRS t0- t ED-arrival
3	To assess the need for rescue analgesia in the treatment groups	3	Need for additional analgesia not in the regimen of the allocated treatment group:	• time of administration • type of medication • dose • route of administration
4	To determine difference in time from scene arrival to IMP administration	4	Difference in time arrival to administration of IMP	Δ tx -t0

Objectives

- To determine if a regimen of methoxyflurane is non inferior to a regimen of intranasal fentanyl or a regimen of intravenous morphine at 5, 10, 20 and 30 min in patients with acutepain with NRS more than 4
- Assess the need for rescue medicine in the groups
- Determine difference in time from scene arrival to administration of analgesic
- Assess diffrences in AE
- Determine efficacy within diagnoisis group
- Determine the need for rescue medicine in relation of painfull procedures, painfull evacuation, reposition of fractures etc

Sample size

With an alfa of 0.05 and a beta of 0.1 (90% power) the sample size required to detect this difference was estimated to be n=88 in each arm by time 10 minutes for administration of IMP.

That **gives a total number of participants of 264, and the plan is to include 3x90 = 270 patients per protocol.**

In order to achieve this number, we plan to enrol approximately 300 subjects, anticipating not all subjects enrolled will adhere to the protocol completely.

BJA Open

BJA Open, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bjao.2023.100204
Original Research Article

ORIGINAL RESEARCH ARTICLE

Haemodynamic effects of methoxyflurane versus fentanyl and placebo in hypovolaemia: a randomised, double-blind crossover study in healthy volunteers

Lars Øivind Høiseth[1,2,*], Lars Olav Fjose[3,4], Jonny Hisdal[2,5], Marlin Comelon[1], Leiv Arne Rosseland[1,2,6] and Harald Lenz[1]

[1]Department of Anaesthesia and Intensive Care Medicine, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Norwegian Air Ambulance Foundation, Oslo, Norway, [4]Division of Pre-hospital Services, Innlandet Hospital Trust, Moelv, Norway, [5]Section of Vascular Investigations, Oslo University Hospital, Oslo, Norway and [6]Department of Research and Development, Division

Background

- Methoxyflurane is approved for relief of moderate to severe pain in conscious adult trauma patients.
- Our patients may sustain injuries causing haemorrhage compromising haemodynamic stability.
- It is therefore important to elucidate whether methoxyflurane may adversely affect the haemodynamic response to hypovolaemia

Methods

- In this randomised, double-blinded, placebo-controlled cross-over study, inhaled methoxyflurane 3 ml, intravenous fentanyl 25 µg and placebo were administered to 15 healthy volunteers exposed to experimental hypovolaemia in the lower body negative pressure (LBNP) model.
- In a recent study,we have demonstrated fentanyl 25 mcg i.v. to be equianalgesic to 3 ml inhaled methoxyflurane in healthy volunteers.
- The primary endpoint was the effect of treatment on changes in cardiac output, while secondary endpoints were changes in stroke volume and mean arterial pressure as well as time to haemodynamic decompensation during LBNP.

Measurements

- A non invasive arterial pressure waveform was obtained by the volume-clamp method around the left middlefinger
- Ascending aortic blood velocity by suprasternal Doppler
- Acral (fingertip) skin perfusion was measured by laser Doppler flowmetry at the left thumb

- There were no statistically significant effects of treatment on the changes in cardiac output, stroke volume or mean arterial pressure during LBNP.

- Time to decompensation was longer for methoxyflurane compared to fentanyl (hazard ratio (HR) 1.9; 95%CI 0.4 to 3.4; P=0.010), while there was no significant difference to placebo (HR -1.3; 95%CI -2.8 to 0.23;

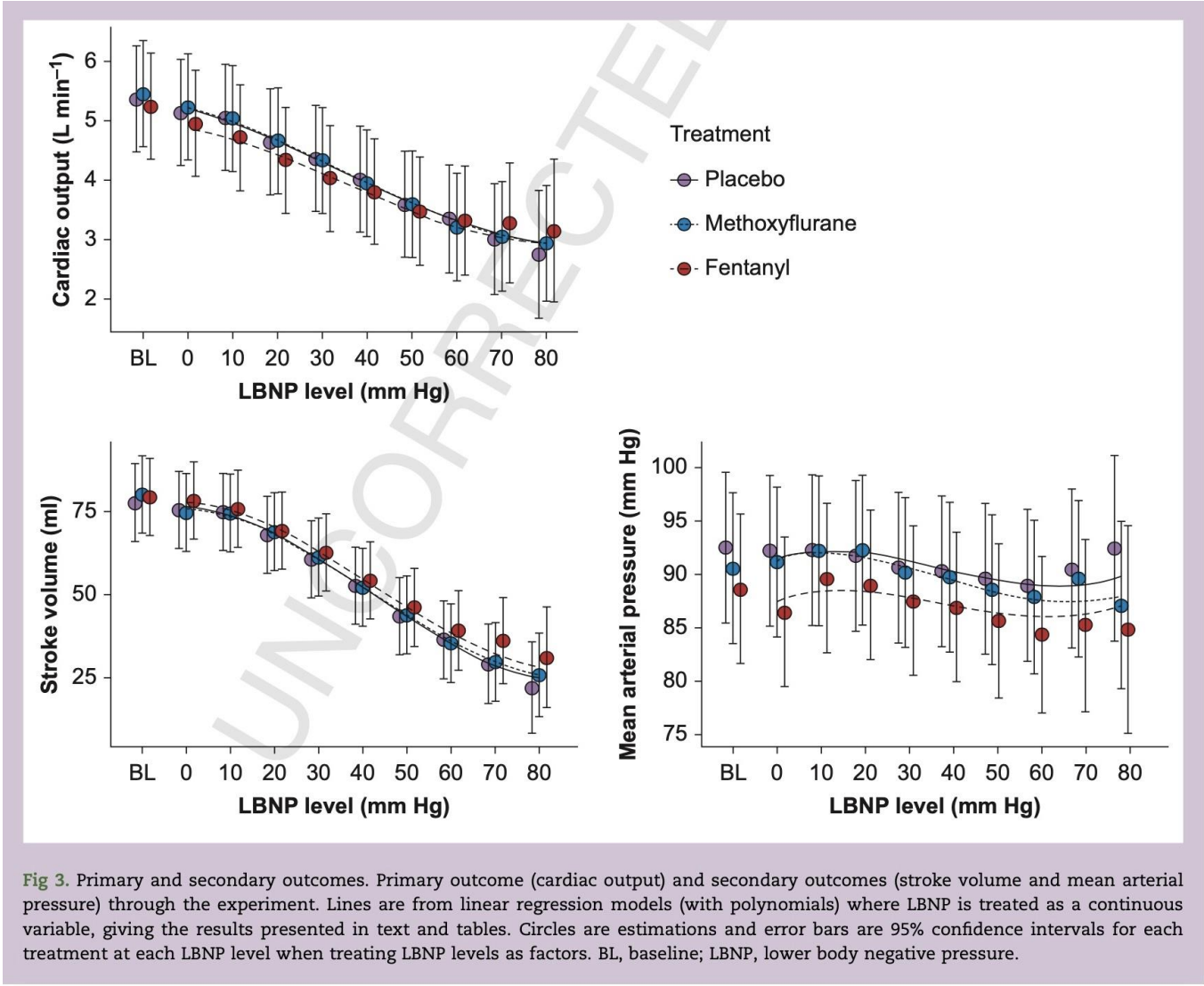


Fig 3. Primary and secondary outcomes. Primary outcome (cardiac output) and secondary outcomes (stroke volume and mean arterial pressure) through the experiment. Lines are from linear regression models (with polynomials) where LBNP is treated as a continuous variable, giving the results presented in text and tables. Circles are estimations and error bars are 95% confidence intervals for each treatment at each LBNP level when treating LBNP levels as factors. BL, baseline; LBNP, lower body negative pressure.

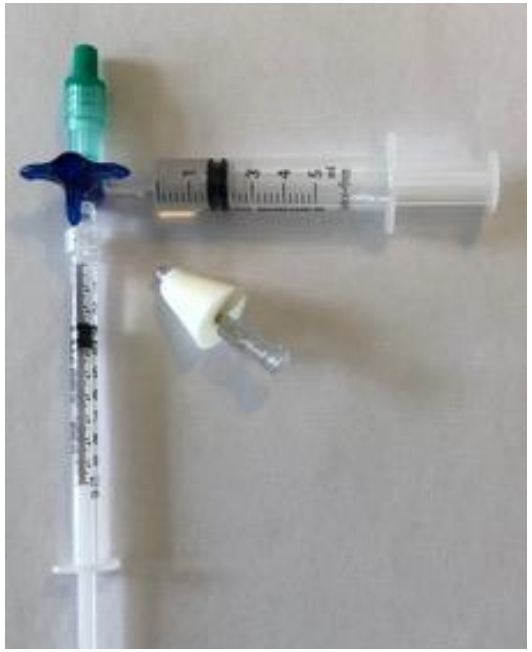
Conclusions

- The present study does not indicate that methoxyflurane has significant adverse haemodynamic effects in conscious adults experiencing hypovolaemia.

Intranasal fentanyl and ketamine in 100 children with severe traumatic pain in pre-hospital setting in the hands of paramedics, a feasibility trial

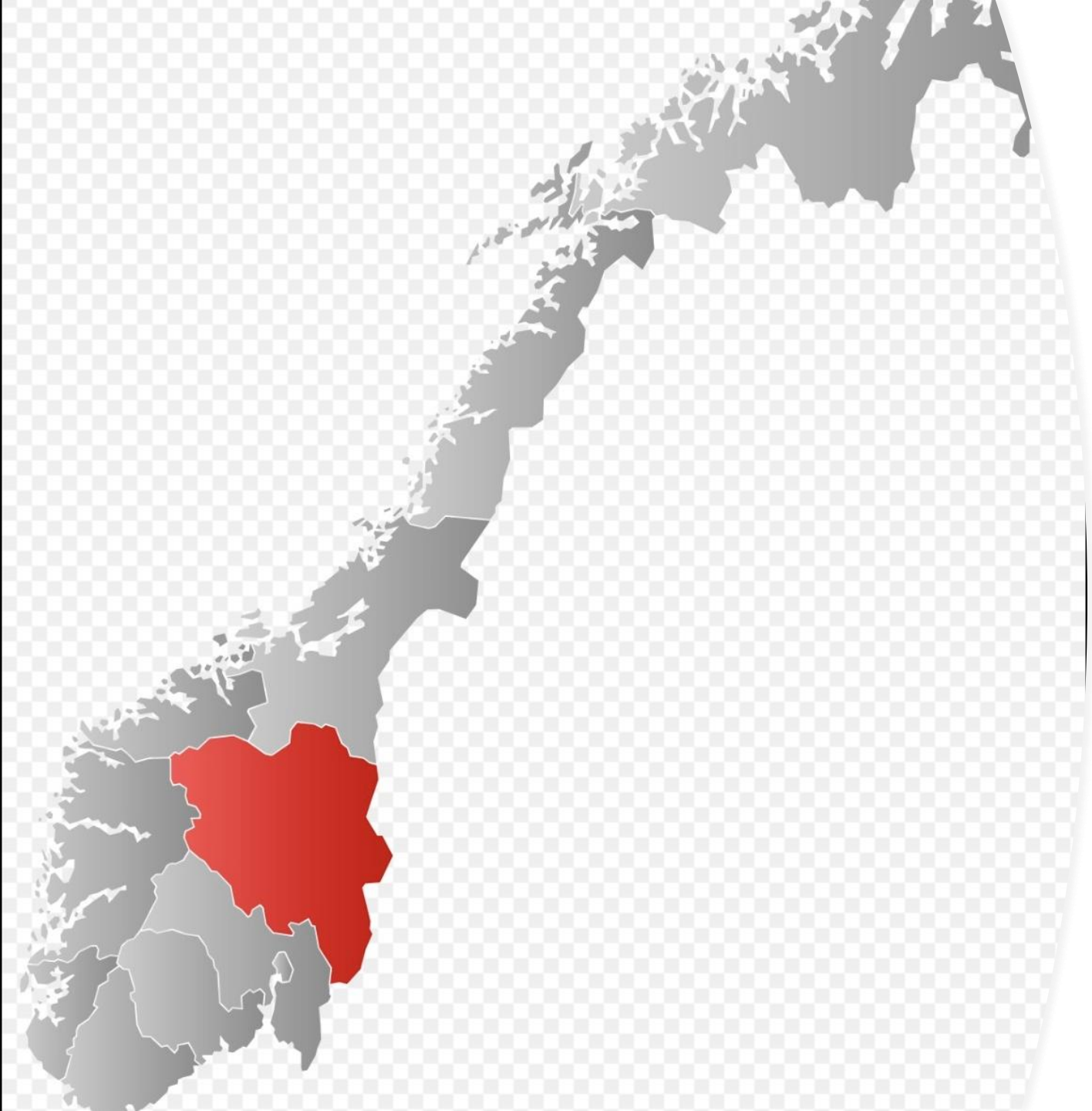
Lars Olav Fjose

MD



NORWEGIAN AIR AMBULANCE FOUNDATION

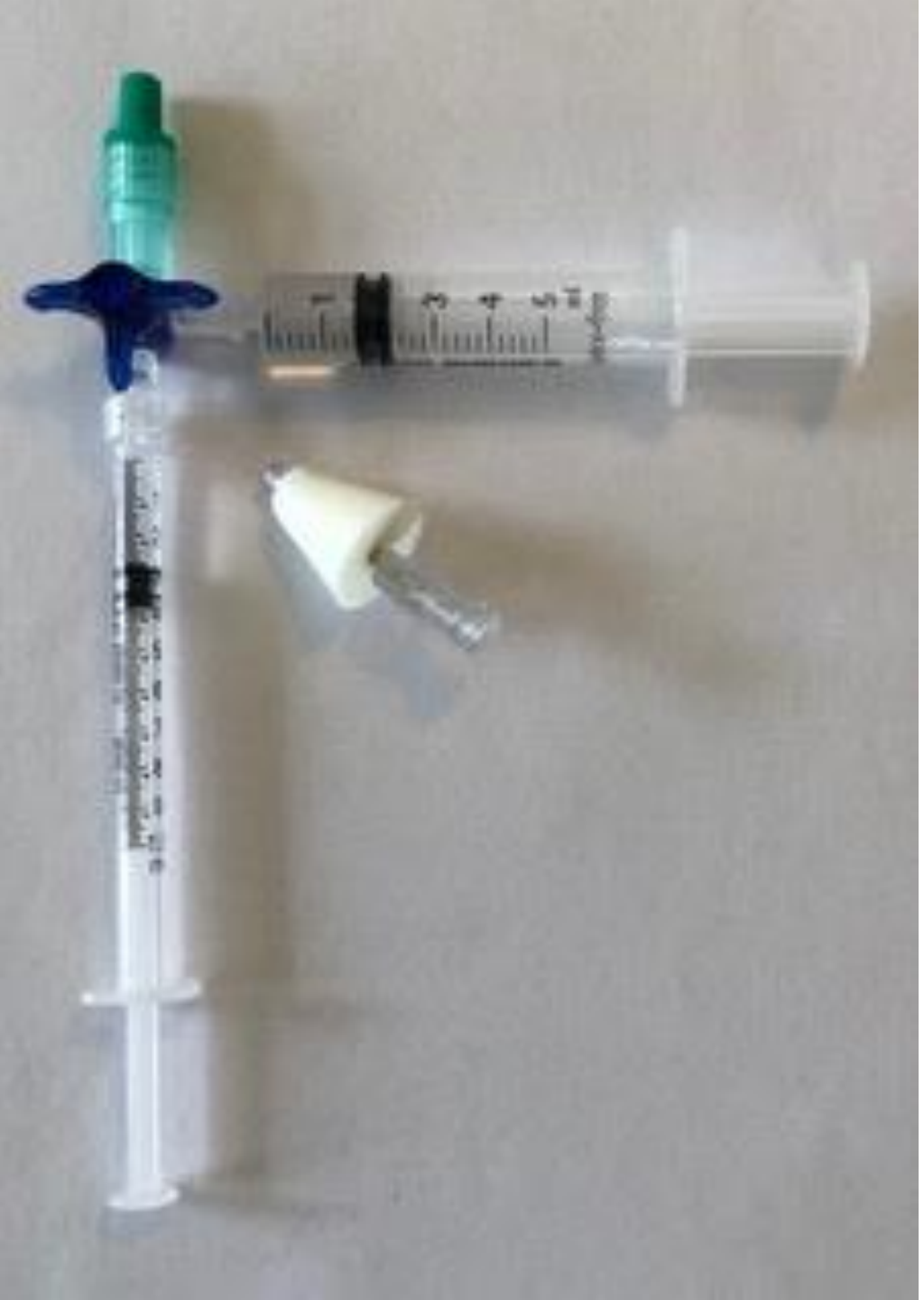
Innlandet Hospital Trust



Why intranasal opioid administration in our ambulanse service?

- Pediatric intravenous morphine in 13 cases during 18 month from 2013, no opioid < 7 years
- Our hospital trust responsible for population 370 000, size of Denmark
- Intranasal administration opioids increased the chance of opioid use due to its ease of administration

- Both IN ketamin and fenatnyl are effective in pediatric pain
- We want to take advantage of both drugs
- Increase effect and reduced risk of AE in ambulance service.
- This study aimes to describe the feasibility of a combination of non-invasive 1,5 mcg/kg intranasal fentanyl (INF) and 1 mg/kg intranasal ketamine (INK) administered by paramedics



- The dose of fentanyl 50 mcg/ml and ketamine 50 mg/ml were to be mixt in a 2 or 5 ml syringe.

- MAD Nasal 300; Teleflex Medical, Morrisville, NC 27560, USA, was used with a 1 ml syringe to vaporize fentanyl and ketamine

Doses of fentanyl and ketamine

mixed in a 2- or 5-ml syringe for IN administration

Weight	IN Fentanyl 50 µg/ml *1,5 µg/kg*	IN Ketamin 50mg/ml *1,0 mg/kg*	IN Naloxone in case of hypoxia/ bradypnea
15-19 kg	**0.5 ml (25 µg)**	**0.25 ml (12,5 mg)**	0.50ml im
20-24 kg	**0.6 ml (30 µg)**	**0.3 ml (15 mg)**	0.5 ml im
25-29 kg	**0.75 ml (37,5 µg)**	**0.5 ml (25 mg)**	0.5 ml im
30-34 kg	**0.8 ml (40 µg)**	**0.6 ml (30 mg)**	0.7 ml im
35-39 kg	**1.0 ml (50 µg)**	**0.7 ml (35 mg)**	0.8 ml im
40-44 kg	**1.2 ml (60 µg)**	**0.8 ml (40 mg)**	1.0 ml im
45-50 kg	**1.35 ml (67,5 µg)**	**1.0 ml (50 mg)**	1.0 ml im

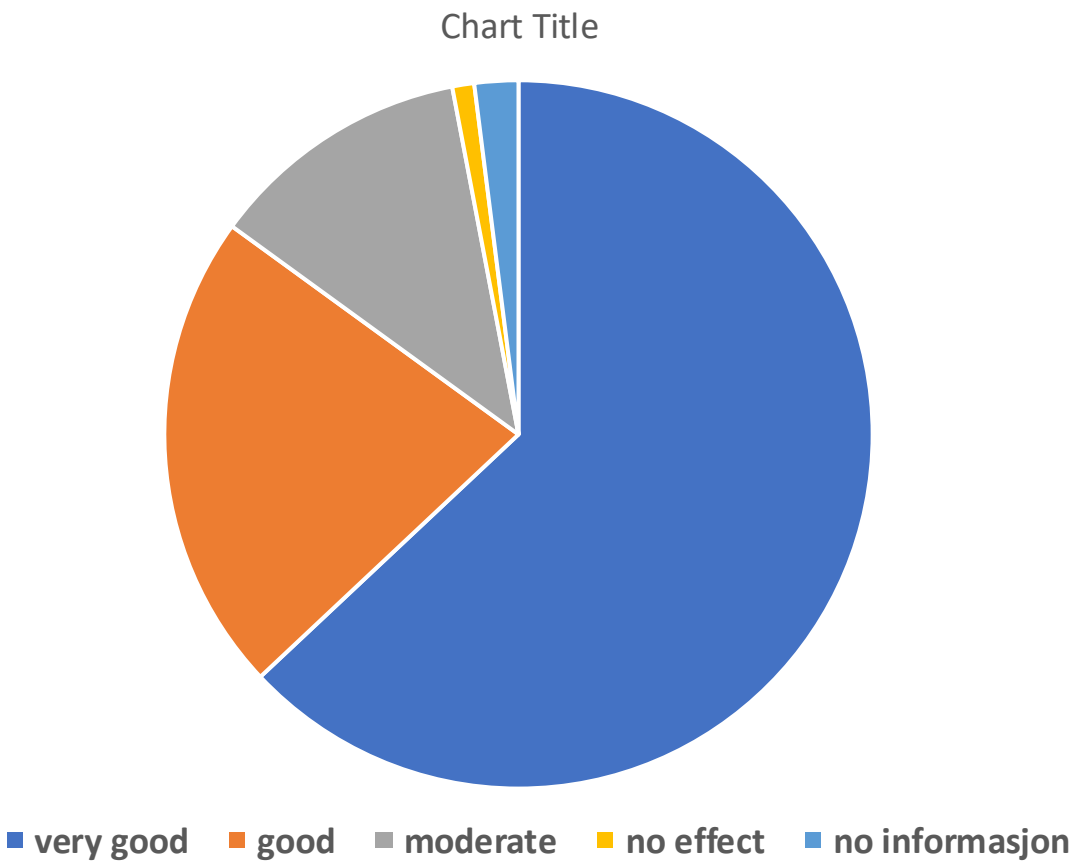
leg/ankle fracture	31
femur fracture	14
lower arm fracture	13
mixt cases	12
wound	7
patella luxation	5
traumatic back pain	4
clavicle fracture	4
shoulder luxation	3
knee pain	3
upper arm fracture	4

	Mean	Min.	Max
Age	9.21	1	16
Gender	Males 66 %		
Weight	34.16	10	80
Fentanyl dose (ug)	54.75	12.5	150
Ketamine dose (mg)	37.41	12.5	150

Adverse Events

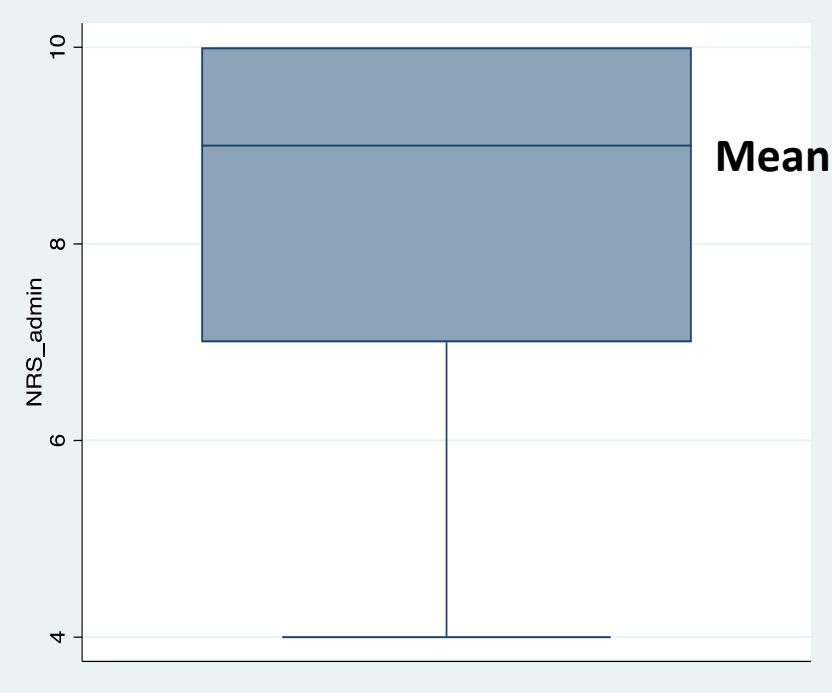
- No AE reported in 92% of cases
- Minor Adverse events reported:
    - Sleepiness 3%
    - Dizziness 1%
    - Nausea 1%
    - Headache 1%
    - Confusion 2%
    - Muscle twitches 1%
    - Flashlight sensation 1%
- No respiration depression, no circulatory events reported
- No need for Naloxone

Paramedics assessment of treatment effect

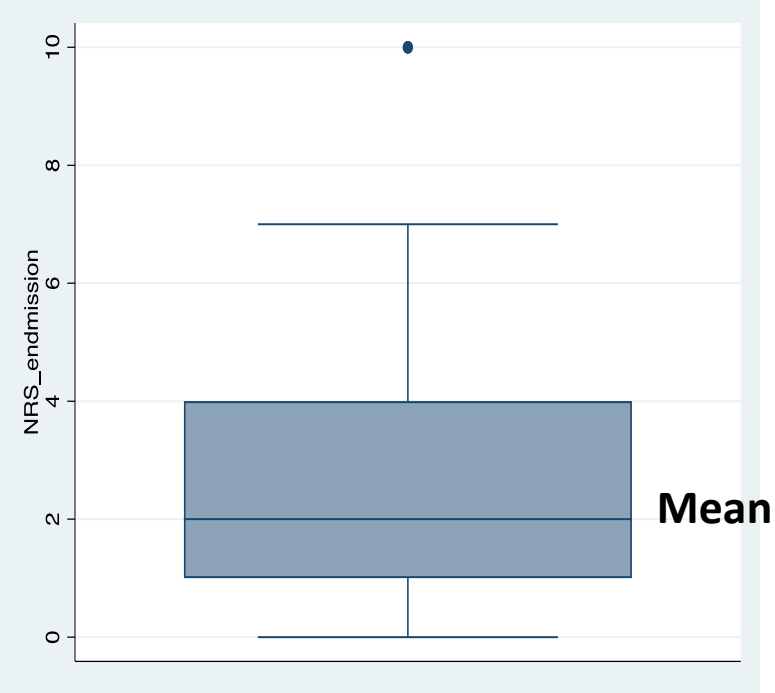


Main effect outcome:

Pre administration



Post administration



Difference in **Face Pain Scale** pre vs post administration:

5.7 (95% CI 5.3-6.1)

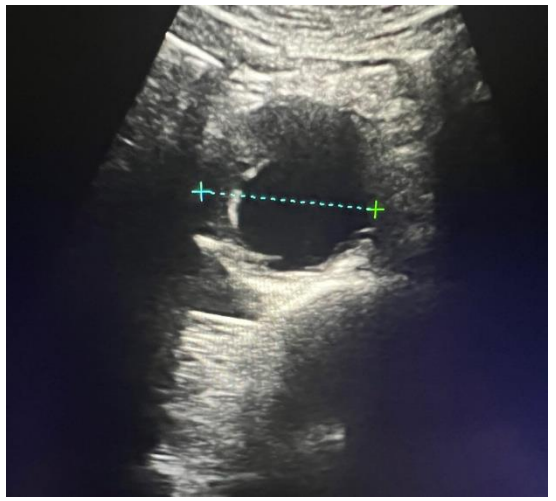
Pain management with inhalation of methoxyflurane by non-medical ski patrol

- By Hanna Sofia Rydlöv,
- Lars Olav Fjose
- Fridtjof Heyerdahl

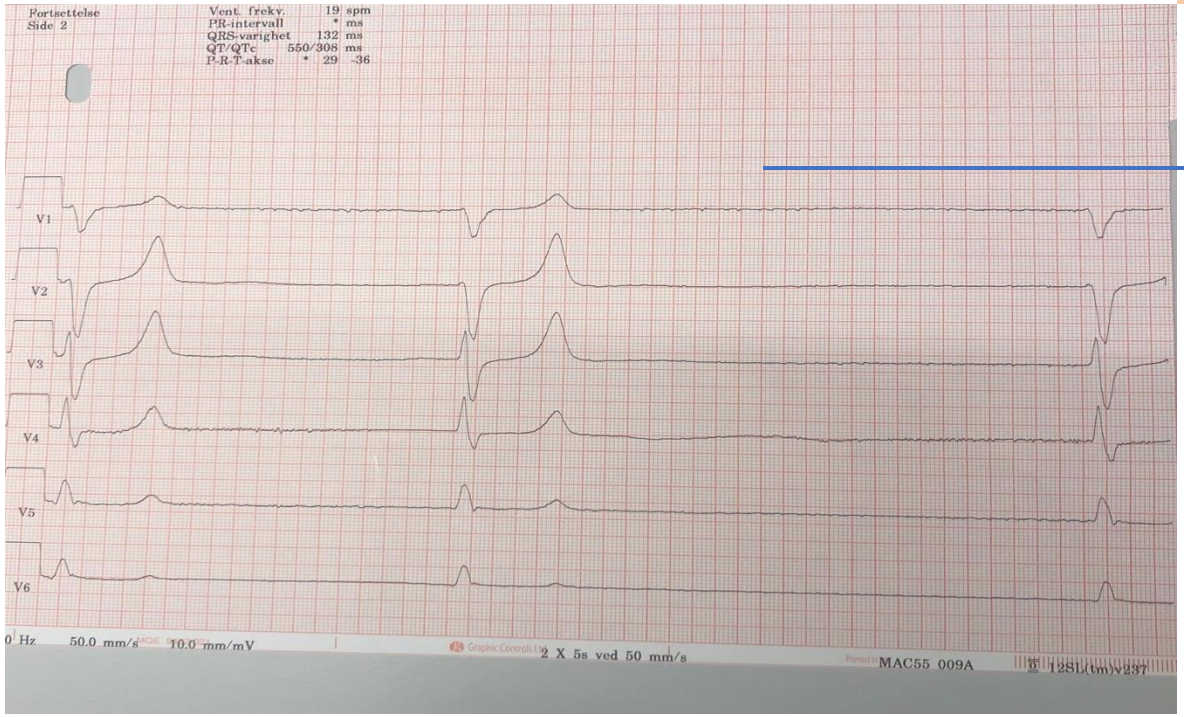
- 53 patients with ski related injuries were treated by ski patrol, 66 % fractures, 13% joint luxations.
- NRS went down in average 3 points, NRS 8 to 5.
- No serous AE
- Early pain management with inhalation of methoxyflurane provides good perceived effect with mild adverse events and can be of great value in settings where few alternatives for pain management are available.

Methoxyflurane to alpine rescue group (NARG)

- Volenter rescue climbers
- Often cooperate with air ambulance in high altitude and difficult terrein.
- In cooperation with air ambulance and after training and delegation



Takk!


Fortsettelse
Side 2
Vent. frekv. 19 spm
PR-intervall * ms
QRS-varighet 132 ms
QT/QTc 550/308 ms
P-R-T-akse * 29 -36
V1
V2
V3
V4
V5
V6
50.0 mm/s
10.0 mm/mV
2 X 5s ved 50 mm/s
MAC55 009A

- There is to our knowledge no study from prehospital peadiatric trauma care involving opioid-sparing effects of ketamine.

- The opioid sparing effect of ketamine is especially attractive in children in the prehospital environment.

Some comments from attending paramedics:

“Very fast and good effect”

“Very successful pain relief”

“Vascular access was unsuccessful, and this was a very good alternative to morphine iv”

“This opens up a new world for us“

5	To determine time difference from scene arrival to pain reduction	5	Time from ambulance personnel arrival to first measure > 2 points reduction in NRS from baseline	Δ tx -to first t with ΔNRS>2
6	To determine any difference in level of sedation	6	Change in level of sedation from t0 to T-10 and T-30	Δ GCS t0 to T-10 and T-30
7	To determine any difference in change in respiratory rate (RR)	7	Change in RR t0 to T-10 and T-30	Δ RR t0 to T-10 and T-30
8	To determine any difference in systolic blood pressure (SBP)	8	Change in SBP t0 to T-10 and T-30	Δ SBP t0 to T-10 and T-30
9	To determine the level of overall health care personnel satisfaction of the treatment	9	Likert scale of HCP satisfaction at end of mission	1–5-point Likert scale
10	To determine the level of overall patient satisfaction of the treatment	10	Likert scale of patient satisfaction at end of mission	1–5-point Likert scale
11	To determine differences in any adverse events or serious adverse events	11	Registration of AE and SAE during study period until end of intervention	AE and SAE t0 to discharge
	Exploratory Objectives		Exploratory endpoints	Assessment
12	To determine efficacy within diagnosis group	12	Analyse Primary and secondary efficacy endpoints stratified by diagnosis or diagnosis groups	ΔNRS t0-t10 stratified by diagnosis group Use of rescue analgesia stratified by diagnosis group ΔNRS t0-t30 stratified by diagnosis group
13	To determine the need for rescue medication in relation to painful procedures (complex evacuation, painful medical procedures)	13	Proportion of patient receiving rescue treatment related to procedures (reposition of fractures, relocation etc)	Use of rescue analgesia stratified by type of procedure
14	To determine any difference in attempts of vascular cannulation with the level of competence of the ambulance worker	14	Attempts of vascular cannulation access	Vascular access attempts from tx to tED and ambulance worker years of experience
15	To determine any difference in NRS reduction or time to pain relief stratified by ambulance worker competence	15	Change in NRS and time to a significant NRS reduction compared to level of competence	ΔNRS from tx to t30mim
16	To determine any difference in patient satisfaction stratified by ambulance personnel competence	16	Ambulance personnel competence and patient satisfaction	Participant Likert scale and ambulance worker years of experience; 1-4, 5-10, 11-20, >21
17	To determine efficacy within ACS groups 1) elevated versus normal Troponin group 2) ACS suspect ECG versus normal ECG	17	Analyze primary and secondary efficacy endpoints stratified by level of troponin after ED admission and sign of ACS on ECG at scene	ΔNRS t0-t10 and/or rescue medication stratified by Troponin groups ΔNRS t0-t10 and/or rescue medication stratified by ECG groups

Pediatric Anesthesiology
Section Editor: **James A. DiNardo**
SYSTEMATIC REVIEW ARTICLE

Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review

Alyssa Zhu, MD,* Hubert A. Benzon, MD, MPH,† and T. Anthony Anderson, MD, PhD*

JAMA Pediatrics | Original Investigation

Effect of Intranasal Ketamine vs Fentanyl on Pain Reduction for Extremity Injuries in Children
The PRIME Randomized Clinical Trial

Theresa M. Frey, MD; Todd A. Florin, MD, MSCE; Michelle Caruso, PharmD, BCPS; Nanhua Zhang, PhD; Yin Zhang, MS; Matthew R. Mittiga, MD

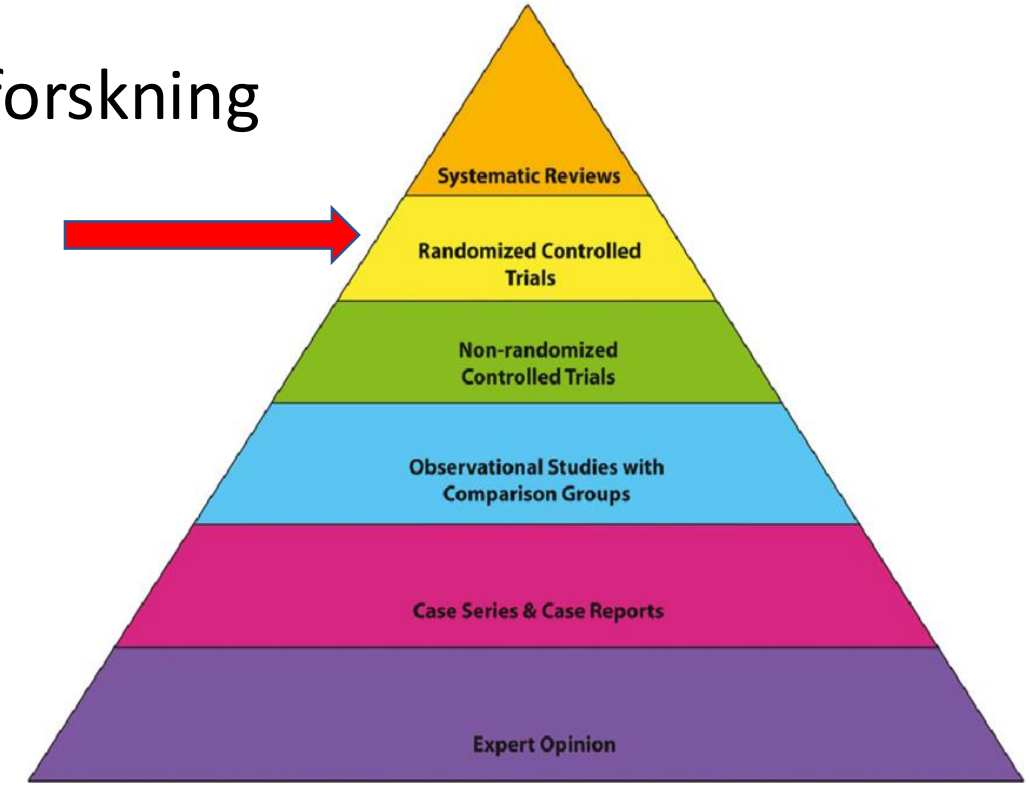
Emergency department, traumatic limb pain, 8-18 years

In this randomized, double-blind, active-control, noninferiority trial, intranasal ketamine (1.5 mg/kg) provided similar and noninferior pain relief when compared with intranasal fentanyl (2 µg/kg) for traumatic extremity injuries in children.

Both medications produced clinically meaningful pain reduction within 15 minutes.

Hva vil det si å rangere høyt i evidens?

- Våre funn får betydning for klinisk praksis – helt direkte!
- Meningsfullt å drive forskning!
- Pasientene forstår at de er med på nyttig forskning
- Regulatorisk tungt
  - Krever mange tillatelser...
  - Krever presisjon av ambulansearbeiderne!



Flytskjema – hva og når?

Opplæringsbehov:

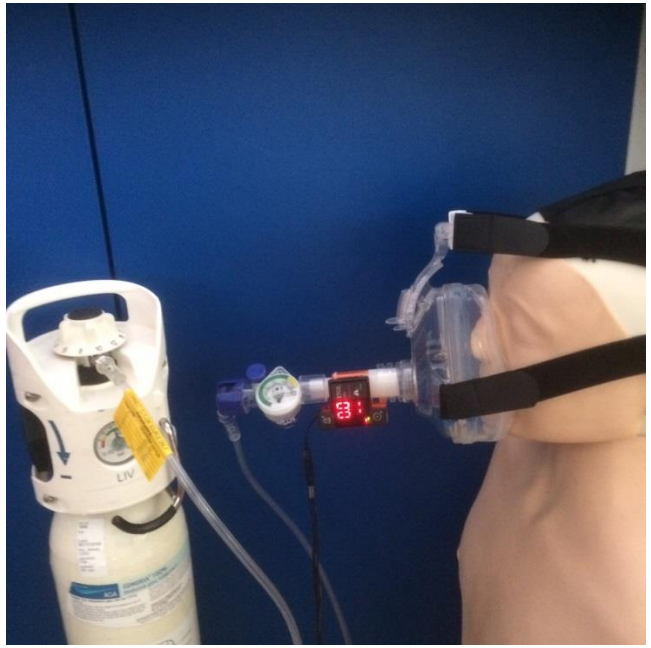
- **Opplæring av superbrukere**
  - Være med på å undervise studiemedarbeidere
  - Være resurspersoner lokalt under inklusjonsperioden
- **Opplæring studiemedarbeidere**
  - Estimert tidsforbruk: 8t
  - Teoretisk del i Nakos
  - Praktisk del / utsjekk- oppmøtebasert

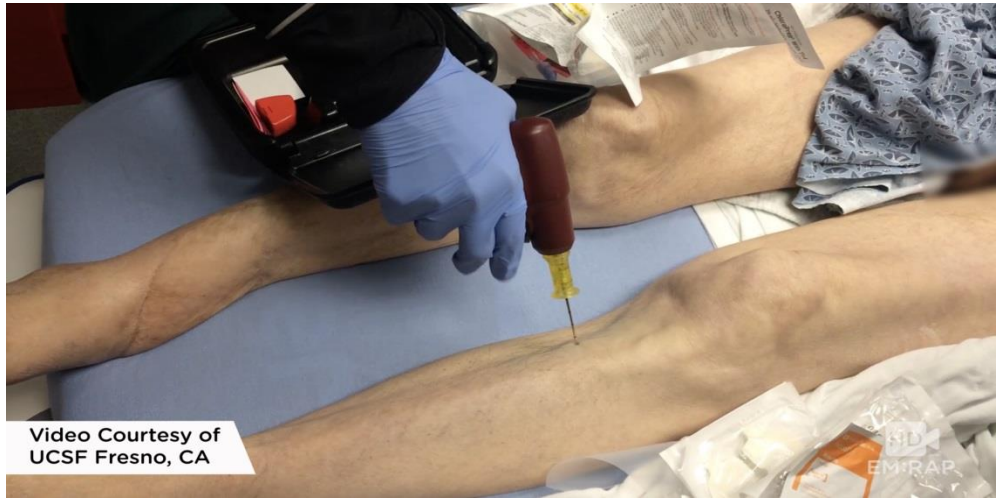
Aktuelle tema:

- Samtykkekompetanse
- Hvordan bli en god studiearbeider
- Innhenting av gyldige data
- Håndtering og rapportering av bivirkninger
- Praktisk trening i studiearbeid

Videokommunikasjon; verktøy for bedre kvalitet i helsevesenet

Fremskritt i akuttmedisin





Bedre hjerneslagsbehandling

Clin Neuroradiol (2020) 30:795–800
https://doi.org/10.1007/s00062-019-00842-9

ORIGINAL ARTICLE

Direct Admission vs. Secondary Transfer to a Comprehensive Stroke Center for Thrombectomy

Retrospective Analysis of a Regional Stroke Registry with 2797 Patients

Fatih Seker[1] · Susanne Bonekamp[1] · Susanne Rode[2] · Sonja Hyrenbach[2] · Martin Bendszus[1] · Markus A. Möhlenbruch[1]

Received: 22 July 2019 / Accepted: 18 September 2019 / Published online: 11 October 2019

Abstract

Background and Purpose This study aimed at comparing short-term clinical outcome after thrombectomy in patients directly admitted (DA) to a comprehensive stroke center with patients secondarily transferred (ST) from a primary stroke center.

Methods In a prospective regional stroke registry, all stroke patients with a premorbid modified Rankin scale (mRS) score 0–2 who were admitted within 24 h after stroke onset and treated with thrombectomy between 2014 and 2017 were retrospectively analyzed. Patients with DA and ST were compared regarding the proportion of good outcome (discharge mRS 0–2), median discharge mRS, mRS shift (difference between premorbid mRS and mRS on discharge) and occurrence of symptomatic intracranial hemorrhage.

Results Out of 2797 patients, 1051 (37.6%) achieved good clinical outcome. In the DA group ($n = 1657$), proportion of good outcome was higher (DA 42.2% vs. ST 30.9%, $P < 0.001$) and median discharge mRS (DA 3 vs. ST 4, $P < 0.001$) and median mRS shift (DA 3 vs. ST 4, $P < 0.001$) were lower. The rate of symptomatic intracranial hemorrhage was similar in both groups (DA 9.3% vs. ST 7.5%, $P = 0.101$). Multivariate analysis revealed that direct admission was an independent predictor of good clinical outcome (adjusted odds ratio, OR 1.32, confidence interval, CI 1.09–1.60, $P = 0.004$).

Conclusion These results confirm prior studies stating that DA to a comprehensive stroke center leads to better outcome compared to ST in stroke patients undergoing thrombectomy.

Keywords Mothership · Drip and Ship · Triage · Regional stroke care · Interhospital transfer

Prehospital video kan gi bedre løsninger for klimaet og ambulansetjenesten

Review

The 2021 report of the *Lancet* Countdown on health and climate change: code red for a healthy future

Marina Romanello, Alice McGushin, Claudia Di Napoli, Paul Drummond, Nick Hughes, Louis Jamart, Harry Kennard, Pete Lampard, Baltazar Solano Rodriguez, Nigel Arnell, Sonja Ayeb-Karlsson, Kristine Belesova, Wenjia Cai, Diarmid Campbell-Lendrum, Stuart Capstick, Jonathan Chambers, Lingzhi Chu, Luisa Ciampi, Carole Dalin, Niheer Dasandi, Shouro Dasgupta, Michael Davies, Paula Dominguez-Salas, Robert Dubrow, Kristie L Ebi, Matthew Eckelman, Paul Ekins, Luis E Escobar, Lucien Georgeson, Delia Grace, Hilary Graham, Samuel H Gunther, Stella Hartinger, Kehan He, Clare Heaviside, Jeremy Hess, Shih-Che Hsu, Slava Jankin, Marcia P Jimenez, Ilan Kelman, Gregor Kiesewetter, Patrick L Kinney, Tord Kjellstrom, Dominic Kniveton, Jason K W Lee, Bruno Lemke, Yang Liu, Zhao Liu, Melissa Lott, Rachel Lowe, Jaime Martinez-Urtaza, Mark Maslin, Lucy McAllister, Celia McMichael, Zhifu Mi, James Milner, Kelton Minor, Nahid Mohajeri, Maziar Moradi-Lakeh, Karyn Morrissey, Simon Munzert, Kris A Murray, Tara Neville, Maria Nilsson, Nick Obradovich, Maquins Odhiambo Sewe, Tadj Oreszczyn, Matthias Otto, Fereidoon Owfi, Olivia Pearman, David Pencheon, Mahnaz Rabbaniha, Elizabeth Robinson, Joacim Rocklöv, Renee N Salas, Jan C Semenza, Jodi Sherman, Liuhua Shi, Marco Springmann, Meisam Tabatabaei, Jonathon Taylor, Joaquin Trinanes, Joy Shumake-Guillemot, Bryan Vu, Fabian Wagner, Paul Wilkinson, Matthew Winning, Marisol Yglesias, Shihui Zhang, Peng Gong, Hugh Montgomery, Anthony Costello, Ian Hamilton

Executive summary

The *Lancet* Countdown is an international collaboration that independently monitors the health consequences of a changing climate. Publishing updated, new, and improved indicators each year, the *Lancet* Countdown represents the consensus of leading researchers from 43 academic institutions and UN agencies. The 44 indicators of this report expose an unabated rise in the health impacts of climate change and the current health consequences of the delayed and inconsistent response of countries around the globe—providing a clear imperative for accelerated action that puts the health of people and planet above all else.

The 2021 report coincides with the UN Framework Convention on Climate Change 26th Conference of the Parties (COP26), at which countries are facing pressure to realise the ambition of the Paris Agreement to keep the global average temperature rise to 1·5°C and to mobilise the financial resources required for all countries to have an eff... negotiations unfold in ... pandemic—a global he... millions of lives, affected ... around the globe, and exposed deep fissures and inequities in the world's capacity to cope with, and human-caused climate change. Although the exact number will not be known for several months, hundreds of people have died prematurely from the heat. Furthermore, populations in countries with low and medium levels of UN-defined human development index (HDI) have had the biggest increase in heat vulnerability during the past 30 years, with risks to their health further exacerbated by the low availability of cooling mechanisms and urban green space (indicators 1.1.1, 2.3.2, and 2.3.3).

Agricultural workers in countries with low and medium HDI were among the worst affected by exposure to extreme temperatures, bearing almost half of the 295 billion potential work hours lost due to heat in 2020 (indicator 1.1.4). These lost work hours could have devastating economic consequences to these already vulnerable workers—data in this year's report shows that the average potential earnings lost in countries in the low HDI group were equivalent to 4–8% of the national gross ... insecurity that still affects the most underserved populations around the world, denying them an essential

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This online publication has been corrected. The corrected version first appeared at thelancet.com on December 9, 2021

See Editorial page 1541

For the Chinese translation of the Executive Summary see Online for appendix 1

For the French translation of the Executive Summary see Online for appendix 2

For the German translation of the Executive Summary see Online for appendix 3

For the Spanish translation of the Executive Summary see Online for appendix 4

Institute for Global Health (M Romanello PhD, A McGushin MSc, L Jamart MSc, Prof I Kelman PhD, Prof A Costello FMedSci),

Ambisjon om bedre kvalitet kommer først

- bedre smertestillende behandling
- bedre hjerneslagsbehandling
- bedre utnyttelse av ressurser og bidrag til et grønnere helsevesen

Presentasjon Flesland 17.11.22
Anestesilege Lars Olav Fjose
SI-HF og Norsk Luftambulanse Stiftelsen

- PreMeFen
- Kombinasjonsbehandling fentanyl og ketamin til 100 til barn
- Videoprosjekt ambulansetjenesten SI

Hensikten med studien

- Undersøke om de non-invasive metodene er like gode/ikke dårligere enn morfin iv
- Er det forskjell i behov for mer rescuemedisin i medikament regimene?
- Se om det er forskjell i tid fra ambulanseankomst til reduksjon i smerte i de 3 regimene
- Se på forskjell i bivirkninger
- Undersøke forskjell i smertestillende effekt av regimene i forskjellige diagnosegrupper
- Undersøke mulighet for å gjennomføre prosedyrer i regimene
- Undersøke forskjell i tilfredshet med regimene hos pasient og ambulansearbeider
- Undersøke forskjell i smertestillende effekt av regimene til pasienter med brystsmerter