Short summary draft study proposal for KCE-ZONMW Benefit call application for discussion

Study title: *Prospective, multicentric randomized, controlled trial comparing midazolam and dexmedetomidine as primary sedative agent in critically ill children*

Background: The alfa-2 agonist dexmedetomidine is increasingly used for analgosedation in critically ill children requiring mechanical ventilation in (Belgian and Dutch) PICUs. The 2022 American guidelines advocate the use of alfa-2 agonists like dexmedetomidine as primary sedative agent. As stated in these guidelines, scientific evidence for the claimed superiority of dexmedetomidine versus usual care analgosedation is however low and the strength of recommendation is classified as conditional.

Primary study objectives:

- To study if dexmedetomidine leads to reduced days on ventilator support

Secondary study objectives:

- To evaluate safety and tolerability
- To study neurodevelopmental outcome

Study design: Individual, multicentric, partially blind, randomized, controlled trial

Inclusion criteria:

- Children between 1 month and 18 years of age
- Mechanically ventilated with estimated duration at least>24h (or>48h?) on ICU
- Informed consent from parents or legal representatives
- Recruitment within maximum 12 hour interval after start mechanical ventilation

Exclusion criteria:

- patients with neurologic conditions that prohibit an evaluation of adequate analgosedation (traumatic brain injury, status epilepticus)
- severe bradycardia (<5th percentile for age)
- severy hypotension (<5th percentile for age)
- patients on extracorporeal treatment
- patients on continuous infusion with neuromuscular blockers
- patients with a life expectancy <72h
- patients with a known allergy to morphine or dexmedetomidine
- congenital or acquired heart block (grade 3)
- previous treatment with α_2-adrenoreceptor agonist within 14 days
- absence of parental consent
- previously participated in this study

Intervention arm:

Patients will receive a sedative infusion of dexmedetomidine shortly after initiation of mechanical ventilation. Dexmedetomidine infusion will be commenced (with or without a loading dose) at a maintenance rate of 0.7 mcg/kg/hr and will be varied between 0 – 1.2 mcg/kg/hr to maintain Comfort Scores and NRS scores within the target range. Dexmedetomidine infusion is continued until sedation is no longer required or to a maximum of 28 days after enrollment. Supplemental sedative agents such as propofol (maximum dose 4mg/kg/hr, maximum duration 24hr), ketamine, chloral hydrate, sedating antihistamines, and phenobarbital according to physician preference are used if dexmedetomidine at the maximum allowable and tolerable dose does not provide adequate sedation. Benzodiazepine

use is permitted only for salvage treatment of refractory agitation. Clonidine is prohibited as a sedative agent with use reserved for management of suspected dexmedetomidine withdrawal (after cessation for 96hr).
As opioid analgesic, fentanyl or morphine are used.

Standard-of-care arm:

The primary sedative agent is at the discretion of the treating clinician, given by bolus dose or infusion (excluding dexmedetomidine or any other alpha-2 agonist) titrated to target sedation range. Sedative agents could include, benzodiazepines, chloral hydrate, propofol (maximum dose 4mg/kg/hr, maximum duration 24hr), ketamine, and barbiturates, guided by individual unit practice. Clonidine can only be used as a supplemental sedative in this group. Dexmedetomidine cannot be used. Comfort B score and NRS scores are used to titrate analgosedation. As opiates fentanyl or morphine is used.

Blinding: statistician and parents remain blinded until the end of data analysis

Endpoints to consider:

Primary endpoint:

Number of ventilator-free days 28 days after randomisation

Secondary endpoints:

Percentage of patients with analgosedation within target range within timeframe 24h, 48h, 72h
Proportion of patients with sedation failure
Cumulative dose of opiates and other sedative drugs
Daily urine output
Proportion of patients with withdrawal
Proportion of patients with delirium
Proportion of patients with unplanned extubation and reintubation
Proportion of patients with loss of vascular cannulae
Proportion of patients with reflex tachycardia
Proportion of patients with fall in blood pressure requiring intervention
Hours of ventilator support
ICU length of stay
Hospital length-of-stay
All cause death 90 days after randomisation
Assessment of cognitive function 6 months after discharge
Assessment of neurodevelopmental outcome 12 years after discharge?

Study period: 6 months (12 years?) follow-up

Setting: approximately 10 (N)/PICUs to be determined in Belgium and the Netherlands.

Sample size: 670 patients

Duration: 3 years patient recruitment

0.5/week *52 weeks *10 units = 260 per year ; 3 years recruitment

Study consortium: One principal investigator per participating centre, trial management team (chief investigator, chief medical advisor, coordinating investigator from the Netherlands, two chief trial coordinators, two data managers from BE and NDL, representatives from the Health Innovation and Research Institute, representatives from patient organization and KCE/ZonMw…

Sponsor and coordination: UZGent

Points for discussion:

- interest in participation
- usual care protocol protocol in different centres
    - position of dexmedetomidine and clonidine at your unit versus the restrictions described in the current draft
    - other suggestions/remarks/questions on draft proposal

- pilot feasibility survey:
    - number of eligible patients per month on invasive mechanical ventilation >24h and >48h per year
    - interference with patient recruitment in other studies