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Title page

Dexmedetomidine with continuous salbutamol inhalation in the treatment of paediatric near-fatal asthma

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.16399

Short running title: Treating paediatric asthma with dexmedetomidine

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Paediatric near-fatal asthma with hypoxia and respiratory failure leads to care in paediatric intensive care unit (PICU). There is unmet need for treatment of near-fatal asthma. Paediatric asthma is usually treated with inhaled beta$_2$-agonists. In PICU, beta$_2$-agonist are administered at large doses. The treatment can cause irritability, tremor and tachycardia, which worsens the status of hypoxic child, decrease cooperation and require the use of sedatives.[1]

Dexmedetomidine is a sedative with favorable respiratory and cardiovascular, and may have anti-inflammatory properties.[2] Importantly, it does not depress the patients' own respiratory drive. As many children are too agitated during a severe asthma attack to tolerate continuous salbutamol inhalation, adding low-dose dexmedetomidine might yield a beneficial therapeutic effect. Although dexmedetomidine in the treatment of near-fatal asthma has been successful in adult studies,[3] paediatric studies are lacking.

We studied the use of dexmedetomidine together with continuous beta$_2$-agonist in the treatment of paediatric near-fatal asthma.

We conducted a record-database, observational study on the treatment of paediatric near-fatal asthma in 2012-2016 at the PICU of Turku University Hospital, Finland. We included 13 consecutive pediatric patients, age 0.9-15 years. The data was collected from the Critical Clinical Care Clinisoft digital patient record system, software 8.0 (GE Healthcare, IL, USA).

All children received standard care for severe acute asthma with two to three repeated inhaled salbutamol doses (0.6 mg via spacer), methylprednisolone 2 mg/kg/day (max 60 mg/day), and supplemental oxygen treatment at the

emergency care prior to the admission to the PICU. At PICU, all children were under continuous cardiorespiratory surveillance, including heart rate, blood pressure, respiratory rate, pulse oximetry and blood exchange gas, lactate, and glucose measurements.

Patients received continuous salbutamol inhalation at 3.5 mg/kg/hr with Aeroneb® Pro (Aerogen, Galway, Ireland) combined with intravenous dexmedetomidine infusion at 1 µg/kg/min, followed by 0.3-1.9 µg/kg/min dose-dependent on their anxiety level. Intravenous esketamine (0.33-0.67 mg/kg/hr) was added to the treatment of two patients, because dexmedetomidine alone did not provide adequate sedation.

This study was approved by the Ethics Committee, Hospital District of Southwest Finland (108/1802/2016). We used IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA) for statistical analysis.

At the admission to PICU, all the patients were restless, desaturated and had tachypnoea. Sixty-one % were males, 39% were females, 53% were atopic and 73 % were cortisone-naïve (Table 1).

Significant proportion of patients corrected saturation levels ($p=0.005$) and decreased heart rate ($p=0.007$) towards normal level within 2 hours. Invasive mechanical ventilation was required with only three patients (23%) and the average time spent in a ventilator was 4 hrs. Subjectively the patients were co-operative, calm, and had fast improvement in clinical condition. Children were transferred to the general paediatric ward after an average of 48.7 hrs.

We found that dexmedetomidine with continuous salbutamol inhalation was well tolerated in children, even in patients as young as 0.9 years. We did not observe any adverse events. Two children developed hypokalaemia (range 2.8-3.2 mmol/l), a common side-effect of high-dose salbutamol. This might also be due to fluids or insulin infusion given to these two children.

Secondly, the children treated with dexmedetomidine plus salbutamol recovered two times quicker in terms of the correction of heart rate and saturation levels compared to a study with continuous salbutamol alone.[4] The quick correction of respiratory and cardiovascular values allows fast reduction of the sedatives. In animal models, intravenous dexmedetomidine blocked histamine-induced bronchoconstriction.[5] During weaning from mechanical ventilation, when neurally mediated airway reflexes dominate, this may be beneficial to prevent a reintubation.

Differences exist between sedatives in inflammation and immunity. The anti-inflammatory properties of dexmedetomidine may offer extra benefit in treating severe asthma. For example, hypoxia upregulates the expression levels of inflammatory NF-kB, which are effectually inhibited by dexmedetomidine.[2]

Treatment with continuous inhaled beta-agonists is effective and mostly well tolerated. Possible side effects include hypokalaemia and tachycardia.[1] Dexmedetomidine dose-dependently decreases heart rate by blocking cardio-accelerator nerves.[2] This cardiac conduction delay not only protects against tachycardia, but also calms patients. Severe hypokalaemia (<2.6 mmol/l) was not observed, but frequent surveillance of plasma potassium

and cardiovascular values is necessary when using continuous beta2-agonist and dexmedetomidine.

This study has several strengths. A comprehensive analysis of the medications used were available from the electronic database. Despite the small size of our cohort, it was the first with paediatric patients and is the largest to date compared with adult studies.[3]

Our study was limited due to the lack of a control group. Further, 73% of the patients were new asthmatics and thus our results may not comply with difficult-to-treat asthma. Although our study provided valuable information on the use of dexmedetomidine in a real-life setting, it is considered preliminary and larger, randomized controlled trials are needed.

In conclusion, the use of dexmedetomidine in paediatric near-fatal asthma did not appear to have any significant side effects even among toddlers. Adding low-dose dexmedetomidine to continuous salbutamol inhalation might improve the tolerance to nebulized beta2-agonists and enhance their therapeutic effect.

Aknowledgements

This work was supported by Tampere Tuberculosis, Finnish Allergology and Immunology, Paulo and TYKS Foundations.

Conflict of interest statement

No conflict of interest.

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Table 1. Patient characteristics.

Category	Patients
n	13
Age, years, mean [range]	4.8 [0-15]
Weight, kg, mean (SD)	23.7 (20.6)
Female, n (%)	5 (39%)
Male, n (%)	8 (61%)
Previous asthma controller therapy, n (%)	3 (23%)
Atopy, n (%)[a]	7 (53%)
Comorbidities, n (%)[b]	9 (69%)
Blood Potassium, mmol/l (SD)	3.5 (0.6)
Saturation at admission to PICU, % (SD)	86.7 (3.9)
after 2 hours, % (SD)	96.5 (2.7)
Heart rate at admission to PICU, b/min (SD)	178.5 (20.6)
after 2 hours, b/min (SD)	147.1 (23.9)
Salbutamol, mg/kg, median [IQR]	482.5 [1045.8]
Dexmedetomidine, µg/kg, median [IQR]	450.0 [1377.1]
Esketamine, ug/kg, median [IQR]	0.000 [0.00]
Methylprednisolone, mg/kg, median [IQR]	3.0 [3.0]

Mean and standard deviation used in normally distributed parameters and median and interquartile range in non-normally distributed. Abbreviations: IQR; interquartile range, PICU; paediatric intensive care unit, SD; standard deviation. [a]*Atopy determined based on diagnosis codes in the medical database.* [b]*Comorbidies were atopic eczema, food allergy, allergic rhinitis and CHARGE syndrome together with atrioventricular septal defect.*