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Research Article

Pharmacodynamics Parameters Determine Analgesic and Sedative Drug Dosing during Neonatal and Pediatric Extracorporeal Membrane Oxygenation

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Abstract

Introduction: Extracorporeal Membrane Oxygenation (ECMO) is a complex highly specialized care facility used in neonates and children with reversible circulatory and/or ventilator failure.

Aim: to evaluate the effect of implementation of the protocolized use of pain, sedation and withdrawal scores on analgosedative drug dosing in ECMO patients.

Materials and Methods: From October 2010 to January 2015 ECMO was performed in 20 patients (12 neonates, 8 children) using a Bio-Medicos centrifugal pump. Patients were stratified according to standardized scoring of pain and sedation in two groups: period-I (n=14) standardized scoring without protocolized use of analgosedation and period-II (n=6) standardized scoring with protocolized use of analgosedative drugs based on validated pain and sedation scores. Pharmacodynamic parameters of analgosedative drugs consisted of COMFORT behavior scale (COMFORT-B) and Sophia Observation Withdrawal Symptoms-scale (SOS). Mean (SEM) cumulative daily dose of midazolam (mg.kg-1.day-1) and sufentanil (µg.kg-1.day-1), and total number of analgosedative drugs per patient were compared between groups using the Student`s t-test and its Welch modification with the 95% confidence interval (CI).

Results: COMFORT-B scores were within target range (11-22) in 62% of all measurements of 14 patients, while 36% of scores were considered to identify over sedation (<11) in 5 patients. 12.5% of two consecutive SOS ≥4 suggested withdrawal in 10 patients (7 patients in period-I, three patients in period-II).Total number of analgosedative drugs per patient decreased significantly in period-II from a median of 8 (IQR) (3-14) to 5 (3-7) in period-I (P=0.047). The mean cumulative dose of midazolam decreased from 5.7 (SEM 0.6) to 3.7 (SEM 0.44) mg.kg-1.day1 (P=0.053), and the mean cumulative dose of sufentanil from 22.3 (SEM 3.63) to 8.1 (SEM 1.27) ug.kg-1. day1 (P=0.002).

Conclusion: Pharmacodynamic parameters using validated assessment instruments for analgosedation result in a significant reduction of analgosedative drug dosing during ECMO.

Keywords: Neonatal Ecmo; Pediatric Ecmo; Analgesia; Sedation; Midazolam; Sufentanil; Comfort-B Score; Withdrawal Syndrome; Sos Score

Abbreviations

ACD: Alveolar Capillary Dysplasia;
COMFORT-B: Behavior Scale;
CL: Clearance;
ECMO: Extracorporeal Membrane Oxygenation;
HT: Hypothermia;
Iv: Intravenous;
LOS: Length of Hospital (PICU) Stay;
MODF: Multiorgan Dysfunction Failure;
NAS: Neonatal Abstinence Score;
Orig: Original;
PD: Pharmacodynamics;
PICU: Pediatric Intensive Care Unit;
PK: Pharmacokinetics;
PPHN: Persistent Pulmonary Hypertension in Neonates;
SIRS: Systemic Inflammatory Response Syndrome;
SOS: Sophia Observation Withdrawal Symptoms-Scale;
VAS: Visual Analogue Scale;
Vd: Volume of Distribution

Introduction

Extracorporeal membrane oxygenation (ECMO) is a complex highly specialised treatment modality used in neonates and children with therapy resistent circulatory and/or respiratory failure. Analgesia and sedation during ECMO is used to provide decreased anxiety, pain, induce amnesia or facilitation of synchronous breathing with the ventilator, the prevention of removing lines as well as for cannulation and decannulation etc. [1,2]. Rapid changes in drug disposition on ECMO are due to decreased plasma concentrations and may result in changed pharmacodynamics (PD) due to altered pharmacokinetics (PK) [2,3]. Analgosedation in ECMO patients should be guided by validated pain and/or comfort scales [4-6]. ECMO increases volume of distribution (Vd) and reduces clearance (CL) of most drugs, lipophilic drugs in particular are sequestered by the ECMO circuits (i.e. midazolam) [2,3]. For drugs with a high hepatic CL (i.e. morphine, fentanyl) increased lipophilicity of drugs may predict increased Vd [3]. For other drugs, this is unknown (i.e. sufentanil, clonidin). Changes in Vd or CL may have as a consequence that the normal dose (i.e. dose of drug per kg) is different in ECMO patients compared to non-ECMO patients [3].

The aim of our study was to evaluate prospectively the effect of implementation of standardized scoring of pain/sedation, and withdrawal on drug dosing during and after ECMO.

Materials and Methods

Design and Setting

This prospective open label observational study included all full term neonates (gestational age ≥ 37 weeks) and children (1 month<18 years of age). Approval of the study was provided by the Ethics Committee of the Department of Ethics General Faculty Hospital, the 1st Faculty of Medicine Charles University in Prague. Written informed consent was obtained of the parents of neonates and children included in the study (as a part of the standardized treatment protocol). Exclusion criteria were neonatal abstinence syndrome, severe congenital abnormalities, intracranial hemorrhage and severe bleeding due to disseminated intravascular coagulopathy (DIC).

Procedure

Patients were stratified in two groups: *period I* (n=14) of standardized scoring and no protocolized use of analgosedation and *period II* (n=6) standardized scoring and protocolized use of analgesia and sedation, and /or withdrawal after completion of the training of caregivers.

Standardized Scoring

In 2010 analgesia and sedation was based on clinical judgment of the attending physicians and care giving nurses using visual analogue scale (VAS), and physiological and behavioral variables (i.e. crying, physical movements, muscle tone, facial tension, blood pressure and heart rate, sleep etc.). ECMO patients were included using unit specific standardized analgesia and sedation in the absence of protocolized scoring and use of analgesia and sedation assessments, and patients were considered oversedated, comfortable or undersedated. For neonatal withdrawal symptoms the neonatal abstinence score (NAS) was used. For NAS a value of ≥7 and higher was considered to represent withdrawal syndrome and therapy was started based on international recommendations and local standardized treatment protocol [7,8].

Assessment tools

a. Period I

Since 2010 nurses and physicians were trained (October 2010 to February 2013) to use validated assessment instruments such as the COMFORT behavior scale (COMFORT-B) and the Sophia Observation withdrawal Symptoms-scale (SOS) [4,8]. The aim was to apply assessments every 3 hours per patient to individualize drug dosing by changes in standardized therapy [4,8,13]. Pain and sedation assesment was titrated according to the desired effect based on the patient´s response and the observed COMFORT-B score. The cut-off value for pain and sedation management failure was COMFORT-B>22: representing

undersedation and dose of sufentanil increased. In case of a COMFORT-B<11: the patient was considered to be oversedated and the dose of sufentanil and or midazolam decreased. In case of values between COMFORT-B=11-22: pain and sedation management was considered sufficient. For SOS a value of 4 and higher of two consecutive meassurements and for NAS a value of 7 and higher suggested withdrawal syndrome and patients were treated by using a cut-off value (SOS<4 or NAS<7) to change therapy.

In *period I* standardized scoring without protocolized use of analgosedation was performed:

• Every 3 hours if a patient was considered sufficiently sedated or more frequent if a patient was considered undersedated or oversedated.

• COMFORT-B, NAS or SOS scores were not used simultaneously during weaning from analgesia and sedation neither if the patients were considered at risk of withdrawal syndrome.

• NAS or SOS scores were used if the symptoms suggested withdrawal syndrome.

b. Period II

Nurses were systematically trained (February 2013 to February 2015) and had to show the adequate use of the COMFORT-B scale during a one-day training (April 2014). In addition, at least six patients were assessed with COMFORT-B scale together but independently with a trained nurse. The corresponding linear weighted Cohen's kappa was calculated and a value of 0.65 or higher was used as a proof of adequate training of individual care givers [14,15] also. Subsequently the protocolized use of COMFORT-B and withdrawal (SOS) scores were implemented in daily clinical practice. Protocolized use of scores (COMFORT-B, and/or SOS) was performed on a daily base with 3 hours interval and simultaneously used during weaning of every patient or patients at risk of withdrawal (≥5 days of combination of analgosedative drugs) as a minimum of 24 hours or longer if needed after a start of weaning. For SOS a value of two consecutive meassurements of 4 and higher suggested withdrawal syndrome and patients were treated by using a cut-off value (SOS<4) to change therapy.

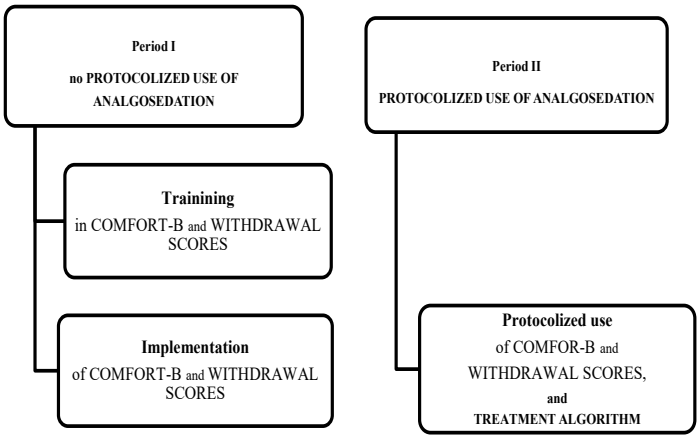
In period II standardized scoring with protocolized use of analgosaedation was performed:

• Every 3 hours if a patient was considered sufficiently sedated or additionaly if a patient was considered undersedated or oversedated.

• COMFORT-B, and SOS scores were used simultaneously during weaning from analgesia as well as in patients who were considered at risk of withdrawal (≥5 days of analgosedative drugs).

• SOS score was used if the patient was considered at risk of withdrawal or withdrawal syndrome was diagnosed (figure 1a).

Figure 1a. Study design -period I: protocolized use of analgosedation (implementation algorithm)



Standardized therapy

Drug dosing for pain management and sedation was based on international recommendations [16-18]. Sufentanil (Sufentanyl inj. Torrex Chiesi, orig. solution 1ml/5μg, per original ampules 10 ml or per 2 ml or orig. solution 1ml/50μg a 20 ml ampules) was diluted with the original ampule: saline solution 1/1, 1:4 (1 ml=1μg); initial bolus 0,1-0.5μg.kg^{-1} i.v., and administered for 5-10 minutes, and to the discretion of the treating physician followed by a continuous infusion of 0.1-0.2 (0.5) μg.kg^{-1} per hour i.v. Midazolam was administered as initial bolus 0.05-0.2 mg.kg^{-1} given over 2-3 min i.v., followed by a continuous infusion of 0.06-0.36 mg.kg^{-1} per hour i.v. (19-22). Other analgosedative drugs, muscle relaxants and anticonvulsive-sedative drugs were administered based on local and international protocols. Dosage regimen of each drug was adjusted to reach desidered effect. Analgosedative drugs (midazolam and sufentanil) were increased 10-25% of an initial dose or decreased 10-25% to reach the target range of scores. If a patient was considered to be in line with target range for 24-48 hours no change in drug dosing took place. Mean (SEM) dose of midazolam (mg.kg^{-1}.hour^{-1}) and sufentanil (μg.kg^{-1}.hour^{-1}0) and the cumulative daily dose of midazolam (mg .kg-1.day^{-1}), and sufentanil (μg.kg^{-1}.day^{-1}) and total number of hours converted to days were determined in all patients from day 1 day (day 0=day of ECMO cannulation, day 1= the first day after ECMO cannulation) during their hospital (PICU) stay. Day zero was not taken into account due to the wide variability of total drugs and dosages used and the effect of drugs given during cannulation.

In period I "Standardized therapy" was as follows:

• No protocolized use of analgosedation.

• Dosages of analgosedation was adjusted based on the desired effect.

• Standardized therapy (sufentanil, midazolam) was not changed or analgosedative drugs increased 10-25 %, or decreased 10-25% of each drug per patient to reach the target range of scores (COMFORT-B, SOS, NAS).

• Withdrawal symptoms were treated if they occurred.

• Boluses of analgosedative drugs given to patients were not limited.

In period II "Protocolized use of standardized therapy":

• Protocolized use of analgosedation.

• Dosages of analgosedation was adjusted based on the target range of assessments.

• Standardized therapy (sufentanil, midazolam) was not changed, or analgosedative drugs increased 10-25 %, or decreased 10-25% to reach the target range of scores (COMFORT-B, SOS, NAS).

• Patients were stratified according to a duration of analgosedative treatment and risk of withdrawal.

• Patients without any risk or presence of withdrawal symptomes (<5 days of analgosedative drugs) were treated based on standardized treatment during weaning .

• Patients at risk of withdrawal (≥5 days of analgosedative drugs) or presence of withdrawal symptomes were weaned from analgosedation according to risk of withdrawal:

• Patients treated 5-10 days of analgosedative drugs: no change, increased/or decreased drug dose 10-25% (12-24h)

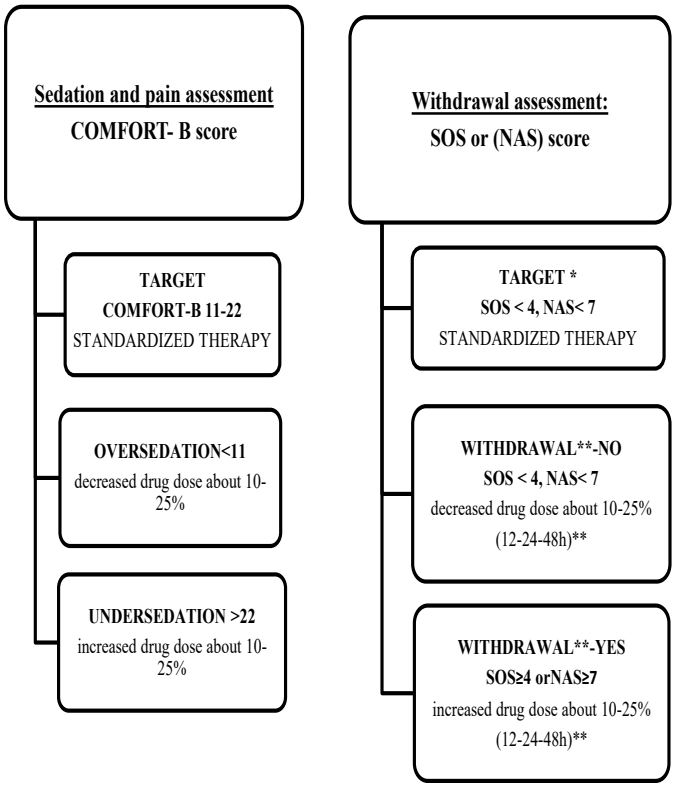
• Patients treated (≥10 days of analgosedative drugs: no change, increased/or decreased drug dose 10-25% (24-48h)

• Boluses of analgosedative drugs were restricted per patients during weaning period (more than 2-3 boluses of each drug were considered therapeutic failure), (figure 1b).

Statistical Analysis

Variables are presented by descriptive statistics (mean, SEM, median, IQR). The results were obtained using two-sample Student's t-test (or its Welch modification in case of heterogenous variances or unequal sample sizes) the 95% confidence interval (CI), median levels were compared by Mann-Whitney U test. Furthermore the paired t-test and the coefficient of variation were used. The significance level was set to 0.05. The data was analysed with the use of Dell Statistica version 12 (Czech). The information about scores percentages between limits was obtained in MS Excel.

Figure 1b. Study design - period II: protocolized use of analgosedation (treatment algorithm)



Legend. *patient without risk (< 5 days of analgosedative drugs) or presence of any withdrawal symptomes,

** patient at risk (≥5 days of analgosedative drugs) or presence of withdrawal (two consecutive SOS≥4)

Results

Patients

From October 2010 to January 2015 ECMO was performed in 21 patients (12 neonates, 9 children) using a Bio-Medicus centrifugal pump. One patient with sepsis who died a few hours after cannulation (i.e. day 0 of ECMO cannulation) was excluded from the study. In the study population 18/20 (80%) patients were weaned from ECMO, 15/20 (75%) patients survived to hospital discharge. The median (IQR) of postnatal age (PNA) of neonates was 8 (5.8-22) days, the age of children was 6 months (1-13.3). All patients were treated for multiorgan

dysfunction failure (MODF: 5 for pneumonia, one for severe PPHN, two for CDH, one for lobar emphysema, and 11 for SIRS and/or sepsis). One patient died due to PPHN and CDH, one patient died due to suspected alveolocapillary dysplasia (ACD), and three patients died after developing severe MODF due to suspected or proven sepsis (one patient due to *Klebsiella species* sepsis, two patients due to sepsis with unclear etiology). For detailed demographics of the study population (table 1).

Table 1. Study Population.

VARIABLE*	Period I	Period II
Patients (n)	14	6
Gender m/f	6/8	4/2
Neonates/children	6/8	6/0
Weight (kg)	5.5 (3.7-8.1)	3.48 (3.4-3.5)
Length of analgosedation (days)	29.5 (23-41)	29.0 (13-59)
Length of hospital (PICU) stay (days)	33 (23-43)	39 (17-66)
ECMO (days)	10 (6-16)	9.5 (6-15)
Mode (v-v/v-a/ vv-va) (n/n/n)	6/6/2	1/5/0
Analgosedative drugs per patient	8 (6-10)§	6 (5-7)§
Decannulated (n/N)	12/14	6/6
Survived (n/N)	10/14	5/6

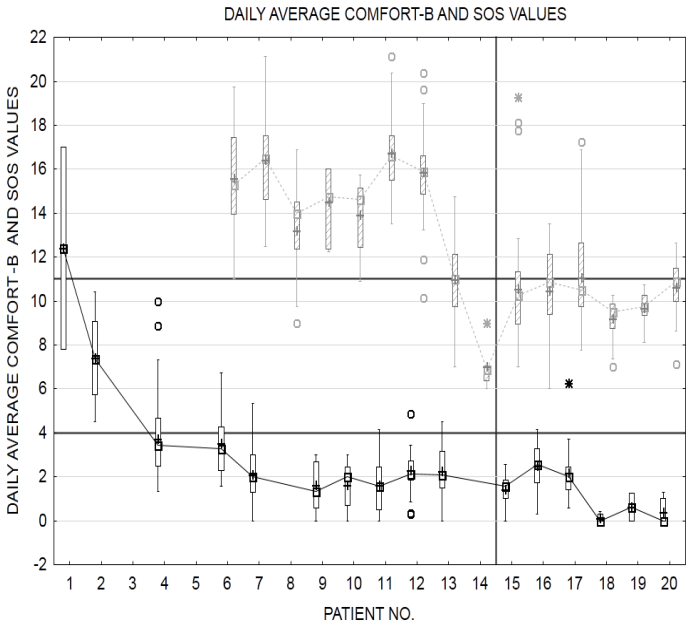
Abbr: *Median (IQR), or (n/N), study population stratified according to protocolized use of therapy (period I no protocolized use, period II protocolized use of therapy), § P value=0.047

Standardized Scoring

All physicians (n=7/7) and nurses n=27/35 (77%) were trained to apply scores in daily clinical practice, of which 16 nurses obtained a linear weighted kappa between 0.65 and 0.95 (median 0.80), of the other 11 nurses a kappa score was not obtained in this period of training. The median (IQR) of daily average COMFORT-B scores were 11.9 (9.9-14.9) in the whole study group. In total 386 COMFORT-B scores were obtained representing 15/20 patients. Sixty two percent of the COMFORT-B scores were within target range (11-22), 36% represented over sedation (<11) in 5 patients, while only 2% indicated under sedation (>22) in one patient. The median and IQR of the daily average COMFORT in period I was 14.8 (12.9-16.5) and in period II 10.1(9.4-11.6) (p<0.001) but not for the neonates. For COMFORT-B scores in period I 83% (265/319) were within target range (11-22), 16.6% (53/319) were <11, and 0.3% >22, while in period II 42% (643/1544) were within target range 58% (897/1544) were <11, and 0.3 % (4/1544) >22.

SOS (n=2236 in total) were determined with the following results: SOS<4=87.5 %; SOS ≥4 or NAS ≥7 = 12.5% representing measurements of 16 patients. The median (IQR) of daily average SOS score was 2.1 (1.3-3.3). 10/20 patients (50%) developed withdrawal syndrome with a median (IQR) SOS of 2.4 (1.3 – 3.3). 7/10 patient were treated for withdrawal syndrome in *period I*, while three neonates (3/10) developed withdrawal syndrome in *period II* (figure 2).

Figure 2. Daily COMFORT-B and SOS scores in period I (patient 1-14) and period II (patient 15-20)



Abbr. median (square), inter-quartile range (box), mean (cross), outliers (circle) and extreme values (star) of daily average Comfort-B (gray) and daily average SOS (black) score for each scored patient. Line indicated between patient No. 14 and 15 suggested patients treated with analgosedation in period I and period II.

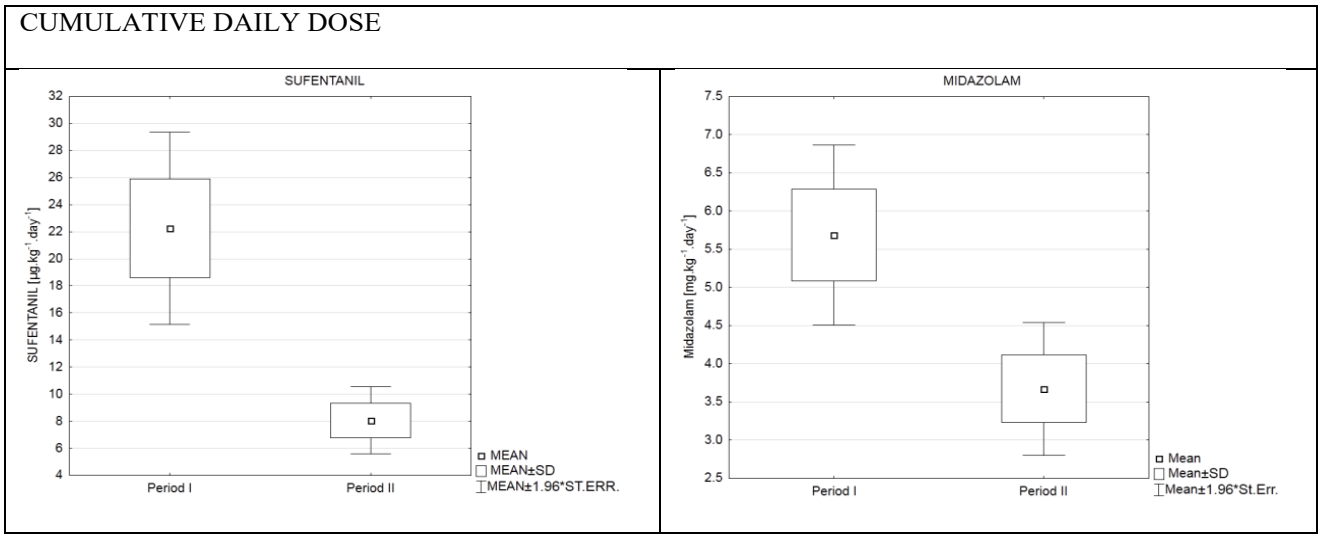
Legend. Box plots showed daily mean (SD) COMFORT-B scores and the target range (dark), and SOS scores and the target range (light)

Standardized Therapy

The total number of analgosedative drugs per patient was 8 (6-10) vs 6 (5-7); (P=0.047) showing a significant reduction in *period II* vs *period I* (table 1). Dosage adjustment of sufentanil was 0.93 (0.57) ug.kg^{-1} per hour in period I vs 0.3 (0.13) ug.kg-1 per hour in period II, while dosage adjustment of midazolam was 0.22 (0.09) mg.kg^{-1} per hour in *period I* and0.15 (0.09) mg.kg^{-1} per hour in *period II*. A signifi-

cant difference in the mean (SEM) cumulative daily dose of sufentanil 22.3 (3.63) vs 8.1 (1.27) ug.kg^{-1} per day was found between *period I* and *period II* (P=0.002). In case of midazolam the mean (SEM) cumulative daily dose of midazolam decreased from 5.7 (0.60) to 3.7 (0.44) mg.kg^{-1} per day (figure 3).

Figure 3. Cumulative daily dose of sufentanil (left) and midazolam (right panel)



Legend. the mean cumulative daily dose of sufentanil (P value=0.002) and midazolam (P value=0.053) period I vs period II

Comparison between the neonates only in both groups revealed no differences in the total number of analgosedative drugs and dosage adjustments of sufentanil or midazolam: the cumulative daily dose of sufentanil 14.39 (4.11) vs 8.1 (1.27) ug.kg^{-1} per day (P=0.16), or midazolam 4.86 (0.98) vs 3.7 (0.44) mg.kg^{-1} per day (P=0.30).

Discussion

Adequate sedation and analgesia is a crucial component of critical care management of neonates, children and adults. Despite widespread recommendations for the use of sedation and analgesia a recent systematic review [7,23] demonstrated a lack of evidence based on six prospective observational studies. (4-6, 23, 24). We showed that the use of validated pain, sedation assessments, and withdrawal assessment tools are feasible in daily clinical practice in the most critically ill patients being treated with ECMO and have a major effect on the amount of drugs etc. After the implementation of protocolized use of analgosedation assessment instruments (period II) the total number of analgosedative drugs per patient (P=0.047) and the cumulative dose of sufentanil decreased (P=0.002), while the cumulative daily dose of midazolam showed a trend towards significance (P=0.053), The same downward sloping trend of cumulative daily dose of sufentanil and midazolam was found in newborns however without reaching statistical significant differences. No significant differences in number of days that analgosedation was needed neither LOS were found between *period I* and *period II*, nor between neonates in the *period I* and *period II*.

Standardized Scoring

In 2010 the standard analgosedative drug therapy was basedon clinical judgment only.Subsequently nurses and physicians were trained in COMFORT-B and SOS scores and after reaching adequate interobserver variability the scores were implemented in daily clinical practice. Kappa was established in 16/ 27 (59%) of care-givers which should be considered as a limitation of our study. In line with the literature we used cut off values of assessment instruments for COMFORT-B (11-22) and SOS (<4) for mechanically ventilated patients. In period I the COMFORT-B score was used every 3 hours with no time limitation of assessments based on the patient condition and/ or changes in analgosedation. In period II the COMFORT-B score was performed for 2 minutes by detailed assessment of every patient every 3 hours to the desired effect. During analgosedation weaning, or difficult analgosedative conditition, or in patients at risk of withdrawal, every patient was scored for a minimum of 24 hours or longer simultaneously COMFORT-B and withdrawal (SOS) scores. SOS score was used every 3 hours (or more often) to the desidered effect also, which is more frequent than validated scores suggested (4, 6, 8). The rationale for intensive assessment was: a. to objectivate withdrawal symptoms as early as possible in every patient at risk for or showing signs of withdrawal (5 days or more of combined-benzodiazepines/opioids analgosedation) b. to clarify a difference between pain/sedation level and withdrawal symptoms and c. to continue with this scoring algorithm not only for this study but more importantly in daily clinical practice [11, 12].

Protocolized Use of Analgosedation

Our results of implementation of the protocolized use of se-

dation and analgesia are based on the analysis of the small study population (n=20), and only 6 patients all neonates were scored in period II. The variety of sedatives and analgesics in the PICU was considered still high among ECMO patients (from three to seven analgosedative drugs per patient) after introduction of the protocolized use of analgosedation The day of ECMO cannulation (day 0) and procedural iv and enteral boluses or muscle relaxants on day 0 were not included to the final pharmacodynamic analysis. In our study group standardized therapy was guided by implementation of the protocolized use of analgosedation and for outcome we used clinical outcomes in a highly vulnerable group of ECMO patients such as length of hospital (PICU) stay, number of sedative and analgesic drugs, and cumulative daily doses of the most frequently administered drugs as sufentanil and midazolam in the PICU. Other reported pharmacodynamic (PD) data were not included in the final analysis (frequency of unplanned extubation, duration of MV etc.) due to the very low incidence in our ECMO group. Compared to other studies [6, 8, 25-28] we investigated only patients on ECMO. Recently Curley et al. was not able to find differences in amount of analgosedative drugs in a large international multicenter study in a mixed PICU population [7, 29]. Compared to other studies, a. no difference was found between period I and period II groups regarding length of stay in PICU and overal mortality, b. duration of mechanical ventilation, c. duration of total sedation.These aspects were found to be decreased in two studies [26,27], consisting of decreased continuous iv sedative-benzodiazepines in one study [27] decreased continuous iv opioids [27] and continuous ketamine in another study (28). Better results were found for iv bolus sedative (for fentanyl, midazolam and lorazepam) [26], or ketamine [28] or enteral bolus sedative (chloralhydrate) [26] d. withdrawal symptoms were decreased after intervention in one study [26]. Still a significant number of patients on ECMO show signs of oversedation guiding continuation of our approach to decrease the number and amount of analgosedative drugs to the desired effect based on validated assessment instruments.

Conclusion

Implementation of protocolized use of analgosedative drugs was successful in neonatal and pediatric ECMO. patients After introduction of standarized pain/sedation assessments the number of sedatives and analgesics as well as the daily dose of sufentanil decreased significantly and resulted in a midazolam sparing effect. Withdrawal was also observed less.

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