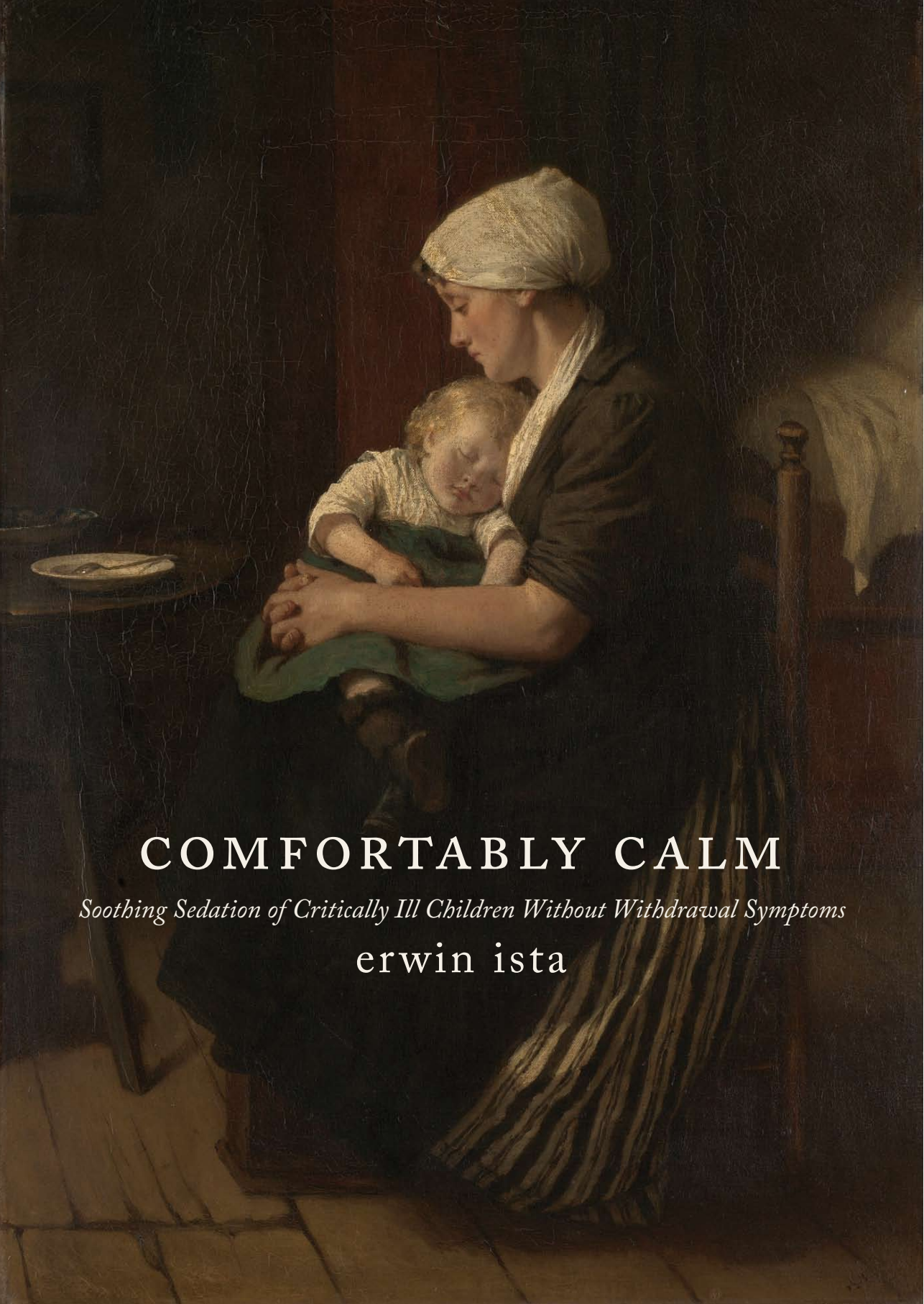

COMFORTABLY CALM

Soothing Sedation of Critically Ill Children Without Withdrawal Symptoms

erwin ista

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Soothing Sedation of Critically Ill Children Without Withdrawal Symptoms

Comfortabel en rustig
Zorgvuldig sederen van ernstig zieke kinderen zonder ontwenningsverschijnselen

Erwin Ista

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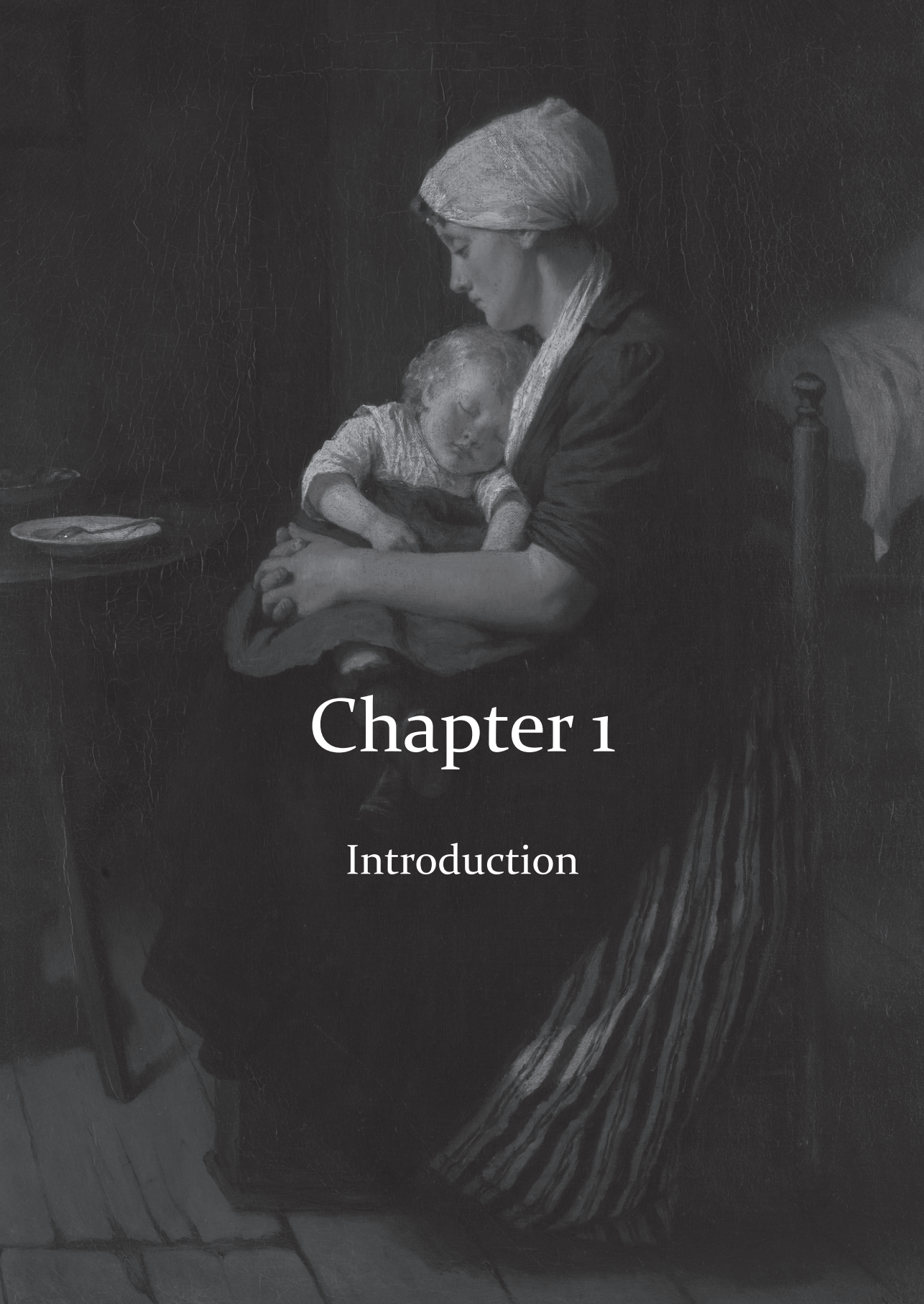
Contents



Chapter 1

Introduction

Introduction

The intensive care unit (ICU) of the Erasmus MC - Sophia Children's Hospital yearly admits some 1100 children aged 0 to 18 years. Many of these are so severely ill that mechanical ventilation or vasoactive therapy is necessary to support organ dysfunction. Pediatric intensive care nurses provide care for critically ill children on a daily basis. Children in this setting inevitably are exposed to a series of painful and stressful events. These include not only invasive procedures like insertion of intravenous lines, catheters and tubes, mechanical ventilation, endotracheal suctioning, but also separation from parents, unfamiliar environment and disruption of the usual day-night cycle in a busy ICU.

Admission to an ICU has a great impact on both child and parents. As adult ICU patients have indicated, and which is now increasingly recognized, the distress and pain experienced during admission are very unpleasant.[1,2] We can only speculate how children who cannot communicate their feelings experience all these things happening to them - often even without understanding where they are. And then, parents have to cope with a miserable and ill child, and will be concerned and insecure about their child's health status.[3-6] Nurses are confronted with the grief of both child and parents. An important part of nursing activities involves providing comfort and minimizing anxiety for both child and parents. Apart from discomfort and pain, stress is a well-recognized negative factor in determining the speed of recovery in children.[7,8] The child will therefore often be given sedative and/or analgesic drugs to diminish anxiety or pain. Ideally, prescription is based on nurses' observations and as such nurses hold a key position and have an advocacy role between child, parents and physician. The sedative of choice in our ICU is midazolam, which is the most commonly used sedative in other European pediatric ICUs as well.[9,10] This drug reduces anxiety and agitation, retrograde amnesia, improves tolerance of ventilator support and facilitates nursing care. It usually given continuously by the intravenous route. Retrograde amnesia for ICU experiences is one of the aims of sedation and is especially reached by midazolam. Many adult and also pediatric patients have a memory of being uncomfortable while in the ICU.[11-16] Opioids such as morphine and fentanyl are most commonly prescribed to relief severe pain in these children.[10]

Optimal sedation has been described as a state in which the patient is somnolent, responsive to the environment but untroubled by it, and with no excessive movements.[17] In ICU practice, this means that a child is conscious, breathes in synergy with the ventilator, and is tolerant or compliant with other therapeutic procedures. Still it can be difficult to reach this stage, because of the variability in drug plasma levels. On the other hand, the available arsenal of sedative drugs is limited in the pediatric ICU. Propofol, for example, drug with a good sedation qualification, is contra-indicated as a sedative in children below 16 years for long term administration.[18,19] Optimal level of sedation varies for each patient and careful consideration should be given to the underlying diagnosis and severity of illness such as pulmonary hypertension.[20] Meanwhile, strong evidence has

emerged that adult patients who are oversedated may need mechanical ventilation for a longer period. A daily drug holiday has a proven beneficial effect on duration of artificial ventilation in adult patients.[21] On the other hand, undersedation is undesirable as it can lead to increased distress, auto-extubation, accidental displacements of catheter, tubes and vital lines, fighting the ventilator and hemodynamic instability.

In clinical practice, it can be difficult to find a balance between under- or oversedation in children. About 65% of these children in the ICU are below 3 year of age.[22] It can be especially hard to distinguish between pain, anxiety and distress in children who cannot communicate verbally.

In the past decade a line of research was concerned with optimal assessment and therapy of pain in children in our ICU or on general ward. Within this context the COMFORT behavior scale as a postoperative pain instrument and the Checklist Pain Behavior in cognitive impaired children were developed.[23-25] In the past years this line of research was extended to sedation in critically ill children. Recently, delirium in pediatric ICU patients has been studied in 877 children over a 4-year period and cumulative incidence of delirium in their patients was 5%.[26]

Pain is closely intertwined with anxiety, fear and other unpleasant emotions and they may reinforce each other. Pain and other forms of discomfort are expressed in change of behavior or changing vital signs. In clinical practice this means that it is very difficult to know if an infant is in pain or distressed, or both. The gold standard of ensuring patient comfort is self-report. This is impossible, however, in pre-verbal children and in critically ill patients who have tracheal tubes in place and are often under effects of sedation. In these cases we have to fall back on the observations of nurses and physicians, but this gives wide range of variable descriptions. The variability in nurses' and physicians' observations arise from different ideas or attitudes toward discomfort, pain, best drugs and treatment, and knowledge of the latest scientific findings. Given this fact, the use of a validated assessment tool that contains behavioral and physiological components reduces this variability. In practice, nursing staff with varying degrees of expertise will change three times over the working day. This means that patients' individual sedation requirements will be assessed by different nurses, and that patients therefore may receive variable dosages of sedatives.[20] A standard tool will counteract this effect and promote continuity of care.

The disadvantage of assessment tools is the fact that it provides a snapshot impression in contrast with continuous monitoring with the Bispectral index (BIS) monitor. The BIS monitor was originally developed for assessing consciousness in adults. It is also used, however, to evaluate depth of sedation in pediatric and adult ICU patients.[27-31]

This brings us to the first important question of this thesis. How should the optimal level of sedation be assessed in critically ill children?

A second question concerns prolonged administration of benzodiazepines and/or opioids in children in an ICU environment. It has been documented that prolonged administration may induce physiological dependency and withdrawal symptoms. Withdrawal symptoms may develop when a drug that causes physical dependence is suddenly stopped, reduced too quickly or antagonized. Prevention and treatment of withdrawal symptoms is another aspect of optimal comfort.[32,33]

Most of our knowledge on tolerance and withdrawal symptoms has been derived from research in newborns of drug-addicted mothers and from literature on adult opium-addicted patients.[34,35] Withdrawal symptoms can also be observed in critically ill children. Physicians recently seem to have greater awareness of the need to prevent withdrawal symptoms in children.[9] On the other hand, there are scarce data about the nature and incidence of benzodiazepines and opioids withdrawal symptoms in children. Incidences of benzodiazepines withdrawal symptoms in critically ill children have been only described in two studies so far, and varied from 17 to 35 %.[36,37] Katz *et al.*[38] evaluated the occurrence of opioids withdrawal symptoms in children after prolonged continuous fentanyl administration. In this study 57% of the children developed withdrawal symptoms.[38]

The intensive care nurse has a key role in providing optimal comfort and especially in ensuring adequate sedation and prevention of withdrawal symptoms. The task of assessing seriously ill children for signs of tolerance, dependence or withdrawal notably falls into the professional domain of the pediatric intensive care nurse. Using a validated and reliable assessment tool could facilitate this task.

The second question therefore is: how do withdrawal symptoms present in pediatric ICU patients and what is the best way to assess withdrawal syndrome?

Objectives of the thesis

The overall aims of the studies presented in this thesis are:

- To study strategies for assessing level of sedation in pediatric intensive care patients by nurses (Chapters 2 and 3).
- To evaluate the value of the BIS monitor for objective assessment of level of sedation (Chapter 4).
- To obtain insight in withdrawal symptoms in critically ill children after long-term administration of benzodiazepines and opioids, and to construct a validated scoring system for assessing these symptoms (Chapters 5-8).

Outline of the thesis

Sedation in critically ill children

Chapter 2 describes the reliability and validity of the COMFORT behavior scale as a scoring system for level of sedation in pediatric intensive care patients aged from 0 to 16 years. Furthermore, new cutoff points are determined for assessing over- and under sedation. Chapter 3 describes the implementation of a sedation treatment protocol in the ICU and analyses nurses' compliance with the protocol. Nurses in this protocol titrated sedatives based on COMFORT behavior assessments. The investigation in chapter 4 focuses on analyses of the usefulness of the BIS monitor for measuring sedation in infants aged up to 12 months. BIS values are compared with COMFORT behavior scores in non-sedated infants and postoperatively sedated infants.

Withdrawal symptoms

Chapter 5 reviews the literature on withdrawal symptoms in critically ill children after long-term sedation. Next, chapter 6 evaluates the frequencies of benzodiazepines and opioids withdrawal symptoms described in the review. Also, possible correlations are determined between withdrawal symptoms and total doses of benzodiazepines or opioids and duration of use. Chapter 7 describes the construction of the 'Sophia Observation withdrawal Symptoms-scale' (SOS). This instrument is based on expert opinions and on the underlying clinical-empirical structure of withdrawal symptoms revealed by multidimensional scaling. Chapter 8 describes the feasibility of weaning at home of sedatives and analgesics in infants with congenital diaphragmatic hernia after extra corporeal membrane oxygenation therapy.

Discussion and perspectives

Chapter 9 contains a general discussion of the results of the investigations presented in this thesis as well as directives for future research.

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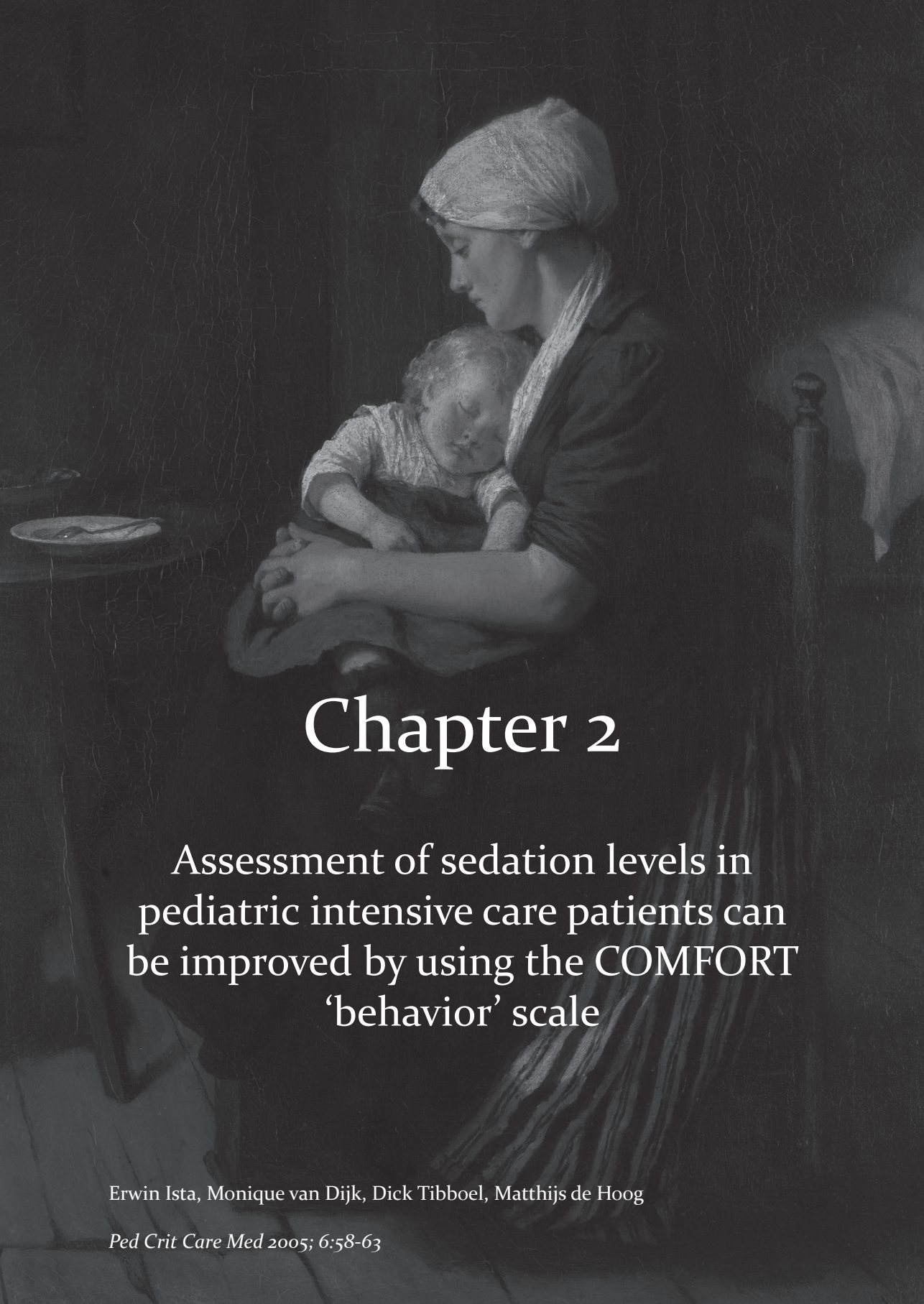

Chapter 2

Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT 'behavior' scale

Erwin Ista, Monique van Dijk, Dick Tibboel, Matthijs de Hoog

Ped Crit Care Med 2005; 6:58-63

Abstract

Objectives: The original COMFORT scale, including both observational and physiologic items, has been validated for measuring distress in children admitted to a pediatric intensive care unit. However, physiologic variables are influenced by drugs given in the pediatric intensive care unit setting. The objectives of this study were to assess the usefulness of physiologic variables in judgment of sedation and to determine new cutoff points for the COMFORT 'behavior' scale (COMFORT-B), using only observational items.
Design: Prospective observational study.
Setting: Pediatric intensive care unit in a university hospital.
Patients: Seventy-eight patients admitted to the pediatric intensive care unit.
Interventions: None.
Measurements and Results: COMFORT scores were obtained in this patient group. Similar to the original COMFORT scale validation, the expert opinion of nurses (Nurse Interpretation Score of Sedation) served to determine optimal cutoff scores for the COMFORT-B scale. A total of 843 combined COMFORT and Nurse Interpretation Score of Sedation scores were obtained in 78 patients. Cronbach's alpha for the COMFORT scale was 0.78, increasing to 0.84 when the physiologic items, blood pressure and heart rate, were excluded. COMFORT scores were significantly different for the three Nurse Interpretation Score of Sedation categories (Kruskal-Wallis, $p < 0.001$). According to the pediatric intensive care unit nurses, undersedation was present in 11% and oversedation in 3% of all observations. Cutoff points for the COMFORT-B scale were < 10 for oversedation and > 23 for undersedation. The area in the COMFORT-B score between 11 and 22 does not adequately predict under- or oversedation, pointing to a need for supplemental observation.
Conclusion: The COMFORT-B scale is a reliable alternative to the original COMFORT scale. The cutoff points of the COMFORT-B scale in conjunction with the Nurse Interpretation Score of Sedation facilitate the use of sedation algorithms on the pediatric intensive care unit.

Introduction

Critically ill children admitted to a pediatric intensive care unit (PICU) will experience physical and psychological discomfort.[1,2] Apart from discomfort, stress is a well-recognized negative factor in determining the speed of recovery in children.[3] Both factors warrant adequate sedation and pain relief in this vulnerable patient group.[4,5]

Although clinical judgment of trained PICU nurses and physicians is important, the development of an optimal scoring system for sedation is needed to both determine the efficacy of sedatives and related interventions and facilitate interinstitutional comparisons.

The Ramsay scale is the sedation scoring system most used in the adult intensive care setting.[6] Several categories in this scale are based on judgment of level of consciousness. Other Ramsay scale categories, such as response to commands, are not relevant for young infants. This calls for other, more specific observations in the PICU setting. Contrary to adult intensive care, no gold standard for sedation is available for PICU use.[7] Several sedation scoring scales have been described for children (Table 1): the Hartwig Sedation Scale,[8] the COMFORT Scale,[1] the University of Michigan Sedation Scale,[9] and recently one for neonates (Neonatal Pain, Agitation, and Sedation Scale).[10] All these scales have been validated by comparison with the 'expert opinion' of attending physicians and/or nurses, and each has its specific strengths and weaknesses (Table 1). At present, the COMFORT scale seems to be the most practical scoring system for PICU use. In contrast to the Hartwig scale, the COMFORT scale does not use reaction to suctioning as an item. This implies that the COMFORT scale can be used in both ventilated and nonventilated pediatric patients.[7,11]

The University of Michigan Sedation Scale is restricted to level of consciousness and has only been validated for short, procedure related observations.[9] Because comfort in children has many more aspects than consciousness alone, and preverbal infants are not able to clearly communicate discomfort, it is necessary to include other behavioral and physiologic variables. An additional advantage of the COMFORT scale is that it takes these variables into account.

Although the COMFORT scale was originally described in and validated for measuring discomfort in ventilated pediatric patients, the use of this instrument in the clinical PICU setting is disputed.[1,12] The correct use of the physiologic variables of the COMFORT scale implies that reference values for heart rate and arterial blood pressure are adjusted each day. Because these physiologic variables are titrated by inotropic and other drugs often used in pediatric intensive care, we questioned whether their use contributes to the overall assessment of sedation in the individual patient. It has already been demonstrated that these two variables have a low interrater agreement.[1] Two other studies have demonstrated insufficient correlation between physiologic and behavioral COMFORT items.[13,14]

We set up a study with a two-fold objective. The first objective was to assess whether

physiologic variables are really useful in the judgment of sedation with the COMFORT scale, and second, we aimed at determining cutoff points for an abbreviated COMFORT scale restricted to behavioral COMFORT items (the COMFORT-B scale).

Table 1 Items in sedation scales used for children

Name of instrument	Conditions measured						Validated for (age)
	Consciousness	Agitation	Ventilation	Pain	Psychological variables	Other	
COMFORT Scale[1]	X	X	X	X	X	Muscle tone	Pediatric
Hartwig Sedation Scale[8]	X	X	X	X		Reaction to tracheal suction	Pediatric
Ramsay Scale[6]	X	X					Adult
Children's Hospital of Wisconsin Sedation Scale[19,20] (modified Ramsay scale)	X	X					Pediatric
Neonatal-PASS[10]	X	X		X	X		Neonate
University of Michigan Sedation Scale (UMSS)[9]	X	X					Pediatric
The Vancouver Sedative Recovery Scale[21]	X						Pediatric

Materials and Methods

Design

Prospective observational study.

Patients

Children aged 0-18 years admitted to the PICU of the Erasmus MC-Sophia Children's Hospital between March 2002 and November 2002 were eligible for this study. Children with severe mental retardation, severe hypotonia, and neuromuscular blockade were excluded because the COMFORT scale has not been validated for these patients. Patients were included when at least one of five study nurses was on call to coordinate data sampling. Because of the strictly observational and noninvasive nature of the study, the institutional review board waived the need for informed consent.

Measurements

COMFORT Scale

The COMFORT scale was originally developed to assess distress in pediatric patients in a PICU environment and has also been validated to assess postoperative pain in children <3 years of age.[1,13] The behavioral items are alertness, calmness, respiratory response (in ventilated patients) or crying (in nonventilated patients), muscle tone, physical movement, and facial tension. It contains two physiologic items, heart rate and mean arterial pressure, the latter requiring an indwelling arterial catheter.

All response categories range from 1, 'no distress', to 5, 'severe distress'. The COMFORT scale has been officially translated into Dutch and adapted to the extent that the item 'crying' was added for nonventilated patients.[13]

Nurse Interpretation of Sedation Score

To facilitate a comparison between the COMFORT scale and the clinical judgment of the attending nurse, we used a reference score, similar to the one used in the original validation by Marx *et al.*[12] The Nurse Interpretation of Sedation Score (NISS) is the nurse's expert opinion of the level of sedation, reflected by one of these categories:

1. Insufficient sedation
2. Adequate sedation
3. Oversedation

Using the expert opinion of a professional is common practice for validation of scales like the COMFORT Scale. Expert opinion can be viewed as the 'silver standard' when a 'gold standard' is not available.[15]

Procedure/Measurement

The care-giving nurse assessed the patient every 8-hr shift at set times (2, 10, and 18 hrs) determining the NISS score before COMFORT score. Paired scores were obtained when the patient was uncomfortable (NISS = 1) or when sedation medication was administered or changed. Individual baseline values for heart rate (HR) and mean arterial blood pressure (MAP) were calculated each day. Severity of illness was scored using the Pediatric Index of Mortality score.[16]

Interobserver Reliability

All nurses at the PICU were trained to use the COMFORT scale by using both videotaped material and bedside instructions. Newly trained nurses performed ten COMFORT assessments together with a trained nurse. When the obtained linearly weighted Cohen's kappa was satisfactory (>0.65),[17] nurses could participate in the study. The median interobserver-reliability linearly weighted Cohen's kappa in our PICU was 0.84 (range 0.67 to 0.96) for 52 nurses.

In a random sample of this study, a second nurse performed a COMFORT score at the

same time as the attending nurse. This test served to check whether the COMFORT score was influenced by the fact that the attending nurse had already performed a NISS score.

Sedation Medication

Administration of sedative drugs was at the discretion of the attending physician. The drug of first choice for sedation purposes in our PICU is midazolam (0.05 - 0.3 mg/kg/hr). When sedation is considered insufficient, morphine, ketamine, or fentanyl is given in addition to midazolam. Other drugs are used very infrequently.

Statistical Analysis

Interrater reliability was tested by using the linearly weighted Cohen's kappa and the intraclass correlation coefficient.

The internal consistency was calculated by using Cronbach's alpha, a reliability index that estimates the internal consistency of several items within a scale. Items were removed when item total correlation was < 0.40. Cutoff scores for the COMFORT-B scale were determined by using the NISS as the silver standard. COMFORT scores were compared for the three NISS categories by using the nonparametric Kruskal-Wallis H test.

Results

Patient Characteristics

A total of 843 paired observations in 78 patients were obtained. Background characteristics of the patients are listed in Table 2. Median age was 17 months (range 0 to 223).

The age distribution of patients in this study and their Pediatric Index of Mortality scores are representative for the total population of our PICU.

Use of analgesics and sedatives is summarized in Table 3. Sixty-five of 78 (83.3%) patients received midazolam, with a median of 100 mcg/kg/hr (50 - 900 mcg/kg/hr).

Interobserver Reliability

In 40 observations, COMFORT scores were simultaneously assessed by two independent nurses, the caregiving nurse and a colleague. The intraclass correlation coefficient of 40 paired observations was 0.99 for the COMFORT scale.[18] The interobserver reliability (linearly weighted Cohen's kappa) for the COMFORT items ranged from 0.77 to 1.00.

Internal Consistency

Cronbach's alpha was 0.78, including all items for 596 observations. Missing data could be attributed to a lack of an arterial catheter. MAP and HR observations were below or equal to the obtained baseline values of the patients in 86.6% and 88.6% of cases, respectively. Table 4 shows the corrected item-total correlation of all comfort items. The internal

consistency, presented by the alpha if item deleted, increased to 0.80 (if MAP deleted) or 0.79 (if HR deleted).

The Spearman's rank order correlation coefficient of HR with the behavioral items ranged from 0.18 to 0.30 and for the MAP items with the other items ranged from 0.05 to 0.20. Cronbach's alpha increased to 0.84 when both MAP and HR were excluded. In this analysis, all corrected item total correlations were ≥ 0.50.

Table 2 Background characteristics of the patient group (N = 78)

Variable	N	%
Gender		
Male	49	63
Female	29	27
Age group		
Neonate	12	15
1 - 6 months	14	18
6 - 12 months	11	14
1 - 3 years	17	22
> 3 years	24	31
Diagnosis		
Cardiac - congenital	15	19
Cardiac - others	3	4
Respiratory failure	26	33
Sepsis, septic shock	14	18
Other diagnosis	20	26
PIM score		
Mean	0.13	
Median	0.07	
Range (min, max)	0.002 - 0.96	
Number of ventilated patients	66	85

Table 3 Sedatives and analgesics use for patient group (N = 78)

Medication	N[a]	%	Doses, median (range)
Sedatives			
Midazolam	65	83.3	100 mcg/kg/hr (50 - 900)
Ketamine	11	14.1	1 mg/kg/hr (1 - 4)
Analgesics			
Morphine	31	39.7	15 mcg/kg/hr (5 - 40)
Fentanyl	4	5.1	1 mcg/kg/hr (1 - 2)

[a] Number of patients

Concurrent Validity

COMFORT scores were significantly different for the three NISS categories (Kruskal-Wallis, Chi-square = 237, $df = 2$, $p < 0.001$). The median COMFORT scores were 7 (range 6 to 14) in the oversedated NISS category, 11 (range 6 to 26) in the adequately sedated category, and 19 (range 11 to 29) in the undersedated category.

Table 4 Corrected Item-Total correlation (N = 596 observations)

COMFORT Scale item	Corrected Item-Total Correlation	Alpha if Item Deleted
MAP	0.27	0.80
HR	0.31	0.79
Alertness	0.60	0.74
Calmness	0.65	0.74
Respiratory response or crying	0.48	0.76
Physical movement	0.71	0.72
Muscle tone	0.43	0.77
Facial tension	0.54	0.76

Cutoff Points for the COMFORT-B Scale

Cutoff points were determined with emphasis on the importance of preventing undersedation in individual patients. Table 5 shows the frequency of different COMFORT-B scores and the relative frequencies of COMFORT-B scores between 6 and 10, 11 and 22, and 23 and 30 within the three NISS categories. In 93 of 843 observations (11%), the impression of nurses was undersedation (NISS = 1), with most COMFORT scores between 11 and 22.

In 85.5% of all observations, nurses considered sedation as adequate, with COMFORT scores ranging between 6 and 22. In 29 of 843 (3.4%) of all observations, nurses considered infants oversedated, with most COMFORT scores between 6 and 10.

The risk of over- or undersedation with a COMFORT score ≥ 23 was 0% and 95%, respectively. The risk of over- or undersedation with a COMFORT score ≤ 10 was 7.8% and 0%, respectively. With COMFORT scores between 11 and 22, patients were under- and oversedated in 15.4% (75 of 488) and 0.4% (2 of 488) of observations, respectively.

COMFORT and NISS Scores

Patients were considered adequately sedated (NISS = 2) in 721 (86%) of all observations. In 57% of these observations, the COMFORT score pointed at adequate sedation.

Patients were considered oversedated (NISS = 3) in 29 observations in 18 patients. In 93% of these observations, the COMFORT score also implied oversedation. Patients were considered undersedated (NISS = 1) in a total of 93 (11%) observations in 35 patients. In 19.4% of these observations, the COMFORT scale also implied undersedation. These 35

(NISS = 1) and 18 (NISS = 3) patients did not differ significantly from the total study group with regard to age, diagnosis, gender, or Pediatric Index of Mortality score.

Some differences between daytime observations (6 *a.m.* until 10 *p.m.*, n = 546) and nighttime (n = 297) observations were observed. Oversedation (NISS = 3) occurred in 4.4% of daytime and 1.7% of nighttime observations. Undersedation (NISS = 1) was seen in 11.7% of observations during the day and 9.8% of observations during the night. The median COMFORT-B scores of 78 patients were significantly higher during daytime than during nighttime (Wilcoxon test, Z = -2.86, $p = 0.004$).

Table 5 COMFORT-B scores, distinguished by level of sedation according to NISS

COMFORT score[a]	Frequency of observations	%	Cumulative %	NISS [b] = 1 Undersedated 93 observations (%)	NISS [b] = 2 Adequately sedated 721 observations (%)	NISS [b] = 3 Oversedated 29 observations (%)
6	11	1.3	1.3			
7	38	4.5	5.8			
8	60	7.1	12.9	0 (0)	309 (42.9)	27 (93.1)
9	128	15.2	28.1			
10	99	11.7	39.8			
11	104	12.3	52.1			
12	96	11.4	63.5			
13	71	8.4	71.9			
14	57	6.8	78.7			
15	49	5.8	84.5			
16	40	4.7	89.2			
17	17	2.0	91.2	75 (80.6)	411 (57.0)	2 (6.9)
18	16	1.9	93.1			
19	13	1.5	94.6			
20	12	1.4	96.0			
21	9	1.1	97.1			
22	4	0.5	97.6			
23	5	0.6	98.2			
24	5	0.6	98.8			
25	3	0.4	99.2			
26	2	0.2	99.4			
27	3	0.3	99.7	18 (19.3)	1 (0.1)	0 (0)
28	0	0.0				
29	1	0.1	99.8			
30	0	0.0				
Total	843	100.0	100.0	100	100	100

[a] low: favorable, high: unfavorable, [b] column percentages, *NISS* Nurse's Interpretation of Sedation Score

Discussion

The main findings of this study are two-fold. First, physiologic variables do not correlate well with the behavioral items of the COMFORT scale. Second, there is a definite gray area, with COMFORT-B scores of ≥ 11 and ≤ 22, where adequate sedation cannot be based on COMFORT-B scores alone.

Our results show a low variance of the MAP and HR items, because these variables are by nature artificially controlled in the PICU. Another explanation for the low variance in the HR and MAP items may be due to the construction of these two items within the COMFORT scale. The HR and MAP scores are compared with baseline values. HR and MAP are scored > 1 when these items are 15% above baseline. First, this may result in low values when baseline values were increased due to stress, and second, the 15% increase has to our knowledge never been tested for adequacy. Additionally, only low correlations of HR and MAP with the other items of the COMFORT scale were seen.

Exclusion of these physiologic items in the present study increased the reliability of the total COMFORT score. These findings are in line with those from two other studies.[13,14] The study by Carnevale and Razack[14] in 18 pediatric patients indicated that physiologic variables have a very limited validity as determinants of the total COMFORT score. In a former study in postoperative patients (0-3 years), we demonstrated insufficient correlation between physiologic and behavioral COMFORT items, indicating that inclusion of physiologic variables was not useful.[13] The surplus value of this study compared with the study of Carnevale and Razack lies in the greater sample size and the determination of cutoff points for the COMFORT-B scale.

This finding has implications for the clinical judgment of sedation. A COMFORT scale restricted to behavioral items needs new cutoff points. In the present study, as in the original study by Marx *et al.*,[12] we used the expert opinion of experienced medical personnel, translated to a 3-point scale, to validate the COMFORT-B scale.[1] Marx *et al.*[12] originally used a 5-point scale, later also reduced to 3 points. Since the COMFORT score obtained by the attending nurse might be biased, a second COMFORT score was performed in a subset of observations. As shown in the results, no bias was detected. We realize the fallibility of using the nurse's opinion (NISS) as the gold standard. There is no true gold standard to compare the COMFORT against. Self-report is either not possible or not reliable in young children. We are, however, confident that the NISS is useful as a silver criterion.[15] Nurses were not only experienced but also trained in comfort and pain assessment. The NISS integrates personal knowledge of the attending nurse on previous hours, illness, medication, idiosyncratic behavior, ventilation, and other PICU aspects of the child. The NISS expert opinion is therefore only valid when applied by the caregiving nurse and is not useful when scored by an observer unfamiliar with the context of the child.

New cutoff points for the COMFORT-B scale were determined with an emphasis on preventing undersedation. In clinical practice, undersedation is a major concern from the viewpoint of patients, parents, doctors, and nursing staff. Regulation of sedative medication based on COMFORT-B scores should reflect this concern. In our population, cutoff points of 10 and 23 reached this goal. Patients with COMFORT-B scores ≤10 were never undersedated. Patients with COMFORT-B scores ≥23 were undersedated in 95% of cases. This means that in these ranges of the COMFORT-B score, changes in sedative medication can be based on the COMFORT-B score alone. With COMFORT-B scores ranging from 11 to 22, patients had a 15.4% chance of being undersedated. The poor relationship between the COMFORT-B score and the clinical judgment of the nurse in this middle COMFORT-B score range can be explained by several factors. COMFORT-B scores are obtained at fixed time points and do not always reflect the overall sedation of the patient over time. This sometimes leads to tapering of sedation medication on the basis of low COMFORT-B scores, where the overall impression of the attending nurse is different. Factors such as day-night rhythm and procedure-related discomfort have to be taken in to account as well.

Daytime COMFORT-B scores in the present study were significantly higher than nighttime scores. This finding might be explained by other factors than day-night rhythm alone. At nighttime there are fewer nursing and medical staff present. Light and noise are reduced, and the children receive only necessary care and interventions.

Overall, COMFORT-B scores are relatively low in this PICU sample, considering the median score of 11 and bearing in mind that, theoretically, the COMFORT-B score may range from 6 to 30. These low scores may be attributed to increased use of sedatives in pediatric intensive care patients. The attention for optimal sedation is perhaps also reflected in the exceptionally low percentage of observations with oversedation (3.4%) by the PICU nurses. This low percentage might be related to the fact that in a PICU environment, care givers do not mind that infants and children are heavily sedated with concomitant retrograde amnesia for the period on the PICU.

A second explanation for the discrepancy between an adequate NISS and low COMFORT-B score in this study is the fact that all children in whom this discrepancy was noted were critically ill, with circulatory and respiratory instability. In these cases, the attending nurse might include a previous negative influence of distress on hemodynamics and respiration in the judgment of the desired level of sedation. An example of this phenomenon was seen in patients with pulmonary hypertension in whom undersedation is a risk factor for recurrent bouts of increased pulmonary resistance. Undersedation according to the caregiving nurses occurred in 11% of all observations. This coincided with COMFORT-B scores > 10.

A limitation of this study is that the data were derived in one PICU with one set of PICU attending physicians and one set of PICU nurses. There is no international consensus about adequate or optimal sedation. Regional and cultural attitudes may influence the

opinion about optimal sedation.

This study shows the feasibility of using the COMFORT-B scale in judging sedation levels in critically ill children. The question remains how this sedation scale can be used in daily practice. Can an adequate sedation algorithm be developed solely on the basis of the COMFORT-B scale? Is there room for the clinical judgment of the attending physician and nurse in such a protocol? The use of sedation observation scales, such as the COMFORT-B scale, as a single measure of patient sedation has drawbacks. It limits observation of sedation to a single point in time, without including prior knowledge of the patient. However, as long as there are no methods to assess sedation as a continuous variable, the use of a score like the COMFORT-B scale in the PICU remains necessary.

The clinical impression of the caregiving nurses (represented by the NISS) showed a relationship with the paired COMFORT-B scale, albeit not a perfect one. Although it is tempting to focus on the statistical significance of these findings, it is more rational to admit that the COMFORT score is fallible. We cannot rely solely on an observational tool without prior knowledge or expertise. Even for experienced PICU nurses, though, it remains difficult to determine the emotional state of their patients. Are they in pain or distressed? Is it possible to distract the child or to apply non-pharmacologic interventions? Our findings suggest that assessment of sedation in pediatric intensive care patients could benefit from adding a second score such as the NISS in the middle range (11-22) of the COMFORT-B score. We believe this would better reflect the inherent difficulties and pitfalls of assessing discomfort in critically ill children.

Conclusion

Our results indicate that the assessment of sedation levels in children admitted to a PICU can be improved by using a COMFORT-B scale, leaving out physiologic variables. The place of a second subjective measure, for instance the NISS, in a sedation protocol based on sedation scores is currently under investigation in our PICU.

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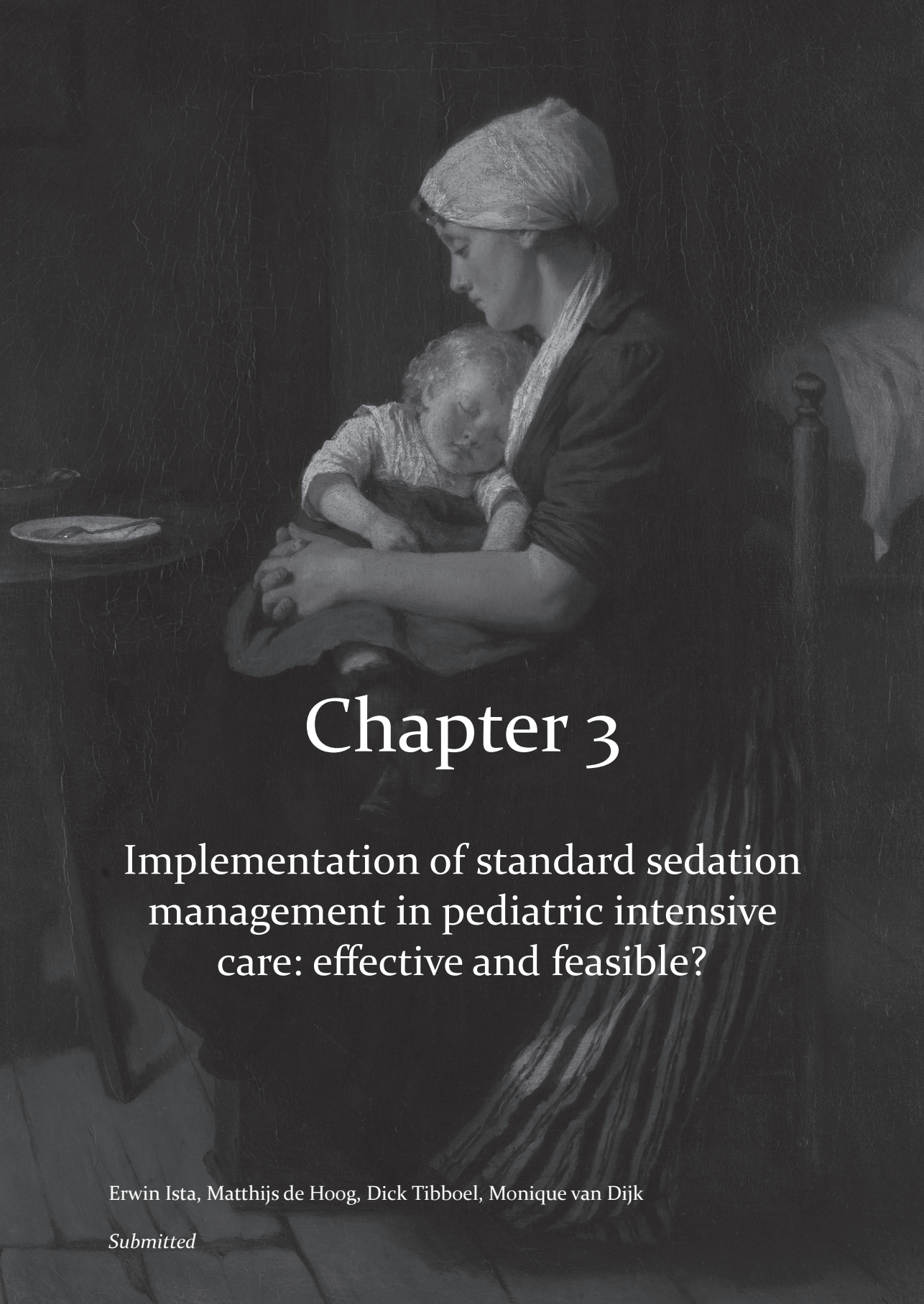


Chapter 3

Implementation of standard sedation management in pediatric intensive care: effective and feasible?

Erwin Ista, Matthijs de Hoog, Dick Tibboel, Monique van Dijk

Submitted

Abstract

Objectives: To study effects of the introduction of a sedation treatment protocol for children in intensive care, and to analyze PICU nurses' compliance with this protocol.
Methods: Administered sedatives and analgesics over the first seven days of admission was documented for convenience samples before and after implementation of standard sedation assessments and a sedation protocol. Pre- and posttest sedation scores were collected for three months with the use of the COMFORT behavior scale, Nurse Interpretation of Sedation Score and the Visual Analogue Scale. Nurses' compliance with the sedation protocol, as well as amounts of sedatives and analgesics administered were evaluated 21 months after the posttest during 12 months.
Results: Sedatives for 27 patients were recorded pretest; and for 29 other patients after the implementation of the sedation protocol. Both median midazolam and median morphine administration was significantly higher in the posttest period. The proportion of patients with COMFORT scores between 11 and 22, indicating adequate sedation, had increased from 63% pretest to 72% posttest and to 75% in the long run. According to the cutoff points of the sedation protocol patients were adequately sedated in 71% of the assessments. In 45% of assessments indicating undersedation the infusion rate was increased according to the protocol. The majority of staff surveyed considered the sedation protocol comprehensible and useful for clinical practice.
Conclusion: This study showed that regular sedation assessment in critically ill children was feasible and was found to be standard practice two years after the first posttest. There is insufficient evidence to conclude whether implementation of a sedation treatment protocol indeed improves sedation treatment.

Introduction

With a view on optimizing sedation and pain treatment in critically ill children, several authors and societies have recommended to assess levels of sedation and pain, and to titrate sedatives and analgesics on the guidance of guidelines, protocols or algorithms.[1-4] Clinical practice guidelines (CPGs) are widely advocated in the evidence-based health care literature, especially by the medical profession, as a method of improving practice, standardization of care and research utilization.[5] Clinical practice, however, seems to lag behind in implementing pain management plans, mainly for lack of resources and motivation.[6,7]

Young children receiving intensive care should be given optimal pain, anxiety and discomfort treatment. Apart from discomfort, they may suffer pain from procedures such as intubation, thoracic drain insertion, or from severe trauma or disease. Being disoriented in a perceived hostile environment and unable to comprehend the situation, they may also be prone to anxiety.[8] It follows that implementation of a standard sedation management strategy might be of benefit.

Several studies evaluated effects of sedation guidelines and/or pain management in adult[9-15] or pediatric intensive care.[16,17] Findings of the studies in the adult setting varied from a significant reduction (33 to 57%) in duration of mechanical ventilation[9-12] to no effect.[13,14] Chanques *et al*.[11] reported also a significantly decrease of pain and agitation after implementation of systematic evaluation of pain and agitation. There is little evidence on use of sedation protocols in the pediatric intensive care (PICU). One study evaluated a sedation and analgesic protocol in 10 PICU patients.[16] Patients received more sedation while on the protocol and the nurses found the protocol easy to use. A recent COMFORT scale study in PICU patients showed significant decreases of duration of mechanical ventilation and doses of sedatives in 21 patients managed with the use of a sedation protocol as compared with controls.[17]

To date no studies of standard pain and sedation management in PICU patients have been reported in the European context for neonates and infants up to 3 years of age. Here we reported a study in a PICU in the Netherlands. The aim of this study was twofold. The main objective was to study effects of a sedation treatment protocol on doses of administered sedatives. The second aim was to investigate nurses' compliance with the sedation protocol.

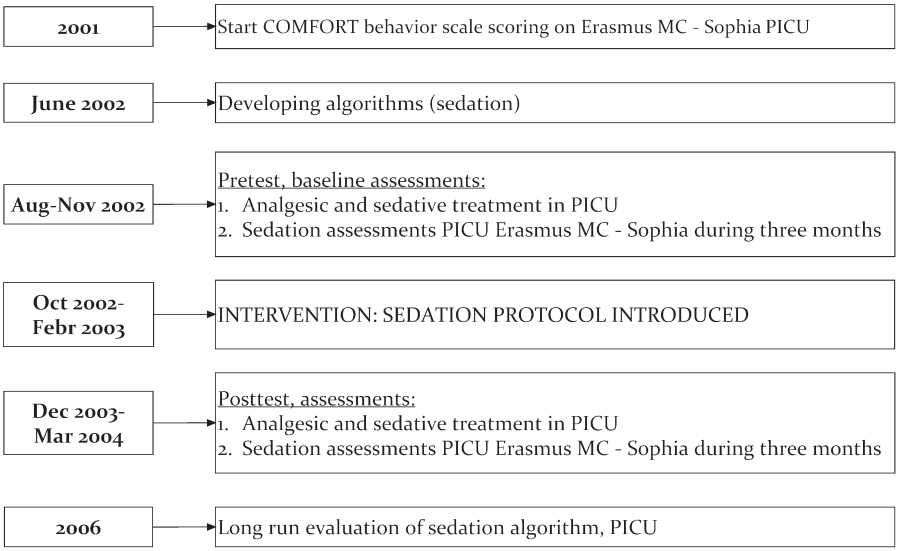
Methods

Design and Setting

This pretest - posttest intervention study (see Figure 1) was conducted in a 15 beds ICU of the Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands. In view of the

strictly observational and non-invasive nature of the study the institutional review board waived the need for informed consent.

Figure 1 Time scheme



Sedation measures

The COMFORT behavior scale

The COMFORT scale was originally developed to assess children's distress in a PICU environment.[18] An adapted version, the COMFORT behavior (COMFORT-B) scale, was validated to assess distress and postoperative pain in young children under the age of 3 years.[19-21] Measurement of its internal consistency had yielded a Cronbach's alpha of 0.92. Nurses rate alertness, calmness, respiratory response (in ventilated patients) or crying (in non-ventilated patients), muscle tone, physical movement and facial tension. With response categories ranging from 1 'no distress' to 5 'severe distress', total scores range from 6 to 30.

Nurses learned to use the COMFORT-B scale through a two-hour training using both videotaped material and bedside training. Inter-observer reliability was ensured by having nurses perform ten assessments together with an experienced nurse, after which linearly weighted Cohen's kappa was calculated.[22] Values > 0.65 are taken to indicate good inter-observer reliability. All nurses met this criterion in the first instance.

Visual Analogue Scale

Pain research frequently uses a Visual Analogue Scale (VAS) as an observational instrument for pain intensity. The VAS is a horizontal continuous 10-cm line with word anchors 'no-pain' at the left end and 'extreme pain' at the right end.[23] A mark on this

line representing pain intensity is converted to distance to give a pain score ranging from 0 - 10 centimeter. Nurses assigned VAS ratings after completing the COMFORT-B scoring form. VAS ratings ≥ 4 were considered to reflect moderate to severe pain.[24]

Nurse Interpretation of Sedation Score

To facilitate a comparison between the COMFORT-B scale and the clinical judgment of the attending nurse, we used a reference score, resembling the one used in the original validation study of the COMFORT scale by Marx *et al.*[25] The Nurse Interpretation of Sedation Score (NISS) is the nurse's expert opinion of the level of sedation, reflected by one of these categories:[21]

1. Insufficient sedation
2. Adequate sedation
3. Oversedation

Procedure

Pretest

COMFORT-B, VAS and/or NISS scores for patients up to three years age admitted to the PICU in the second half of the year 2002 served as baseline assessment. Use of sedatives and analgesics over the first 7 days of admission was documented for a convenience sample of patients ventilated for > 48 hours and/or receiving midazolam or morphine. Pediatric Index of Mortality (PIM)[26] was used to determine severity of illness. The primary investigator (MvD) acted as a focal point and supervised the study.

Intervention

The intervention consisted of implementation of standard sedation assessment scales; COMFORT-B scale, VAS and NISS, and a sedation treatment protocol developed by a pediatric intensivist and nursing scientist. It provides medication decision trees for hemodynamic stable and unstable patients (increasing medication) as well as weaning of medication (see Appendix). Within the boundaries of the protocol, nurses were allowed to titrate medication (midazolam and/or morphine) on the guidance of assessments. The cutoff points for sedation scores were established in a previous prospective study.[21] Undersedation: COMFORT-B scores of 23 or higher; or COMFORT-B scores of 11 to 22 (also called grey area) in combination with NISS of 1. Adequate sedation: COMFORT-B scores of 11 to 22 (grey area) in combination with NISS of 2. And oversedation: COMFORT-B scores of 6 to 10; or COMFORT-B scores 11 to 22 in combination with NISS of 3.

Posttest

From December 2003 until March 2004 types and doses of sedatives and analgesics over the first 7 days of admission to the ICU were documented in a convenience sample of patients ventilated for > 48 hours and/or receiving midazolam or morphine. COMFORT-B,

VAS and/or NISS scores were collected during three months.

Long run evaluation

Long run compliance with the sedation treatment protocol was assessed in 2006 (Figure 2). All eligible scores over this year were compared with the cutoff points of the sedation protocol. If the score indicated undersedation or oversedation, assessment and treatment doses of administered midazolam and morphine were compared to the protocol.

Survey

A closed-ended survey was carried out to determine nurses' and physicians' attitude and satisfaction regarding the utility and feasibility of the treatment protocol.[27] The respondents were asked to rate their opinion on statements of use of the sedation protocol, titration of medication, as well as comprehensibility and feasibility.

Statistical analyses

Background characteristics of pretest and posttest groups were compared using Chi-square analysis for dichotomous variables and Mann-Whitney tests for continuous variables (*e.g.* medication, scores). We considered $p < 0.05$ to be statistically significant. Data were analyzed using Statistical Package for Social Sciences (SPSS), version 14.0.

Results

Study population

We recorded sedative and analgesic treatment of altogether 27 patients admitted (at least seven days) in the period August 2002 - November 2002 (pretest); and of 29 other patients admitted in the period December 2003 - March 2004, after the intervention.

Background characteristics of these patients are listed in Table 1. Sex, median age, diagnoses and median PIM score did not significantly differ between the pretest and posttest groups.

In the long run group, in total 246 patients below the age of 3 years were admitted during 2006. Evaluation of the sedation protocol was performed in 131 patients (see Figure 2).

Sedation treatment

Table 2 gives an overview of administered sedatives and analgesics in pretest, posttest and long run groups. Morphine and midazolam were the most frequently administered drugs. Both median morphine and median midazolam doses were significantly higher in the posttest period. Morphine administration rose from 6.9 mcg/kg/hr to 11.2 mcg/kg/hr (Mann-Whitney, $Z = -2.9$, $p = 0.004$) for 63% versus 55% of patients, midazolam from

54.0 mcg/kg/hr to 112.8 mcg/kg/hr (Mann-Whitney, Z=-3.34, $p=0.001$) for 59% versus 79% of patients (Table 2). Several patients received additional drugs such as esketamine, clonidine, paracetamol or alimemazine to relieve distress and/or pain.

Table 1 Background characteristics of pretest and posttest patients 0-3 years

	Pretest (N=27)	Posttest (N=29)	*p* value*
Sex			
Female / Male	6 / 21	13 / 16	0.08
Age			
Neonate (< 28 days)	8	4	
1 – 6 months	8	18	
6 – 12 months	4	2	
1 – 3 years	7	5	
Median age (months)	4.1	3.1	0.81
Ventilation (yes)	17	21	0.79
Diagnosis			0.89
Congenital heart disease	15	10	
Sepsis	1	2	
Respiratory failure	4	9	
Other	7	8	
PIM score			
Median	0.04	0.05	0.80
min-max	0.002-0.97	0.002-0.78	

PIM score Pediatric Index of Mortality score, * Mann-Whitney test used

Table 2 Frequency and doses of analgesics and sedatives

	Pretest 2002 (N=27)	Posttest 2003-2004 (N=29)	Long run 2006 (N=131)
Analgesics			
Morphine			
Median (mcg/kg/hr)*	6.9	11.2	10.0
Minimum – maximum	3.4-30.2	7.4-31.5	4.5-80.0
N(% of group)	*17 (63%)*	*16 (55%)*	*80 (61%)*
Sedatives			
Midazolam			
Median (mcg/kg/hr)**	54.0	112.8	118.2
Minimum – maximum	32.3-125.7	39.9-246.0	31.3-400.0
N(% of group)	*16 (59%)*	*23 (79%)*	*95 (73%)*
COMFORT-B scale			
Number of assessments	214	832	4067
Median score (IQR)	12 (11-13)	12 (11-13)	12 (11-15)
Number of patients	*22*	*24*	*131*

Mann-Whitney test for pre-posttest morphine ($p=0.004$)* and midazolam ($p=0.001$)**, *IQR* interquartile range, *N* number of patients, Additional medication administered in pretest / posttest / long run groups: Esketamine, 2 / 3 / 28 patients; Alimemazine, 4 / 7 / 54 patients.

For the long run group, median doses for midazolam and morphine equaled those of the posttest group. COMFORT-B, VAS and NISS score distributions are shown in Table 3. The proportion of COMFORT-B scale scores between 11 and 22, indicating adequate sedation, increased from 63% during pretest period to 72% posttest and to 75% in 2006. Proportions of NISS scores indicating adequate sedation were nearly equal for the three stages. Proportions of VAS scores ≥ 4, indicating pain, were 4.6% and 5.5% for respectively the posttest group and the long run group.

Table 3 Sedation and pain assessments, COMFORT-B scale scores

	Pretest 2002	Posttest 2003-2004	Long run 2006
COMFORT-B scale			
Median (IQR)	11 (10-13)	12 (10-14)	12 (11-15)
Score ≤10	35.7%	26.3%	22.5%
Score 11-22	63.2%	72.0%	74.5%
Score ≥23	1.1%	1.8%	3.0%
Number of assessments	*440*	*1256*	*4067*
VAS*			
Median (IQR)	-	0 (0-1)	1 (0-1)
Score ≥4	-	4.6%	5.5%
Number of assessments	-	*675*	*3541*
NISS			
Under sedated	9.4%	8.8%	13.8%
Adequate sedation	87.5%	88.8%	83.7%
Over sedated	3.1%	2.4%	2.5%
Number of assessments	*425*	*784*	*3573*
Patients			
N	*48*	*60*	*131*
Median age (months)	6.5	3.1	4.0

NISS Nurse Interpretation of Sedation Score, *VAS* visual analogue scale, *IQR* interquartile range, *N* number,
* During the pretest period the VAS was not assessed on the PICU; nurses instead scored level of sedation

Feasibility

All nurses (n=44) involved reached the inter-observer reliability required for use of the COMFORT-B scale in the first instance. The mean number of assessments increased slightly from 11 (440 assessment in 48 patients) pretest to 12 (1256/60) posttest.

Long run - utilization and compliance of sedation protocol

In the long run, the sedation protocol was still being used and sedation assessments were analyzed. Sedatives were prescribed in 131 patients according to the sedation protocol. For these patients nurses' compliance with interventions dictated by the protocol and with control assessments was evaluated. In total 3573 paired COMFORT-B and NISS

assessments were performed. Patients were adequately sedated in 64% (2273/3573) of the assessments correspondingly to cutoff point for sedation protocol, which implied no medical intervention was necessary according the sedation protocol. In 45% (209/461) of assessments indicating undersedation the infusion rate was increased according to decision tree (Table 4). A medical treatment intervention outside of the protocol was performed in 26% of the assessments indicating undersedation. Control assessments were performed in 197/330 (60%) of cases in which the infusion rate or other medical treatment was increased by protocol. Sedation was weaned by protocol in 85/704 of the assessments indicating oversedation. Only in 12 of 85 cases of weaning a control assessment was performed. Forty-six percent of these assessments were performed during the night.

Figure 2 Inclusion patients long run evaluation

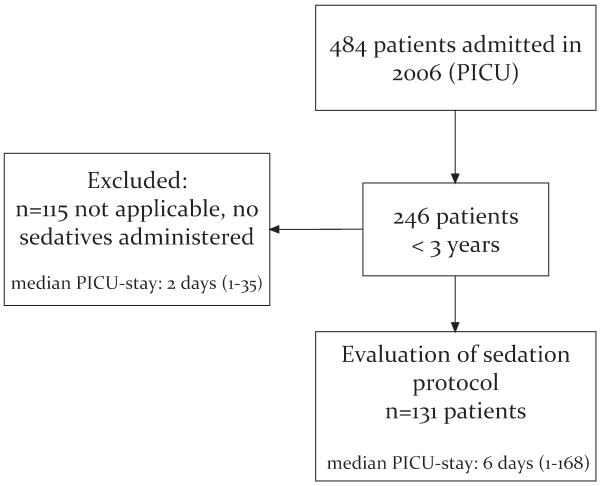


Table 4 Adherence of sedation protocol in long run evaluation (2006)

Condition	Treatment according to protocol	n (%)	Number of control assessments
Under sedated		461 (100)	
	No treatment	131 (28)	19
	Infusion rate increased	209 (45)	137
	Other medication increased (outside of protocol)	121 (26)	60
Over sedated		704 (100)	
	No treatment	619 (88)	1
	Infusion decreased/ stopped	85 (12)	12

Survey

The posttest survey on the use of the sedation protocol was completed by 26 nurses and 4 physicians (response rate of 60%). The results are summarized in Table 5. Twenty-five of

the nurses (96.2%) considered the sedation protocol comprehensible and 88.5% of them considered it was useful for clinical practice. 76.9% of nurses titrated medication within the bounds of the protocol and based on the guidance of assessments.

Table 5 Results posttest survey of pain and sedation protocol (n=30)

Items of posttest survey	**Answer (%)**		
Statements	**Yes/yes!**	**No/no!**	**?**
1. Nurses independently titrated medication within the bounds of the protocol and based on the guidance of COMFORT-B assessments.*	76.9	19.2	3.8
2. The sedation protocol in combination with the COMFORT-B scale is comprehensible, joined with.*	96.2	3.8	
3. The sedation protocol is useful for clinical practice.*	88.5	3.8	7.7
4. Independent administering of medicines within the bounds of the sedation protocol is a too large a responsibility.*	19.2	80.8	
5. Independent administering of medicines within the bounds of the protocol is a challenge.*	61.5	34.6	3.8
6. The sedation protocol is only useful for postoperative patients.	10.3	82.8	6.9
7. Implementation of the sedation protocol on the ward has little impact.	44.8	51.7	3.4
8. The protocol increases quality of care.	62.1	27.6	10.3

* nurse specific statements

Discussion

After the introduction of a sedation protocol, administered amounts of midazolam and morphine increased significantly. The implementation proved relatively successful in the long run in PICU.

Effect of the implementation?

Proportions of patients receiving morphine or midazolam did not significantly change. However, higher doses did not lead to significantly lower sedation scores. In contrast, the proportion of COMFORT-B scores 11-22 ('adequately sedated') increased slightly for the posttest group. The variety of sedatives (propofol, ketamine and alimemazine) administered in addition shows that optimal sedation and quality of sleep remain challenging for this patient group. Alexander *et al.*[16] found also significantly higher doses of midazolam and fentanyl after implementation of a sedation protocol. The study population was small, however, and the authors did not provide a reason for the increase. In the long run evaluation, we found that median doses of midazolam and morphine were equal to those in the posttest group. These results, however, pertained to a larger

population. Furthermore, doses recorded for the long run evaluation concerned patients' total ICU stay, in contrast to the posttest group for which doses over the first 7 days were recorded.

Most of the studies of nurse implemented pain and/or sedation protocols were performed in adult-ICU care. The effects of implementation were different, however, and therefore these cannot be generalized to our practice.[10,11,14]

Several questions may be raised how we can explain the effect on the implementation in this study. Does higher dosing of sedatives and analgesics indeed reflect improved sedation treatment? Does higher number of COMFORT scores ≥ 23 point at undersedation, or at caregivers' increased awareness of the necessity of adequate sedation? We selected midazolam and morphine to be used in our protocol for sedation treatment, but administered other additional sedatives and analgesics as well. Given the lack of solid data these preferences are not evidence-based.[4,28] Seeing that pediatric drug studies are still scarce, physicians may tend to draw on personal experiences.

Compliance

Sedation assessment is the first step in multidisciplinary sedation management. In general, we may conclude that regular sedation assessment was feasible for the study period. What's more, it was found to be standard practice two years after the first posttest, with acceptable compliance. We would like to propose three explanations. One, the research nurse's continuous involvement in sedation issues was conducive to regular sedation assessment. Two, a patient data management system was in place, which is valuable when set to alert caregiving nurses to assess their patient(s) comfort and pain each shift. Also, it is essential to have the commitment of at least one physician on the PICU, not only to develop an protocol but also to supervise its use. Further, we may conclude that staff was satisfied with implementation of the sedation protocol. Regrettably, this proved no assurance for strict adherence to guidelines of sedation management and application of the protocol. We have seen this also in the long run evaluation. There were several reasons for violation of the treatment protocol. First, nurses were reluctant to decrease sedatives during nighttime. COMFORT-B scores were significantly lower during nighttime than daytime.[21] This might be explained by physiological sleep pattern, less noise and light and children receiving only necessary care and interventions. Sedatives were mostly decreased after daily rounds and based on nighttime and daytime sedation scores. This would be discussed with nurse and physician during rounds. Reluctance and anxiety may be other factors why nurses did not titrate sedatives or analgesics as prescribed in the protocol. Relatively few control assessments for evaluating medical treatment were performed, especially in oversedated patients. We speculated nurses were occasionally not focused on reduction of length of stay but more engaged with comfort of the patient.

Cabana *et al.*[6] have identified several barriers that refrain physicians and nurses from following guidelines, such as lack of awareness, familiarity and agreement. Such

factors may well have played a role in our study as well. On the other hand we agree with Alexander *et al*.[16] that the use of a sedation and pain protocol, which transfers some of the decision-making process from physicians to nurses, requires a change in culture.

In our opinion it is important to incorporate standard sedation assessment in a treatment protocol. The nurses can thus be given the authority to act on the basis of sedation assessment, albeit within the borders of the treatment protocol. Correcting inadequate sedation is inefficient in the absence of a protocol since it requires the nurse to first communicate her/his assessment, obtain a prescription, adjust the sedation and wait for the drug to take effect. This is a time-consuming process which can lead to conflicts. The use of a protocol enables efficient interventions and avoids the need to negotiate with physicians. The success of nurse-directed protocols can be achieved, at least partly, by allowing more rapid clinical decision making to occur at the patient's bedside.[10]

The general purpose of the study was implementation of a sedation assessment tool and a related treatment protocol. Our study had some limitations. The time frame from start to finish was relatively long. This was needed, we felt, because of the well-known problem of introducing new protocols on a ward. However, during this period a number of unknown influences might have led to the increased use of midazolam and morphine. The chosen design in this study had some weaknesses in contrast with a RCT. Other potential outcomes such as morbidity or duration of mechanical ventilation require much larger sample sizes. It proved difficult to find optimal outcome parameters for this study. Patient satisfaction cannot be tested in very young children, as they lack the ability for self-report. Caregivers may be satisfied with their sedation treatment but their view may be biased. Finally, it proved difficult to check whether nurses worked according to the protocol. Sedation assessment scores could be retrieved from PDMS but determining if nurses indeed increased midazolam or morphine dosing themselves when scores were high proved very complex.

We conclude that the implementation of sedation assessment was successful in our PICU. Satisfactory implementation of the protocol - *i.e*. treatment based on sedation assessment itself - remains questionable, however. We hypothesize that compliance was moderate, like with many other treatment protocols.[1,29] Nurses may find it easier to ask an attending doctor to adjust dosing of sedatives rather than to consult a treatment protocol. Physicians, in turn, like to follow their clinical impression instead of providing treatment on the guidance of sedation scores. The higher dosages of midazolam and morphine noted in this study might well result from greater awareness of pain or anxiety invoked by the very study. Unfortunately, the relatively low level of evidence for these specific populations does not yet provide for solid based guidelines.[4,28]

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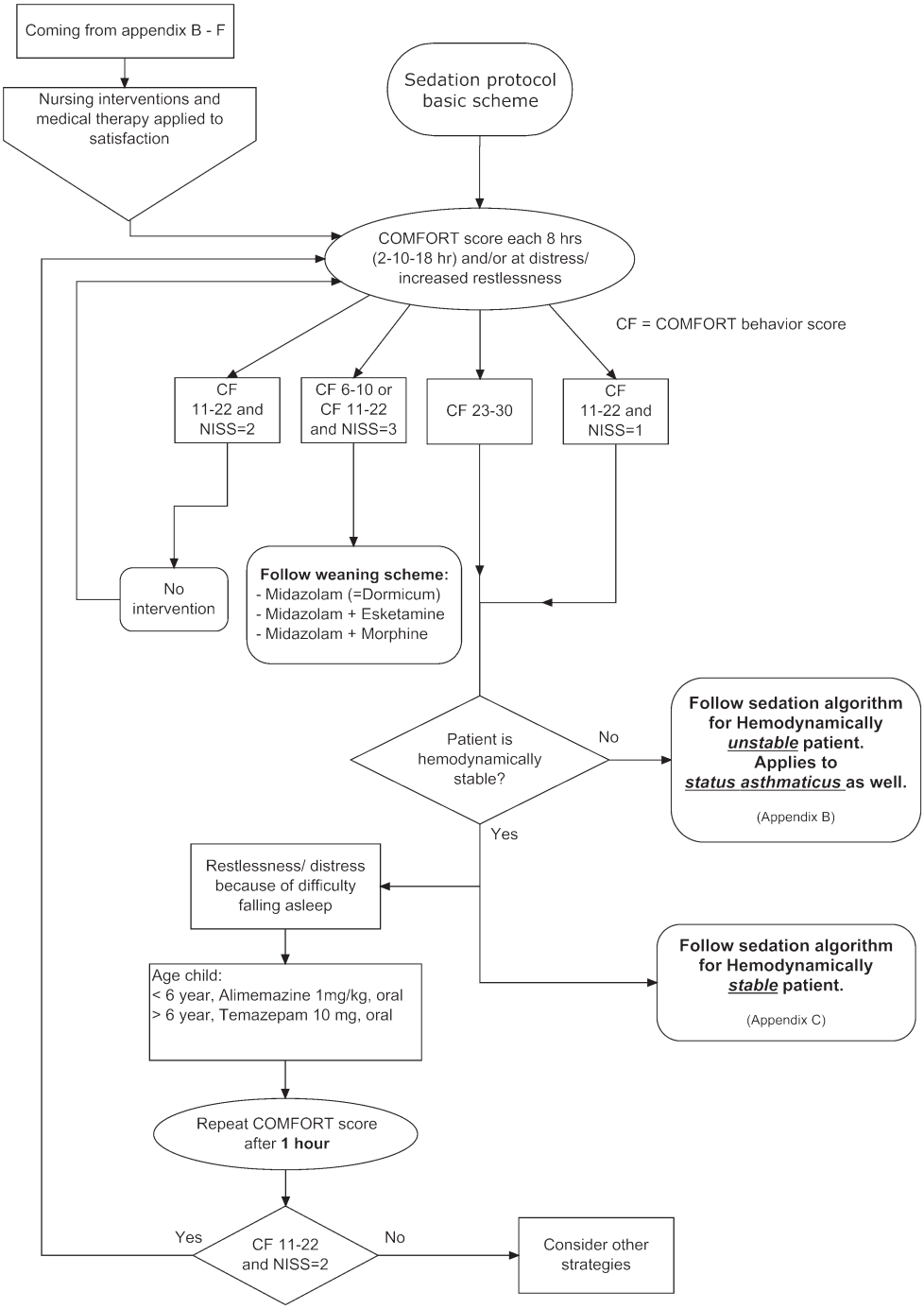
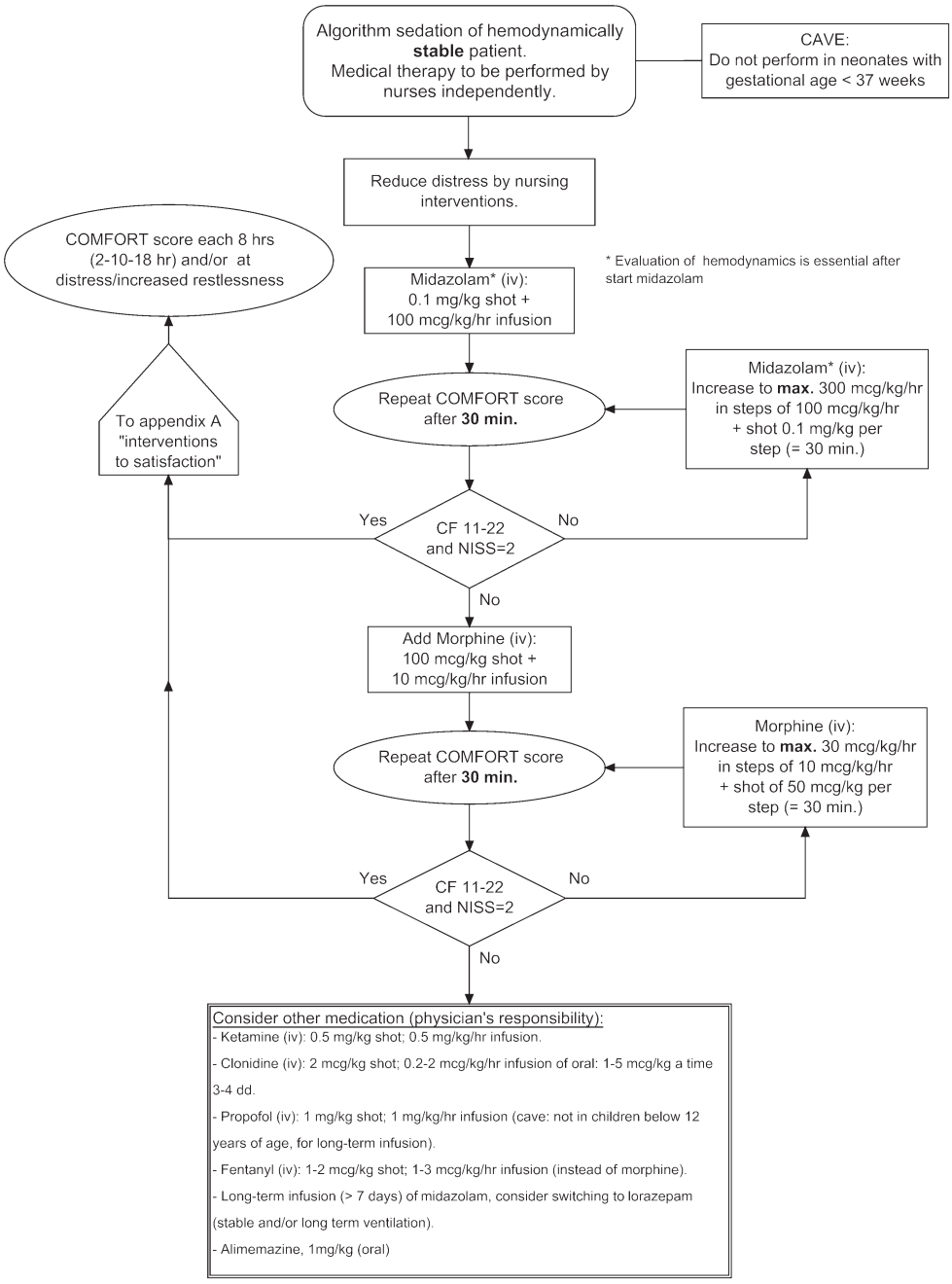
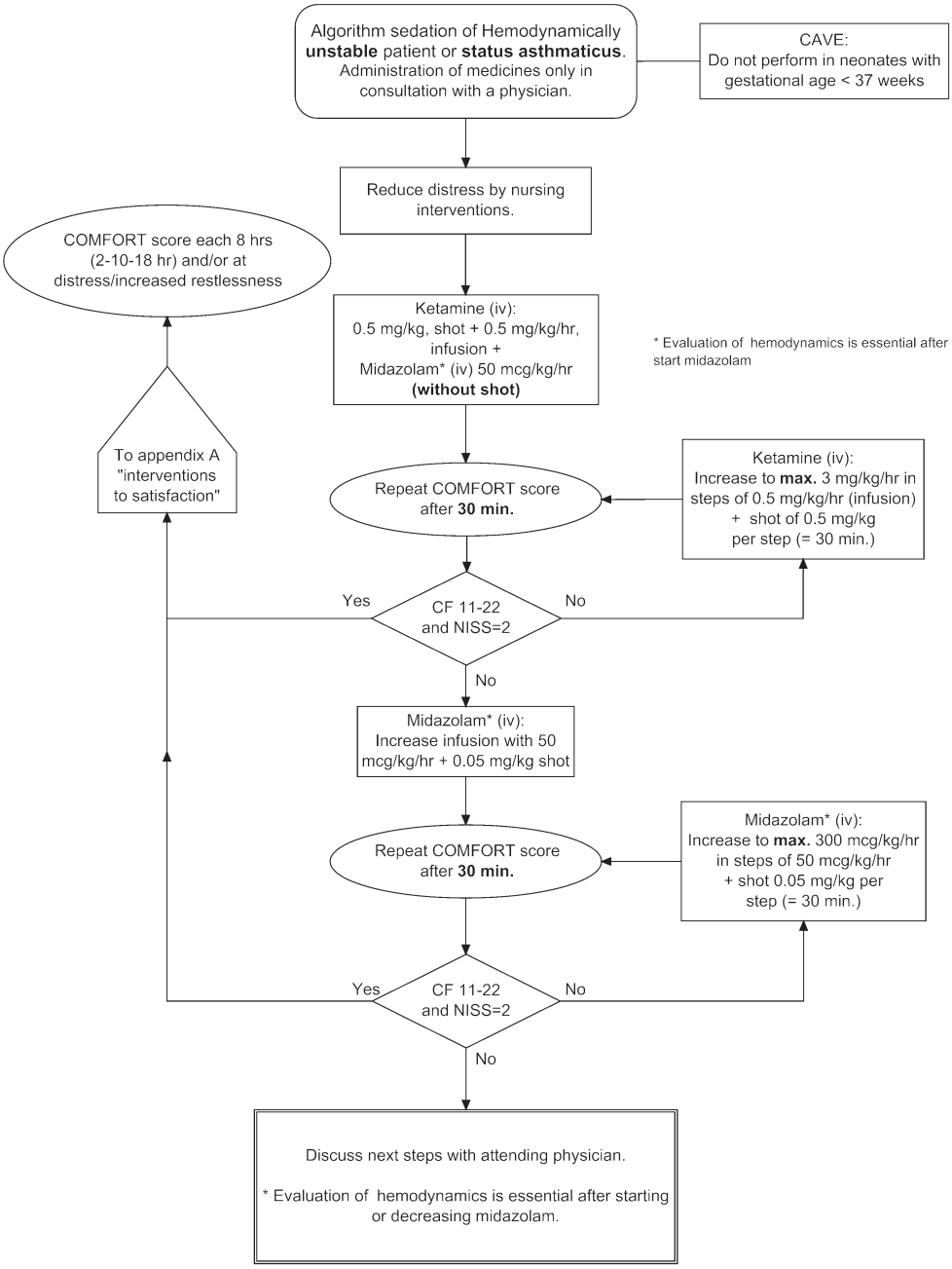
Appendix A Basic scheme sedation protocol



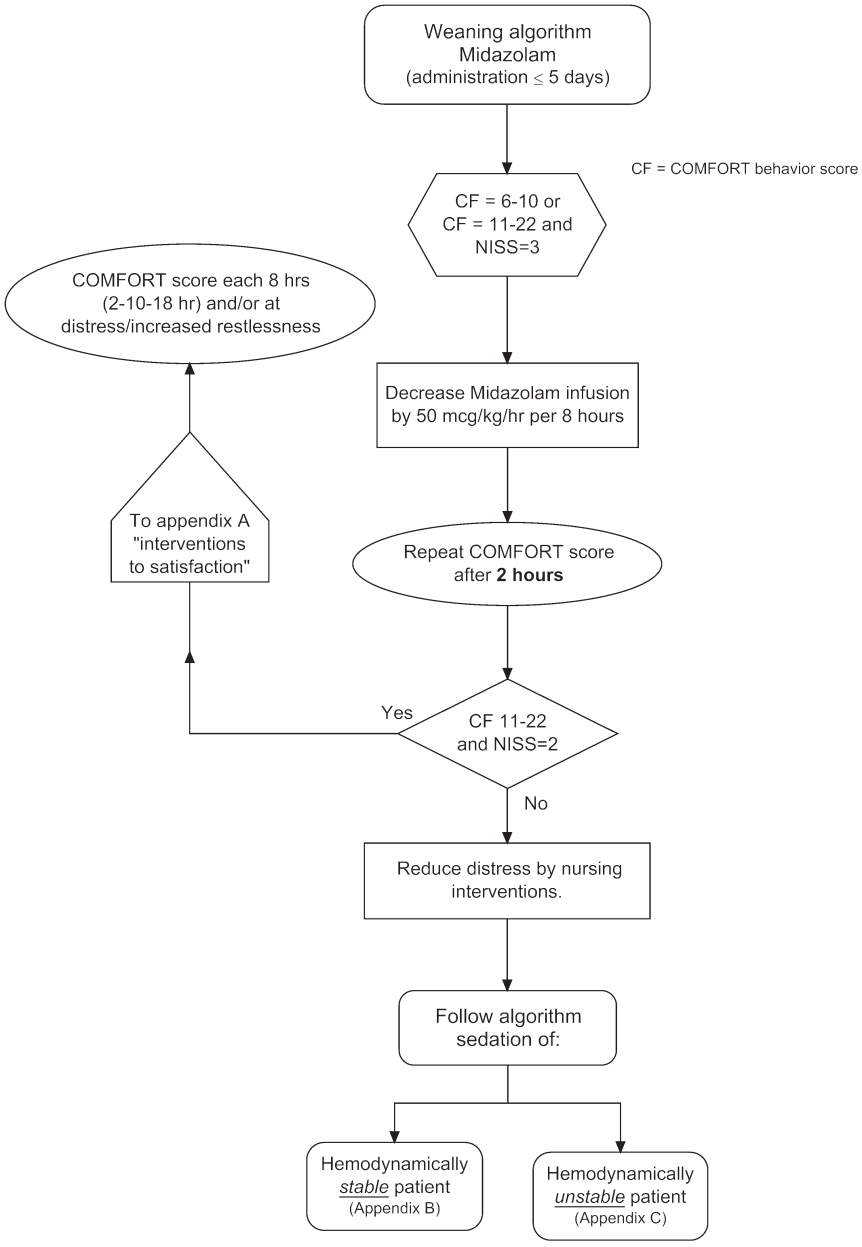
Appendix B Decision tree for hemodynamic stable



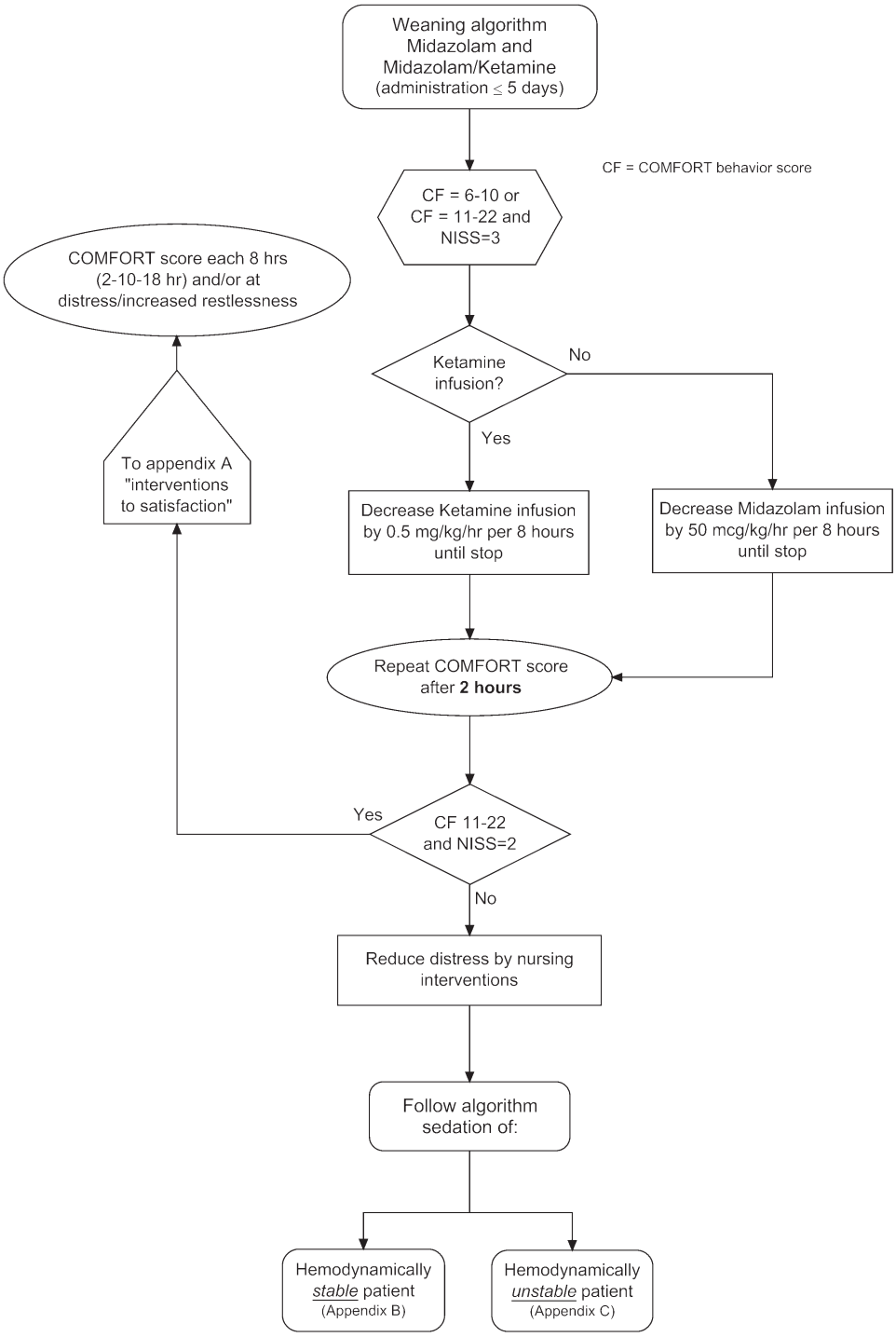
Appendix C Decision tree for hemodynamic unstable



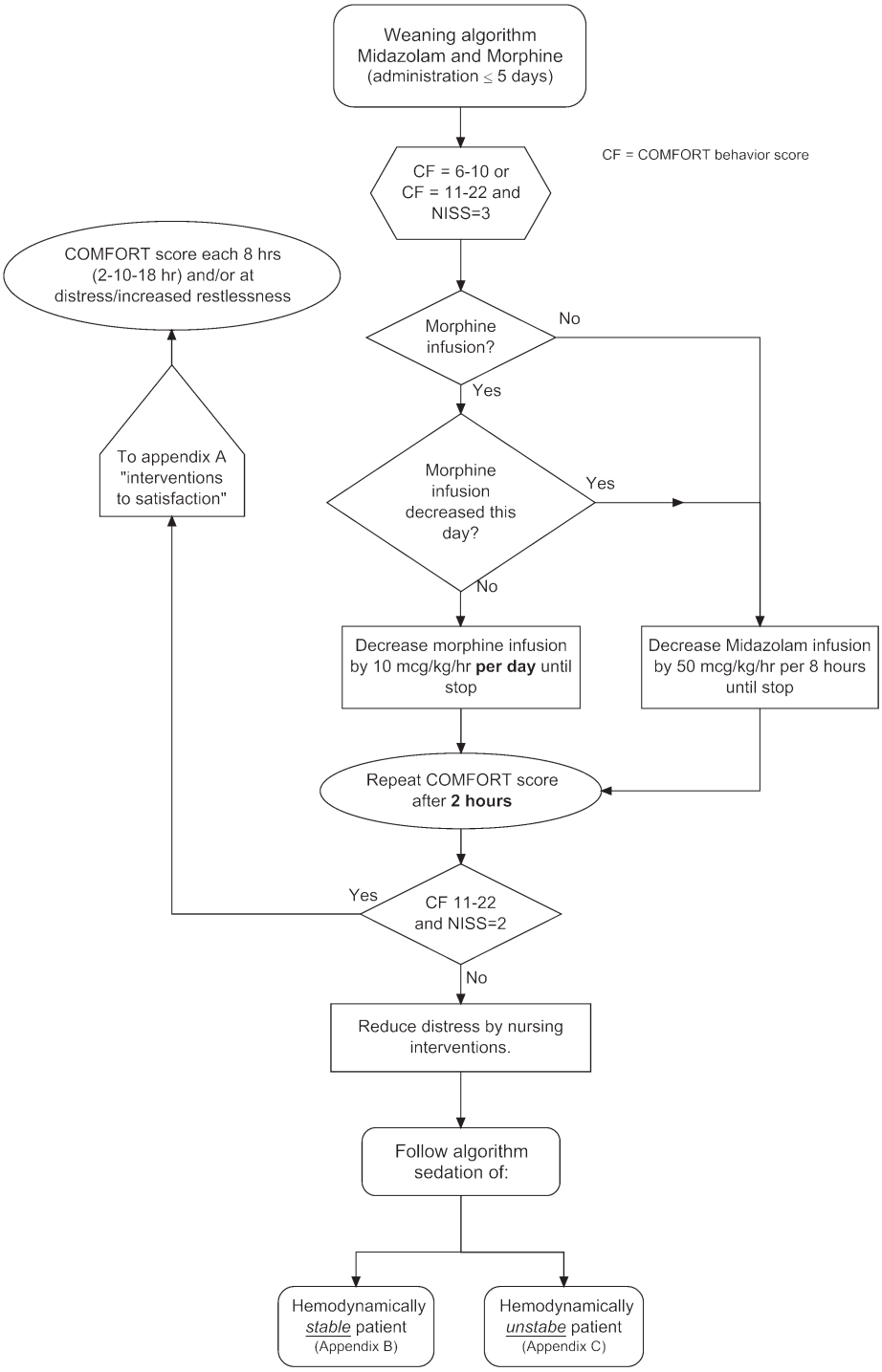
Appendix D Decision tree weaning midazolam

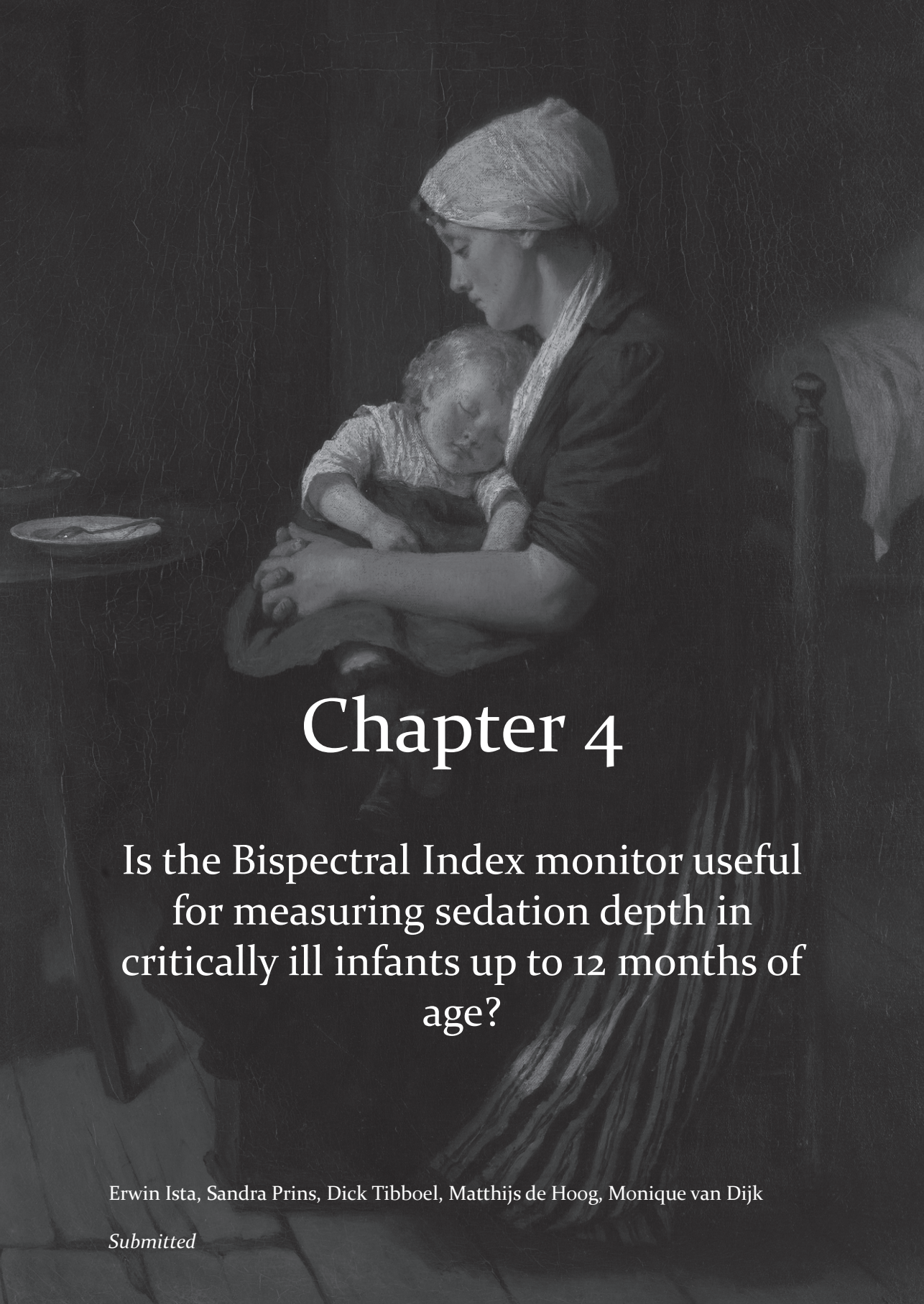


Appendix E Decision tree weaning midazolam and ketamine



Appendix F Decision tree weaning midazolam and morphine





Chapter 4

Is the Bispectral Index monitor useful for measuring sedation depth in critically ill infants up to 12 months of age?

Erwin Ista, Sandra Prins, Dick Tibboel, Matthijs de Hoog, Monique van Dijk

Submitted

Abstract

Background: The BIS monitor has been validated for assessment of sedation levels in adults and children above one year of age. Normal BIS values are available for adults, but not yet for infants.
Aim: We aimed to examine the correlation between the BIS monitor and COMFORT behavior scale in infants up to 12 months and to evaluate the usefulness of the BIS for the assessment of consciousness in infants.
Methods: We created two groups. Infants in the 'natural sleep' group were drug free and free from intra-cerebral pathology, and were monitored with BIS and COMFORT behavior scale (COMFORT-B) for 24 hours. Infants in the 'postoperative sedation' group were monitored likewise during the first 48 hours postoperatively. The correlations and prediction coefficient (Pk) for BIS and the COMFORT-B item alertness were calculated.
Results: 264 paired observations were collected for 32 hospitalized infants (median age 58 days; range 1 to 363) without any opioids and sedatives. The Spearman correlation coefficient between the BIS and COMFORT-B was $r_s = 0.62$ and $r_s = 0.72$ for the age groups 0 - 6 months and 6-12 months, respectively. The Pk for the BIS compared with alertness scores was slightly higher for the older age group.
Thirty-nine infants were enrolled in the postoperative sedation group (median age 39 days; range 4 to 97 days). In total 203 paired observations were obtained with a median BIS value of 67 (range 12 to 98) and a median COMFORT-B score of 12 (range 6 to 30). The overall Spearman's correlation coefficient was 0.50 ($p < 0.0001$). BIS values were significantly different for the five COMFORT-B alertness categories (Kruskal-Wallis, $p < 0.0001$).
Conclusion: BIS values obtained using the present algorithm software during natural and pharmacological sleep (sedation or anaesthesia) should be interpreted with caution in infants up to 12 months of age. A new algorithm, derived from BIS values for this age group during 'natural sleep' and awake state needs to be developed.

Introduction

Critically ill children requiring mechanical ventilation almost always receive sedative and analgesic drugs. These will reduce possible distress, anxiety, pain, and facilitate intensive care therapy and nursing care. While undersedation fails to produce the desired effects, oversedation will lead to prolonged intensive care, longer duration of mechanical ventilation, and drug tolerance possibly with withdrawal syndrome.[1,2] Optimal level of sedation will vary with age and severity of illness, among other things. Titrating optimal doses for each child is a difficult task therefore. In order to achieve this, a number of sedation scoring systems have been devised for use in the critically ill.[3] Only three validated sedation scales assess distress in ventilated critically ill children; the COMFORT behavior scale, the Hartwig sedation scale and the State Behavioral Scale.[4-8] The COMFORT-B scale has been recommended for regular sedation assessment.[9] Concerns have been raised about the subjectivity of clinical sedation scales and their inability to differentiate between deep and moderate sedation. Furthermore, they assess sedation at single points in time, so that information about sedation levels in the intervening periods is lacking.

As an alternative, brain monitors such as Bispectral Index (BIS) monitor have been developed and validated for assessing depth of sedation (consciousness) - mostly during anaesthesia in adults and children over one year of age.[10-15] Experience with the BIS monitor has been gained meanwhile in pediatric intensive care.[16,17] Several BIS monitoring validation studies have been performed in critically ill infants and children in the intensive care setting (see Table 1).[18-24] All studies showed from moderate to good correlation (0.54 to 0.89) between BIS values and clinical sedation scores. However, the BIS monitor has a major limitation when applied in young children. It makes use of an algorithm derived from adult electroencephalograms (EEG), which are known to differ from those in young children. Furthermore, in clinical practice it seems to be a moderate predictor of sedation level in the individual infant.

Steriade[25] reported that characteristic changes in EEG signals during general anaesthesia also occur to some degree during naturally occurring sleep; it would seem logical, therefore, to determine BIS values during 'natural sleep'. Only for children undergoing surgery a correlation was established between BIS values based on the 'adult algorithm' and sevoflurane concentration with the.[26] It seems likely, however, that BIS values for young children differ from adult ones and will change during the first years of life.[27]

The aim of this study was to examine the correlation between the BIS monitor and COMFORT behavior ratings in infants up to 12 months of age, and to evaluate the usefulness of the BIS assessment of consciousness level in infants. To this aim we compared BIS values and COMFORT behavior scores in 'natural sleep' infants without sedatives and postoperative (sedation) infants.

Table 1 Overview of BIS monitor studies in PICU patients

Reference	Aim	Setting	N	Age	BIS versus	Correlation
Twite *et al.*[24]	Assess degree of correlation between COMFORT Scale - BIS	PICU	75	1 month - 12 yrs (25% <6 months)	COMFORT Scale	$r_s = 0.54$ ($p < 0.0001$) overall
Triltsch *et al.*[23]	Evaluate the use of BIS to monitor level of sedation	PICU	40	0-16 yrs (n = 21, 0 - 6 months)	COMFORT Scale	$r_s = 0.65$ ($p < 0.001$) total group $r_s = 0.78$ ($p < 0.001$) 0 - 6 mo $r_s = 0.47$ ($p < 0.041$) 6mo - 16 yrs
Hsia *et al.*[22]	Examine correlation BIS and GCS	PICU	17	10 months - 16 yrs	GCS	$R = 0.76$ ($p < 0.001$)
Aneja *et al.*[18]	Compare BIS versus Ramsay score	PICU	48	1 - 16 yrs	Ramsay scale	$R = 0.77$ ($p < 0.0001$)
Courtman *et al.*[20]	Examine the BIS as reliable indicator of depth of sedation	PICU	40	1 month - 16 yrs	COMFORT Scale	$r_s = 0.50$ ($p < 0.0001$) overall
Berkenbosch *et al.*[19]		PICU	24	1 month - 20 yrs	PICU scale Ramsay scale TSS Scores	$R^2 = 0.21$ ($p < 0.001$) $R^2 = 0.12$ ($p < 0.001$) $R^2 = 0.09$ ($p < 0.001$)
Crain *et al.*[21]	Compare BIS versus COMFORT scale	PICU	31	53 ± 11 months [a]	COMFORT Scale	$R^2 = 0.29$ overall $R^2 = 0.89$ BIS categorized

GCS Glasgow Coma Scale, *PICU scale* pediatric intensive care unit sedation score, *TSS score* tracheal suctioning score, r_s spearman's rank correlation coefficient, *R* linear regression coefficient, R^2 squared regression coefficient, *mo* months, *yrs* years, [a] mean ± SD (standard deviation)

Methods

To examine the correlation between the BIS monitor and the COMFORT behavior scale we performed an observational prospective study in two different study groups. All patients were infants aged 0 up to 12 months and included in this study after written parental informed consent. The Erasmus MC institutional review board approved the research of the BIS monitor.

Natural sleep group

Infants, free of opioids and midazolam and free from intra-cerebral pathology, were included in this study group between March 2003 and April 2004. BIS electrodes were applied at the forehead of the infants as instructed by the manufacturer during 24 hours at a medium care unit of the tertiary Erasmus MC - Sophia Children's hospital. The BIS monitor was connected to a laptop, which collected all BIS data. During these 24 hours, hourly COMFORT behavior observations were planned. Simultaneously, BIS values were collected continuously, read afterwards and paired with the COMFORT observations.

Postoperative sedation group

Infants were included for this study between March 2002 and April 2003 if they were expected to undergo postoperative sedation for more than 48 hours after surgery. We evaluated the BIS monitor during sedation of infants admitted to the surgical pediatric intensive care unit of the Erasmus MC - Sophia Children's Hospital using the COMFORT behavior scale. An independent observer (SP) randomly scored the COMFORT behavior scale together with BIS values during the first 48 hours postoperatively.

The COMFORT behavior scale

The COMFORT behavior scale is an adapted version of the scale that was originally developed by Ambuel and colleagues[8] in 1992 and consisted of six behavioral items and two physiological parameters, heart rate and blood pressure. Marx and colleagues[5] showed that this scale was useful to assess sedation. We showed that, leaving out the physiological items, the scale was still valid for both postoperative pain and sedation in children aged 0 - 3 years.[28] Six patterns of behavior are assessed: Alertness, Calmness/Agitation, Muscle tone, Physical movement, Facial tension, Crying (non-ventilated children) or Respiratory response (ventilated children). Each item is scored from 1 to 5; the total score thus ranges from 6 to 30: the higher the score, the more uncomfortable the child is thought to be. All nurses were trained to use the scale, as reported in our earlier analgesia study.[28] Inter-observer reliability, represented by linearly weighted kappa, was satisfactory, with kappa > 0.65 for all nurses and the principal investigator.[28] Scores < 9 are thought to represent over-sedation, scores between 9 and 16 no distress, scores ≥ 17 distress.

BIS monitor

The BIS monitor uses a frontal, two channel electroencephalogram (EEG) to quantify hypnotic effects of anaesthetic and sedative drugs on the brain. First mainly used during surgery, over the years it has found its way to the pediatric intensive care unit as well.[10,19] Fourier transformation of the information and bispectral analysis are used to compute a number between 100 (fully awake) and zero (absence of brain electrical activity).[11] BIS values above 60 are considered to be indicative of inadequate sedation and even risk of awareness in adults.[12,13] A Bispectral A 2000 version 3.12 monitor (Aspect Medical Systems, Natick, MA, USA) with commercially available BIS sensor strips designed for children was used. A BIS sensor was placed on the patient's forehead in accordance with the manufacturer's instructions. The algorithm within the BIS monitor sets limits for electrode impedance and signal quality. Consequently, no value is displayed if the signal has too much noise or artefacts. We used the limits set in the monitor; if the BIS value was displayed, meaning a Signal Quality Index (SQI) >50, it was recorded. BIS values of <40 were defined as very deep sedation, 41-60 as deep sedation, 60-79 as moderate sedation, 80-89 as light sedation, and >89 as awake.

Statistical analyses

The data were analyzed using SPSS for Windows (version 14.0; SPSS, Chicago, IL). Correlations between BIS values and COMFORT scores were expressed by the Spearman rank correlation coefficient (r_s). In this study scores on the COMFORT behavior item alertness represented the level of consciousness. These scores were compared with BIS values using the Kruskal-Wallis H test. Furthermore, to detect any age related differences, we created two age groups: 0 to 6 months of age and 6 months to 12 months of age. In anaesthesia the prediction probability coefficient (Pk) is commonly used as a measure of association between a clinical monitor such as the BIS monitor and consciousness (anaesthetic depth) reflected by observation.[16,29] Pk gives the probability that the index values of two randomly selected data points predict correctly which of the data points correspond to the deeper or lighter level of anaesthesia. A Pk of 1 means that the values of the predicting index (BIS) will always correctly predict the level of consciousness. A Pk value of 0.5 means that the values of the predicting index will predict level of anaesthesia no better than a 50-50 chance. Pk values depend on the number of levels of the observation scale.[30] Statistical differences were considered significant if $p < 0.05$.

Results

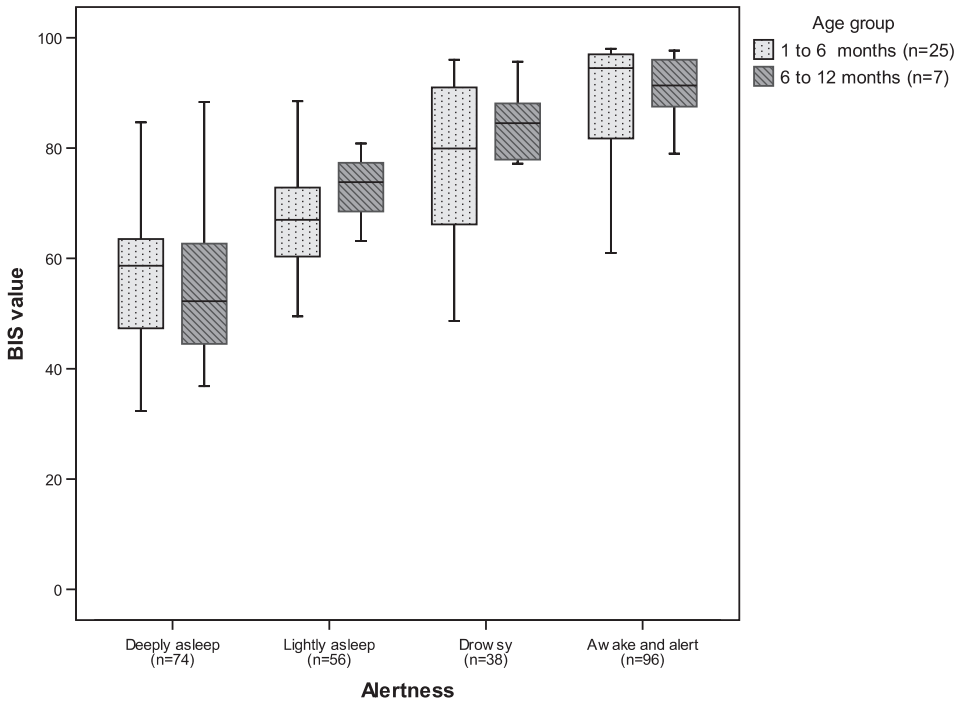
Natural sleep group

Thirty-two infants (22 boys and 10 girls) were included in the 'natural sleep' group. Their median age was 58 days (range 1 to 363 days). Twenty-five were 0 to 6 months of age and

seven infants were 6 months to 12 months of age. All patients were free of opioids and benzodiazepines. Nine (28%) were on acetaminophen (paracetamol) at the time of the observations.

In total 264 COMFORT behavior scale observations were done, with a median of 8 observations (range 2 to 17) per patient. The median BIS value for these observation moments was 73 (range 32 to 98); the median COMFORT behavior score was 13 (range 6 to 23). The BIS-COMFORT behavior correlation was r_s= 0.62 for the age group 0 - 6 months and r_s = 0.72 for the age group 6 - 12 months. The overall correlation for all observations was r_s = 0.67 ($p < 0.0001$). Correlations between separate COMFORT behavior scale items and BIS ranged from 0.58 for facial tension to 0.79 for body movement. BIS values corresponding with the various response categories of the item alertness are shown in Figure 1. In spite of large overlaps, BIS values were significantly different for these categories (Kruskal-Wallis test, Chi-square 64.85, $df = 4$, $p < 0.0001$). The association between BIS values and the item alertness reflected by the prediction coefficient (Pk) was 0.86 (SE 0.02) for the overall group. The Pk was slightly better in the age group 6 - 12 months (Table 2).

Figure 1 BIS values for infants in the 'natural sleep' group in relation to the various response categories for the COMFORT item alertness



The response category Hyper-alert did not contain data.

Table 2 Correlation and prediction probability coefficients

	Postoperative sedation group			Natural sleep group		
	Total (N = 39)	0 - 6 months (N = 37)	6 - 12 months (N = 2)	Total (N = 32)	0 - 6 months (N = 25)	6 - 12 months (N = 7)
Spearman Correlation	0.50	-	-	0.67	0.62	0.72
$Pk_{(BIS\text{-}alertness)}$	0.76 (0.02)	0.76 (0.02)	-	0.86 (0.02)	0.84 (0.020)	0.89 (0.037)
$Pk_{(BIS\text{-}COMFORT\text{-}behavior)}$	0.69 (0.02)	0.69 (0.02)	-	0.75 (0.016)	0.73 (0.019)	0.78 (0.039)
Number of assessment	*203*	*198*	*5*	*264*	*210*	*54*

Pk prediction coefficient (SE), *N* number of patients

Postoperative sedation group

Thirty-nine infants (32 boys and 7 girls) were enrolled in the postoperative sedation group. Their median age was 39 days (range 4 to 97 days). Two of them were > 6 months. These infants received analgesics and sedatives in the PICU after major abdominal (n = 30), craniofacial (n = 4) urological (n = 2), or other surgery (n = 3).

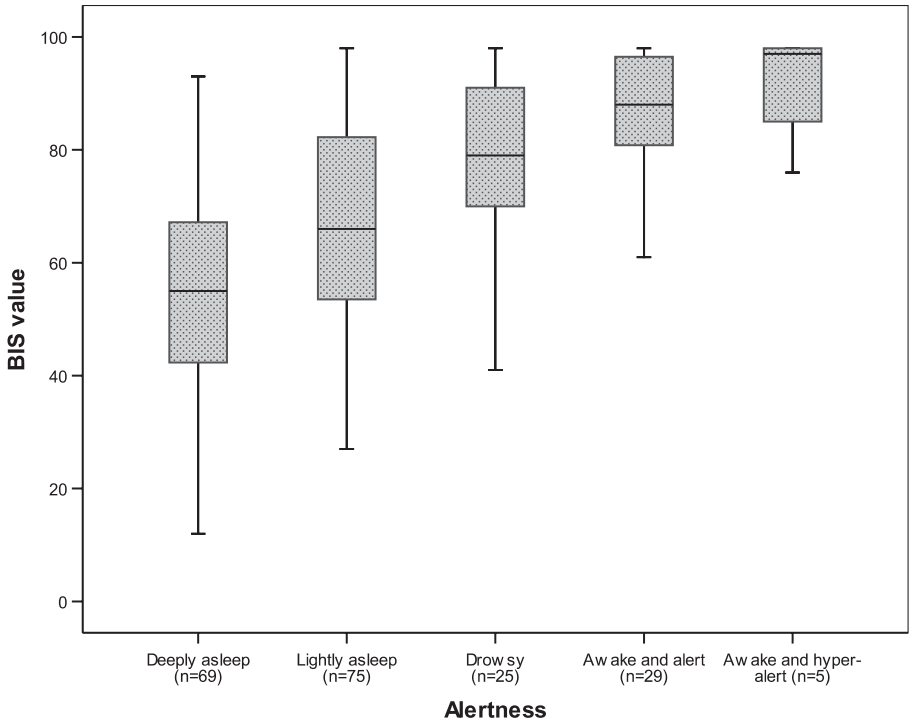
Fifteen infants received only morphine, 2 infants only midazolam and 16 a combination of the two. Median dosages of morphine and midazolam were 10 mcg/kg/hr and 100 mcg/kg/hr respectively. Six infants received only acetaminophen during the observations.

In total 203 COMFORT behavior observations were done with a median of 4 observations (range 2 to 14) per patient. The median COMFORT behavior score was 12 (range 6 to 30) and the median BIS value for the observation moments was 67 (range 12 to 98). The overall Spearman correlation coefficient for all observations was $r_s = 0.50$ ($p < 0.0001$). Correlations between separate COMFORT behavior items and BIS ranged from 0.20 for crying to 0.60 for alertness.

Figure 2 shows BIS values corresponding with the various response categories of the item alertness. BIS values were significantly different for these categories (Kruskal-Wallis, Chi-square 64.8, $df = 4$, $p < 0.0001$). The association between BIS values and the item alertness reflected by the prediction coefficient (Pk) was 0.76 (SE 0.02) (see Table 2)

In 56.7% of the observations the infants were considered appropriately sedated on the basis of the BIS score (BIS 41 - 79 (deep and moderate)); in 10.8% they were considered oversedated (BIS < 40). On the other hand, in 69.0% of the observations the infants were adequately sedated on the basis of the COMFORT behavior score (9 - 16) and in 11.8% oversedated (< 9).

Figure 2 BIS values for infants in the postoperative group in relation to the various response categories for the COMFORT behavior scale item alertness.



Discussion

To our knowledge this is the first study describing effects of sedation and physiological sleep on BIS values in infants up to 12 months of age. Our main finding is a moderate overall correlation between BIS monitor and COMFORT behavior scale for infants less than 12 months. For infants 6 to 12 months in the 'natural sleep' group, however, the correlation (r_s = 0.72) was better than that in younger infants, and the prediction coefficient (Pk = 0.89) was good.

Maintaining adequate sedation in children in intensive care is a great challenge and often a difficult task. Appropriate RCTs in this field have not been performed yet.[31] A disadvantage of the use of sedation scales is that completion takes much time, with inherent risk of low compliance. What's more, these 'objective' scales still carry the risk of some subjectivity in assessing sedation depth, such that sedation requirements may be set differently by different practitioners caring for a patient.[32] A really objective method such as BIS monitoring could therefore be a helpful instrument to guide administration of sedatives and analgesics.[17]

To date, relevant studies performed have primarily focused on validating BIS measurements by correlating BIS with existing clinical sedation scales (Table 1).[18-24] Except for Aneja *et al.*[18] all authors included infants less 12 months of age. However, only two studies distinguished between young infants (< 6-12 months) and older children (>6 months).[23,24] While Twite *et al.*[24] found a similar correlation as in our study, Triltsch *et al.*[23] found a higher correlation in infants less than 6 months compared with the older children. Surprisingly, they could not explain the higher correlation in the younger children. Also, other authors have noted BIS scores in infants <6 months of age to be unreliable during general anaesthesia.[14,15,26] Like Twite *et al*.[24] we conclude that the BIS monitor and the COMFORT behavior scale do not measure the same variables. The former measures level of consciousness (sedation), whereas the latter was designed for assessing overall distress. Although different, these variables yet are related and affect each other. For example, an infant may be awake and alert as shown from a high BIS value and comfortable on account of a moderately low COMFORT behavior score. Alternatively, a stimulus may awaken a sedated infant, increasing the BIS value but not changing the COMFORT behavior score to a great extent. BIS and COMFORT behavior scale detected the same proportion of undersedation, however, there was a discrepancy for the proportions of adequate sedation detected.

In this study the Pk measure was used to examine the association of BIS measures and 'alertness' in infants.[16,29] We hold the view that level of consciousness is best reflected by the item 'alertness' of the COMFORT behavior scale. The results of this study indeed underpin this view (Table 2). Patients in the 'natural sleep' group showed a higher Pk association and Spearman correlation coefficient than those in the postoperative group. This suggests that assessing pharmacological sedation with the BIS monitor may be less reliable in infants less than 1 year old.

Age-related differences in EEG patterns also are thought to affect the validity of BIS monitoring in children. The algorithm used in the BIS monitor is derived from adult EEG patterns, which differ from those of children and especially infants. The 'normal awake' EEG changes with brain maturation. With increasing age the frequency of the awake dominant background activity increases; at 6 months of age the dominant frequency is 5 Hz, from 6-18 months 6-7 Hz, at 2 years 7-8 Hz, by 7 years it is 9 Hz and by 15 years of age reaches adult levels at 10 Hz. Under 5 year olds also have specific EEG patterns associated with the transition to, and from, sleep and drowsiness. Children aged 6 months to 4 years have short bursts of 4-8 Hz activity lasting 1-5 seconds. Also, longer periods of 1-Hz to 3-Hz activity may be seen in 3 months to 5 year old children, predominantly at 12 months. Therefore the difference in EEG pattern is the most important limitation in the use of BIS monitor in infants.[16,33,34]

The BIS monitor does not distinguish between various stages of natural sleep and pharmacologically induced sleep[20,35]. BIS values during REM sleep in adults and children have been found to range from 16 to 45. This range is equivalent to that used to define deep

sedation. In our study we found BIS values as low as 32 in infants without any medication. In contrast, in both study groups high BIS values were observed in infants supposedly 'deeply asleep' according to the COMFORT score. The BIS is sensitive in reflecting changes in the EEG pattern that accompany the various stages of natural sleep. More specifically, BIS values decrease progressively as sleep becomes deeper. On the other hand, BIS values may surge to 88 on reawaking.[35] The COMFORT behavior scale, however, does not differentiate between the different stages of REM sleep.

This study has several limitations. Firstly, it was hardly feasible to create two age groups for the postoperative group into, because we included only two patients aged 6 to 12 months. Secondly, number of observations per patient widely ranged in the 'natural sleep' group. In addition, the observations gave us only snapshot views. Video recordings would be a means to get continuous data.

A particular strength of this study is the clinical relevance. Because the results of this study give insight in the usefulness of the BIS monitor for assessing sedation in infants up to 12 months.

Conclusion

The BIS monitor was not designed as a monitor for assessing the depth of sedation in children. BIS values obtained during pharmacological sleep (sedation or anaesthesia) with the standard algorithm should therefore be interpreted with caution in infants up to 12 months of age. A new algorithm, derived from prospective raw EEG data of infants of this age during 'natural sleep' and wake, needs to be developed.

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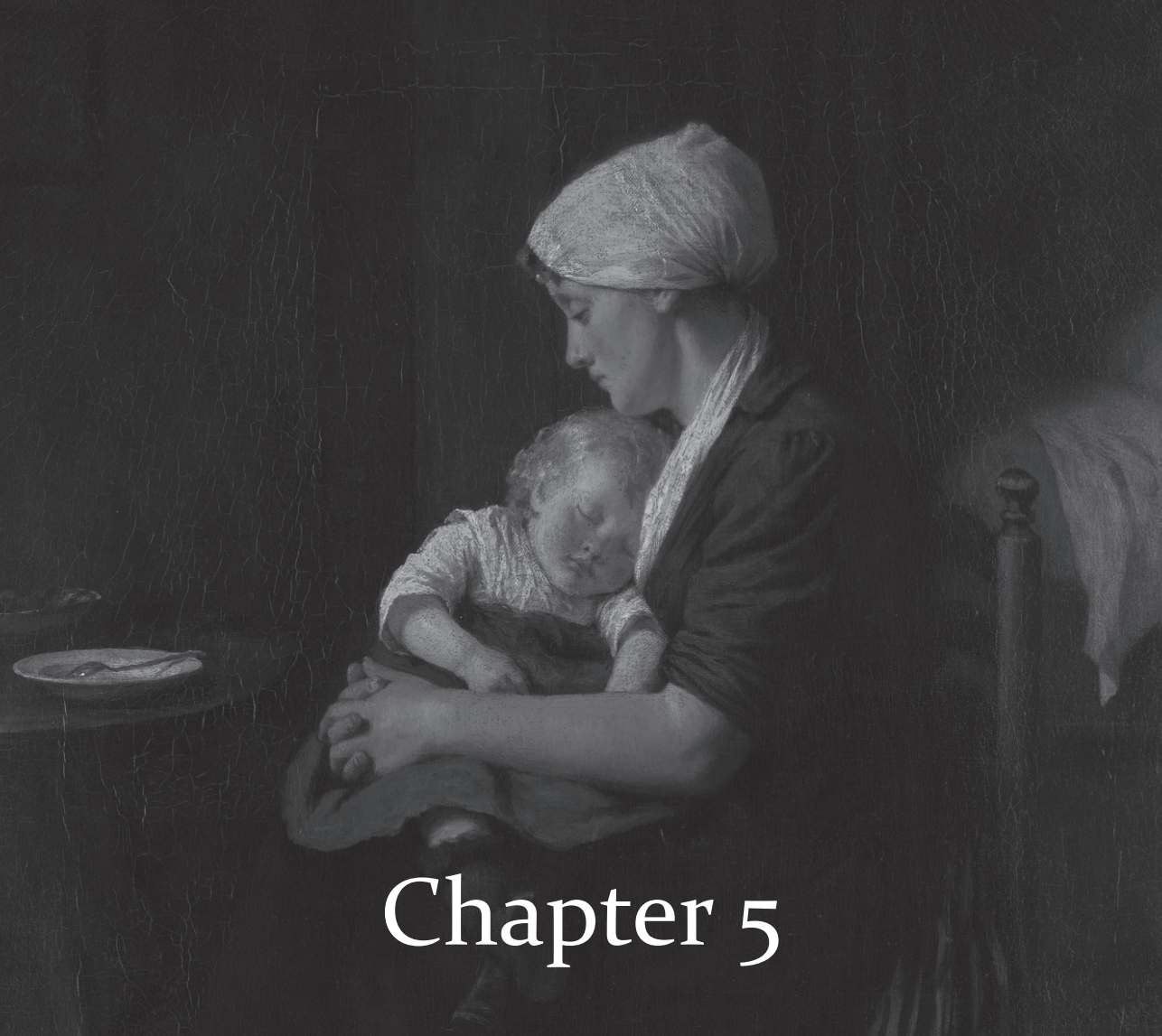

Chapter 5

Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: a literature review. 'Assessment remains troublesome'

Erwin Ista, Monique van Dijk, Claudia Gamel, Dick Tibboel, Matthijs de Hoog

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Abstract

Background: Prolonged administration of benzodiazepines and/or opioids to children in a pediatric intensive care unit (PICU) may induce physiological dependence and withdrawal symptoms.
Objective: We reviewed the literature for relevant contributions on the nature of these withdrawal symptoms and on availability of valid scoring systems to assess the extent of symptoms.
Methods: The databases PubMed, CINAHL, and Psychinfo (1980-June 2006) were searched using relevant key terms.
Results: Symptoms of benzodiazepine and opioid withdrawal can be classified in two groups: central nervous system effects and autonomic dysfunction. However, symptoms of the two types show a large overlap for benzodiazepine and opioid withdrawal. Symptoms of gastrointestinal dysfunction in the PICU population have been described for opioid withdrawal only. Six assessment tools for withdrawal symptoms are used in children. Four of these have been validated for neonates only. Two instruments are available to specifically determine withdrawal symptoms in the PICU: the Sedation Withdrawal Score (SWS) and the Opioid Benzodiazepine Withdrawal Scale (OBWS). The OBWS is the only available assessment tool with prospective validation; however, the sensitivity is low.
Conclusion: Withdrawal symptoms for benzodiazepines and opioids largely overlap. A sufficiently sensitive instrument for assessing withdrawal symptoms in PICU patients needs to be developed.

Introduction

Ventilated, critically ill children commonly receive sedative and analgesic drugs to ease their mental burden, anxiety and pain, induced by frightening or painful interventions and environmental factors in the pediatric intensive care unit (PICU). Intravenous opioids (such as morphine and fentanyl) and benzodiazepines (such as midazolam) are the most commonly used drugs for this purpose.[1,2] Tolerance and physiological dependence may develop during long-term administration of opioids and/or benzodiazepines and are risk factors contributing to withdrawal symptoms precipitated by too rapid tapering or cessation of these medications.[3] Tolerance is defined as a decrease in a drug's effect or the need to increase the dose to achieve the same effect.[3,4] Physiological dependence is the requirement for continued administration of a sedative or analgesic to prevent signs of withdrawal.[4] Psychological dependence is the need for a substance because of its euphoric effects and is encountered in the care and treatment of drug addicts.[5] Discontinuation of medication in dependent patients leads to symptoms of withdrawal.[5]

Most of our knowledge on tolerance and withdrawal symptoms has been derived from research in newborns of drug-addicted mothers[6,7] and from the literature on adult opium-addicted patients. Benzodiazepine withdrawal is also reported in adult psychiatric and drug-addicted populations.[8-10] Two retrospective and one prospective randomized controlled trial have been reported on opioid and/or benzodiazepine withdrawal after long-term administration of analgesics or sedatives in the adult ICU setting.[11-13] The reported incidence of withdrawal syndrome in adult ICU patients ranges from 32.1% (9/28) to 100%.[11,12] Each of these studies used a different assessment tool, however, which makes it difficult to describe symptoms in a uniform manner. Symptoms in these patients are mostly agitation, irritability, anxiety, insomnia, tachycardia, hypertension, and sweating. High total doses and exposure to medication for longer than 7 days are risk factors for developing withdrawal symptoms in the adult ICU. This knowledge may serve to gain a better insight into problems of tolerance, dependence, and withdrawal in pediatric intensive care, which are still insufficiently recognized.[14] Recognition of withdrawal in PICU patients is difficult because the symptoms may strongly overlap clinical signs of inadequate sedation, such as agitation, anxiety, and movement disorder. An objective instrument to establish withdrawal symptoms of critically ill children in clinical practice is necessary to establish severity and course of the symptoms and to evaluate efficacy of withdrawal treatment.

This review of the literature addresses two questions. First, what withdrawal symptoms resulting from long-term use of sedatives (opioids and/or benzodiazepines) in critically ill children in a PICU have been described and might be useful in an assessment tool? Second, are there any validated, reliable tools to assess withdrawal symptoms in children in a PICU in clinical practice?

Methods

The databases PubMed, CINAHL, and Psychinfo were searched for relevant literature on (a) benzodiazepine and opioid withdrawal symptoms or (b) assessment tools for withdrawal symptoms. Time limits were set at January 1980 and May 2006. Only articles published in English or Dutch were included in the study. The following exploded MeSH terms were used: 'withdrawal symptoms', 'abstinence syndrome', 'tolerance' with 'opioid', 'benzodiazepine', and with 'PICU', 'critically ill children', or with 'assessment tool', 'scoring system'. The age limits were set at 0 and 16 years. Preterm neonates (< 37 weeks gestation) and neonates of addicted mothers were excluded because generally they are not admitted to a PICU. A first search for reviews retrieved seven relevant articles which were used to delineate the domain of withdrawal symptoms.[3-5,15-17] Two of these reviews relate to patients in a neonatal ICU.[7,15] They were nevertheless included because PICUs admit surgical neonates as well. Also, these two reviews did not focus on neonates of addicted mothers.

In total, abstracts of 53 articles were evaluated. Articles on withdrawal symptoms had to meet two criteria for inclusion in this review: describing a study of benzodiazepine and/or opioid withdrawal symptoms and relating to the age restriction. In total 20 articles, either case studies, retrospective or prospective studies, met these criteria.[18-37] Table 1 lists the studies from which the withdrawal symptoms were derived, grouped by type of medication, study design, and methodological quality. Studies on assessment tools for identifying withdrawal symptoms had to meet the following criteria: (a) the tool should be aimed at identifying symptoms of benzodiazepine and/or opioid withdrawal; (b) the tool should be appropriate for children. Two articles met these criteria.[17,29]

Results

Withdrawal symptoms

Opioid withdrawal symptoms

Clinical signs of opioid withdrawal in newborns include those of the neurological system (high-pitched crying, irritability, increased wakefulness, hyperactive deep tendon reflexes, increased muscle tone, tremors, exaggerated Moro-reflex, seizures, intraventricular hemorrhage), those of the gastrointestinal tract (poor feeding, uncoordinated and/or constant sucking, vomiting, diarrhea, dehydration), autonomic signs (increased sweating, nasal stuffiness, fever, mottling), and others (poor weight gain, increased rapid-eye movement sleep, skin excoriation).[6,15] Symptoms of opioid withdrawal in newborns of drug addicted mothers are generally divided into three main groups: overstimulation of the central nervous system (CNS), gastrointestinal dysfunction, and autonomic dysregulation or sympathetic hyperactivity.[4,15,38] Table 2 lists the described signs and symptoms of withdrawal in children relating to either opioids or benzodiazepines,

or combined use, broken down for these three groups. (a) Common manifestations of CNS overstimulation are: tremors, increased muscle tension, anxiety, restlessness, irritability, and insomnia.[21,23-27,29,30,32,33] In addition, Lane *et al.*[26] and French and Nocera[30] described the development of choreoathetoid movements as a withdrawal symptom of fentanyl administration in five children and one child, respectively, as well as intermittent muscle contractions and uncontrolled movements after long-term use of fentanyl. (b) The most frequent gastrointestinal symptoms of opioid withdrawal are vomiting and diarrhea.[23-25,27,29,32] Carnevale and Ducharme[32] in addition reported reduced oral intake. (c) Autonomic phenomena are: fever, perspiration, sneezing, yawning, increased heart rate, and blood pressure.[23-25,29,30] Note that increases in heart rate and blood pressure should be seen in relation to the normal values for the child's age and disease. In summary, the clinical signs of opioid withdrawal in children (Table 2) are largely congruent with those in newborn babies of drug-addicted mothers.

Benzodiazepine withdrawal symptoms

Classical characteristics of benzodiazepine withdrawal described for the domains of adult psychiatry and drug addicts care are: severe anxiety, involuntary muscle tremors, confusion, insomnia, perception disorders, depression, and generalized convulsions.[4,9] In contrast to opioids, a systematic classification of benzodiazepine withdrawal symptoms is not available in the literature. For the sake of uniformity, however, the grouping for opioid withdrawal symptoms will be used here as well. Table 2 lists the observed withdrawal symptoms for benzodiazepines. Strikingly, most symptoms have been described on the basis of single case-reports and case series with small numbers of patients. Only two articles describe larger patient groups of 40 and 53 patients, respectively.[28,31] Symptoms observed in these two studies were different, however, and the used observation forms included no more than five and seven symptoms, respectively. These qualitative and quantitative limitations, notably in the case studies, provide only limited insight into the symptoms of benzodiazepine withdrawal. The benzodiazepines studies were all of a descriptive nature, in contrast to the opioids studies. (a) Regarding CNS overstimulation, Sury *et al.*[22] in a case-report first described withdrawal symptoms resulting from long-term use of midazolam in children. Three children aged 4, 11, and 12 years received midazolam as a sedative for 7, 14 and 17 days, respectively. Within 24 h after discontinuation they showed signs of (visual) hallucinations, irritability, confusion, restlessness/agitated behavior and generalized convulsions. These are all manifestations of CNS overstimulation. Other studies report tremors, anxiety, agitation, restlessness, inconsolable crying, muscle twitching, and myoclonic movements of the extremities.[18,19,21,28,29,31-33] (b) Regarding sympathetic hyperactivity, a case study of two children observed tachycardia and fever as benzodiazepine withdrawal reactions.[19] Others observed perspiration, insomnia and severe coughing.[29,31] (c) Regarding gastrointestinal dysfunction, one case study of a 14-day-old newborn reported vomiting caused by a distended stomach resulting from swallowing air.[19] This single case report provides insufficient evidence to include this symptom as

Table 1 Overview of studies of benzodiazepine and/or opioid withdrawal symptoms

Reference	Study design	Population (age)	Nature of study	Medication			Withdrawal symptoms	
				Type	Duration (days)	Total doses (mg/kg)	Assessment tool	Observed symptoms
Sury *et al.*[22]	Case series	3 children (4, 11, 12 yrs)	Descriptive	BZDs	7, 14, 17	37.3, 58.8, 230	-	Irritability, hallucinations, confusion, restlessness, convulsions
Van Engelen *et al.*[19]	Case series	2 children (14 days, 15mo)	Descriptive	BZDs	12, 29	0.14, 0.57 per h (mean doses)	-	Restlessness, tachycardia, fever, vomiting (as result of swallowing air)
Hughes *et al.*[28]	Prospective	53 children (0-11 yrs)	Incidence, Descriptive	BZDs	4.9 (1.2-17.9)[a Inf] 3.5 (1-14.8)[a Child]	14.6 (1.8-46.2)[a Inf] 9.6 (0.9-39.0)[a Child]	-	Hallucinations (visual and audio), disorientation, not recognizing parents, abnormal movements (puppet-like movements), inappropriate laughter
Fonsmark *et al.*[31]	Retrospective	40 children (6 mo-14 yrs)	Incidence, descriptive	BZDs	4 (1-13)[a W] 3 (1-11)[a NW]	30.9 (0.01-99.2)[a W] 4.6 (0.3-33.3)[a NW]	OC	Agitation, anxiety, muscle twitching, sweating, tremor
Bergman *et al.*[33]	Case series	3 children (3, 5, 15 mo)	Descriptive	OP/ BZDs	1-38	29.8 (1.4-286)[a Mida] 0.18 (0-2.9)[a Fent]	-	Irritability, high-pitched crying, abnormal movements, choreoathetotic movements
Tobias[21]	Case series	3 children (15, 27 mo, 11 yrs)	Descriptive	OP/ BZDs	4-28	ND	-	Choreoathetoid movements, restlessness, irritability, tremors
Yaster *et al.*[18]	Case series	2 children (4 mo, 8 yrs)	Descriptive	OP/ BZDs	> 5	ND	-	Agitation, restlessness
Carnevale *et al.*[32]	Case series	3 children (15, 27 mo, 11 yrs)	Descriptive	OP/ BZDs	4-57	ND	OC	Tremors, twitching, jitteriness, inconsolable crying, irritability, agitation, grimacing vomiting, poor feeding
Tobias[20]	Retrospective	9 children (4.4 ± 1.8yrs)[b]	Efficacy of switching to subcutaneous fentanyl	OP/ BZDs	16-24	ND	NAS	-
Franck *et al.*[29]	Prospective	15 children (1.5-28 mo)	Descriptive, validation instrument	OP/ BZDs	9 (4-18)[a]	7.4 (2.5-19.2)[a OP] 26.4 (0-154)[a Mida]	OBWS	Crying/agitation, sleeplessness, hyperactive Moro Reflex, tremors, pupil dilation, movement disorder, hallucinations, fever, tachypnea, frequent suction required, sweating, yawning sneezing, nasal stuffiness, vomiting, diarrhea
Ducharme *et al.*[34]	Prospective, case study	27 children (0-19 yrs)	Examine effects of O/B weaning rates	OP/ BZDs	1- >21	ND	-	Tremors/twitching/jitteriness, Inconsolable crying, grimacing, agitation/irritability/ fussiness, gagging/vomiting, poor feeding, difficulty sleeping [c]

Table 1 Continued

Reference	Study design	Population (age)	Nature of study	Medication			Withdrawal symptoms	
				Type	Duration (days)	Total doses (mg/kg)	Assessment tool	Observed symptoms
Arnold *et al.*[35]	Retrospective	37 neonates	Incidence of NAS, identified risk factors	OP	ND	3.4 ± 2.5[b Fent] 1.8 ± 1.5[b Fent]	NAS	
Lane *et al.*[26]	Retrospective	13 children (5.35 ± 5.1yrs)[b]	Descriptive	OP	7.8 ± 4.9[b]	0.6 ± 0.5[b Fent]	-	Tremors, ataxia, choreaothetosis (movement disorder), myoclonus, irritability, insomnia
French *et al.*[30]	Prospective	12 children (0-25 mo)	Descriptive, incidence	OP	6.7 ± 5.0[b]	0.56 ± 0.52[b Fent]	NAS	Agitation, irritability, tremors, increased muscle tone, choreoathetoid movements, insomnia, increased respiratory rate and effort
Katz *et al.*[27]	Prospective	23 children (0-22 mo)	Descriptive, incidence	OP	13.1 ± 11.3[b W] 3.8 ± 1.5[b NW]	2.96 ± 4.1[b W, Fent] 0.53 ± 0.37[b NW, Fent]	NAS	Irritability, tremors, decreased sleeping, diarrhea, vomiting
Franck *et al.*[37]	Prospective/ retrospective	34 neonates	Descriptive, prevalence withdrawal after ECMO	OP	20.7 ± 12.0[b Fent] 13.5 ± 8.0[b Morp]	1.3 ± 0.9[b Fent] 3.0 ± 1.8[b Morp]	NAS	
Robertson *et al.*[24]	Prospective	10 children (6 mo-18 yrs)	Descriptive, evaluation opioid weaning protocol	OP	15 (7-53)[a]	ND	-	Tremors, irritability, diarrhea, sweating
Lugo *et al.*[25]	Retrospective	22 children (6.1 ± 5.4yrs)[b]	Descriptive evaluation withdrawal protocol	OP	17.8 ± 8.4[b]	1.3 (0.35-7.54)[a Fent]	NAS	Agitation/irritability, crying/inconsolability, tremors, tachypnea, disorientation, hypertension, sweating, diarrhea
Siddappa *et al.*[23]	Retrospective	30 children (0-16 yrs)	Descriptive evaluation withdrawal protocol	OP	12.5 (7-26)[a W] 10 (7-41)[a NW]	4.2 (1-10.5)[a W, Fent] 1.3 (0.5-5.9)[a NW, Fent]	OC	Sleep disturbance, agitation, tremors, seizures, choreoathetoid movements, vomiting, diarrhea, hypertension, tachycardia, tachypnea, fever, sweating, yawning, mottling[c]
Berens *et al.*[36]	Prospective	37 children (9.8 ± 26.2mo)[b]	Descriptive evaluation weaning withdrawal protocol	OP	15.5 ± 10.7[b]	2.2 ± 1.7[b Fent]	NAS	

Type of medication BZDs benzodiazepines, *OP* opioids, *Duration* number of days administrating of sedatives/analgesics, [a] median (range), [b] mean ± SD (standard deviation), [c] only assessing items, *ND* no data, *W* Withdrawal, *NW* No withdrawal, *mo* months, *yrs* years, *Fent* Fentanyl, *Morp* Morphine, *Mida* Midazolam, *Inf* Infants, *Child* Children, *NAS* Neonatal Abstinence Score, *OC* Own checklist

a benzodiazepine withdrawal symptom. Dysfunction of the gastrointestinal tract as a symptom of benzodiazepine withdrawal has not been described in adults.[9,12] In summary, the major symptoms of benzodiazepine withdrawal in children are anxiety, tremors, and other involuntary muscle movements, irritability, perspiration and insomnia. These correspond to the classical manifestations of benzodiazepine withdrawal in adults.[4,9]

Table 2 Described signs and symptoms of benzodiazepine and opioid withdrawal in children

	Central Nervous System irritability	**Gastrointestinal dysfunction**	**Autonomic dysfunction**
Opioids	Increased muscle tone Myoclonus Ataxia Abnormal movements Pupil dilation (>4 mm) High pitched crying	Vomiting Poor feeding Diarrhea	Tachypnea Yawning Sneezing Hypertension Mottling
Benzodiazepines	Muscle twitching Inconsolable crying Grimacing Jitteriness Visual, auditory hallucinations Disorientation Seizures Movement disorder		Frequent suction required
Opioids & Benzodiazepines	Tremor Anxiety Agitation/Crying Irritability Insomnia/sleep disturbance Choreoathetoid movements (of upper extremities)		Fever Sweating Tachycardia

Combined benzodiazepine-opioid withdrawal symptoms

Differences between opioid and benzodiazepine withdrawal symptoms are marginal.[4] Symptoms associated with CNS overstimulation and sympathetic hyperactivity largely overlap after long-term use of benzodiazepines or opioids in children (see Table 2). However, benzodiazepine withdrawal is not associated with symptoms of the gastrointestinal tract.[4,12] The Moro-reflex is used as an opioid withdrawal symptom in neonates.[6,15] The Moro-reflex disappears between the ages of 1 and 3 months and is therefore never observed in children older than 3 months. The study by Franck *et al*.[29] included 1.5- to 28 month-old children, and the Moro-reflex was one of the items in their assessment tool. In view of the age limitation we feel it is not feasible to use this symptom as a withdrawal symptom for PICU patients.[3] Several studies found it hard to determine whether the withdrawal symptoms were specifically caused by benzodiazepines dependence because in these studies opioids (morphine, fentanyl) were administered for sedation as well.[18,21,28,29,33] This illustrates the

practical limitation for describing specific benzodiazepine-related withdrawal symptoms in the PICU. From clinical experience we know that benzodiazepines and opioids are usually administered in combination for sedation and analgesia, from several days to weeks as reflected in the literature.[1,38] Given the overlap in symptoms, it is hard to ascribe withdrawal symptoms to either opioids or benzodiazepines.[21,29,32]

Incidences and influencing factors of benzodiazepine and opioid withdrawal

Knowledge on the incidences of benzodiazepine and opioid withdrawal symptoms in general as well as the frequencies of the separate phenomena provide clues for the symptoms to be used in an assessment tool. Furthermore, knowledge of possible risk factors for the development of withdrawal symptoms enables physicians and nurses to identify patients at risk. Only five articles describe incidences and influencing factors for the development of withdrawal symptoms after long-term use of benzodiazepines or opioids in children.[27,28,31,35,37]

Incidence

Fonsmark *et al.*[31] in a retrospective study found that 14 of 40 (35%) of sedated children (6 months-14 years) developed withdrawal symptoms. A prospective study of abrupt discontinuation of midazolam in critically ill children (0-11 years) reports adverse side effects in 17% of the 53 patients.[28] Opioid withdrawal symptoms were seen in 13/23 (57%) children aged 0-22 months after prolonged continuous fentanyl administration.[27] Methods differed between these three studies. Katz *et al.*[27] used the Neonatal Abstinence Score (NAS) developed by Finnegan *et al.*[6] which has only been validated for use in newborns. Hughes *et al.*[28] and Fonsmark *et al.*[31] did not use existing tools but recorded withdrawal symptoms through self-developed observation lists. These lists included a limited number (five) of behavioral items.[28,31] Fonsmark *et al.*[31] included 'sweating' as a physiological item. The authors did not provide data on reliability and validity of their observation lists.[28,31] Patients who required extracorporeal membrane oxygenation (ECMO) therapy comprised a specific PICU population. In these populations opioid withdrawal (NAS > 8) was seen in 9-57% of children.[35,37]

Influencing factors

Various authors have shown that dosing and duration of benzodiazepines or opioids influence development of withdrawal symptoms.[27,30,31] Fonsmark *et al.*[31] found a total midazolam dose higher than 60 mg/kg to be associated with the occurrence of withdrawal symptoms. Katz *et al.*[27] found a total fentanyl dose of 2.5 mg/kg or higher or a fentanyl infusion for at least 9 days to result in withdrawal symptoms in 100% of cases. Arnold *et al.*[35] found that neonates receiving ECMO therapy with total doses greater than 1.6 mg/kg fentanyl or an ECMO duration of longer than 5 days had a significantly greater incidence of withdrawal symptoms reflected by the NAS. In another study in ECMO patients the authors demonstrated that neonates who received total fentanyl doses higher than 1.2 mg/kg were

13 times more likely to experience opioid withdrawal after ECMO.[37] Evaluation of the various studies reveals that children in a PICU receiving benzodiazepines and/or opioids for 5 days or longer are at risk for developing withdrawal symptoms.[17,23-25,27-31] Benzodiazepine and/or opioid withdrawal symptoms may occur if these medications are abruptly stopped or tapered off too rapidly in children showing physical dependence.[38] Manifestations typically occur 8 - 48 hr after discontinuation.

Systematic clinical assessment of withdrawal symptoms

The task of assessing seriously ill children for signs of tolerance, dependence, or withdrawal notably falls to the pediatric critical care nurse.[4] This requires particularly awareness, knowledge of and insight into these phenomena. For clinical purposes a validated and reliable assessment tool would be very helpful. Table 3 provides details of six assessment tools for withdrawal symptoms in children that are used in practice and in research. Four of these were developed and validated for application in neonates after long-term use of opioids or in newborn babies of drug-addicted mothers.[6,39-41] The most widely used is the NAS.[6] These four instruments have not been validated for use in older children. However, in the absence of a validated and reliable instrument for children, several authors have opted for the NAS.[24,25,27,30] Other authors designed observation checklists themselves, including 5 - 13 symptoms.[25,28,31] These observation checklists have not been properly validated for use in children.[25,31] Two recent articles describe assessment tools for observing withdrawal symptoms after long-term use of opioids and/or benzodiazepines in children in a PICU: the Sedation Withdrawal Score (SWS)[17] and the Opioid Benzodiazepine Withdrawal Scale (OBWS).[29]

Sedation Withdrawal Score

The SWS includes 12 symptoms of withdrawal (see Table 3) and was developed in 2004 by Cunliffe *et al.*[17] Each symptom is scored on a three-point scale, ranging from absent (0), mild (1), to severe (2). Thus a maximum score of 24 is possible. The authors provide instructions for the regimen for decreasing sedatives based on cutoff points. However, a justification for these cutoff points is not given. The authors consider the SWS to be clinically sensitive in detecting abstinence in a child of any age with signs of withdrawal from sedatives and/or opioids.[17] However, data on sensitivity, specificity, validity, and reliability are lacking.

Opioid Benzodiazepine Withdrawal Scale

The OBWS is a 21-item checklist with 16 withdrawal items for determining frequency and severity of withdrawal symptoms in children (see Table 3).[29] Franck *et al.*[29] tested the predictive validity of the OBWS by performing 693 assessments in 15 children aged 6 weeks-28 months. Sensitivity of the OBWS at scores 8 (cutoff) or higher was 50%, which implies that the scale is not better than chance prediction. Specificity was 87%, which implies that the scale rightly classifies 87% of the children without withdrawal symptoms. The predictive value expressed in terms of positive and negative likelihood ratio, 4.0 and 0.57,

Table 3 Survey of tools for clinical assessment of withdrawal symptoms in critically ill neonates and children.

Instrument	Population	Observation items				Structure		Validation		Withdrawal cut-off scores
		CNS	GI	Auto	Other	Total items	Score range	Reliability	Validity	
Neonatal Abstinence Score[6]	121 addicted infants	High pitched crying, sleeplessness, HMR, tremors, convulsion, HT, frantic sucking of fists	Poor feeding, vomiting, diarrhea, dehydration	RR, T, sneezing, sweating, yawning	Mottling, nasal stuffiness,	21 Numerical	0-43	IRR: $r=0.82$ (0.75-0.96), $p<0.005$).	ND	0-7 none 8-12 mild 13-16 moderate ≥17 severe
Neonatal Drug Withdrawal Scoring system[40]	36 newborns, 8 infants of addicted mothers	Tremors, irritability, reflexes, muscle tone,	Stools, vomiting	RR, sneezing, yawning, fever	Skin abrasions	11 Numerical	0-20	ND	Probability of successful identification = 77%	≥5 withdrawal
Neonatal Withdrawal Inventory[41]	80 neonates	Tremors, HMR, HT	Diarrhea	Sweating, sneezing, yawning	(Continuous) crying, irritability	8 Numerical	0-19	IRR: $r=0.93$ (0.89-0.98) Cronbach's alpha 0.98	sen.= 100% (kappa=1.0, SE=0.14) spec.=100%	≥ 8 withdrawal
Neonatal Narcotic Withdrawal Index[39]	50 full-term infants	Tremors, crying, HT, HMR, seizure	Vomiting, diarrhea	RR, T, sweating, sneezing	Weight loss, skin abrasion	15 Numerical	0-14	IRR: $r=0.77$	t=5.632 ($p<0.001$)[a]	≥ 5 withdrawal
Sedation withdrawal score[17]	Children	Tremor, irritability, HT, high pitched cry, convulsions, hyperactivity	Vomiting, diarrhea	RR, T, sweating, sneezing		12 Numerical	0-24	ND	ND	<6 -, 6-12 don't decrease, 12-18 revert to former regimen, >18 seek advice
Opioid Benzodiazepine Withdrawal Scale[29]	15 pediatric patients	Crying/agitation, tremors, sleeplessness, movement disorder, HMR, Hallucinations	Vomiting, diarrhea	RR, T, sweating, sneezing, PD, yawning	Nasal stuffiness, frequent suction required	21 (16 withdrawal symptoms) Numerical	0-16	IRR: $r=0.8$	sen.= 50%, spec.= 87%	≥ 8 withdrawal

CNS Central Nervous System irritability, *GI* Gastro-intestinal dysfunction, *Auto* Autonomic dysfunction or Sympathetic hyperactivity, *IRR* interrater-reliability, *ND* no data/ not described in article, *r* correlation coefficient, *sen.* sensitivity, *spec.* specificity, *SE* standard error, *HT* hyper tonicity (increased muscle tone), *HMR* hyperactive moro reflex, *RR* respiratory rate, *T* temperature/fever, *WL* weight loss, *PD* pupil dilation (> 4 mm), [a] Twp groups compared: healthy newborns (n=40) and newborn babies of drug-addicted mothers (n=50)

respectively, is moderate for a diagnostic instrument. The interrater reliability was higher than 0.8; the agreement procedure, however, was not published. Neither age range nor diagnoses of the patients in this study are representative for a general PICU. Finally, including the Moro-reflex is questionable in view of the inherent age restriction, and reduces the scale's content validity. In summary, although both instruments include relevant withdrawal symptoms associated with benzodiazepine and/or opioid withdrawal in children, we feel that psychometric issues of the measurements have been given insufficient attention.

Discussion and conclusion

Nurses and physicians could give more priority to the observation and treatment of withdrawal symptoms in children in a PICU. This literature study describes observable withdrawal symptoms related to benzodiazepines and opioids use in children in a PICU. It appears that vomiting cannot be included as a symptom of benzodiazepine withdrawal in this population.[4] The same is true for the hyperactive Moro-reflex as a symptom of opioid withdrawal, given the age limitation.[27] Furthermore, withdrawal symptoms for benzodiazepines and opioids had a large overlap for symptoms such as agitation, anxiety, tremors, insomnia, fever, sweating, and tachycardia. Symptoms such as seizure and hallucinations have been described only as benzodiazepine withdrawal in PICU patients.

As clinical practice tends to combine medication from both groups, symptoms cannot easily be ascribed to either group. Several authors studied only either benzodiazepine or opioid withdrawal symptoms in patients who received both medications.[25,27,28,31] Then it was not possible to determine whether the withdrawal symptoms were specifically caused by benzodiazepine or opioids because in these studies additional benzodiazepine or opioids were administered for sedation as well. For treatment and management purposes we should preferably distinguish between withdrawal symptoms caused by weaning of benzodiazepines or opioids. Therefore assessment tools should be sensitive enough to discriminate between benzodiazepine and opioid related withdrawal symptoms.[3,24,42] Generalization of the identified withdrawal symptoms is hampered by the fact that most are based on case series and case reports and consequently on small numbers of patients. Furthermore, most studies considered only few withdrawal symptoms. Thus representative incidence numbers based on the full spectrum of withdrawal symptoms are lacking.

In this review high total doses, duration of opioid, and/or benzodiazepine infusion and ECMO therapy are described as risk factors in developing withdrawal symptoms in PICU patients. These factors are also described in adult studies.[11,12] The diagnosis of withdrawal in patients must be made carefully. Withdrawal symptoms vary from patient to patient in number, severity and presentation. However many PICU patients show relatively subtle clinical symptoms that can easily be confused with responses to other factors in the PICU. Symptoms such as agitation, anxiety, insomnia, irritability, fever, tachycardia, hypertension,

and sweating are also an expression of inadequate sedation or pain management, ventilator distress, infection, noisy environment, paradoxical reactions, or delirium.[43-47] These key confounders may mask withdrawal symptoms. With Tobias[3], we maintain that the diagnosis of withdrawal symptoms remains one of exclusion. For example, fever or vomiting should never be attributed to withdrawal until other possible causes are excluded. Key confounders must be excluded as well. We feel that the occurrence of withdrawal symptoms must be time-related to a decrease or cessation of benzodiazepines and/or opioids.

Strategies to reduce the incidence of withdrawal symptoms begin by making efforts to reduce the total doses of benzodiazepines and/or opioids administered. Based on a few prospective studies several authors recommend a daily tapering rate of 10 - 20% for children who receive benzodiazepines and/or opioids for more than 5 - 7 days.[23-25,29] This strategy did not result, however, in the absence of withdrawal symptoms. Adult sedative and analgesic guidelines recommend that daily dose decrements of opioids should not exceed 5 - 10% in high-risk patients.[48] Playfor *et al.*[49] support use of this practice in the PICU in spite of the fact that there is little evidence for its efficacy. Several studies evaluating withdrawal symptoms, incidence and risk factors in the PICU used an assessment tool (NAS) not validated for use in children in a PICU. The results of these studies therefore may not be reliable, and symptoms may have been overlooked. Most of these scoring systems (four of six, see Table 3) were developed to assess the severity of withdrawal in infants and drugs-addicted mothers. They have some limitations, however. First, they were developed to assess neonatal behavior and opioid withdrawal.[3,49] Certain reflexes such as the Moro can only be judged in children below 3 months, and this implies that they cannot be used in the total PICU age group. Second, cutoff points for other patients than newborns of addicted mothers are not defined. For these reasons the NAS is less useful in PICU patients because most receive both opioids and benzodiazepines.

The available literature demonstrates that a good assessment tool for clinical use in children is lacking.[49] A good assessment tool can be defined as a tool, which is valid reliable, and clinically useful. This means that a cutoff point is established, and that the tool shows sensitivity to change.[50,51] Furthermore Franck *et al.*[29] stated that clinical utility may be improved with fewer items and longer intervals between assessments. The OBWS displays moderate validity and includes an item that is not representative for the target population. We agree with Cunliffe *et al.*[17] that the SWS includes clinically relevant items for the observation of withdrawal symptoms in children on the basis of the described withdrawal symptoms in our literature study. However, it lacks a good methodological foundation. The OBWS is the only available assessment tool with prospective validation; however, its sensitivity is low. In general, assessment tools must preferably be tested in a multicenter study with a larger patient population and an extensive patient mix. The criterion validity can be tested using an independent expert's opinion because there is no gold standard for opioid and benzodiazepine withdrawal

in children. Further assessments should be carried out before and after tapering off of opioids or benzodiazepines. At least key confounders that mask withdrawal must be excluded. In conclusion, the OBWS can be feasible for assessing benzodiazepine and/or opioid withdrawal symptoms in children in a PICU when additional validation has been completed.

This review clearly provides directions for further research. First, quantification of withdrawal symptoms in children based on the symptoms and signs listed in this review is needed to clearly define the spectrum of withdrawal in PICU patients. Second, an adapted withdrawal assessment tool based on this quantification needs to be developed and psychometric issues must be tested before application in the PICU population.

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Chapter 6

Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics, a first evaluation

Erwin Ista, Monique van Dijk, Claudia Gamel, Dick Tibboel, Matthijs de Hoog

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Abstract

Objectives: To establish frequencies of benzodiazepines and opioids withdrawal symptoms as well as correlations with total doses and duration of administration.
Design: A prospective, repeated measures design.
Setting: Two pediatric intensive care units in a university children's hospital.
Patients: Seventy-nine children, aged 0 days to 16 years, who received intravenous midazolam and/or opioids for more than 5 days.
Interventions: None.
Measurements and Main Results: PICU nurses assessed withdrawal symptoms using the Sophia Benzodiazepine & Opioid Withdrawal Checklist (SBOWC), which includes all withdrawal symptoms (n=24) described in the pediatric literature. Over six months, 2188 observations in 79 children were recorded. Forty-two percent of observations were performed within 24h after tapering off or discontinuation of medication. Symptoms representing overstimulation of the central nervous system, such as anxiety, agitation, grimacing, sleep disturbance, increased muscle tension and movement disorder, were observed in more than 10% of observations. Of symptoms reflecting gastrointestinal dysfunction, diarrhea and gastric retention were most frequently observed. Tachypnea, fever, sweating and hypertension as manifestations of autonomic dysfunction were observed in more than 13% of observations. The Spearman rank correlation coefficient between total doses of midazolam and maximum sum score (of the SBOWC) was 0.51 ($p < 0.001$). The correlation between total doses of opioids and the maximum sum score was 0.39 ($p < 0.01$). A significant correlation (0.52; $p < 0.001$) was also found between duration of use and maximum sum score.
Conclusions: This is the first study to report frequencies of all 24 withdrawal symptoms observed in children after decrease or discontinuation of benzodiazepines and/or opioids. Agitation, anxiety, muscle tension, sleeping less than 1 hour, diarrhea, fever, sweating and tachypnea were observed most frequently. Longer duration of use and high dosing are risk factors for development of withdrawal symptoms in children.

Introduction

Ventilated, critically ill children commonly receive sedatives and analgesic drugs to ease their anxiety, pain and mental burden induced by the pediatric intensive care unit (PICU) setting. Usually these medications are intravenous opioids and benzodiazepines.[1,2] Long-term exposure to these drugs, however, carries the risk of physical dependence. Abrupt discontinuation or too rapid tapering down of sedatives and analgesics in physically dependent children may result in withdrawal syndrome.[3] High total cumulative doses, long-term infusion (>5-7 days) and too rapid tapering off or abrupt discontinuation of sedatives and/or analgesics have been found to increase the risk of withdrawal syndrome in children in a PICU.[4-7]

Symptoms observed in withdrawal syndrome in children include: (1) central nervous system irritability (*e.g.* agitation, anxiety, tremors, increased muscle tension, sleep disturbance, abnormal movements); (2) gastrointestinal dysfunction (vomiting, diarrhea and poor feeding); and (3) autonomic dysfunction (*e.g.* sweating, fever, tachycardia, hypertension and tachypnea).[4-18]

The reported incidences of benzodiazepine withdrawal syndrome in critically ill children range from 17 to 35%.[5,6] So far, only Katz and colleagues have documented opioid withdrawal in critically ill children; it was found in 13 of 23 PICU patients (57%) receiving fentanyl.[7]

Diagnosing withdrawal syndrome in PICU patients is a complex matter, because some symptoms may strongly overlap with clinical signs of inadequate pain or sedation management, ventilator distress, delirium and stress induced by the noisy environment.[19-23] Furthermore, symptoms of benzodiazepine withdrawal largely overlap with those of opioid withdrawal. Yet we should be able to distinguish between opioid and benzodiazepine related withdrawal as well as confounders, as each requires a different treatment approach. Therefore, a clinically validated and sensitive assessment tool is needed to determine the presence and nature of different withdrawal symptoms and their relative frequencies. Such a tool is still lacking,[24,25] leaving aside the Neonatal Abstinence Score (NAS) developed for infants of drug-dependent mothers[26] which has been used in several studies in critically ill children.[7,11,13,27,28]

Documenting the prevalences of relevant withdrawal symptoms is an essential first step in the development of an assessment tool. To our knowledge, prevalences of the whole spectrum of withdrawal symptoms have not yet been prospectively studied in PICU patients. We therefore conducted a study evaluating all withdrawal symptoms in critically ill children described in the literature and recently reviewed by us.[24] A second aim was to establish possible correlations between withdrawal symptoms and total doses of benzodiazepines or opioids and duration of use.

Materials and Methods

Design

A prospective, repeated-measures design was used to estimate occurrences of withdrawal symptoms using a self-designed observation form that included withdrawal symptoms described in the literature.

Patients

Children aged ≤16 years admitted to the pediatric and pediatric surgical intensive care units of our level three children's hospital between September 2005 and February 2006 were eligible for this study if they received midazolam (a benzodiazepine), morphine or fentanyl (opioids) by continuous infusion for at least 5 days. These units serve as a referral centre for all critical care patients (medical and surgical, 0-16 years) except postoperative open heart surgery. Exclusion criteria were: status epileptic treated with midazolam, use of neuromuscular blocking agents (NMBA), and severely disturbed behavior pattern on account of underlying neurological disease.

The Erasmus MC institutional review board reviewed and approved this study. Because of the strictly observational and noninvasive nature of this study, the need for informed consent was waived. The parents of enrolled subjects received an information sheet explaining the study.

Severity of illness was scored using the Pediatric Index of Mortality (PIM) and the Pediatric Risk of Mortality (PRISM II).[29,30]

Weaning from midazolam and/or morphine was by protocol. This provides for midazolam administered by continuous infusion to be decreased by steps of 50 mcg/kg/hr per 8 hours, and for morphine by steps of 10 mcg/kg/hr per 24 hours.

Measurement

For this study we composed a checklist which we named Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC). It contains all symptoms of benzodiazepine and opioids withdrawal described in the literature specific to critically ill children.[24] The final checklist was approved by 10 experienced pediatric intensivists to guarantee content validity. The 24 items of the SBOWC are listed in Table 3.[31] Tachycardia was defined as a heart rate of more than 15% above the baseline value.[32,33] The latter criterion accordingly was applicable to the items tachypnea and hypertension. For heart rate, respiratory rate and arterial blood pressure, the highest values within the past four hours were automatically generated by the patient data management system (PDMS) when the nurse completed the SBOWC. The daily baseline values for the physiological items were also computed from PDMS data.

All nurses of the two PICUs received verbal and written instruction on how to use the SBOWC. In addition, an instruction manual was available at each patient's bedside. Items

were to be scored 'yes' if the symptom had been present during the past 4 hours. For the purpose of analysis, items assigned 'yes' were recoded in the numeric value '1'; all other items were recoded in '0'. The sum score for each assessment was computed by summating the numeric values. The SBOWC sum score thus can range from 0 to 24 (no symptoms versus all symptoms of withdrawal were observed).

Procedure

The attending nurse completed the SBOWC every shift at set times (4 *a.m.*, 2 and 8 *p.m.*). These set times had been determined on the basis of the daily nursing staff schedule, *i.e.* three 8 hours shifts, taking into account that a nurse must have been able to look after the child for a minimum of 4 hours before scoring. Scores were entered into the PDMS, which system also 'reminds' the nurse when to complete the SBOWC. For logistical reasons data collection ceased after the child's discharge from the PICU.

Statistical analyses

Descriptive statistics were used to present demographics, administered medication and withdrawal symptoms. The doses for fentanyl were converted to morphine equivalents by the formula 0.1 $mg \cdot kg^{-1}$ of fentanyl = 10 $mg \cdot kg^{-1}$ of morphine.[34]

Spearman's rank correlation coefficient (r_s) was used to explore association between the variables total dose, duration of infusion and maximum SBOWC sum score. For every r_s a 95% confidence interval (CI) was computed. The maximum sum score of the SBOWC was computed for each patient.

The observations were divided into four groups. First, the total group, 2161 observations made in all 79 children. Second, a 'weaning group', 932 observations in 76 children obtained within 24 hours after decrease and/or discontinuation of midazolam and/or opioids. Third, a 'high doses' group as a subset of the second group, 496 observation in 19 children with the highest total doses of midazolam during admission (> 70 mg/kg). These are children at particular risk of developing withdrawal symptoms. Fourth, an 'unsuccessful weaning' group, 93 observations in 27 children. These observations were obtained before increasing midazolam and/or opioids during the weaning process in order to counteract possible withdrawal related symptoms.

Interobserver reliability was tested for the dichotomous items by Cohen's kappa and the intraclass correlation coefficient (ICC) for continuous data.[35] A Cohen's kappa below 0.65 was considered unsatisfactory.[36] SBOWC assessments were excluded for analysis when three or more (>10%) items were missing. A p value of <0.05 indicated a statistical significance.

Results

Patients

During the study period a total of 687 patients were admitted; 91 patients received prolonged midazolam and/or opioids, however, 12 patients were excluded. Of these, 10/12 patients were admitted with status epilepticus and treated with midazolam, and two patients had severely disturbed behavior pattern (one patient with syndrome of West and another patient with infantile encephalopathy with choreoathetosis) on account of underlying neurological disease. Thus, 79 (11%) patients fulfilled the inclusion criteria and were enrolled in this study. Median age was 3.4 months (range 0 days to 15.5 years). Demographic data and background characteristics are listed in Table 1.

Table 1 Patient characteristics (N=79)

Variables	N	%
Sex		
Male	45	57
Female	34	43
Age		
Neonate (< 28 days)	19	24
1 – 6 months	26	33
6 – 12 months	12	15
1 – 3 year	11	14
3 – 10 year	9	11
> 10 year	2	3
Age in months, median (range)	3.4 (0-185)	
Diagnosis		
Respiratory insufficiency	34	43
Cardiac (pre- en postoperative (after ≥48 hours)	21	27
Postoperative	9	11
Congenital defects	5	6
Sepsis	4	8
Other	6	5
Surgery (yes)	56	71
ECMO therapy (yes)	11	14
Ventilation		
Number of patients	76	96
Number of days*	8 (1 to 107)	
Length of stay PICU‡ (days)	11 (7 to 21)	
Pediatric Index Mortality score* (%)	3.2 (0.4 to 43.7)	
Pediatric Risk of Mortality* (%)	13 (0 to 32)	

ECMO extracorporeal membrane oxygenation, * median (min-max), ‡ median (P25-P75)

Medication

Specifics of dosing and duration of medication are given in Table 2. All 79 patients were sedated with midazolam at a median dose of 176 mcg/kg/hr (range 25 to 397). Seventy-three (92%) also received opioids. Midazolam was administered for a median 10 days (range 3 to 108 days). The median total dose of midazolam administered was 33 mg/kg (range 2 to 595) and of opioids 4 mg/kg (range 0 - 682). Opioids were administered for a median of 8 days (range 1 to 41 days).

The first line drugs were midazolam, morphine and fentanyl. Several patients received additional drugs such as ketamine (n = 26), propofol (n = 14) and clonidine (n = 26) to relieve distress and/or pain.

Table 2 Continuous midazolam and opioid iv infusion

	Midazolam	**Opioids** (Morphine and fentanyl‡)
Number of patients	79	73
Number of days*	10 (3-108)	8 (1-41)
Mean continuous doses (mcg/kg/hr)*	176 (25-397)	14 (5-559)
Maximum doses (mcg/kg/hr)*	300 (25-700)	20 (2-1200)
Total doses during admission (mg/kg)+	33 (2-595) [20-70]	3.8 (0-682) [1-11]

* median (min-max), + median (min-max) and [P25 - P75], ‡ the doses for fentanyl were converted to morphine equivalents[34]

Interobserver reliability

Twenty-three observations were scored simultaneously by the attending nurse and the principal investigator (EI). The intraclass correlation coefficient was 0.85 (95% CI 0.69 to 0.94). The interobserver reliability (Cohen's kappa) of the individual items of the SBOWC ranged from 0.59 to 1.0. Interobserver reliability for the items high pitched crying (0.59), and mottling (0.62) showed a kappa below 0.65.

Withdrawal symptoms

A total of 2188 assessments were performed in 79 children. Twenty-seven observations in 14 patients were excluded from analysis because more than 2 items were missing. The median number of assessments in individual patients was 14 (range 2 to 198) over a median of 6 days (range 1 to 67 days). In 3 patients there were no observations performed after weaning or cessation of midazolam and/or opioids because they were discharged. The frequencies of withdrawal symptoms for the groups defined above are summarized in Table 3.

Table 3 Frequencies of observed withdrawal symptoms

Observation item	Total group 2161 observations in 79 patients		Weaning group 932 observations in 76 patients		High doses group [a] 496 observations (after decreasing medication) in 19 patients		Unsuccessful weaning group 93 observation in 27 patients	
	n (%)	*N*	*n (%)*	*N*	*n (%)*	*N*	*n (%)*	*N*
Central nervous system irritability								
Agitation	440 (20.4)	57	197 (21.1)	50	110 (22.2)	17	43 (46.2)	17
Anxiety	334 (15.5)	41	139 (14.8)	35	85 (17.1)	13	23 (24.7)	11
Increased muscle tension	322 (14.9)	38	121 (13.0)	30	92 (18.5)	15	26 (28.0)	13
Motor disturbance								
Slight muscle jerks	151 (7.0)	30	65 (7.0)	21	37 (7.5)	8	8 (8.6)	5
Uncoordinated, robust movements	296 (13.8)	43	120 (12.8)	34	60 (12.1)	15	27 (29.0)	15
Tremors								
Spontaneous	42 (1.9)	9	17 (1.8)	6	17 (3.4)	6	2 (2.2)	1
In response to stimuli	23 (1.1)	11	9 (1.0)	5	4 (0.8)	2	1 (1.1)	1
Inconsolable crying	141 (6.5)	38	68 (7.3)	31	39 (7.9)	14	10 (10.8)	7
High pitched crying	57 (2.6)	18	34 (3.6)	15	18 (3.6)	6	4 (4.3)	3
Grimacing	212 (9.8)	36	94 (10.1)	23	58 (11.7)	10	18 (19.4)	9
Sleep pattern								
Sleeps <1 hour	307 (14.2)	54	135 (14.6)	47	63 (12.7)	17	20 (21.5)	15
Sleeps >1 and <3 hours	1262 (58.7)	73	535 (57.7)	69	310 (62.5)	19	57 (60.2)	22
Seizures	6 (0.3)	4	3 (0.3)	2	3 (0.6)	2	0	0
Pupil dilatation	30 (1.4)	14	11 (1.2)	9	8 (1.6)	6	2 (2.2)	2
Hallucinations	16 (0.7)	8	10 (1.1)	5	4 (0.8)	2	1 (1.1)	1
Gastro-intestinal dysfunction								
Vomiting	102 (4.7)	21	42 (4.5)	16	27 (5.4)	8	11 (11.8)	5
Diarrhea	312 (14.5)	45	166 (17.8)	36	87 (17.5)	12	20 (21.5)	10
Increased gastric residuals after feeding	280 (13.0)	32	115 (12.4)	26	75 (15.1)	12	24 (25.5)	10
Poor feeding	34 (1.6)	9	15 (1.6)	8	9 (1.8)	4	0	
Autonomic dysfunction								
Tachycardia	168 (7.8)	53	87 (9.3)	40	42 (8.5)	13	15 (16.1)	9
Tachypnea	610 (28.3)	72	276 (29.6)	62	160 (32.3)	19	29 (31.2)	17
Hypertension [b]	169[1] (15.0)	42	82[2] (14.6)	33	35[3] (13.1)	12	8[4] (13.6)	6
Fever	397 (18.4)	39	164 (17.6)	28	97 (19.6)	9	23 (24.7)	10
Sweating	411 (19.0)	32	120 (12.9)	23	71 (14.3)	10	21 (22.6)	7
Sneezing	27 (1.2)	11	9 (1.0)	6	5 (1.0)	3	1 (1.1)	1
Yawning	63 (2.9)	23	18 (1.9)	12	9 (1.8)	5	4 (4.3)	4
Mottling	203 (9.4)	19	86 (9.2)	13	73 (14.7)	6	14 (15.1)	7

n number of observations scored with yes, *N* number of patients, [a] cumulative doses of midazolam ≥ 70 mg/kg, [b] hypertension only determined in patients with arterial line: n=1130[1]; n=560[2]; n=267[3];n=58[4]

Central Nervous System irritability

Symptoms such as anxiety, agitation, grimacing, sleep disturbance, increased muscle tension and movement disorder were observed in more than 10% (10 to 22.1%) of all observations. Their frequencies differed little between the total, weaning and high doses groups.

Symptoms such as seizures, tremors, high pitched crying, pupil dilatation and hallucinations were rarely seen (0 to 4%) in all groups.

The group 'unsuccessful weaning' showed much higher frequencies of the symptoms agitation, anxiety, increased muscle tone, motor disturbance, grimacing and sleep <1 hour (20.4 to 46.2%) than observed in the two other 'weaning' groups. Figure 1 illustrates this finding. Administration of additional sedatives and analgesics, including ketamine, clonidine and propofol, was slightly higher (10.5%) in the unsuccessful weaning group as compared to the total group. On the other hand, in 45 (48%) of the 93 assessments in this group midazolam, morphine and fentanyl were tapered off before administering additional medication. Strikingly, in 13 of 45 observations the tapering rate was between 10-20% per step. In 32 of 45 cases these medications were tapered off faster (>20% of initial doses) indicating that tapering rate might be a factor of influence.

Gastrointestinal dysfunction

Diarrhea and increased gastric residuals after feeding were most frequently observed (respectively 14.5 to 21.5% and 12.4 to 25.5%) in all four groups. Vomiting was seen twice more frequently (11.8%) in the unsuccessful weaning group than in the three other groups. Frequency of increased gastric residuals after feeding was higher in this group as well.

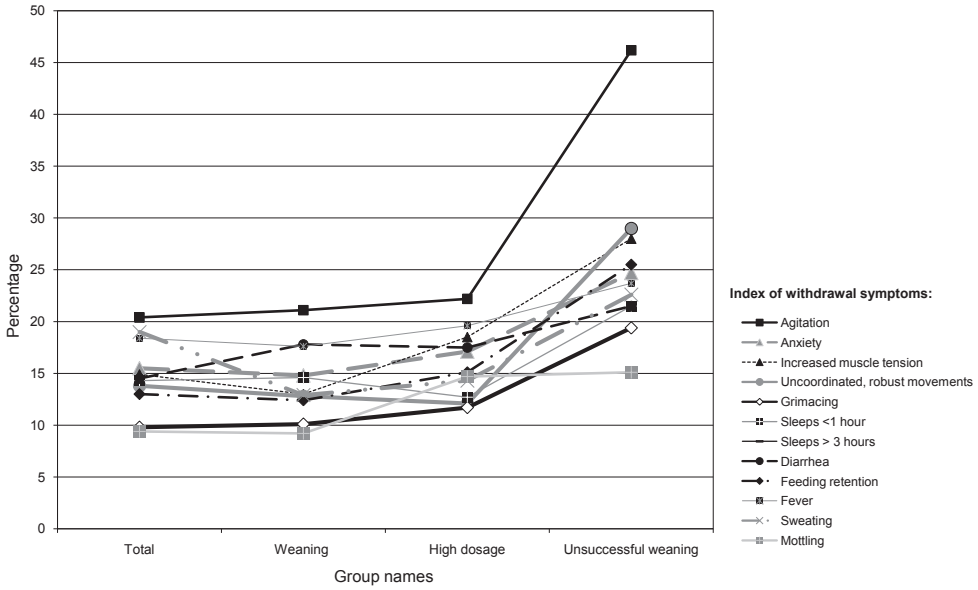
Autonomic dysfunction

Tachypnea, fever, sweating and hypertension were observed in more than 13% of assessments in all four groups. Sneezing and yawning were rarely observed in all the groups. The unsuccessful weaning group showed higher frequencies of notably the symptoms sweating and mottling with a relative increase of 10% or more (see Figure 1).

Correlation between SBOWC sum scores and doses medication

The maximum SBOWC sum scores per patient ranged from 1 to 12 with a median of 6. The r_s between total doses of midazolam and maximum SBOWC sum score in 76 children was 0.51 (95% CI 0.32 to 0.66, $p<0.001$). The r_s between total doses of opioids and the maximum SBOWC sum score was 0.39 (95% CI 0.17 to 0.57, $p<0.01$, n=71). The correlation between duration of medication and maximum SBOWC sum score was 0.52 (95% CI 0.34 to 0.67, $p<0.001$, n=76).

Figure 1 Withdrawal symptoms with percentage of > 10%



Discussion

This study in a large PICU population is the first that prospectively evaluates occurrences of all 24 benzodiazepine and opioids withdrawal symptoms described in the literature for PICU patients. Previous publications included fewer symptoms or focused on either opioid or benzodiazepine withdrawal symptoms.[4,5,7,9]

Only Franck *et al.*[10] prospectively studied both benzodiazepine and opioid withdrawal symptoms. The number of symptoms was limited to 16, however, and the study group included only 15 patients with a complex congenital heart disease. Their findings demonstrate that symptoms like sleeplessness, temperature above 37.2°C, diarrhea, tremors and pupil dilation were most frequently observed, which coincides with findings in the present study, except for tremors. Based on the literature we did not expect GI symptoms such as diarrhea and vomiting as withdrawal symptoms in patients with midazolam[37] However, two of six patients who received only midazolam showed GI symptoms not caused by viral infection or use of antibiotics. Still, this is no clear evidence to state that GI symptoms can be seen as benzodiazepine withdrawal symptoms.

Several authors found correlations between withdrawal symptoms and total cumulative doses (mg/kg) of midazolam or opioids.[4,5,7,10,11,38] In this study we found similar significant correlations. We also found correlations between duration of use and total dose of midazolam administration on the one hand, and maximum SBOWC sum score on

the other hand (respectively 0.52 and 0.51). The correlation between total doses of opioids and maximum sum score (r_s = 0.39) is moderate.

We found that patients whose medication is tapered off (weaning group) and those with high cumulative total doses (high doses group) were at risk for developing withdrawal symptoms during weaning. Surprisingly, frequencies of withdrawal symptoms hardly differed between total group and these subsets of observations, in which higher frequencies would have seemed likely. Thus, the observed symptoms need not necessarily have been withdrawal symptoms, but may have been expressions of discomfort, pain or ventilator distress. Based on these findings and in line with other authors, we recommend awareness of possible over diagnosis of withdrawal symptoms.[25] For example, fever or vomiting should never be attributed to withdrawal until other possible causes are excluded. With other authors we agree that the occurrence of withdrawal symptoms must be time-related to a decrease or discontinuation of sedatives and analgesics.[5-7,10,13,14,27,39] Furthermore, the results of this study underscore that withdrawal symptoms are more likely to occur in patients receiving high (cumulative) doses of midazolam and/or morphine.

Strikingly, a particular set of symptoms stood out clearly in this 'unsuccessful weaning' group (agitation, increased muscle tension, anxiety, grimacing, sleeping less than 1 hour, poor feeding and tachypnea). These symptoms therefore need to be included in an assessment tool. Of symptoms occurring less frequently yawning and sneezing require constant observation and may therefore be difficult to assess in a reliable manner. Symptoms such as tremors, hallucinations and seizures may have a high positive predictive value, even if seen less frequently.

Based on the findings of this study, we propose that the SBOWC could form the basis for an assessment tool for withdrawal symptoms in PICU patients. Still we believe it is questionable if all items in the SBOWC were clinically relevant. Therefore, it is necessary to prospectively study the co-occurrences of several symptoms. In a further study it would be advisable to have independent observers assess videotaped material, so as to increase the validity and reliability. Also, items of the checklist should be further clarified so as to ensure there is no misinterpretation possible for nurses. Item reduction would seem advisable to achieve easier clinical use. Particularly the two items for which low interobserver reliability was obtained should be investigated for their relevance. A way of dealing with these items is giving them more emphasis during training of nurses. On the other hand, it would be worthwhile to investigate if the items with a kappa below 0.65 are relevant for the final assessment tool.

Some limitations of this study must be pointed out. First, there may have been observer bias arising from the fact that the observers were the ones who nursed the children. Second, when completing assessment forms in the PDMS, nurses were not blinded to earlier recorded assessments. This may have influenced objectivity. Third, the frequencies of benzodiazepine and opioid withdrawal symptoms may have been influenced by administration of additional sedatives. Long-term administration of these sedatives

is known to cause withdrawal symptoms as well.[25,38,40] Fourth, The fact that weaning in this study might differ from weaning strategies in other centres might influence the prevalences of withdrawal symptoms.

For treatment purposes, opioid withdrawal symptoms need to be distinguished from those of benzodiazepines because each type of withdrawal syndrome is treated differently.[24,25] This was not possible, however, in the present study, because 73 of 79 children received both types of medication, as is common practice in PICU patients.[41,42] The subset of six patients receiving only midazolam is too small to allow conclusions on specific benzodiazepine withdrawal symptoms.

Conclusion

This is the first study which gives a complete overview of frequencies of all 24 known withdrawal symptoms after tapering off or cessation of benzodiazepines and/or opioids in PICU patients. Both longer duration of administration and higher total doses of midazolam and opioids were clearly related with the occurrence of withdrawal symptoms, and may therefore be considered risk factors.

The checklist (SBOWC) used in this study now forms the basis for a psychometric validation study aimed at establishing a clinically useful assessment tool for PICU patients that could facilitate prevention of withdrawal syndrome and application of a treatment algorithm.

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Chapter 7

Construction of the Sophia Observation withdrawal Symptoms-scale (SOS) for critically ill children

Erwin Ista, Monique van Dijk, Matthijs de Hoog, Dick Tibboel, Hugo Duivenvoorden

Submitted

Abstract

Objectives: To construct a reliable and clinically practical instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric ICU patients.
Design: Instrument development.
Setting: Intensive care unit in an academic children's hospital.
Patients and participants: 79 patients up to age 16 years on intravenous midazolam and/or opioids for ≥5 days. An expert panel of 85 physicians and nurses rated clinical relevance of withdrawal symptoms.
Intervention: During drug weaning repeated observations were performed with a checklist of 24 withdrawal symptoms described in the literature.
Measurements and results: For 76 children, 932 observations were obtained within 24 hours after decreasing and/or discontinuation of midazolam or opioids. Most frequent symptoms were tachypnea, agitation, motor disturbance, diarrhea, fever, anxiety, sleep disturbance and hypertension (14.6 to 29.6%). Multidimensional scaling (MDS) was performed to detect the underlying empirical structure of co-occurrences of symptoms. An expert panel judged clinical relevance of each withdrawal symptom using a four-point scale ranging from 'definitively so' to 'definitively not'. Agitation, anxiety, inconsolable crying, increased muscle tension, tremors, tachycardia and sweating were considered relevant by 85% to 95% of the experts. On the basis of the MDS results and the expert opinions, 15 symptoms were selected for inclusion in the final instrument.
Conclusions: We are the first to develop an assessment tool for withdrawal symptoms in pediatric ICU patients on the basis of the underlying empirical structure of co-occurrences of withdrawal symptoms that experts considered relevant. Future studies need to define cutoff points and clarify psychometric issues.

Introduction

Many critically ill children, admitted to a specialized intensive care unit (ICU), receive benzodiazepines and/or opioids to reduce pain and anxiety. Long-term exposure to these medications may result in physical dependency. These patients are at risk for withdrawal symptoms after abrupt discontinuation or too rapid tapering-off of these medications.[1]

Symptoms of withdrawal can be categorized into three main groups, *i.e.*: overstimulation of the central nervous system (CNS), gastrointestinal dysfunction, and autonomic dysregulation.[1-3]

A reliable, validated and clinical useful assessment tool is indispensable for monitoring withdrawal syndrome. Two such tools are available, the Sedation Withdrawal Score (SWS) and the Opioid Benzodiazepine Withdrawal Scale (OBWS).[4,5] Yet each has its limitations. The Sedation SWS was designed includes 12 symptoms. While all these symptoms seem clinically relevant for assessing withdrawal, data on validity and reliability are lacking. The OBWS was evaluated in a small sample of PICU children (n = 15) comparing OBWS scores and nurses' clinical judgment. Sensitivity of the OBWS at scores 8 (cutoff) or higher was 50% and the specificity was 87%, which implies moderate validity of the scale.[5] Symptoms of the OBWS were indirectly adapted from the Neonatal Abstinence Score.[6]

Within our line of research we studied the (co-)occurrences of withdrawal symptoms in critically ill children with the ultimate objective to develop a valid assessment tool. Specifically, we estimated the (co-)occurrences of the withdrawal symptoms, both bivariately and multivariately. The objective was to find out which symptoms were sufficient for developing of a reliable and valid instrument tailored to adequately assess withdrawal symptoms in critically ill children.

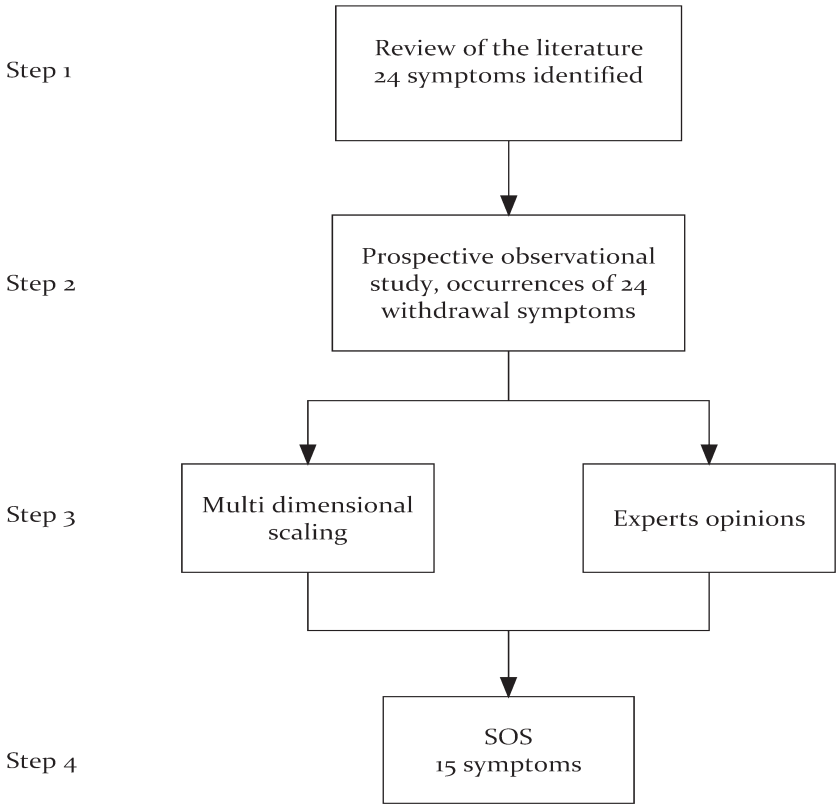
Materials and methods

Methods

Several steps of scale development involved in the construction of the Sophia Observation withdrawal Symptoms-scale (SOS) were taken. Figure 1 shows the outline of the study. The institutional review board approved the study and because of the strictly observational and non-invasive nature of this study, they waived the need for informed consent.

The first step was a review of the literature on withdrawal symptoms in critically children admitted to a PICU based on an extensive evaluation of the literature as recently published by our group.[3] Based on this review, we selected 24 symptoms for in a preliminary scale, which we called the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC). Twelve symptoms concerned the central nervous system, four the gastrointestinal tract, and eight the autonomic nervous system (see Table 1).

Figure 1 Outline of the steps taken to construct the Sophia Observation withdrawal Symptoms-scale (SOS)



The second step was a prospective observational study in critically ill children admitted to the intensive care of the Erasmus MC - Sophia Children's Hospital between September 2005 and February 2006. Eligible for inclusion were children aged ≤16 years who had received midazolam (benzodiazepine), morphine or fentanyl (opioids) by continuous infusion for at least 5 days.

The SBOWC was assessed within 24 hours after tapering-off or cessation of midazolam and/or opioids (morphine or fentanyl). All nurses had received verbal and written instruction on the SBOWC. An instruction manual explaining the symptoms to be observed was available at each patient's bedside. Details about reliability and validity of the SBOWC have been presented in earlier work.[7]

The third step was twofold. In step 3a the underlying structure was identified by multidimensional scaling. Step 3b was to obtain expert opinion on the relevance's of the SBOWC symptoms. To this end we mailed a questionnaire to all pediatric intensivists and their clinical fellows in pediatric intensive care of all eight PICUs in the Netherlands and to critical care nurses of our own PICU.

Step 4 selected the relevant items; symptoms which had insufficient discriminative

value were eliminated.

Study population

The observations were stratified into two groups. First, a 'weaning group' (WEAN), in which 932 observations in 76 children were obtained within 24 hours after decrease and/or discontinuation of midazolam and/or opioids. Those children were at risk for developing withdrawal symptoms. Second, an 'unsuccessful weaning' group (WEAN-), 93 observations in 27 children. These observations were obtained before increasing midazolam and/or opioids during the weaning process in order to counteract possible withdrawal related symptoms. In this 'unsuccessful weaning' group we expect more withdrawal related symptoms compared to the 'weaning group'.

Statistical analyses

As the frequency distribution of the symptoms of SBOWC was skewed, the response categories were dichotomized. Of clinical interest is to determine the interrelationship of the symptoms. Conventionally, one or another kind of correlation technique as an association measure is used. To our belief, in this study it is not of interest to estimate the association between symptoms, but preferably to estimate the co-occurrences of these symptoms. To that end, Jaccard's measure of similarity tailored to estimate these occurrences will be applied.

Expert opinions

The experts were asked to rate the relevance of each withdrawal symptom in critically ill children using a four-point scale ranging from 'definitively so' to 'definitively not'. In addition we asked them to state which symptoms were absolutely necessary for an assessment tool. Each symptom of the checklist was recoded. A symptom was coded relevant if the expert scored the first question as 'that's definitely so' or 'that's true' or the second question with 'absolutely necessary'. We considered a symptom was deemed relevant if 50% or more of the respondents agreed on relevance.

Multidimensional scaling

The goal of multidimensional scaling (MDS) analysis technique in this study is to detect meaningful underlying dimensions of observed similarities and dissimilarities (distances) between withdrawal symptoms.

The (dis)similarities between the withdrawal symptoms identified by MDS are based on the co-occurrences of these symptoms. Then, MDS attempts to arrange 'objects' (withdrawal symptoms) in a space of as few dimensions as possible without substantial loss of information. This enables reproducing the observed distances adequately. Nevertheless, in general, the more dimensions we use in order to reproduce the distance matrix, the better the fit of the reproduced matrix to the observed matrix. We considered

Table 1 Co-occurrences of withdrawal symptoms (values were percentages of symptoms scored with yes) Empty fields were zero

	Agitation	Anxiety	Muscle tone	Motor	Tremors	Crying	High pitched crying	Grimacing	Sleeping	Seizures	Pupil dilation	Hallucination	Vomiting	Diarrhea	Feeding retention	Poor feeding	Tachycardia	Tachypnea	Hypertension	Fever	Sweating	Sneezing	Yawning	Mottling	Frequency of unsuccessful weaning group (n=94)
Agitation		18.1	24.5	25.8	1.1	9.6	3.1	15.9	15.9		2.1		2.1	7.4	11.7		9.6	17.0	8.6	12.8	15.9	1.1	4.3	9.6	**46.2**
Anxiety	8.5		15.9	15.1		8.5	4.3	7.4	12.8		2.1		4.3	4.3	9.6		4.3	8.5	3.4	7.4	8.5		3.2	7.4	**24.7**
Muscle tone	7.7	5.8		19.4	1.1	9.6	3.2	11.7	11.7		2.1		2.1	6.4	8.5		7.4	15.9	5.2	10.6	9.6	1.1	3.2	4.3	**28.0**
Motor	9.5	5.4	7.2		1.1	4.4	2.2	10.8	15.0		2.2		1.1	7.6	9.7		8.6	13.9	10.3	10.8	9.7	1.1	3.3	8.6	**37.6**
Tremors	1.2	1.1	1.9	1.4														2.2	1.7	1.1					**3.3**
Crying	5.4	4.5	4.0	2.3	0.4		4.3	5.3	4.3		1.1		2.1	1.1	5.3		1.1	6.4	1.7	3.2	6.4		1.1	1.1	**10.8**
High pitched crying	4.3	4.3	3.3	1.6	0.7	6.6		3.2	2.1		1.1		1.1		2.1		1.1	2.1	1.7	1.1	1.1				**4.3**
Grimacing	5.9	3.6	4.9	5.3	1.0	2.0	1.7		9.6		1.1		1.1	5.3	3.2		4.3	8.5	6.9	4.3	5.3		1.1	2.1	**19.4**
Sleeping	6.8	5.0	4.0	4.4	0.8	3.0	1.4	2.9			2.1		1.1	2.1	6.4		7.4	9.6	6.9	9.6	8.5		2.1	5.3	**21.5**
Seizures			0.2	0.2	0.1																				**0**
Pupil dilation	0.4	0.3	0.3	0.4	0.1	0.2			0.2						2.1		1.1	1.1	1.7		1.1			1.1	**2.2**
Hallucination	0.4	0.3	0.2	0.4	0.2		0.3	0.3	0.5		0.1				1.1										**1.1**
Vomiting	1.6	1.2	0.5	0.6		0.5	1.7	0.6	0.5	0.1		0.1		5.3	5.3			5.3		3.2	2.1		1.1	1.1	**11.8**
Diarrhea	4.9	2.0	3.3	4.9	0.7	1.2	2.6	3.4	3.1	0.1		0.1	1.5		7.4		4.3	6.4	3.4	8.5	1.1		1.1	1.1	**21.5**
Feeding retention	4.9	4.1	3.6	4.8	0.2	1.6	1.2	2.8	2.5		0.1	0.3	2.5	2.5			5.3	5.3	6.9	10.6	7.4		2.1	5.3	**25.5**
Poor feeding	4.2	7.0		5.6		1.4	1.4		7.0		0.3	2.8	1.4	2.8	1.4										**0**
Tachycardia	3.4	2.1	1.3	1.8	0.2	1.4	2.6	1.2	2.3		0.1		0.9	2.1	1.2	1.4		8.5	3.4	5.3	4.3		1.1	2.1	**16.1**
Tachypnea	7.2	4.5	4.2	5.5	0.4	2.3	3.3	2.7	5.9	0.3	0.4	0.1	1.5	5.2	4.4	5.6	4.8		5.2	7.4	8.5	1.1	2.2	1.1	**31.2**
Hypertension	3.8	2.0	1.6	4.3	0.1	1.3	0.3	2.4	2.9			0.2	1.1	2.4	1.9	1.4	2.6	5.6		5.2				5.2	**13.6**
Fever	3.7	3.9	3.5	5.6	1.3	1.4	1.7	2.6	2.9	0.1	0.5	0.2	0.8	4.9	3.7	2.8	1.0	5.5	2.4		6.4		1.1	3.2	**24.7**
Sweating	4.3	3.9	4.0	3.0	0.4	2.4	1.7	1.7	3.7		0.2	0.2	0.8	2.0	3.6	4.2	1.8	5.5	2.4	3.3			1.1	4.3	**22.6**
Sneezing	0.3	0.2	0.3	0.3	0.1	0.3		0.1	0.5				0.3	0.3	0.3		0.2	0.3			0.1				**1.1**
Yawning	0.5	0.1	0.3	1.1					0.4	0.2			0.2	0.2	0.5	2.8	0.1	0.4		0.1		0.1			**4.3**
Mottling	1.8	2.1	2.3	2.4	0.7	0.6	1.0	1.1	1.8	0.1	0.2	0.3	0.4	2.3	1.3	4.2	0.9	2.1	0.7	3.3	1.3	0.1	0.2		**15.1**
Frequency weaning group (n=932)	**21.1**	**14.8**	**13.0**	**19.8**	**2.8**	**7.3**	**3.6**	**10.1**	**14.6**	**0.3**	**1.2**	**1.1**	**4.5**	**17.8**	**12.4**	**1.6**	**9.3**	**29.6**	**14.6**	**17.6**	**12.9**	**1.0**	**1.9**	**9.2**	

the Jaccard measure as a similarity measure of co-occurrences. The fit of the models were represented by the normalized raw stress, a measure of model performance. This coefficient varies from 0 to 1 and should be < 0.05 as a good fit. The Tucker's ϕ coefficient of congruence is a measure of correspondence between the distances of the empirical data and the distance derived from the model. Ideally, this coefficient should be > 0.95. To identify the clinical-empirical structure the computer algorithm PROXSCAL (Proximity Scaling) was used. Two symptoms were excluded from analysis. First, hypertension since it was not always possible to measure arterial blood pressure, *i.e.* when the child did not have an indwelling arterial catheter, in 386/932 (41%) observations. Second, high pitched crying, since this symptom could only be observed if patients did not have an endotracheal tube, which was not always the case (629/932, 67%). Furthermore, as the SBOWC asked for observation of either feeding retention or poor feeding, these items were taken together in the MDS procedure. Final item selection was based on the expert opinions and the results of MDS. Inclusion in the SOS required symptoms to have a substantial score (z-score) ≥ 0.30 on at least one dimension of the MDS solution. And, a symptom was deemed relevant if 50% or more of the respondents agreed on relevance. The robustness of the normalized raw stress and the Tucker's ϕ coefficient of congruence of the MDS solution was tested with tenfold cross-validation and presented by the mean (SD) value.

Interobserver reliability was tested for the dichotomous items by Cohen's kappa and the intraclass correlation coefficient (ICC) for continuous data.[8] A Cohen's kappa below 0.65 was considered unsatisfactory.[9]

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS), version 14.0.

Results

Characteristics study sample

Seventy-nine children - 43% girls; 57% boys - met the inclusion criteria. Their median age was 3.4 months (range 0 days to 15.5 years). All 79 received midazolam at a median dose of 176 mcg/kg/hr. Seventy-three children (92%) also received opioids at a median dose of 14 mcg/kg/hr. Midazolam was administered for a median of 10 days (range 3 to 108 days); opioids were administered for a median of 8 days (range 1 to 41 days). The median total dose of midazolam was 33 mg/kg (range 2 to 595 mg/kg), and of opioids 4 mg/kg (range 0 to 682 mg/kg).

For 76 children, 932 observations were obtained within 24 hours after decreasing and/or discontinuation of midazolam and/or opioids (WEAN). In 3 patients there were no observations performed after weaning or cessation of midazolam and/or opioids because they were discharged. Ninety-four 'unsuccessful weaning' observations were obtained for

27 children in the 'unsuccessful weaning' group (WEAN-). The latter observations were obtained before midazolam and/or opioids were increased during the weaning process in order to counteract possible withdrawal related symptoms.

Interobserver reliability

Twenty-three observations were scored simultaneously by the attending nurse and the principal investigator (EI). The intraclass correlation coefficient was 0.97 (95% CI 0.92 to 0.98). The interobserver reliability (Cohen's kappa) of the individual items of the SOS ranged from 0.73 to 1.0.

Bivariate analysis of co-occurrences of withdrawal symptoms

Table 1 presents (co)-occurrences of symptoms for the two conditions, *i.e.* observations performed within 24 hours after weaning (WEAN, n=932) of opioids/benzodiazepine

Table 2 Construction of the SOS based on two methods (MDS and Expert opinion)

SBOWC	SBOWC - MDS	SBOWC - Expert opinion		SOS
Anxiety	+	+	95.3	+
Agitation	+	+	84.7	+
Increased muscle tension	+	+	85.9	+
Motor disturbance	+			+
Slight muscle jerks		+	72.9	
Uncoordinated, robust movements		+	78.8	
Tremors	+	+	92.9	+
Inconsolable crying	+	+	88.2	+
High pitched crying	*	+	68.2	-
Grimacing	+	+	76.5	+
Sleep disturbance				
< 1 hour	+	+	71.8	+
Seizures	-	-	35.3	-
Pupil dilation	-	+	56.6	-
Hallucinations	+	+	76.5	+
Vomiting	+	+	61.2	+
Diarrhoea	+	+	50.6	+
Feeding	+			
Poor feeding		+	55.3	-
Feeding retention		-	43.5	
Tachycardia	+	+	89.4	+
Tachypnea	+	+	69.4	+
Hypertension	*	+	67.4	-
Fever	+	+	50.6	+
Sweating	+	+	90.6	+
Sneezing	-	-	24.7	-
Yawning	-	-	44.7	-
Mottling	+	-	45.9	-

* not performed in the MDS analysis because of many missing observations, + meet criteria for inclusion, - do not meet inclusion criteria

(lower triangle) and observations performed before decreasing medication (WEAN-, n = 94) (upper triangle).

For WEAN, high prevalence's were noted for tachypnea (29.6%), agitation (21.1%), diarrhea (17.8%), fever (17.6%) anxiety (14.8%), sleep pattern (14.6%) and hypertension (14.6%) showed. On the other hand, for WEAN- , symptoms such as agitation (46.2%), motor disturbance (37.6%), tachypnea (31.2%), increased muscle tension (28.0%) and feeding retention (25.5%) showed the highest prevalence's. The symptoms tremors, hallucination, seizure, pupil dilatation, sneezing and yawning demonstrated very low prevalence's (from 0.3 to 1.9).

With regard to co-occurrences (Table 1) the highest percentage was seen for agitation co-occurring with motor disturbance, both in the WEAN (9.5%) and WEAN- (25.8%). Groups substantially differed in frequencies of the following co-occurrences: agitation/anxiety, agitation/muscle tone, agitation/motor disturbance, agitation/grimacing, agitation/sleeping, agitation/sweating, muscle tone/motor disturbance. The co-occurrences with symptoms such as seizures, pupil dilatation, hallucinations, yawning and sneezing were very low.

Table 3 Multidimensional scaling, dimensional quantifications (z-scores)

Withdrawal symptoms	**Dimension**		
	1	2	3
Agitation	**0.909**	0.274	-0.190
Anxiety	**-0.594**	**-0.591**	0.223
Increased muscle tension	**-0.609**	**0.696**	0.173
Motor disturbance	**-0.820**	0.032	-0.280
Tremors	0.126	**0.350**	**-0.417**
Crying	-0.090	0.168	**0.678**
Grimacing	0.232	-0.006	**-0.668**
Sleep disturbance (less 1 hour)	**0.465**	**-0.605**	-0.177
Pupil dilation	0.153	-0.052	-0.236
Seizures	0.102	-0.200	0.070
Hallucinations	-0.144	0.167	**0.326**
Vomiting	0.014	**0.523**	-0.259
Diarrhea	-0.050	**-0.520**	**0.456**
Feeding	**0.523**	**-0.391**	**0.340**
Tachycardia	**-0.437**	-0.108	0.227
Tachypnea	0.064	**0.719**	0.273
Fever	**0.632**	0.198	0.296
Sweating	**-0.360**	-0.178	**-0.646**
Yawning	-0.174	0.121	-0.259
Sneezing	0.168	0.003	0.289
Mottling	-0.110	**-0.600**	-0.218

Z-scores > 0.30 were highlighted, these symptoms has substantial score on one of the three dimensions.

Expert opinions

In total 85 experts, 22 physicians and 63 nurses responded to the questionnaire. Most of them (84.7%) were female. The median work experience was 8 years, for physicians (IQR 4 - 11.3) and nurses (IQR 4.5 - 15) alike.

The following symptoms were considered most relevant: agitation, anxiety, inconsolable crying, increased muscle tension, tremors, tachycardia and sweating (84.7% to 95.3%) (see Table 2). For five symptoms less than 50% of the experts agreed on relevance, *i.e.* seizures, feeding retention, yawning, sneezing and mottling.

Multidimensional analysis of co-occurrences

The PROXSCAL-procedure was applied with random starts was chosen as initial configuration. Twenty-one symptoms were entered and the solution of the MDS procedure turned out to be three-dimensional. The normalized raw stress was 0.0498, indicating a good fit. The Tucker's ϕ coefficient of congruence equaled 0.97. Decompositions of normalized Raw Stress ranged from 0.02 to 0.06. The tenfold cross-validation of the MDS solution identified a mean normalized raw stress of 0.0501 (SD = 0.002) and a mean Tucker's ϕ coefficient of congruence of 0.97 (SD = 0.0009).

The symptoms seizures, pupil dilatation, sneezing and yawning had a z-score below 0.30 on either of the three dimensions (see Table 3). Finally, based on the MDS results as well as the expert opinions, 15 symptoms (Table 2) were selected for inclusion in the SOS (see also Appendix).

Discussion

To our knowledge, this is the first study to identify the underlying empirical structure of co-occurrences of withdrawal symptoms that experts (physicians and nurses) considered to be of relevance in critically ill children. The co-occurrences of these symptoms could be adequately represented in a three-dimensional solution. Nevertheless, the heterogeneity suggested that the symptoms did not constitute homogeneous clusters within the three-dimensional solution. In all probability, this should be attributed to the low levels of occurrences of withdrawal symptoms, and, consequently, low levels of co-occurrences. This finding suggests that the nature of withdrawal symptoms varies between individuals which is supported.

As withdrawal symptoms of children in the PICU are usually treated immediately, extreme reactions are seen for short times only. Ethically this is correct because we strive for comfortable patients. This, however, makes it difficult to determine co-occurrences of withdrawal symptoms. Although the underlying empirical structure of the symptoms was unraveled nicely, the question arises whether the composed SOS based on MDS and expert opinion adequately covers all phenomena of the withdrawal syndrome. The symptoms included in the SOS have been extensively described in the literature.[3-5,10] Also,

the tenfold cross validation on children showed that the empirical solution was robust. Therefore, we could conclude the SOS covers true the withdrawal symptoms.

Several items were excluded from MDS analysis. We do not preclude that assessment of arterial blood pressure (ABP) might be of additional value, particularly in children being ventilated for a long time. This item was excluded because not all children had an indwelling arterial catheter. High-pitched crying can only be assessed when children are not ventilated. This item was excluded, therefore, even though experts identified it as relevant. The item feeding was eliminated. 'Poor feeding' was judged as relevant by 55% of the experts, but 'Feeding retention' was judged irrelevant. Both Feeding items were combined in the MDS analysis and it was impossible to distinguish which feeding item had a substantial z-score. Therefore, we decided to eliminate the item Feeding and not incorporate it in the SOS.

The OBWS and SWS largely overlap with our SOS scale, except for the symptoms hyperactive Moro-reflex, high pitched crying, sneezing, yawning, frequent suction required, seizures and pupil dilation.[4,5] These symptoms were not included in the SOS. Given the inherent age restriction for the symptom Moro-reflex this item cannot be included in the scale for all ages. We included three other symptoms - anxiety, grimacing and tachycardia - which the two other scales do not contain. On the basis of the literature, however, these symptoms were identified as withdrawal symptoms.[3]

A particular strength of the SOS is that it incorporates the opinions of health care workers, so as to make it clinically relevant. Also, it does not ask the raters to assess severity of the symptoms, unlike the Sedation Withdrawal Score. Therefore we feel that it is not only more simple in use, but also more reliable, seeing that the reliability of an assessment tool will increase as symptoms are unambiguous.[11]

In future research, we will explore the sensitivity to change of the SOS in critically ill children. Furthermore, cut off scores, sensitivity and specificity must be defined for treatment purposes.

In conclusion, the SOS is feasible for assessing benzodiazepine and/or opioid withdrawal symptoms in critically ill children in an ICU environment.

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Appendix A - SOS

SOS - Sophia Observation withdrawal Symptoms-scale
(Children 0 – 16 years)

Sticker with patient's name

Date _____

Time _____

Observer _____

Step 1		Explanation
Heart rate	/min.	*Enter highest rate in past 4 hours if present, otherwise read the monitor first or feel pulse.*
Breathing rate (tachypnoe)	/min.	*Enter highest rate in past 4 hours if present, otherwise read the monitor first or count breathing.*
Baseline value heart rate	/min.	*Please turn over for instruction on determining baseline value.*
Baseline value breathing rate	/min.	*Please turn over for instruction on determining baseline value.*

Step 2	Tick if yes	
Autonomic dysfunction		
1 Tachycardia	☐	*Yes if heart rate exceeds baseline value by ≥ 15%.*
2 Tachypnea	☐	*Yes if breathing rate exceeds baseline value by ≥ 15%.*
3 Fever	☐	*Yes if body temperature exceeded 38.4 °C in past 4 hours.*
4 Sweating	☐	*Not caused by room temperature, clothing, swaddling e.g.*
Central nervous system irritability		
5 Agitation	☐	*Yes if child shows at least one of these signs: irritable, restless, agitated, fidgety.*
6 Anxiety	☐	*Unrest or anxious face (eyes wide open, eyebrows tense and raised). Behavior can vary from panicky to draw back.*
7 Tremors: ***(pick one)***		*Slight, involuntary rhythmic movements of hand and/or feet.*
• Spontaneous	☐	*Note: please turn over for instructions.*
• In response to environmental stimuli	☐	
8 Motor disturbance: ***(pick one of four)***		
Slight muscle jerks:		*Involuntary, of forearms/lower legs, muscle twitching.*
• Spontaneous	☐	
• In response to environmental stimuli	☐	
Uncontrolled, robust movements:		*Choreoathetosis of arms, legs and/or head.*
• Spontaneous	☐	
• In response to environmental stimuli	☐	
9 Increased muscle tension	☐	*Clenched fists or tense clenched toes.*
10 Inconsolable crying	☐	*Yes if child cannot be consoled by parents or by offering distraction, e.g. pacifier, food; or game playing for older children. Score silent crying in intubated children.*
11 Grimacing	☐	*Eyebrows contracted and lowered, nasolabial fold visible.*
12 Sleeplessness	☐	*Sleeps not more than 1 hour at a stretch.*
13 Hallucinations	☐	*During the past 4 hours child seems to see, hear or feel things that are not there.*
Gastrointestinal dysfunction		
14 Vomiting	☐	*At least once in past 4 hours, not related to feeding changes.*
15 Diarrhea	☐	*Watery stools, not related to feeding changes (do not score e.g. when the result of breastfeeding).*
Count ticked boxes	☐	***Maximum score is 15***

Please turn over for further instructions

Appendix B - SOS Instructions

SOS - Sophia Observation withdrawal Symptoms-scale

Instructions

Target group:

Children, up to 16 years old, who have received benzodiazepines and/or opioids for more than 4 days, start from the 5th day.

Excluded are children who:

- Receive neuromuscular blocking agents continuous;
- Have been admitted with status epilepticus (and therefore receive midazolam);
- Show severely disturbed behavioral pattern on account of underlying neurological disease.

For assessing abstinence in infants of drug-dependent mothers, we recommend the Neonatal Abstinence Score (NAS) of L.P. Finnegan (1975).

Procedure:

- Observe the child:
  - At 4 a.m., 2 p.m. and 8 p.m.
  - At suspicion of withdrawal syndrome.
  - 2 hours after an intervention for treatment of withdrawal symptoms.
- Please fill in the form carefully after observation;
- Please score for each item the most extreme/ worst moment during the **past 4 hours**;
- Check the explanation if a particular item is not clear.

Step 1

Determining baseline values for heart rate and breathing rate:

The baseline value is the mean value over the past 24 hours. Dependent on type of 'patient data management system' it could be automatically generated, otherwise it must be computed by hand.

For example:

The baseline value of heart rate is 100. Compute baseline "exceeded by 15 %" as follows:

100 x 1.15 = 115. The highest rate observed in the past 4 hours is 124. This is higher than 115, so tick yes for tachycardia (step 2).

Step 2 ***Items 7 and 8***

Instructions for tremors and motor disturbance:

Tremors and motor disturbance can present in two ways:

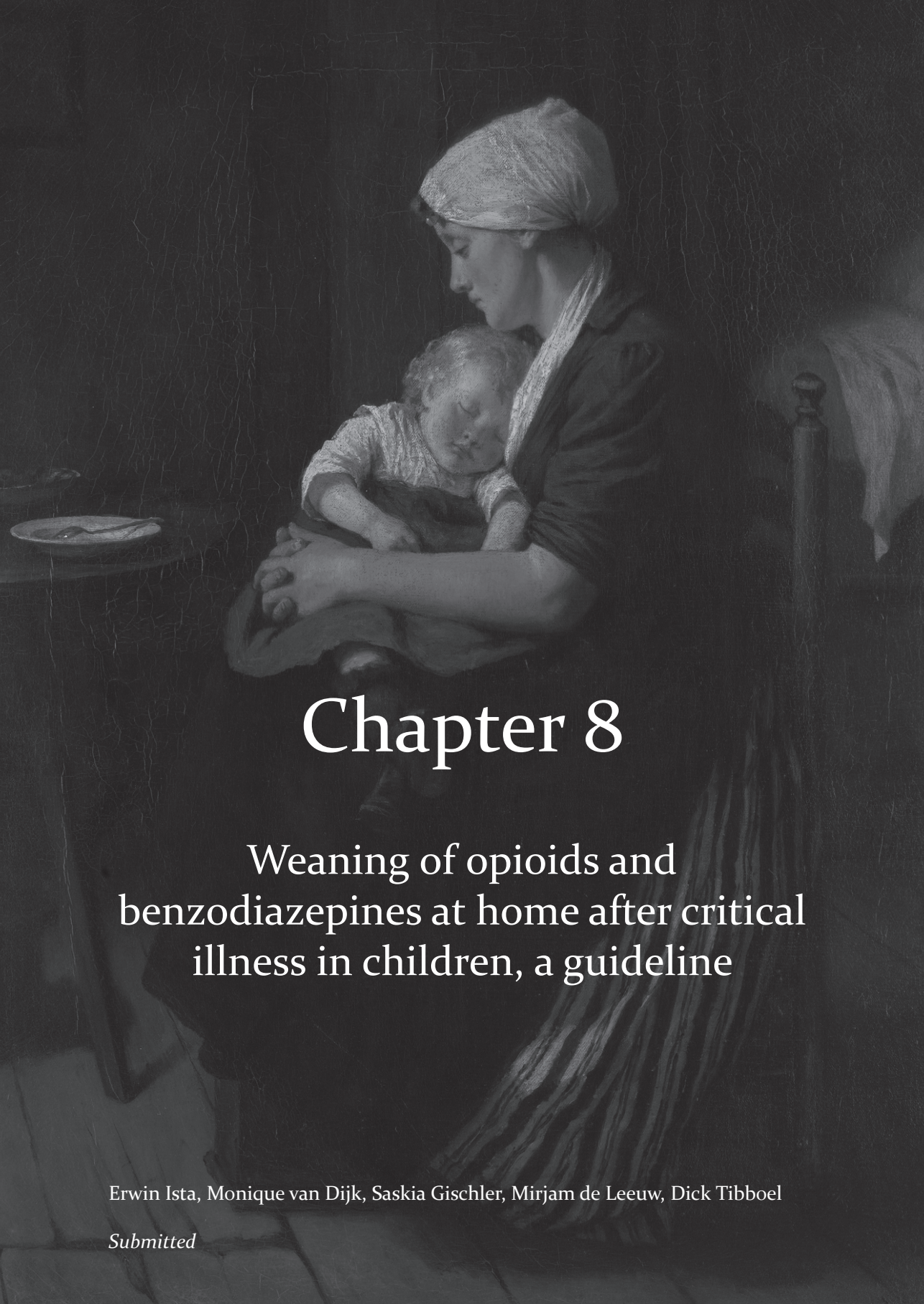
1. spontaneous, not related to environmental stimuli or touching of the child;
2. in response to environmental stimuli (caretaking, noise, etc.).

Please take this into account when completing the form.

Example: a child show tremors when you attend to it. The tremors stop when you have finished.

In this case, please tick yes for 'tremors – in response to environmental stimuli'.

For clarification and questions please send email to w.ista@erasmusmc.nl



Chapter 8

Weaning of opioids and benzodiazepines at home after critical illness in children, a guideline

Erwin Ista, Monique van Dijk, Saskia Gischler, Mirjam de Leeuw, Dick Tibboel

Submitted

Abstract

Objectives: To evaluate the feasibility of weaning sedatives and opioids at home in children.
Design: Retrospective observational study.
Participants: 30 neonates treated for congenital diaphragmatic hernia (CDH) with extra corporeal membrane oxygenation (ECMO).
Setting: Intensive Care Unit of the Erasmus MC - Sophia Children's Hospital
Results: Of the 30 neonates treated for CDH with ECMO from 2003 through 2005, 15 survived. Five children were weaned at home, though telephone contact once a week. The mean infusion rates of midazolam and morphine for the weaned at home children were significantly higher than those for other children (Midazolam: Kruskal-Wallis, Chi-Square=7.44, *df*=2, *p*=0.024; Morphine: Kruskal-Wallis, Chi-Square=6.86, *df*=2, *p*=0.032). Weaning at home took respectively 11, 42, 107, 173 and 180 days. Two parents reported inconsolable crying, agitation, sleeplessness and irritability especially on days when doses were tapered off. As a consequence, dosages for two patients had to be kept at the same level for two weeks because of serious withdrawal symptoms.
Conclusions: Home weaning reduces length of hospital stay by a median of 107 days in the five infants presented in this study. Parents should be well informed about possible withdrawal symptoms and should consent in this strategy. The strategy of final weaning with the aid of weekly telephone consultations with a consultant pediatric intensivist was feasible and satisfying for these parents.

Introduction

To minimize patients discomfort in the pediatric intensive care unit (ICU), sedation and pain relief has become an integral part of critical care practice. After prolonged exposure of sedatives and opioids, physical dependence may develop, placing the critically ill children at risk for withdrawal symptoms after abrupt discontinuation or tapering too fast.[1,2] This is a significant problem and too less recognized. Although the exact incidence of iatrogenic withdrawal is unknown.

Neonates born with a congenital diaphragmatic hernia (CDH) often need life-saving Extra Corporeal Membrane Oxygenation (ECMO) treatment. In contrast to many other patient groups they treated with ECMO, CDH patients often remain hospitalized for prolonged artificial ventilation due to the high incidence of bronchopulmonary dysplasia and pulmonary hypertension. This subset group is especially at high risk for developing an iatrogenic withdrawal syndrome. They receive intravenous sedatives and opioids at high doses and for long periods of time, which requires cautious monitoring. For one thing, sudden discontinuation of this medication carries the risk of withdrawal syndrome.[3,4] Furthermore, animal studies have suggested that neurodegeneration, with possible cognitive sequela, is a potential long-term risk of sedatives and anesthetics in neonates and young children.[5]

The gradual tapering of intravenous sedatives and opioids to prevent or limit the occurrence of withdrawal symptoms is a time consuming process and may result in even longer hospital stay. A possible alternative is a switch to oral agents such as methadone, lorazepam, clonidine and alimemazine. The switch to oral administration eliminates the need for intravenous sedatives. Patients then could be discharged earlier to complete final weaning at home. Stepwise weaning in the home environment might even facilitate the weaning process, and, for that matter, considerably shortens hospital stay.

Physicians should nevertheless be well aware of the differences in potency, half-life and oral availability between the sedatives and opioids. Regrettably, guidelines for weaning of benzodiazepines and opioids are scarce. The few available reports all describe an ICU hospital setting.[1,6-8]

Home weaning of iatrogenic drug dependent infants has been evaluated in two studies.[9,10] Tobias *et al.*[9] evaluated this strategy for three children (15 months, 17 months and 11 years) and found that tapering of oral sedatives and opioids was feasible within 4 to 6 weeks, without signs of withdrawal. Meyer *et al.*[10] evaluated weaning of methadone in 29 children with a mean age of 26 months. Sixteen children had been discharged to complete their weaning schedule at home. In this study, however, withdrawal symptoms at home were not assessed.

The aim of the present study was to describe aspects of home weaning of benzodiazepines and opioids for five children with CDH after prolonged sedation. A second aim was to develop a guideline for this treatment mode.

Methods

We retrospectively reviewed data of patients with CDH who received ECMO treatment in the Intensive Care Unit of the Erasmus MC - Sophia Children's Hospital from January 2003 up to and including December 2005.

During ECMO to our unit-specific protocol all patients received both opioids (such as morphine and fentanyl) and benzodiazepines (such as midazolam) to relieve pain and physical and psychological discomfort, respectively.[11] These were administered intravenously by continuous infusion or as intermittent bolus. Doses and durations were retrieved from the patient data management system.

Opioids and benzodiazepines were weaned stepwise by 10 to 20% per 24 hours.[1,6] If weaning procedures required a longer time or were unsuccessful and resulted in withdrawal symptoms, opioids were replaced by methadone and midazolam was replaced by clonidine according to our protocol. Methadone was administered orally; clonidine first by continuous intravenous infusion and later by mouth.

As from 2003, selected patients with CDH who had undergone ECMO treatment were discharged home with the intention to complete drug weaning at home. Parents were recruited for weaning at home if they were sufficiently motivated and capable. They received support from one of the pediatric intensivist consultants (DT). In weekly telephone consultations parents described possible withdrawal symptoms after which the consultant advised on decreasing or maintaining doses. Furthermore, the child was regularly examined in the outpatient clinic for disease specific morbidity, on the guidance of the interdisciplinary and protocollized care plan for patients with CDH.

Once weaning was completed, a researcher (MvD) or nurse (MdL) interviewed the parents. Interviewing had a twofold aim. First, parents were asked to identify the withdrawal symptoms they had observed, both in hospital and at home, from a 24-item withdrawal symptom checklist (Sophia Benzodiazepine and Opioid Withdrawal Checklist).[12] The second aim was to gain insight in parents' views on the feasibility of weaning at home.

Statistical analysis

The data were analyzed using SPSS for Windows (version 14.0.1; SPSS Inc., Chicago, IL, USA). With regard to drug administration we calculated total duration of administration (days), and mean doses (mcg/kg/hr). We distinguished three patient groups: weaned before discharge, transferred to other hospital and weaned at home (see Figure 1). Mean doses of midazolam and morphine for these groups were compared with the nonparametric Kruskal-Wallis test.

Results

In the three-year study period, 30 neonates with CDH (20 boys, 10 girls) underwent

ECMO treatment (see Figure 1). Fifteen of them died during hospitalization due to therapy resistant pulmonary hypertension with a variable amount of pulmonary hypoplasia. Table 1 summarizes doses and durations of sedatives and analgesics administered to the 15 survivors. The mean infusion rates of midazolam and morphine for the weaned at home group were significantly higher than those for the two other groups (Midazolam: Kruskal-Wallis, Chi-Square=7.44, $df=2$, $p=0.024$; Morphine: Kruskal-Wallis, Chi-Square=6.86, $df=2$, $p=0.032$). Clonidine and methadone were almost exclusively administered to the patients who were weaned at home.

Five survivors were transferred to other hospitals for additional treatment, of whom three required further weaning. One of these five had been judged eligible for home weaning, but the parents nevertheless could not face the responsibility. This child was weaned in the other hospital within 6 weeks after transfer. The other two patients were lost to follow-up.

Five of the remaining ten infants were weaned in hospital before discharge home. The other five were weaned at home from various combinations of methadone, midazolam, clonidine and alimemazine (Table 2). Successful weaning at home took respectively 11, 42, 107, 173 and 180 days (Table 2). Parents most commonly identified withdrawal symptoms such as agitation, inconsolable crying, increased muscle tension, sweating and mottling during hospital stay. At home, parents reported inconsolable crying, agitation, sleeplessness and irritability as occasional withdrawal symptoms, especially on days when doses were tapered off. This necessitated dosages for two patients to be kept at the same level for two weeks because of serious withdrawal symptoms.

Parents of the five patients weaned at home quite appreciated the support from our quarters, including the weekly telephone consultations with a pediatric intensivist.

Figure 1 Flowchart patients

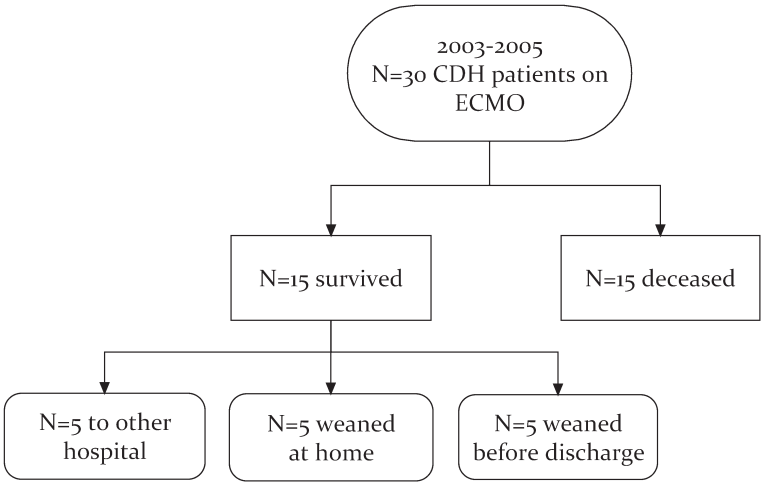


Table 1 Medication (sedatives and analgesics) during hospital stay of survivors (N=15)

	Transferred to other hospital (N=5)		**Weaned before discharge** (N=5)		**Weaned at home** (N=5)	
	Continuous (mcg/kg/hr)	Bolus (mg/kg/day)	Continuous (mcg/kg/hr)	Bolus (mg/kg/day)	Continuous (mcg/kg/hr)	Bolus (mg/kg/day)
Midazolam						
Mean doses	105 (83-318)	2 (0.2-3.9)	110 (81-180)	0.3 (0.1-0.9)	285 (196-330)	5 (0.4-10)
Duration (days)	10 (9-37)	2 (1-46)	21 (6-29)	6 (3-13)	32 (29-88)	66 (4-128)
N	5	3	5	5	5	5
Clonidine						
Mean doses	0.15	2.9			0.3 (0.3-0.5)	8.1 (5.4-14.3)
Duration (days)	25	37			27 (22-40)	74 (20-114)
N	*1*	*1*			3	*4*
Morphine						
Mean doses	9.8 (7-23.9)	0.02	10.5 (4.9-17)		23.3(15.4-36.2)	0.1 (0.07-0.7)
Duration (days)	13 (7-55)	4	15 (10-25)		53 (30-64)	3 (1-13)
N	5	*1*	5		5	*4*
Fentanyl						
Mean doses	2.6	10 (1.7-16.2)*		6.6 (5.7-16.2)*	2.3 (1.5-3)	8.3 (6.3-12.9)*
Duration (days)	11	4 (1-24)		6 (3-9)	19 (10-28)	18 (2-62)
N	*1*	5		5	2	5
Methadone						
Mean doses		1.2				0.6 (0.3-3.9)
Duration (days)		43				78 (19-128)
N		*1*				*4*

* Mean doses fentanyl bolus in mcg/kg/day, mean doses and duration: median (min-max)

Table 2 Weaning medication at home (N=5)

	Type of sedatives / analgesics				PICU stay (days)	Duration of home weaning (days)
	Midazolam	Methadone	Clonidine	Alimemazine		
Patient 1	X	X	X		44	11
Patient 2	X				73	42
Patient 3	X	X			167	107
Patient 4		X	X	X	136	173
Patient 5	X	X	X	X	184	180

X type of agent weaned at home

Discussion

Prolonged exposure to benzodiazepines, opioids and other sedatives has been associated with withdrawal syndrome after abrupt cessation or too rapid tapering off. Our study showed that parents can cope with weaning at home, provided they are given structural medical back up. This is in line with the findings demonstrated in three cases by Tobias *et al.*[9]

Methadone is used increasingly for treatment of opioids withdrawal in infants and children because of its demonstrated efficacy in opioid-dependent adults and infants of drug-addicted mothers. Its enteral administration is easy and it has a long duration of action. Several methadone weaning strategies in PICU patients have been studied prospectively in the past years. These strategies largely vary, however, as they are determined by duration of exposure, type of opioid and practitioner bias and preference.[7,10,13] Robertson *et al.*[13] used a weaning strategy based on duration of exposure. This strategy involved a 20% daily decrease of methadone dose for patients who had been exposed to opioids for 7-14 days, and a 20% decrease every other day for patients exposed longer than 14 days. Successful weaning was achieved in 80% percent (16/20), *i.e.* with minimal withdrawal symptoms regardless of duration of weaning. Another study showed successful weaning from opioids without withdrawal symptoms in 25 of 29 patients over a 10-day period (NAS<8).[10] These patients had received fentanyl for 14.5±9.2 days. Sixteen of them had been discharged to complete their weaning schedule at home, but withdrawal symptoms were not assessed at home. Berens *et al.*[7] performed a RCT comparing two systematic opioid weaning protocols in critically ill children at high risk for opioid withdrawal. They found that opioid-tolerant children could be weaned with oral methadone as effectively in 5 days as in 10 days. Effects of benzodiazepines withdrawal were mostly not taken along in these studies. Moreover, patients in these studies had been exposed to opioids for much shorter times (mean 36 days) than the patients weaned at home in our study (median 53 days). Therefore, weaning strategies must be performed carefully in infants after ECMO therapy.

The first step in preventing withdrawal syndrome is the identification of risk factors. For children in intensive care these factors include high cumulative doses of benzodiazepines and/or opioids,[14,15] long exposure to these drugs, and long duration of ECMO therapy.[3,16]

The next step is careful monitoring of patients found to be at risk of withdrawal symptoms, preferably with the help of an assessment tool. The Neonatal Abstinence Score (NAS) is commonly used.[17] This tool, however, is only applicable for opioid withdrawal. As pediatric patients are also given benzodiazepines, with risk of withdrawal symptoms as well, we have proposed an assessment tool sensitive enough to assess both opioids and benzodiazepines withdrawal symptoms.[2]

A weaning strategy for gradual decreasing opioid and benzodiazepine dosages is essential to prevent withdrawal symptoms. Strategy options include slowly tapering

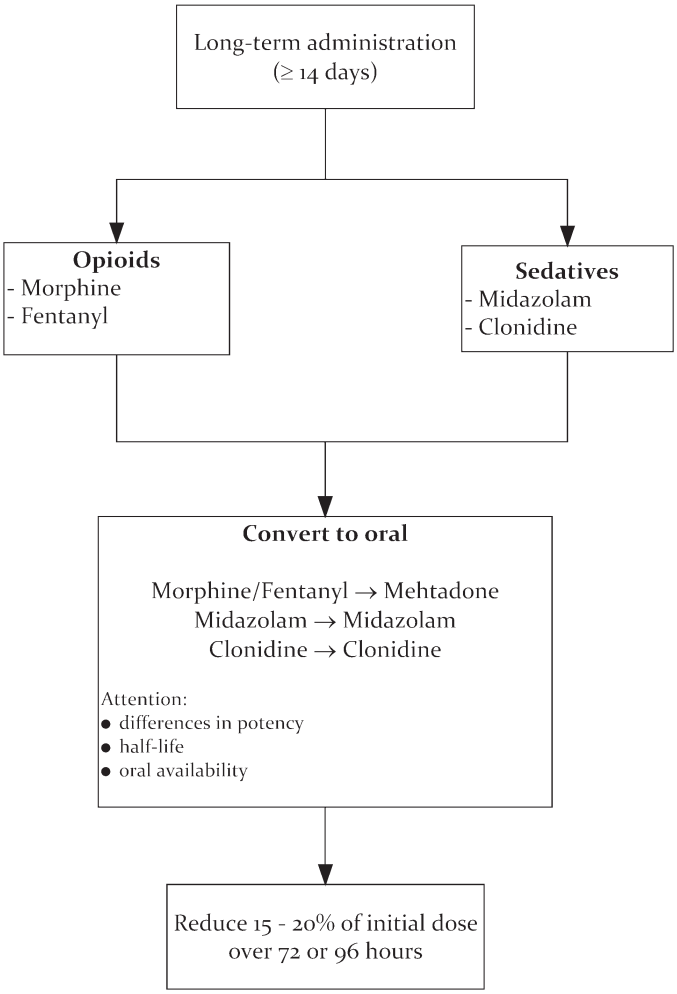
off the intravenous infusion rate over time or using an alternative route, like the subcutaneous or enteral routes. Subcutaneous administration of fentanyl and midazolam has been described in PICU patients.[18] This may be helpful for children who are not yet tolerating enteral nutrition. In line with several other authors we prefer the enteral route for prevention of opioid and benzodiazepine withdrawal because it provides for reliable symptom control and allows for discharge home to complete weaning.[1,10]

Based on our experience we proposed the following steps to wean children from long-term high-dose sedatives and opioids administered by continuous infusion: a) replace intravenous route by enteral route; b) gradually decrease doses by 15 to 20% of initial dose per 72 of 96 hours; c) wean one agent at a time; d) weaning sedatives first, then opioids (Figure 2). At each step in the weaning process, possible withdrawal symptoms should be carefully monitoring with the help of a validated assessment tool applied by nurses in the clinical setting and by parents in the home situation.

Conclusion

Final weaning at home with the aid of weekly telephone consultations with a pediatric intensivist was satisfying for these parents. Nevertheless, they still observed withdrawal symptoms. Weaning of sedation is usually completed in hospital, but home weaning reduces length of hospital stay by a median of 107 days in the five infants presented in this study. This resulted in a €156,220 reduction of health care related costs. Parents should be well informed about the nature of withdrawal symptoms and how to observe these. Parental use of an observation tool such as the SBOWC is highly recommended.

Figure 2 Proposed weaning algorithm



Attention:
- Decrease one agent at a time;
- Observe for withdrawal symptoms.

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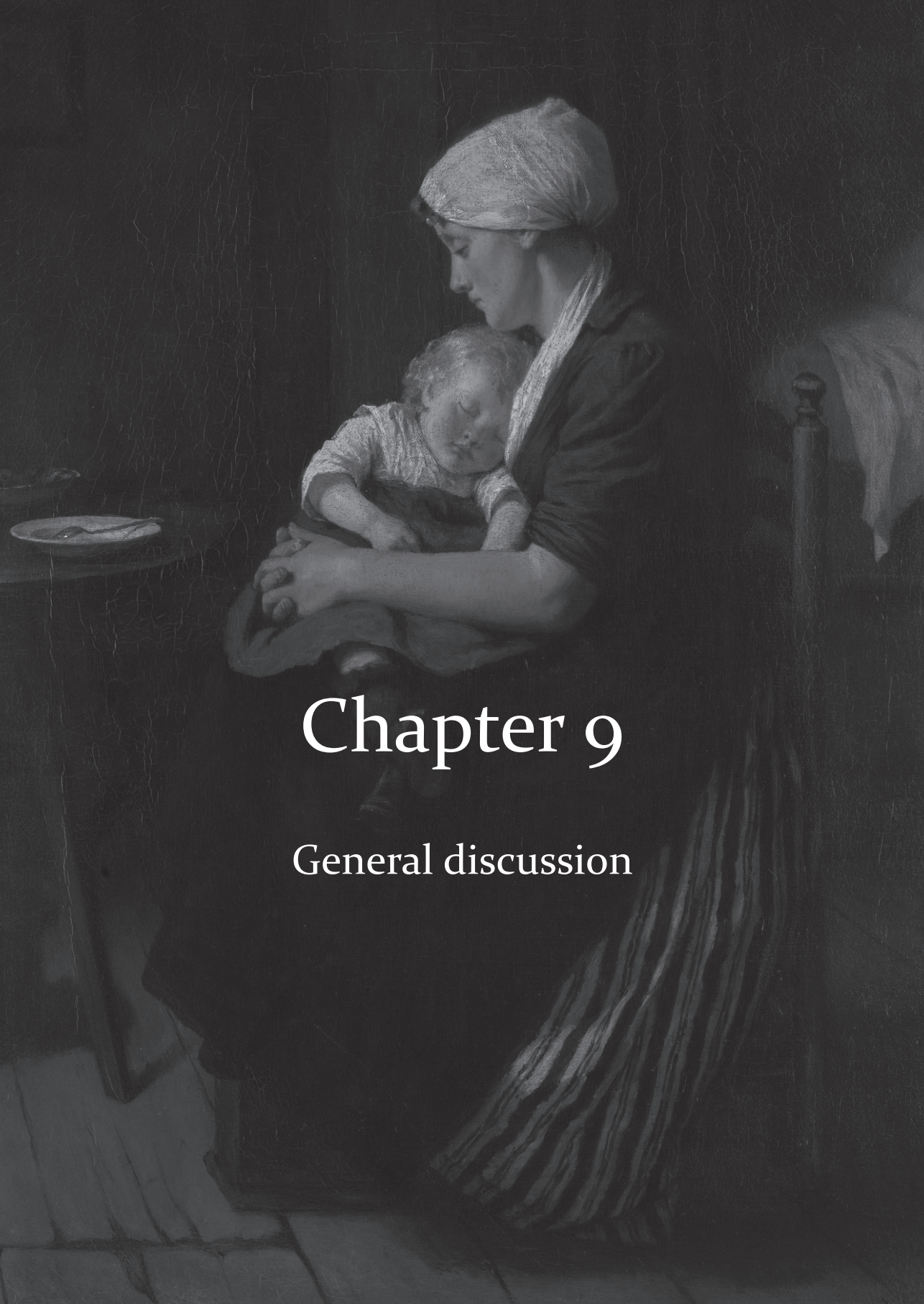

Chapter 9

General discussion

Prologue

The papers presented in this thesis basically concern the question how to provide optimal, consistent sedation and prevent withdrawal in critically ill children - with an important role for the intensive care (IC) nurse.

The overall aims of this thesis were twofold. First, to study strategies by which nurses can accurately assess level of sedation in pediatric intensive care patients. Second, to develop a valid and reliable scoring system for possible withdrawal symptoms after long-term administration of benzodiazepines and opioids. This final chapter evaluates the main findings in relation to other studies and gives suggestions for further research.

What have we learned?

Sedation in critically ill children

In the past decades, several sedation scales have been developed for PICU patients. These are reviewed in Chapter 2.

COMFORT scale

At the time when the studies in this thesis were planned, the COMFORT scale was the most used instrument for assessing pain and sedation level in ventilated children.[1] This observational scale consists of two physiological items - Heart rate and Arterial blood pressure - and six behavioral items - Alertness, Calmness/Agitation, Respiratory response, Physical movement, Muscle tension and Facial tension. The COMFORT scale was originally designed and validated for measuring discomfort in ventilated pediatric patients[2,3] and later also validated for postoperative pain.[4] The COMFORT scale - or the adapted version for postoperative use, COMFORT behavior scale, which does not include the two physiological items - has been applied in a number of randomized controlled trials comparing different types of analgesics or sedatives. Many psychometric properties of this scale have been tested,[5] but some essential information, for instance on sensitivity to change, is still lacking. Validation of scales should therefore be an ongoing process. We chose to use the COMFORT behavior scale because assessment of mean arterial pressure and heart rate would require comparison with baseline values. In critically ill children, however, 'true' baseline values may be confounded by for instance medication such as inotropics, or other confounding variables.

COMFORT behavior scale

In chapter 2 we studied the relationship between behavioral and physiological items of the COMFORT scale in a large sample of PICU patients (N=78) and calculated cutoff scores

after having excluded the physiological items. Nurses' interrater reliability proved to be good, and so was internal consistency, which increased to 0.84 when both physiological items were excluded. Furthermore, concurrent validity of the COMFORT behavior scale was tested by comparison with a 'silver criterion', the Nurse Interpretation of Sedation Score (NISS). COMFORT scores were significantly different for the three categories of the NISS, indicating good concurrent validity.

Cutoff points that may guide treatment are essential to improve the clinical utility of the COMFORT behavior scale. Nevertheless, as well-sedated children do not always show unambiguous behavior, it seemed more realistic to define score ranges rather than cutoff points. Score range 6-10 was defined to indicate oversedation; score range 23-30 was defined to indicate undersedation. Score range 11-22 was defined as a grey area in which a second assessment, for example NISS, is recommended for clinical purposes. We concluded that the COMFORT behavior scale in the PICU setting is reliable and valid to assess children's wellbeing on a sliding scale from comfort to distress or pain.

New sedation tool; State Behavioral Scale versus COMFORT behavior scale

In 2006 Curley and colleagues developed a new sedation assessment tool for mechanically ventilated children, the State Behavioral Scale (SBS).[6] The SBS appraises seven behavioral dimensions; 'Respiratory drive/ response to ventilation', 'Coughing', 'Best response to stimulation', 'Attentiveness to care provider', 'Tolerance to care', 'Consolability' and 'Movement after consoled'.

The psychometric properties of the SBS are presented in Table 1 for comparison with the original COMFORT scale and the COMFORT behavior scale. Curley *et al.*[6] tested its reliability and validity in 198 paired assessments in 91 children aged 6 weeks to 6 years old. The weighted kappa ranged from 0.44 (consolability) to 0.76 (respiratory drive) for the seven SBS dimensions, indicating low to moderate interrater agreement. Cluster analysis yielded five distinct state profiles, with mean numeric rating scale (NRS) ratings of 1.1, 2.5, 4.0, 5.3 and 7.6. The five profiles of each dimensions were significant different with the mean scores on the NRS. With this, the authors supported the discriminant validity of the SBS.

One drawback of the SBS is the necessity of a progressive stimulus with an incremental level (from 'say patient name aloud' to endotracheal suctioning or nail bed pressure). It would seem unethical, for example, to apply nail bed pressure to obtain a reaction from a sleeping child. Furthermore, when the assessment is not performed during suctioning, the observer has to ask the bedside nurse to score this item based on the last suctioning procedure. This may lead to information bias.

Some categories in the SBS and the COMFORT behavior scale share several items. The latter, however, has the advantage of being applicable in non-ventilated high care patients as well. In future research it may be interesting to study both scales simultaneously and compare their psychometric properties in situations such as weaning from mechanical ventilation.

Table 1 Characteristics of the COMFORT (behavior) scale and the State Behavior Scale

Instrument	Parameter measured	Population (age)	Exclusion criteria	Observation items	Score range	Psychometric properties		Cutoff points
					Item / Total	Reliability	Validity	
COMFORT scale[2,3]	Distress	37 (newborn to 17 yrs)	Seriously compromised neurological status[a], Profound mental retardation, Recent multiple trauma, Altered muscle ton or contractures, Severe acute pain	Heart rate, Mean arterial pressure, Alertness, Calmness/agitation, Respiratory response, Physical movement, Muscle tone, Facial expression	Numerical Item: 1 to 5 Total: 8 to 40	$r = 0.84$; $p < 0.01$ (n = 50 paired obs)	COMFORT vs. VAS $r = 0.75$; $p < 0.01$	OS ≤ 16 AS 17 - 29 US ≥ 30
COMFORT behavior scale[7]	Distress / sedation	78 (0 to 16 yrs)	Children with severe mental retardation, Children with severe hypotonia, Patients receiving neuromuscular blockade	Alertness, Calmness/agitation, Respiratory response or crying, Physical movement, Muscle tone, Facial tension	Numerical Item: 1 to 5 Total: 6 to 30	Kappa = 0.77 - 1.0 (n = 40 paired obs) ICC = 0.99	COMFORT behavior vs. NISS (Kruskal-Wallis, $p < 0.001$)	OS ≤ 10 AS 11 - 22 US ≥ 23
State Behavioral Scale[6]	Sedation/ agitation level	91 (6 wks to 6 yrs)	Patients receiving neuromuscular blockade, Postoperative patients, Patients assessed to be in pain, Unstable patients, Patients at risk for opioid withdrawal	Respiratory drive, Coughing, Best response to stimulation, Attentiveness to care provider, Tolerance to care, Consolability, Movement after consoled	Bipolar numeric Item: -3 to +1 Total: -21 to 7	Kappa = 0.44 - 0.76 (n = 198 paired obs) ICC = 0.79	SBS vs. NRS (F = 75.8, $p < 0.001$)	Not done

PICU pediatric intensive care unit, *VAS* visual analogue scale, *NISS*, nurse interpretation of sedation score, *SBS* state behavioral scale, *NRS* numeric rating scale, *Kappa* linearly weighted Cohen's kappa, *r* pearson product correlation coefficient, *yrs* years, *wks* weeks, *obs* observations, *OS* oversedation, *AS* adequate sedation, *US* undersedation, *ICC* intraclass correlation coefficient, *vs.* versus

Sedation protocol

International sedation guidelines promote the use of standardized assessment of sedation levels, both in adults and children.[8,9] Still, the level of evidence is relatively low due to the lack of appropriately conducted randomized controlled trials (RCTs). To improve effectiveness, assessment should be incorporated in a sedation protocol or algorithm. An additional advantage of this strategy is standardized treatment that does not depend on the caregiving nurse or doctor's attitude towards sedation.

In the past years we have seen growing attention to evidence-based practice in nursing (and especially in intensive care). Nurses appear to obtain knowledge from policy and procedure manuals rather than from (research) literature.[10] It follows that protocols and care pathways must be evidence-based, relevant to local contexts and readily accessible to nurses. Several studies support the use of nurse-implemented protocols and guidelines of weaning sedatives or ventilation both in adult[11-16] and pediatric ICUs.[17-20] Some of these studies indeed report significant decreases in dosages of sedatives and duration of mechanical ventilation in adults[11,16] and children[18] after implementation of a nurse-implemented sedation protocol.

Supported by the literature and the need felt in clinical practice, we developed our own sedation protocol.

This sedation protocol shown in Chapter 3 provides decision trees for increasing or weaning of sedatives and analgesics in both hemodynamically stable and unstable patients. It standardizes sedation management and allows nurses themselves to adapt medication based on COMFORT behavior and NISS scores.

Midazolam and morphine dosages increased significantly after implementation of this sedation protocol. The implications of these dosage changes are hard to define. Our studies did not consider the effects on duration of mechanical ventilation and length of ICU stay. Adult studies have shown that daily interruption of sedatives decreases duration of mechanical ventilation and length of ICU stay.[21,22] Future RCTs are needed to study the effects of daily interruption in critically ill children. Nurses may be reluctant, however, to apply such a 'drug holiday', feeling that waking up ventilated critically ill children is inhumane. Good communication may solve this problem.

Implementation of the sedation protocol also increased the proportion of 'adequately sedated' assessments according to the COMFORT behavior scale, *i.e.* from 63% to 75%. On the other hand, the proportion of assessments indicating 'oversedated' decreased from 36% to 23%. Eighty per cent of the nurses who completed a questionnaire on the sedation protocol considered it useful and clear.

Although staff in general was satisfied with the sedation protocol, this was no guarantee of strict adherence. We found that in more than 50% of assessments indicating undersedation the infusion rate was not increased according to the protocol. We conclude, therefore, that adherence is far from perfect. There are several possible reasons

for violations of the treatment algorithm. An important question is: Why don't nurses and physicians adhere to protocols and standardized care? Evidently, in some instances it may be unavoidable to deviate from the protocol, but caregivers may also prefer their own treatment plan, based on intuition and previous experiences. Furthermore, studies have shown that adherence to sedation protocols[23,24] may be hampered by differences in values between protocol's developers and its users, ignorance of aspects of a protocol, and nurses being uneasy with the responsibility for medication changes without specific doctor's order.[23-26]

Another important role for nurses lies in the application of non-pharmacological interventions as complementary treatment. This strategy should be part of standard nursing care; we speculate these interventions may be so effective that sedatives dosing can be reduced. Generally, there is a choice of music therapy, distraction, aromatherapy, and massage therapy.[9,27-30] Massage and music therapy have been found to decrease anxiety in critically ill adults.[31-34] We feel distraction should be offered to children in collaboration with the play specialist. Nevertheless, non-pharmacological interventions are not often used in our ICU. This may be due to several factors, such as insufficient knowledge, lack of evidence, and attitude of nurses regarding the usefulness of complementary treatment. Recently, however, a randomized controlled trial was started in our ICU to compare aromatherapy and massage. This study stimulated the use of massage outside this trial as well.

Another strategy nurses may apply is adaptation of the environment, like noise reduction. Noise is a major environmental factor to cause anxiety and sleep disturbance in critically ill patients.[35,36] In a way, noise reduction could well be effective in decreasing anxiety. It would be worthwhile, therefore, to reduce noise in the PICU as much as possible, so as to create a comfortably calm environment for child and parents.

Bispectral index monitor

Although behavioral sedation scoring tools are valid and reliable, they do not allow continuous evaluation of level of sedation or agitation. The bispectral index (BIS) monitor continuously measures level of consciousness. This method has been extensively investigated in children older than 1 year. We studied the BIS monitor in younger infants, divided into two groups: postoperative sedation and natural sleep (without sedatives). In the postoperative sedation group we found a moderate overall correlation ($r_s = 0.50$) between BIS monitor and COMFORT behavior scale. In the natural sleep group, this correlation for infants 6 to 12 months ($r_s = 0.72$) was better than that for younger infants ($r_s = 0.62$). This suggests that assessing pharmacological sedation with the BIS monitor may be less reliable in infants less than 1 year old. Possibly these children's EEG pattern deviates too much from the adult pattern on which the BIS is based. This forms the most important limitation for the use of BIS monitor in infants.[37-39] Until this major flaw has been amended and a specific BIS algorithm for this age group has been established,

the routine use of the BIS monitor for assessing sedation in children under one year is questionable. Rather than the absolute values, trends in BIS values are potentially more useful in daily clinical practice.

Withdrawal symptoms

Benzodiazepine and opioid withdrawal syndrome remains a significant problem in the PICU, despite increased caregivers' awareness and measures taken to prevent it. The reported incidence of withdrawal syndrome in pediatric ICU patients ranges from 35% to 57%.[40,41] Better understanding of the occurrence of withdrawal symptoms and the risk factors involved is needed. To bridge the knowledge gap, we performed the series of studies presented in the second part of this thesis (Chapter 5-8).

We started our 'expedition' with a literature review that revealed the broad spectrum of opioid and benzodiazepine withdrawal symptoms (Chapter 5). The review yielded 24 such symptoms observable in children in a PICU. Symptoms such as agitation, anxiety, tremors, insomnia, fever, sweating, and tachycardia have been described for both benzodiazepines and opioids withdrawal. Symptoms such as seizure and hallucinations have only been observed as benzodiazepine withdrawal.

Generalization of the identified withdrawal symptoms is hampered by the fact that most are based on case series and case reports, and consequently on small numbers of patients. Furthermore, most studies considered only a few withdrawal symptoms and did not relate symptoms to times when medication was tapered off. Thus, representative incidence numbers of the full spectrum of withdrawal symptoms are lacking. Our next step, therefore, was a prospective study aimed at quantifying the withdrawal symptoms listed in this review, because earlier studies gave insufficient insight in the real incidence of withdrawal syndrome on the PICU.

Incidence and risk factors

In Chapter 6, the 24-items Sophia Benzodiazepine & Opioid Withdrawal Checklist (SBOWC) was used to assess the occurrence of withdrawal symptoms in practice. We created two subgroups of observations. First, a 'weaning group', observations obtained within 24 hours after decrease and/or discontinuation of midazolam and/or opioids. Second, an 'unsuccessful weaning' group. These observations were obtained before midazolam and/or opioids were increased in order to counteract possible withdrawal related symptoms. A particular set of symptoms stood out clearly in a so-called 'unsuccessful weaning' group. These symptoms were: agitation, increased muscle tension, anxiety, grimacing, sleeping less than 1 hour, poor feeding and tachypnea. Although symptoms such as tremors, hallucinations and seizures were rare, they may still have a high positive predictive value.

We found statistically significant correlations between duration of use and total dose of midazolam administration on the one hand, and maximum SBOWC sum score on the

other hand (respectively 0.52 and 0.51). The correlation between total dose of opioids and maximum sum score ($r_s = 0.39$) was moderate. We conclude that both longer duration of administration and higher total doses of midazolam and opioids are clearly related with the occurrence of withdrawal symptoms, and may therefore be considered risk factors. These findings are in line with other studies.[40-43] We suggest that tapering off (weaning) too rapidly increases the risk of withdrawal symptoms. Thus, strategies to reduce the incidence of withdrawal symptoms should begin by making efforts to reduce doses of benzodiazepines and/or opioids. Based on a few prospective studies several authors recommend a daily tapering rate of 10-20% for children on benzodiazepines and/or opioids for more than 5 to 7 days.[43-46] This strategy, however, did not prevent withdrawal symptoms in these studies. There is a great need for effective weaning strategies in clinical practice, which can be used in a PICU, general hospital or in particular circumstances at home. For home weaning we proposed a strategy in Chapter 7, based on our experience.

Withdrawal symptoms scoring tool

For objective assessment of withdrawal symptoms, nurses cannot do without a valid and sensitive tool. Our literature review nevertheless revealed that a good assessment tool for clinical use in children is lacking. The Opioid Benzodiazepine Withdrawal Scale (OBWS) is the only tool with prospective validation, but regrettably shows low sensitivity.[43] Our next step, therefore, was constructing a new scale, the Sophia Observation withdrawal Symptoms-scale (SOS). It is based on the underlying empirical structure of co-occurrences of all previously identified 24 withdrawal symptoms. In addition, experts (physicians and PICU nurses) were asked to indicate relevant and essential symptoms. The final construct contained 15 symptoms. The co-occurrences of these symptoms could be adequately represented in a three-dimensional solution. Nevertheless, the heterogeneity suggested that the symptoms did not constitute homogeneous clusters within the three-dimensional solution, indicating that withdrawal symptoms vary from patient to patient in number, severity and presentation. Many PICU patients, however, show relatively subtle clinical symptoms that can easily be confused with responses to other factors in the PICU. Symptoms such as agitation, anxiety, insomnia, irritability, fever, tachycardia, hypertension, and sweating are also expressions in response to inadequate sedation or pain management, ventilator distress, infection, noisy environment, paradoxical reactions, or delirium.[36,47-50] These key confounders may mask withdrawal symptoms. We maintain that the diagnosis of withdrawal symptoms remains one of exclusion and must be time-related to decrease or cessation of benzodiazepines and/or opioids.

After data collection for the study in Chapter 6, we continued to collect SOS scores in daily practice. The aim was to determine a cutoff for high probability of withdrawal as well as the tool's sensitivity to change. Between July 2006 and November 2007, 440 SOS scores in 16 children with a median age of 6 months (range 0 to 74) were collected. SOS scores of 4 (75th percentile) or higher were taken to reflect a high probability of withdrawal.

Sensitivity to change was confirmed in 26 paired observations before and after administration of extra sedation (*e.g.* midazolam, morphine, clonidine, alimemazine) and showed that: the median SOS score significantly decreased from 6 to 2 (Mann-Whitney test, $Z = -5.79$, $p < 0.0001$). In future research, we will explore interrater reliability more extensively. To this aim, we will collect videotaped material of patients with varying levels of withdrawal. This material will be observed and scored with the SOS by at least eight experienced PICU nurses. Also, we will collect more data to test sensitivity to change.

Recently, a new withdrawal assessment tool has been developed and tested in pediatric ICU patients, the Withdrawal Assessment Tool version-1 (WAT-1).[51] Table 2 presents characteristics of this tool, side by side with those of the SOS. Reliability and validity of both instruments look promising. Validation is a never-ending process and it will be worthwhile to compare the two instruments in a multicenter study.

Transition of care - weaning at home

In selected cases, children do no longer need medical treatment for their primary disease, but remain in hospital, or even in the ICU, for weaning of sedatives or opioids. We assumed that some of these children could be discharged earlier, to continue stepwise weaning at home, albeit supervised by a pediatric intensivist.

We studied the feasibility of this approach in a selective patient group, infants with congenital diaphragmatic hernia treated with extra corporeal membrane oxygenation. They were at risk for development of withdrawal symptoms. Final weaning at home with the aid of weekly telephone consultations with a pediatric intensivist proved satisfying for parents. Nevertheless, some of these children still showed withdrawal symptoms. For the five studied infants home weaning reduced hospital stay by a median of 107 days, which is beneficial for child and parents and reduces costs of hospitalization. We feel it would help parents to apply the SOS as a helpful checklist. Then, if symptoms are confirmed, the proposed weaning schedule could be adjusted.

Table 2 Characteristics of the SOS and the WAT-1

	SOS - Sophia Observation withdrawal Symptoms-scale	**WAT-1 Withdrawal Assessment Tool - version 1**[51]
Scale symptoms	Tachycardia	Loose /watery stools
	Tachypnea	Vomiting/retching/gagging
	Fever (≥ 38.5°C)	Temperature > 37.8°C
	Sweating	State*
	Agitation	Tremor
	Anxiety	Sweating
	Tremors	Uncoordinated/repetitive movement
	Increased muscle tension	Yawning of sneezing
	Inconsolable crying	Startle to touch
	Grimacing	Time to gain calm state (SBS ≤ 0)
	Sleeplessness	
	Motor disturbance:	
	• Slight muscle jerks/twitching or	
	• Uncontrolled, robust movements	
	Hallucinations	
	Vomiting	
	Diarrhea	
Number of items	15	11
Total score	0 - 15	0 - 12
Time to assess	2 minutes	7 minutes
How information obtained?	Patient record, observation (most extreme moment during past 4 hours)	Patient record, observation during: pre-stimulus, stimulus, post-stimulus
Instructions provided?	Yes	Yes
Psychometric evaluation		
Number of patients	79	83
Age patients	3.4 months (0 - 16 years)†	35 months (7 months - 10 years)‡
Number of observations	932	1040
Number of centers included	1	2
Reliability		
Internal consistency	MDS, 3 dimensions	PRINCALS, 4 factors
Interrater	N=23 paired observations	N=30 paired observations
	ICC = 0.97 (95% CI 0.92 to 0.99)	ICC = 0.98
	Cohen's kappa = 0.73 - 1.0 (items)	Cohen's kappa = 0.80
Validity		
Content	85 experts	ND
Construct	+ ∞	sen.= 0.87, spec. = 0.88
Sensitivity to change	+	ND
Cutoff point	SOS ≥ 4	WAT-1 score ≥ 3
Advantages	Development based on empirical structure of co-occurrences and expert opinions	Multi centre
Disadvantages	Single centre	Stimulation (painful) required

*(asleep/awake/calm or awake/distressed), *SBS* state behavioral scale[6], *sen.* sensitivity, *spec.* specificity, *ND* not done, † median (range), ‡ median (IQR), *MDS* multidimensional scaling, *PRINCALS* principle components analysis, ∞ significant correlations between total doses of midazolam /opioids and maximum sum score of withdrawal symptoms[52]

Future research perspectives

The studies in this thesis are part of a larger series of pain and sedation studies from our research group since 1993. On the whole, they have resulted in pain and sedation tools for different groups of patients. In addition, pharmacological studies have improved our knowledge on pharmacokinetics and pharmacodynamics in the developing human being. We hope this thesis will be a source of inspiration for future studies. Several topics of interest present themselves.

- Interrupting sedation by means of daily 'wake-ups', so-called drug holidays. These were found to shorten duration of sedation and ventilation in adult intensive care.[22] RCTs are needed to assess these effects in critically ill children.
- As discussed, several non-pharmacological interventions are recommended for sedation in children. Prospective studies should determine effects of these interventions on pain, distress, and sedatives administration.
- The use of methadone and clonidine as a means to counteract withdrawal symptoms has increased over the last few years - yet without solid data on pharmacokinetics, efficacy and side effects. This warrants further study.
- We suggested that the SOS is a feasible scoring tool for withdrawal symptoms. Psychometric properties such as validity and reliability need to be established in prospective studies.
- Implementation of the SOS in all PICUs in the Netherlands could help increase our knowledge through multicenter studies.

Epilogue

Providing comfort and minimizing anxiety in critically ill children is a very important part of our daily activities as IC nurses. In this thesis we point at possible means to accomplish this in clinical practice, namely assessment tools for sedation and withdrawal syndrome. Judicious use of these tools may indeed prevent inadequate sedation and recognize withdrawal syndrome in time.

Fraser and Riker[53] have remarked, 'it may be time to add the evaluation of sedation, agitation and delirium to that of pain assessment, making all aspects of patients' comfort to the fifth vital sign for the critically ill'. We fully agree with this statement. Assessments of patients' *comfort* should be done before and after a (non-)pharmacological intervention that affects level of comfort. We as IC nurses take care of critically ill children and partly replace the loving care of the parents. We succeed if they say: we're happy to see our child so 'comfortably calm'.

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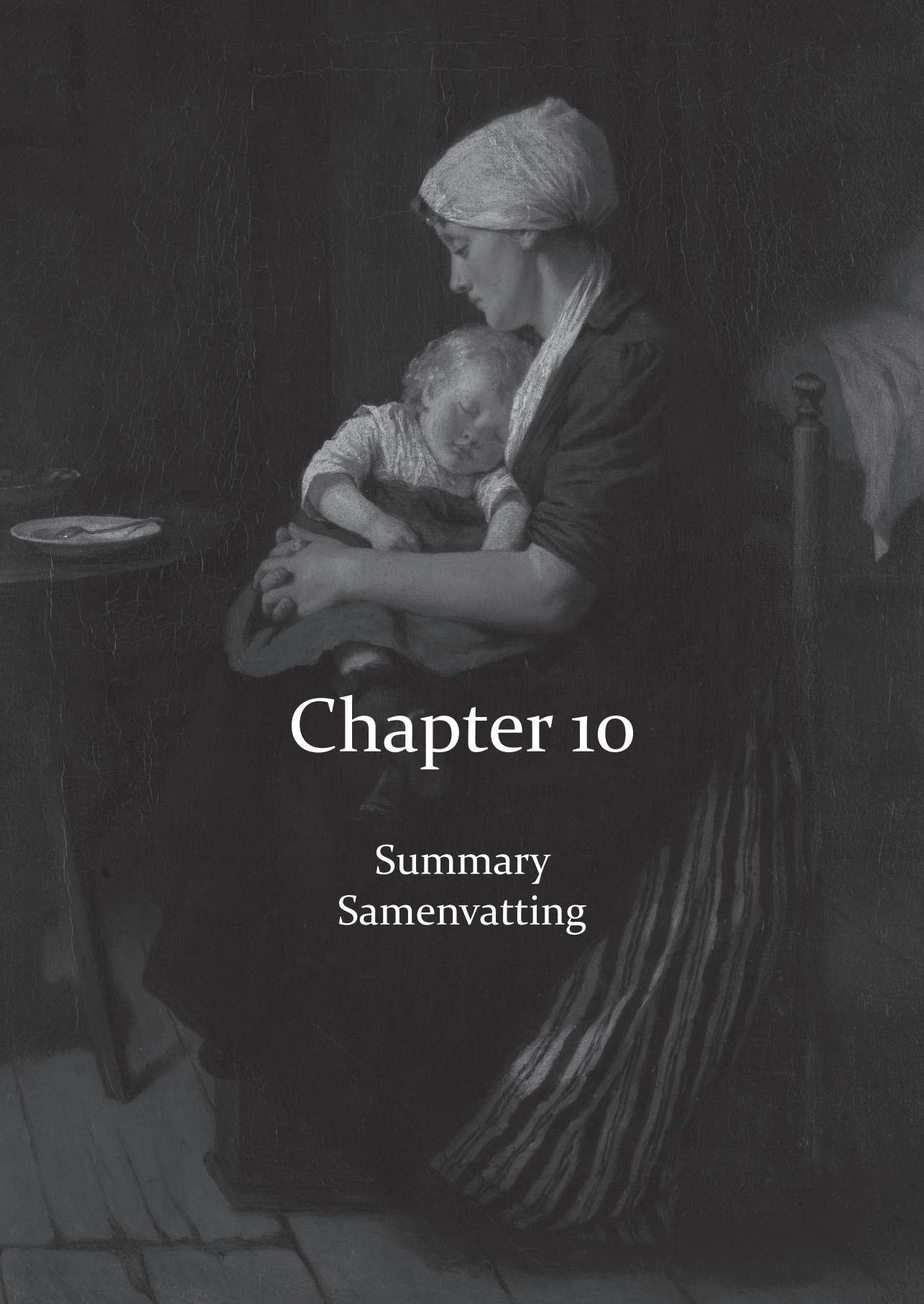


Chapter 10

Summary
Samenvatting

Summary

Critically ill children admitted to an intensive care unit (ICU) are bound to experience some degree of discomfort, distress and pain, more than in other settings in a children's hospital. Inserting intravenous lines, catheters and tubes is a major source of these adverse effects. Other sources are: mechanical ventilation, suctioning of the ventilation tube, removing adhesive plasters and electrodes, as well as manipulating tubes and catheters. In addition, the child may feel threatened by the ICU environment, not being able to communicate, burdened by lights, sounds, noise of alarms going off, and unpredictable events.

In order to achieve that children will experience ICU stay less consciously they will regularly receive sedatives, such as midazolam, and analgesics, such as morphine, fentanyl).

One of the nurse's responsibilities is observing the degree of discomfort and the effect of the sedatives and analgesics used. Adequate sedation is very important. Scoring tools may help to objectivize evaluation. This thesis explores how to best determine depth of sedation in children in an ICU. To this aim we evaluated the application of a scoring tool that assesses sedation depth from the child's behavior, heart rate and blood pressure. In addition we explored the feasibility of developing a standard sedation guideline on the basis of an scoring tool. Finally we evaluated the usefulness of a brain function monitor for determining depth of sedation in young children.

Long-term administration of sedatives and analgesics in critically ill children may lead to various complications. For example, too rapid tapering or abrupt discontinuation of this medication may result in withdrawal symptoms. We therefore studied frequencies of occurrence of withdrawal symptoms in critically ill children. On the basis of the findings we then developed a tool with which nurses can assess withdrawal symptoms.

Sedation of critically ill children

In our studies, nurses assessed levels of sedation of critically ill children with the use of the COMFORT scale. This instrument was opted for because it is a multi-dimensional instrument including both behavioral and physiological stress indicators. The COMFORT scale, for that matter, was originally developed for this purpose. In clinical practice, however, the physiological indicators (heart rate and blood pressure) are influenced by many other factors as well, such as: severity of illness and use of drugs that raise blood pressure.

In *Chapter 2* we evaluated the psychometric properties of the COMFORT scale as well as the relation between behavioral and physiological indicators. We found that nurses were able to reliably observe level of sedation. Interrater reliability appeared to be satisfactory to good for all items of the COMFORT scale.

In total 843 COMFORT scores were obtained for 78 children aged from 0 to 16 years.

The physiological stress indicators, *i.e.* 'Heart rate' and 'Mean arterial blood pressure' showed little variation between measurements. On the other hand we found low statistical correlation with the behavioral items of the COMFORT scale. These items are: 'Alertness', 'Calmness/Agitation', 'Respiratory response' or 'Crying', 'Physical movement', 'Facial tension', and 'Muscle tone'. We concluded that on the basis of the behavioral items, which form the COMFORT behavior scale, nurses are capable of assessing level of sedation in critically ill children in a reliable and valid manner.

As a next step we defined new cutoff points for the COMFORT behavior scale. Score ranges 6 to 10 and 23 to 30 are associated with a high degree of certainty that a child is 'oversedated' or 'undersedated', respectively. The intervening score range 11 to 22 forms a grey area that requires the nurse's clinical expertise expressed in the Nurse's Interpretation of Sedation Score (NISS).

Chapter 3 describes the implementation of a sedation protocol in our pediatric ICU. The aim of a sedation protocol is twofold: on the one side setting uniform policy around sedation, and on the other side facilitating nurses to increase or decrease dosing of sedatives on the basis of the COMFORT behavior scale and the NISS. The ultimate goal is achieving adequate sedation of children in intensive care.

The first step was implementing the COMFORT behavior scale as standard assessment tool for sedation. Next we developed a sedation protocol in the shape of decision-trees for increasing and decreasing dosing of sedatives and/ or analgesics, based on the cutoff points of the COMFORT behavior scale and the NISS. After implementation of the sedation protocol the use of sedatives and the application of the protocol was evaluated. Nurses' routine assessment of sedation depth in critically ill children in intensive care appeared to be feasible. The first follow-up measurement showed that after implementation mean doses of midazolam and morphine had significantly increased. Correspondingly, the proportion of observations with the indication 'adequately sedated' rose from 63 to 75%. In almost half of the observations in which the patient was found undersedated on the basis of the cutoff points, doses of sedatives were increased on the guidance of the 'increase decision-tree'. In very few observations medication was tapered off on the guidance of the 'decrease decision-tree'. In spite of the fact that the steps in the sedation protocol are not always followed correctly, the large majority of the nurses assert that the sedation protocol (decision-trees) is clear and well applicable in practice.

It is of importance that nurses regularly assess level of sedation in children in intensive care. This should prevent complications or too deep or inadequate sedation. There is no gold standard, however, for the assessment of sedation in very young children or in children who cannot communicate verbally. Self-report is the gold standard for older children and adults. In our target group behavioral observation instruments are the only instruments so far. The COMFORT behavior scale is one of those. A relatively new

method to measure sedation depth is the brain function monitor. The bispectral index (BIS) monitor is a brain function monitor that can reflect depth of narcosis and sedation. The technique of the brain function monitor is based on the principle that the wave patterns of an electroencephalogram (EEG) change with different level of consciousness. If a person is deeply sedated, the frequency decreases and the amplitude increases. The monitor generates a number on a continuous scale of 0-100, with 0 indicating cortical electrical silence. The BIS has been extensively evaluated in adults and children during narcosis and during ICU stay. It proved valuable to this aim. Its use in children younger than one year staying in the IC is still underdocumented. In *Chapter 4* we report a study on assessment of state of consciousness in two groups of children younger than one year. Assessment was both by the BIS and the COMFORT behavior scale. One group of 39 children was studied during postoperative sedation. Correlation between the BIS and the COMFORT behavior scale proved moderate. Further more it appeared that sedation level measured with the BIS corresponds best with the item 'Alertness' of the COMFORT behavior scale. This is not surprising, seeing that this item serves to assess state of consciousness. In the second group of 32 children in medium care we assessed state of consciousness during natural sleep state. BIS values were found to be less accurate in determining state of consciousness, especially in the younger children aged from 0 to 6 months. As an illustration, when children were deeply asleep as assessed with the COMFORT behavior scale, the BIS monitor generated values indicative of an alert and awake child. We encountered the reverse of this phenomenon as well. From this study we concluded that in view of the typical EEG pattern of children younger than one year - deviating from that of older children and adults - the BIS is not reliable enough to serve as a gold standard for assessing level of sedation.

Withdrawal in children in intensive care

Chapter 5 provides an overview of the English-language literature on withdrawal symptoms in children in intensive care and available instruments to ascertain this phenomenon in children aged from 0 to 16 years. An emphasis was placed on studies that describe symptoms of withdrawal as a consequence of long-term administration of benzodiazepines and/ or opiates.

Long-term use of benzodiazepines and/or opiates may result in physical dependence and withdrawal symptoms. Withdrawal occurs when drugs (sedatives/analgesics) are tapered off too rapidly in children who have developed physical dependence. Symptoms of benzodiazepines- and opiates withdrawal can broadly be distinguished into three groups: overstimulation of the central nervous system (CNS) and autonomous disregulation. A third group is gastro-intestinal symptoms, which have only been described in opiates withdrawal.

Two assessment tools have been designed to assess withdrawal symptoms in children:

Sedation Withdrawal Score (SWS) and the Opioid Benzodiazepine Withdrawal Scale (OBWS). We came to the conclusion that neither is sufficiently valid and reliable for use in the pediatric ICU.

The literature search yielded 24 possible symptoms of withdrawal in the above mentioned three main categories. As a valid tool to assess frequencies of occurrence of withdrawal was lacking, we compiled a checklist including these 24 symptoms, the Sophia Benzodiazepine & Opioid Withdrawal Checklist (SBOWC). On the guidance of the SBOWC we performed 2188 observations in 79 children *(Chapter 6)*. These children had been receiving midazolam, morphine or fentanyl for five days or longer. Of all observations, 932 had been performed within 24 hours after medication had been tapered off. CNS overstimulation symptoms anxiety, agitation, grimacing, disturbed sleep pattern, increased muscle tension, and movement disorder were observed in over 10% of observations. Of gastro-intestinal symptoms, diarrhea and food retention occurred most frequently. Tachypnea, fever, sweating and hypertension as symptoms of autonomous disregulation were observed in more than 13% of the observations. Furthermore, we established correlations between total amount of midazolam, duration of midazolam use and number of withdrawal symptoms (maximum sum score) per patient. This allowed us to conclude that longer duration of use and high dosing are risk factors for development of withdrawal symptoms in critically ill children. This study provided a comprehensive overview of frequencies of occurrence of all 24 different withdrawal symptoms after tapering off or cessation of benzodiazepines and/or opiates in children. It was concluded, too, that the SBOWC required further validation in order to develop it into a clinically useful tool.

For this reason we performed a psychometric validation study on the basis of the SBOWC. Apart from psychometric evaluation, we aimed at reducing the number of symptoms included in the checklist, leaving only the essential ones in an assessment tool for withdrawal symptoms. The construction of the Sophia Observation withdrawal Symptoms-scale (SOS) is described in *Chapter 7*. The underlying clinical-empirical structure of the interrelationship of the 24 withdrawal symptoms was explored with a statistical method called multidimensional scaling (MDS). Input parameters were the observations made after weaning of medication in the preceding study (*Chapter 6*). Withdrawal symptoms such as 'agitation', 'anxiety', sleeplessness', 'movement disorder' and 'increased muscle tension' showed the highest interrelationships. Nevertheless, the MDS analyses yielded insufficient evidence for reduction of number of symptoms. Some symptoms, such as 'tremors' and 'hallucinations', are very specific to withdrawal, but occurred infrequently. We therefore asked a panel of experts, both pediatric intensive care nurses and pediatric intensivists, to rate the relevance of each of the 24 withdrawal symptoms. By combining the results from this survey with the findings of the MDS analysis we were able to reduce the number of symptoms relevant to a withdrawal scale

to 15. This stepwise approach enabled us to construe the SOS in a meticulous manner. Further reduction of the number of withdrawal symptoms would seem inadvisable, as we know from experience that withdrawal in critically ill children has diverse manifestations. Further studies are required to validate the SOS and to define cutoff points to be included in a treatment algorithm that provides for adequate treatment of children showing withdrawal symptoms.

Research indicates that specific types of patients have higher risk of developing withdrawal symptoms. Higher risk is mainly associated with high dosing and long-term administration of sedatives and analgesics administered to provide comfort. For example, newborns with congenital diaphragmatic hernia who undergo extra corporeal membrane oxygenation are at higher risk. Since 2003 these children may be eligible for earlier discharge from hospital, and continue gradual drug weaning at home under the supervision of a consultant pediatric intensivist. In weekly telephone calls the parents of these children report possible withdrawal symptoms, where upon recommendations on dose decreases are given. *Chapter 8* reports the results of a first evaluation study among five children weaned at home. The strategy of final weaning with the aid of weekly telephone consultations with a consultant pediatric intensivist was feasible and satisfying for the parents involved. Weaning at home provides an opportunity to reduce length of hospital stay. In the future it would be advisable to ask parents to use the SOS in the home situation.

In *Chapter 9* the findings from the studies reported in this thesis are discussed with a view on future perspectives.

Samenvatting

Het noodgedwongen verblijf van ernstig zieke kinderen op een intensive care (IC) afdeling is, meer nog dan in andere settings binnen een kinderziekenhuis, een bron van ongemak, onrust en pijn. Ze staan bloot aan een reeks pijnlijke en stressvolle prikkels, zoals het inbrengen van infusen, katheters en sondes, de beademing, het wegzuigen van slijm uit de beademingsbuis, en het verwijderen van pleisters en elektrodes. Daarbij kunnen ze onrustig worden door de hectiek van de kinder-IC met alle licht, lawaai en onvoorspelbare gebeurtenissen. Daarbij zijn ze vaak ook nog in een positie waarin ze dit alles niet kunnen communiceren.

Om kinderen het verblijf op een IC minder bewust te laten ervaren krijgen ze regelmatig kalmerende middelen (sedativa, zoals midazolam) en pijnstillers (analgetica, zoals morfine, fentanyl) toegediend. Adequate sedatie is heel belangrijk. Een van de verantwoordelijkheden van de verpleegkundigen is dan ook het observeren van de mate van ongemak en het effect van de gebruikte sedativa en analgetica. Om dit te objectiveren kunnen speciale observatie-instrumenten worden gebruikt. In dit proefschrift hebben we onderzocht hoe de diepte van sedatie bij kinderen op een IC het best kan worden bepaald. Voor dit doel is de toepassing geëvalueerd van een observatie-instrument dat de mate van sedatie bepaalt aan de hand van gedrag, hartslag en bloeddruk van het kind. Tevens hebben we onderzocht of het mogelijk is om op basis van dit observatie-instrument een sedatierichtlijn te ontwikkelen. Tenslotte is gekeken of een hersenfunctiemonitor (BIS) bruikbaar is voor het bepalen van de diepte van sedatie bij jonge kinderen.

Langdurige toediening van sedativa en analgetica kan leiden tot allerlei complicaties. Zo kan te snel afbouwen of abrupt stoppen van deze medicatie leiden tot ontwenningsverschijnselen. We hebben daarom onderzocht hoe vaak dit soort ontwenningsverschijnselen voorkomt bij ernstig zieke kinderen op de IC. Daarnaast is een meetinstrument ontwikkeld waarmee verpleegkundigen de ontwenningsverschijnselen kunnen scoren.

Sedatie van ernstig zieke kinderen

Verpleegkundigen kunnen de diepte van sedatie van ernstig zieke kinderen bepalen met de COMFORT schaal. Er is voor dit instrument gekozen omdat het een multidimensioneel instrument is met zowel gedrag- als fysiologische stressindicatoren. De gedragsitems zijn: 'alertheid', 'kalmte', 'reactie op beademing' of 'huilen', 'lichaamsbeweging', 'gelaatsspanning' en 'spierspanning'. Als fysiologisch indicatoren worden hartslag en bloeddruk gemeten. De COMFORT schaal is oorspronkelijk voor dit doel ontwikkeld. Echter in de klinische praktijk worden hartslag en bloeddruk ook beïnvloed door vele andere factoren, zoals: mate van ziek zijn en gebruik van bloeddrukverhogende medicijnen.

In *Hoofdstuk 2* hebben we de psychometrische eigenschappen van de COMFORT

schaal geëvalueerd en de relatie tussen gedrag- en fysiologische indicatoren. We vonden dat verpleegkundigen op een betrouwbare manier het sedatieniveau konden observeren. De interbeoordelaarsbetrouwbaarheid bleek voldoende tot goed te zijn voor alle items van de COMFORT schaal.

Van 78 kinderen, in de leeftijd van 0 tot 16 jaar, werden in totaal 843 COMFORT scores verzameld voor dit onderzoek. De fysiologische stressindicatoren, 'hartslag' en 'gemiddelde arteriële bloeddruk' vertoonden weinig variatie gedurende de metingen. Aan de andere kant vonden we geringe statistische samenhang van deze indicatoren met de gedragsitems van de COMFORT schaal. We kwamen tot de conclusie dat met een schaal die alleen de gedragsitems bevat, de zogenaamde COMFORT gedragschaal, de verpleegkundige betrouwbaar en valide het niveau van sedatie bij ernstige zieke kinderen kan bepalen.

Vervolgens hebben we nieuwe beslispunten gedefinieerd voor de COMFORT gedragschaal. De mogelijke score loopt uiteen van 6 tot 30. Bij scores van 6 tot 10 en 23 tot 30 kan met een hoge mate van zekerheid worden gesteld dat een kind respectievelijk 'overgesedeerd' dan wel 'ondergesedeerd' is. Verder is er een grijs gebied voor scores van 11 tot 22. Om in dit gebied te kunnen vast stellen of een kind adequaat gesedeerd is, is de klinische expertise van de verpleegkundige nodig, uitgedrukt in de Verpleegkundige Interpretatie Sedatie Score (VISS).

Hoofdstuk 3 beschrijft de implementatie van een sedatieprotocol op onze kinder-IC. Het primaire doel van dit sedatieprotocol is tweeledig. Enerzijds om te komen tot een uniform beleid rondom sedatie, en anderzijds om de verpleegkundigen de mogelijkheid te geven op basis van de COMFORT gedragschaal en de VISS sedatie op te hogen dan wel te verlagen. Vanzelfsprekend is het uiteindelijke doel: er voor te zorgen dat kinderen op een IC adequaat gesedeerd zijn.

Allereerst is de COMFORT gedragschaal als een standaard meetinstrument voor sedatie geïmplementeerd. Vervolgens hebben we een sedatieprotocol ontwikkeld, bestaande uit beslisbomen voor verhogen en verlagen van sedativa en/of analgetica, gebaseerd op de beslispunten van de COMFORT gedragschaal en de VISS. Na de implementatie van het sedatieprotocol is het gebruik van sedativa en de toepassing van het protocol geëvalueerd. Uit de eerste nameting bleek dat de kinderen nu gemiddeld significant hogere doseringen midazolam en morfine kregen toegediend. Het percentage metingen met de kwalificatie 'adequaat gesedeerd' steeg van 63 naar 75%. In bijna de helft van de metingen, waarbij de patiënt volgens de beslispunten ondergesedeerd was, werden sedativa volgens de 'beslisboom-ophogen' verhoogd. In een zeer gering percentage werd volgens de 'beslisbomen-verlagen' medicatie afgebouwd. Ondanks dat de stappen in het sedatieprotocol niet altijd correct worden gevolgd, geeft een overgrote meerderheid van de verpleegkundigen aan dat het sedatieprotocol begrijpelijk en toepasbaar is in de praktijk.

De verpleegkundigen dienen de mate van sedatie bij kinderen op een IC regelmatig te bepalen. Dit om complicaties van te diepe of inadequate sedatie tegen te gaan. Voor kleine kinderen of kinderen die verbaal niet kunnen communiceren is dit echter moeilijk. Waar voor volwassen zelfrapportage als de gouden standaard wordt gezien, vormden bij onze doelgroep observatie-instrumenten voor het gedrag tot voor kort de enige mogelijkheid. De COMFORT gedragschaal is er daar één van. Er is nu echter een betrekkelijk nieuwe manier, het gebruik van de Bispectral index (BIS) hersenfunctiemonitor. De techniek van de hersenfunctiemonitor is gebaseerd op het principe dat de golven van een elektro-encefalogram (EEG) veranderen bij een verschillend niveau van bewustzijn. Als een persoon diep gesedeerd is neemt de frequentie af en de amplitude toe. De hersenactiviteit wordt omgezet in een numerieke waarde van 0 tot 100. Bij 0 is er een volledige onderdrukking van het EEG. De BIS is uitgebreid onderzocht en waardevol gebleken bij volwassenen en kinderen tijdens narcose en op de IC. Het gebruik van de BIS monitor bij kinderen jonger dan één jaar op de IC is nog onvoldoende onderzocht. In *Hoofdstuk 4* beschrijven we een onderzoek naar de waarde van de BIS monitor voor het meten van de diepte van sedatie bij kinderen jonger dan één jaar. Voor dit doel keken we naar de relatie tussen de BIS-waarden en de COMFORT gedragschaal scores. Dit werd voor twee verschillende groepen gedaan. De eerste bestond uit 39 kinderen die voor postoperatieve sedatie op onze kinder-IC lagen. Bij deze groep vonden we een matige samenhang tussen de BIS monitor en de COMFORT gedragschaal. Verder bleek dat het sedatieniveau gemeten met de BIS het beste overeenkomt met het item 'alertheid' van de COMFORT gedragschaal. Dit is ook begrijpelijk omdat 'alertheid' refereert aan het bewustzijn. De tweede groep bestond uit 32 gezonde kinderen. Bij deze kinderen werd de bewustzijnstoestand tijdens slapen en wakker zijn gemeten. Vooral bij de kinderen van 0 tot 6 maanden was het bewustzijnsniveau met de BIS monitor minder goed te bepalen. Als ze diep in slaap waren volgens de COMFORT gedragschaal werden met de BIS monitor waarden gemeten die horen bij een staat van alertheid en wakker zijn. Het omgekeerde van dit fenomeen zagen we ook. De belangrijkste conclusie was derhalve dat het EEG patroon van kinderen jonger dan 1 jaar zo afwijkt van dat van oudere kinderen en volwassen dat voor hen de BIS monitor onvoldoende betrouwbaar voor het bepalen van de mate van sedatie.

Ontwenning bij kinderen op IC

Hoofdstuk 5 geeft een overzicht van de Engelstalige literatuur op het gebied van ontwenningsverschijnselen bij kinderen op een intensive care en de beschikbare instrumenten voor verpleegkundigen om dit fenomeen bij kinderen vast te stellen. De nadruk lag op artikelen die de symptomen beschrijven van ontwenning als gevolg van langdurige toediening van benzodiazepinen en/of opiaten. Voor de meetinstrumenten werd gekeken of ze geschikt zijn voor kinderen in de leeftijd van 0 tot 16 jaar.

Langdurige toediening van benzodiazepinen en/of opiaten kan lichamelijke afhankelijkheid en ontwenningsverschijnselen veroorzaken. Ontwenning (afkicken)

treedt op wanneer deze medicijnen te snel worden afgebouwd bij kinderen met lichamelijke afhankelijkheid. De symptomen van benzodiazepinen- en opiatenontwenning zijn te verdelen in drie groepen: overprikkeling van het centraal zenuwstelsel en autonome disregulatie. Een derde groep bestaat uit gastro-intestinale symptomen, maar die zijn alleen bij opiatenontwenning beschreven.

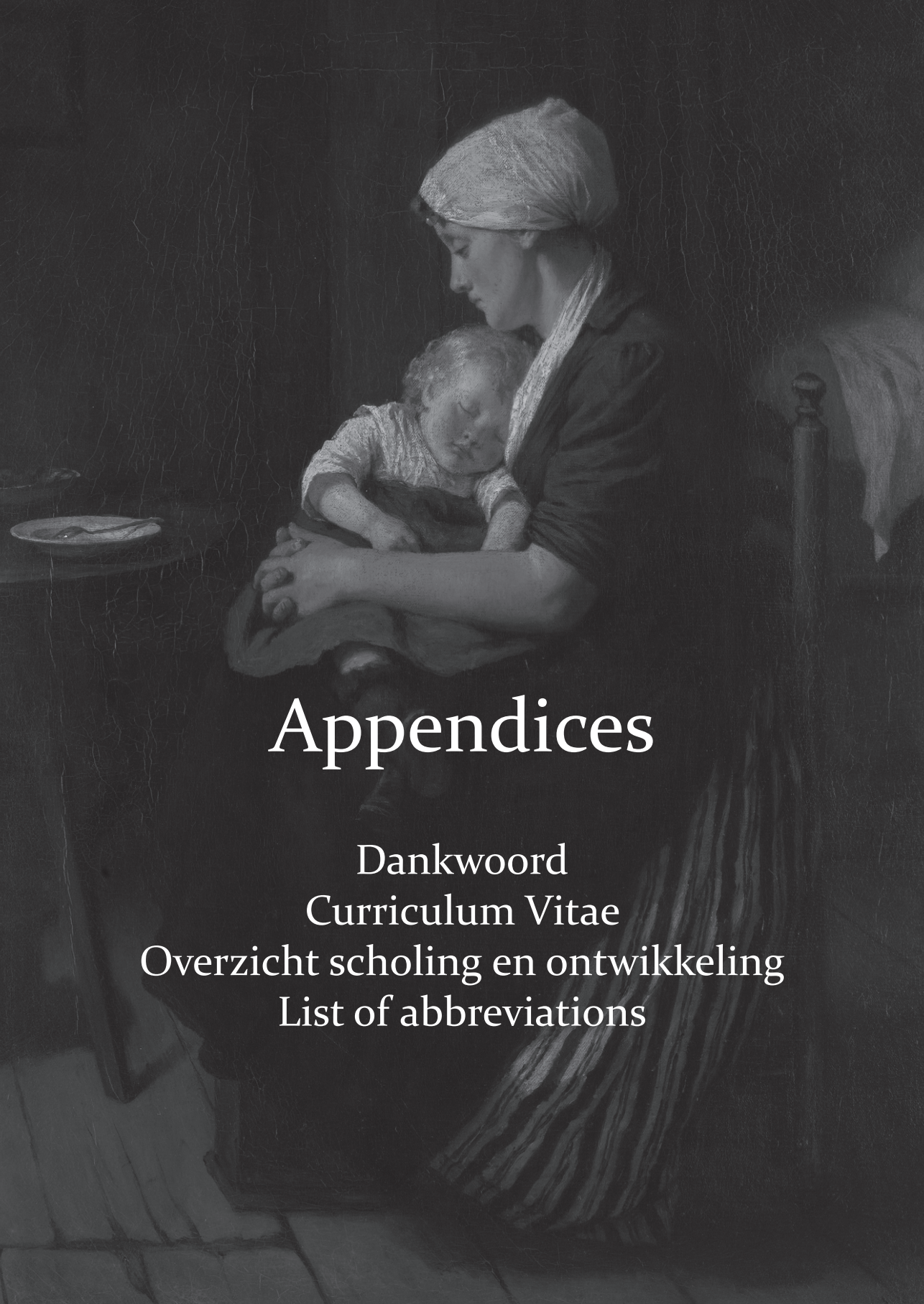
Er bestaan twee meetinstrument om ontwenningsverschijnselen op de kinderleeftijd te bepalen: Sedation Withdrawal Score (SWS) en de Opioid Benzodiazepine Withdrawal Scale (OBWS). We hebben vastgesteld dat beide meetinstrumenten onvoldoende valide en betrouwbaar zijn voor gebruik op de kinder-IC.

Het literatuuronderzoek leverde 24 verschillende symptomen van ontwenning op. Omdat er geen valide meetinstrument voorhanden was om de frequentie van voorkomen van ontwenningsverschijnselen te onderzoeken, hebben we met deze 24 symptomen een checklist gecreëerd, en hiermee 2188 observaties uitgevoerd bij 79 kinderen (*Hoofdstuk 6*). Deze kinderen kregen al minimaal vijf dagen midazolam, morfine of fentanyl toegediend voor hun comfort of pijnstilling. Van deze observaties waren er 932 uitgevoerd binnen 24 uur na afbouw van genoemde medicatie. Binnen de hoofdgroep 'overprikkeling centraal zenuwstelsel' werden angst, agitatie, grimassen, verstoord slaappatroon, toegenomen spierspanning en motorische onrust in meer dan 10% van de observaties waargenomen. Als gastro-intestinale symptomen kwamen diarree en voedingsretentie het meest voor. Tachypnoe, koorts, zweten en hypertensie werden in meer dan 13% van de observaties waargenomen als uiting van autonome disregulatie. Verder bleek er verband te zijn tussen de totale hoeveelheid midazolam, aantal dagen midazolam gekregen en het aantal ontwenningsverschijnselen per patiënt. Daarmee kunnen we stellen dat langere duur van toediening en een hogere totale dosis midazolam of opiaten risico's vormen voor het optreden van ontwenningverschijnselen bij ernstig zieke kinderen. Ons onderzoek geeft een volledig overzicht van de frequentie van voorkomen van elk van de 24 mogelijke ontwenningsverschijnselen na afbouwen en/of stoppen van benzodiazepinen en/of opiaten bij kinderen. Om te komen tot een valide en betrouwbaar instrument waarmee verpleegkundigen ontwenningsverschijnselen kunnen vast stellen bij ernstig zieke kinderen is nader onderzoek gedaan naar de gebruikte checklist. De centrale vraag hierbij was: hoe kunnen we een goed onderbouwd instrument ontwikkelen en kan het aantal symptomen worden teruggebracht tot de belangrijkste, die werkelijk nodig zijn voor een meetinstrument ontwenningsverschijnselen. De constructie van de Sophia Ontwenningsverschijnselen Scorelijst (SOS) wordt beschreven in *Hoofdstuk 7*. Met behulp van een statistische procedure, multi-dimensionale schaaltechnieken (MDS), is gekeken naar de onderlinge samenhang van de 24 symptomen. Hiervoor zijn de observaties na afbouw van medicatie uit het vorige onderzoek (hoofdstuk 6) gebruikt. We vonden dat ontwenningsverschijnselen zoals 'agitatie', 'angst', slapeloosheid', 'motorisch onrust' en 'toegenomen spierspanning' de grootste onderling samenhang

vertoonden. Sommige symptomen zoals 'tremoren' of 'hallucinaties' zijn zeer specifiek voor ontwenning, maar kwamen weinig voor. Daarnaast hebben we aan kinder-intensive care verpleegkundigen en kinder-intensivisten gevraagd het belang van elk van de 24 afzonderlijke ontwenningsverschijnselen aan te geven. Door deze resultaten te combineren met de resultaten van de MDS procedure konden we het aantal relevante symptomen terugbrengen tot 15. Vervolgonderzoek is nodig om de SOS te valideren en beslispunten te definiëren zodat kinderen met ontwenningsverschijnselen op een IC ook adequaat behandeld kunnen worden.

Uit eerder onderzoek is bekend dat bepaalde groepen patiënten een verhoogd risico hebben op het ontwikkelen van ontwenningsverschijnselen. Dit wordt voornamelijk veroorzaakt door hoge doseringen en langdurige toediening van sedativa en analgetica die nodig zijn om er voor te zorgen dat ernstig zieke kinderen comfortabel zijn. Een voorbeeld van een dergelijke risicogroep zijn pasgeborenen met een aangeboren afwijking van het middenrif (congenitale hernia diafragmatica) die een ECMO (extra corporale membraan oxygenatie) behandeling ondergaan. Tijdens het afbouwen van de sedativa en analgetica bij deze kinderen kunnen ontwenningsverschijnselen optreden. Enige jaren geleden is besloten om sommige van deze kinderen eerder te ontslaan uit het ziekenhuis en dan thuis de medicijnen langzaam af te bouwen. Over een periode van 2 jaar (2003 - 2005) kwamen hiervoor vijf kinderen in aanmerking. Dit afbouwen gebeurde onder begeleiding van een arts van de intensive care. De ouders van deze kinderen hadden wekelijks telefonisch contact met de arts om de ernst van de ontwenningsverschijnselen te bespreken alsmede de mogelijkheid om de dosering te verlagen. In *Hoofdstuk 8* worden de resultaten van dit evaluatieonderzoek besproken. Het blijkt goed mogelijk te zijn om onder begeleiding van een arts in de thuissituatie medicatie af te bouwen bij kinderen met ontwenningsverschijnselen. Hierdoor kunnen kinderen eerder uit het ziekenhuis worden ontslagen wat leidt tot een verkorting van de opnameduur op een kinder-IC. Het verdient nadere overweging om ook ouders in de thuissituatie de SOS te laten gebruiken.

In *Hoofdstuk 9* worden de resultaten van dit onderzoek in toekomstperspectief besproken.



Appendices

Dankwoord
Curriculum Vitae
Overzicht scholing en ontwikkeling
List of abbreviations

Dankwoord

Toen ik in 2002 met 'mijn eerste onderzoek' begon en tegelijk startte met de studie verplegingswetenschappen had ik het niet voor mogelijk kunnen houden dat zes jaar later dit boekje er zou liggen. Het is dan ook alleen maar gelukt met de hulp en bijdragen van vele anderen. Graag wil ik deze onmisbare krachten persoonlijk bedanken.

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Curriculum Vitae

Erwin Ista werd geboren op 17 februari 1973 te St. Maartensdijk. Na opleidingen LTS, MTS en propedeuse HTS begon hij in 1993 aan de opleiding tot A-verpleegkundige en behaalde het diploma in 1997. Hij volgde daarna de specialistische vervolgopleiding tot kinderverpleegkundige (1998) en de vervolgopleiding intensive care neonatologie/ kinderen (2000) in het Sophia Kinderziekenhuis. Van 2002 tot en met 2006 studeerde hij in deeltijd verplegingswetenschappen aan de Universiteit Utrecht. Hij behaalde het doctoraalexamen cum laude in 2006. Voor zijn afstudeerscriptie 'Sedativa en Pijnstilling; Ontwenningsverschijnselen op de Kinder-IC' ontving hij de Talma Eykman Prijs van het Universitair Medisch Centrum Utrecht. De prijs werd toegekend wegens de bijzondere kwaliteit van het door hem verrichte wetenschappelijk onderzoek.
Vanaf 2000 tot heden is hij werkzaam op de afdeling IC Kinderen - voorheen Intensive Care Pediatrie - van het Erasmus MC - Sophia te Rotterdam. Eerst als kinder-IC verpleegkundige en sinds 2006 als zorgonderzoeker.

Vanuit zijn functie als kinder-IC verpleegkundige is hij zich vanaf 2002 bezig gaan houden met de kwaliteit van sedatie bij ernstig zieke kinderen. Het bepalen van de diepte van sedatie bij kinderen door verpleegkundigen is een onderdeel hiervan. De verschillende onderzoeken in het kader hiervan hebben geleid tot dit proefschrift.

Hij is getrouwd met Anneke Heiwegen en heeft 2 kinderen, Annelot (2004) en Frederiek (2006).

Overzicht scholing en ontwikkeling

Scholing

Jaar	Activiteit	Instelling	Belasting (ECTS)
2006	Randomized Controlled Trials, Challenges and Pitfalls	Erasmus MC	
2006	Minicursus Methodologie van patiëntgebonden onderzoek en voorbereiden subsidieaanvraag	Erasmus MC	
2007	Academic writing in English for PhD students.	Erasmus Universiteit	1.5
2007	Erasmus Summer program, cursus Regressie analyse.	Erasmus MC	1.4
2008	Erasmus Winter program, Pediatric Drug Research	Erasmus MC	1.4

Ontwikkeling

Jaar	Activiteit	Waar	Belasting (uren)
2003	Congres bezoek en (voorbereiding) voordracht: 'Validation of an abbreviated COMFORT Scale for assessing sedation in PICU patients'	World Congress on Paediatric Intensive Care, Boston	36
2004	Congres bezoek en (voorbereiding) voordracht: 'Usefulness of a sedation algorithm for critically ill children'	ESPNIC congress, London	32
2004	Congres bezoek en (voorbereiding) voordracht: 'Successful early enteral feeding of critically ill children'	ESPNIC congress, London	32
2005	Congres bezoek en (voorbereiding) voordracht: 'Withdrawal symptoms of sedatives and analgesics in PICU'	Efccna congress, Amsterdam	32
2006	Congres bezoek en (voorbereiding) voordracht: 'Occurrence of withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics in PICU'	ESPNIC congress, Barcelona	36

List of abbreviations

ABP	Arterial blood pressure
BIS	Bispectral index
CDH	Congenital diaphragmatic hernia
CI	Confidence interval
CNS	Central nervous system
CPG	Clinical practice guideline
ECMO	Extra corporeal membrane oxygenation
EEG	Electroencephalogram
GCS	Glasgow coma scale
GI	Gastrointestinal
HR	Heart rate
IC	Intensive care
ICC	Intraclass correlation coefficient
ICU	Intensive Care Unit
IQR	Interquartile range
MAP	Mean arterial blood pressure
MDS	Multidimensional scaling
NAS	Neonatal Abstinence Score
NISS	Nurse interpretation of sedation score
NMBA	Neuromuscular blocking agent
NRS	Numeric rating scale
OBWS	Opioid Benzodiazepine withdrawal Scale
PDMS	Patient data management system
PICU	Pediatric intensive care unit
PIM	Pediatric Index of Mortality
Pk	Prediction probability coefficient
PRINCALS	Principle components analysis
PRISM	Pediatric Risk of Mortality Score
PROXSCAL	Proximity scaling
RCT	Randomized control trial
SBOWC	Sophia Benzodiazepine & Opioid Withdrawal Checklist
SBS	State Behavioral Scale
SD	Standard deviation
SE	Standard error
SOS	Sophia Observation withdrawal Symptoms-scale
SQI	Signal Quality Index
SWS	Sedation Withdrawal Score
VAS	Visual Analogue Scale
WAT-1	Withdrawal Assessment Tool - version 1