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Eight Years Later, Are We Still Hurting Newborn Infants?

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Key Words
Procedures · Pain · Neonatology · Analgesia

Abstract
Objective: To study whether new pharmacological and nonpharmacological guidelines lowered numbers of painful procedures in neonates and changed the amount and frequency of analgesic therapy as compared to the results of our previous study in 2001. ***Design:*** A prospective observational study. ***Setting:*** Level III NICU of the Erasmus MC-Sophia Children's Hospital, Rotterdam. ***Participants:*** Neonates admitted at postnatal ages less than 3 days with length of stay at least 72 h. ***Main Outcome Measures:*** Number of all potentially painful procedures and analgesic therapy recorded at the bedside during the first 14 days of NICU stay. ***Results:*** A total number of 21,076 procedures were performed in the 175 neonates studied during 1,730 patient-days (mean 12.2). The mean number of painful procedures per neonate per day was 11.4 (SD 5.7), significantly lower than the number of 14.3 (SD 4.0) in 2001 ($p < 0.001$). The use of analgesics was 36.6% compared to 60.3% in 2001. Sixty-three percent of all peripheral arterial line insertions failed versus 37.5% in 2001 and 9.1% venipunctures failed versus 21% in 2001. ***Conclusions:*** The mean number of painful procedures per NICU patient per day declined. Nonpharmacological pain- or stress-reducing strategies like NIDCAP and sucrose were fully embedded in our pain management. As further reduction of the number of painful procedures is unlikely, we should apply more nonpharmacological interventions and explore newer pharmacological agents.

Introduction

In 2001, in a prospective study on procedural pain and analgesia in our level 3 NICU, neonates underwent a mean of 14.3 painful procedures a day [1]. In 2008, the EPIPPAIN study reported a median of 115 procedures during a study period of 14 days; in almost 80% of cases analgesics were not given [2]. Johnston et al. [3] in 2010 reported a drop in the number of tissue-damaging procedures in Canadian NICUs over a 12-year period; still, half of the procedures were performed without analgesics. In our previous study, 60.3% of patients were given analgesics [1]. Caregivers may be reluctant to prescribe analgesics to neonates for fear of adverse effects, drug tolerance and dependence. Moreover, dosing guidelines and pharmacokinetic data on common drugs for neonates of different gestational ages and birthweights are often lacking [4].

Neonates can feel pain from 23 to 24 weeks' gestation [5], and early exposure to repetitive untreated pain portends immediate and long-term consequences on behavioral and neurological outcome [6–8]. Animal and human studies have shown significant risk for neurological im-

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pairment, besides learning, cognitive and behavioral effects [8, 9]. If this holds true for the longer term is not known because longitudinal data are largely lacking. De Graaf et al. [10] showed negative effects on cognitive functioning in 5-year-old children who as a neonate received morphine. In 2001, we introduced NIDCAP on our ward, placing a focus on nonpharmacological pain management [11, 12]. Several guidelines for procedural pain management in neonates have been published since our previous studies [1]. As a result of this, we routinely administer sucrose 24% orally before painful procedures such as heel lancing, line insertion, and retinopathy screening since 2005. Sucrose has been proven to alleviate pain in mildly to moderately painful procedures in neonates [13–16].

Based on the results of our former study, current pain management includes repeated pain assessments with the COMFORTneo Scale (Appendix 1), analgesic treatment according to a decision tree (Appendix 2), NIDCAP care, and other nonpharmacological pain-relieving interventions.

In the current study, we evaluated whether these policy changes lowered the number of notably painful procedures and investigated what types of procedures often failed. Finally, we quantified analgesic therapy and compared findings with those from the previous study.

Methods

Data Collection

The study design was prospective and observational. From February 6, 2009, to August 5, 2009, nurses and medical staff collected bedside data on all procedures (successful and failed) children underwent during the first 14 days of admission to the level III NICU of the Erasmus MC-Sophia Children's Hospital Rotterdam, the Netherlands. Patients older than 3 days at admission and those transferred or discharged within 72 h after admission were excluded. Data collection for children discharged from the unit between 4 and 14 days was stopped on the day of discharge.

A procedure was defined as any medical, nursing, surgical, diagnostic or therapeutic intervention. Invasive or painful procedures were defined as interventions that cause mucosal or skin injury from removal or introduction of foreign material [2]. Pain guidelines of our Department prescribe sucrose for minimal invasive or mild to moderate painful procedures and opioids for invasive and severe painful procedures (chest tube insertion). Intubations are performed with propofol. All procedures are conducted with parental or caregiver containment (NIDCAP).

Per calendar day, data were recorded on a case record form and combined with the electronic patient's chart data in the Patient Data Management System® (PDMS). Data included background characteristics, type and duration of respiratory support and CRIB® (Clinical Risk Index for Babies) scores [17], as well as administration of pain medication.

Data on analgesics and pain scores during the study days were retrieved from the PDMS. Nurses assessed the neonates' pain with the Numeric Rating Scale (NRS; from 1 to 10) and the COMFORTneo Scale at least once during every 8-hour shift [18, 19]. The COMFORTneo Scale has been validated, and its cutoff value for pain is a score of 14 and higher combined with an NRS score of 4 and higher. A COMFORTneo score of 14 and higher combined with an NRS score below 4 is considered a sign of distress and not pain. Extra assessments are performed after administration of sedatives or analgesics, or if pain, or over- or undersedation are suspected.

The performed study was purely observational. No additional tests or interventions were done. According to the Dutch law, no ethical approval was necessary in this purely observational trial.

Statistical Analysis

Numbers of procedures were counted per calendar day and corrected for the actual length of stay on the first and last study days. Data are presented as mean (SD) for normally distributed variables and as median (interquartile range) for nonnormally distributed variables. Numbers of painful procedures and background characteristics were compared between 4 gestational age groups (24–28, 29–32, 33–36 and 37–42 weeks) using ANOVA with Bonferroni correction. Findings from 2001 are compared with those of 2009 using the independent t test for continuous variables and the χ^2 test for proportions. Analyses were performed with the SPSS statistical program (v17.0).

Results

Patients

Table 1 lists the background characteristics of the 175 enrolled neonates. Mean gestational age was 31.6 weeks (range 24 1/7 to 41 6/7 weeks); 37.1% had a gestational age less than 29 weeks; median birthweight was 1,770 g, and 26.3% patients were small for gestational age.

The overall CRIB score was 2.7 (SD 2.6) on a 0–10 scale. Sixty percent of all patients received conventional ventilation or high-frequency oscillation/ventilation as maximum ventilatory support. The incidences of IRDS, intraventricular hemorrhage and patent ductus arteriosus were highest (81.5, 26.2 and 49.2%, respectively) in infants with a gestational age less than 29 weeks. Asphyxia was diagnosed in 8 patients (26.7%) in the age group of 37–42 weeks and in 6 patients (13.1%) with a gestational age less than 37 weeks. Nine patients (5.1%) died during the study period.

Compared to the study population of 2001, the present population included significantly more preterm infants (145/175 vs. 104/151 patients in 2001, p = 0.003).

Incidences of Procedures

Table 2 shows the incidences of procedures in this study and in the 2001 study, ranked in order of frequency

Table 1. Background characteristics

	Total population (n = 175)	24–29 weeks (n = 65; 37.1%)	30–32 weeks (n = 49; 28.0%)	33–36 weeks (n = 31; 17.7%)	37–42 weeks (n = 30; 17.1%)
Male	89 (50.9)	28 (43.1)	23 (46.9)	19 (61.3)	19 (63.3)
Birthweight, g	1,775 (1,080–1,380)	935 (710–1,110)	1,405 (1,188–1,705)	2,200 (1,725–2,620)	3,545 (3,277–3,962)
Small for gestational age	46 (26.3)	20 (30.8)	18 (36.7)	7 (22.6)	1 (3.3)
CRIB score	2.7±2.6	4.5±3.0	1.3±1.7	1.8±1.9	2.2±1.6
Maximum respiratory support					
Mechanical ventilation	105 (60.0)	58 (89.2)	18 (36.7)	14 (45.2)	15 (50.0)
CPAP/noninvasive ventilation	36 (51.4)	7 (10.8)	21 (67.7)	6 (35.3)	2 (13.3)
Nasal prongs	16 (47.1)	–	5 (50.0)	6 (54.5)	5 (38.5)
No respiratory support	18 (10.3)	–	5 (10.2)	5 (16.1)	8 (26.7)
Duration of maximum respiratory support					
Days on mechanical ventilation	4 (1–9)	5 (1–13)	2 (1–4)	3 (1–4)	4 (3–5)
Days on CPAP	4 (2–7)	9 (3–14)	3 (4–5)	3 (2–4)	1 day both
Days on nasal prongs	3 (1–5)	–	5 (2–10)	2 (2–3)	1 (1–8)
IRDS	76 (43.4)	53 (81.5)	14 (28.6)	8 (25.8)	1 (3.3)
Asphyxia	14 (8.0)	3 (4.6)	1 (2.0)	2 (6.5)	8 (26.7)
Intraventricular hemorrhage	20 (11.4)	17 (26.2)	1 (2.0)	1 (3.2)	1 (3.3)
Patent ductus arteriosus	42 (24.0)	32 (49.2)	4 (8.2)	2 (6.5)	4 (13.3)
Surgery during study period	8 (4.6)	6 (9.2)	–	1 (3.2)	1 (3.3)
Died during study period	9 (5.1)	5 (7.7)	1 (2.0)	1 (3.2)	2 (6.7)

Data are presented as n (%), median (IQR) or mean ± SD. CPAP = Continuous positive pressure ventilation; IRDS = infant respiratory distress syndrome.

established in the 2001 study. The total number of procedures in the current study was 21,076 during 1,730 patient-days or mean 12.2 per patient-day. The mean number of painful procedures per neonate per day equaled 11.4 (SD 5.7) versus 14.3 (SD 4.0) in 2001 ($p < 0.001$). Broken down for age groups, it was highest in age group 24–29 weeks at 14.1 (SD 5.2), followed by age group 30–32 weeks at 9.9 (SD 3.8) and age group 33–36 weeks at 9.1 (SD 5.7).

Suctioning (endotracheal, nasopharyngeal and nasal) was the most frequent painful procedure, comprising 60.3% of all procedures versus 63.6% in 2001.

The second most commonly performed procedure was heel lancing, comprising 10.7% of all procedures versus 7.1% in 2001. Nasal pharyngeal tube insertion accounted for 3.3% of all procedures in 2009 versus 2.4% in 2001; intubation for 0.6% of all procedures versus 0.9% in 2001.

Sixty-three percent of all peripheral arterial line insertions failed versus 37.5% in 2001. Umbilical arterial line insertions failed in 49.5% of cases, umbilical venous line insertions in 36.6% of cases (34.6% in 2001). Intravenous cannula insertions failed in 38% of cases versus 30.9% in 2001, venipuncture in 9.1 versus 21% in 2001 (fig. 1). Of all intubations 22.5% needed more than 1 attempt.

Although the present population included significantly more preterm infants, the mean number of painful procedures was lower in the age groups of 30–32.6 weeks (12.0 in 2001 vs. 9.9 in 2009) and 33–36.6 weeks (12.3 vs. 9.1 in 2009) but not in the more premature infants of 24–29.6 weeks (15.2 in 2001 vs. 14.0 in 2009).

Analgesics

Sixty-four neonates (36.6%) received one or more doses of analgesics. Twenty-one of those (12%) received rectal paracetamol during a median of 2 days (range 1–11 days). Forty-eight neonates (27.4%) received continuous morphine, whether or not combined with bolus morphine for a median of 3 days (range 1–12 days); 8 of those underwent an operation during the study period. Three neonates received fentanyl as bolus medication 1–3 times (fig. 2).

Pain Assessments

Almost all patients (169; 96.6%) underwent pain assessment during the study period, i.e. a median of 16 assessments (range 1–61) per patient. The number of COMFORTneo assessments was 2,962 during 1,690 patient-

Table 2. Incidences of procedures in 2001 and 2009, with frequencies per infant per day and p values comparing frequencies

Procedure	Percent of total procedures		Frequency per infant per day (mean ± SD)		SDM	p value
	2001 (n = 151)	2009 (n = 175)	2001	2009		
Nasal suctioning	31.2	31.6	4.5±2.3	3.4±2.2	0.49	<0.001
Endotracheal suctioning	23.0	23.0	3.3±4.0	2.5±3.5	0.21	0.06
NPT suctioning	9.4	5.7	1.3±2.4	0.6±1.2	0.37	<0.001
Heel lancing	7.1	10.7	1.0±1.6	1.5±1.1	0.36	0.001
Intravenous cannula insertion	3.8	3.2	0.5±0.6	0.4±0.3	0.21	0.06
Nasogastric tube insertion	3.8	1.9	0.5±0.6	0.2±0.1	0.70	<0.001
Intravenous cannula removal	3.2	2.2	0.5±0.7	0.3±0.2	0.39	<0.001
Nasogastric tube removal	3.1	1.0	0.4±0.5	0.1±0.1	0.83	<0.001
X-ray	2.9	2.8	0.4±0.9	0.3±0.3	0.15	0.17
NPT insertion	2.4	3.3	0.3±0.6	0.4±0.4	0.20	0.08
Failed intravenous cannula insertion	1.7	2.0	0.2±0.9	0.2±0.3	0	1.0
Laxative or enema	1.2	1.1	0.2±0.5	0.1±0.1	0.28	0.01
Nasal oxygen cannula insertion	1.0	1.0	0.2±0.4	0.1±0.2	0.32	0.004
Intubation	0.9	0.6	0.1±0.4	0.08±0.08	0.07	0.52
Peripheral arterial line insertion	0.8	0.4	0.1±0.3	0.05±0.07	0.23	0.04
Extubation	0.7	0.5	0.1±0.3	0.06±0.08	0.18	0.09
Peripheral arterial line removal	0.6	0.3	<0.1±0.3	<0.1±0.06		
Failed peripheral arterial line insertion	0.5	0.8	<0.1±0.5	<0.1±0.06		
Venipuncture	0.4	0.2	<0.1±0.3	<0.1±0.1		
Insertion umbilical line	0.4	0.3	<0.1±0.2	<0.1±0.05		
Removal umbilical line	0.3	0.4	<0.1±0.2	0.1±0.1		
Failed umbilical line insertion	0.2	0.2	<0.1±0.2	<0.1±0.06		
Insertion central line	0.2	0.4	<0.1±0.2	<0.1±0.05		
Insertion chest tube	0.1	0.2	<0.1±0.2	<0.1±0.1		
Failed central line insertion	0.1	0.2	<0.1±0.2	<0.1±0.09		
Venipuncture attempt	0.1	0.02	<0.1±0.2	<0.1±0.03		
Removal central line	0.1	0.2	<0.1±0.1	<0.1±0.05		
Removal chest tube	0.1	0.07	<0.1±0.1	<0.1±0.04		

NPT = Nasopharyngeal tube; SDM = standardized mean difference.

days, corresponding to 1.7 per patient-day. Out of 2,962 assessments, 2,901 involved complete assessments meaning COMFORTneo, NRS pain and NRS distress scores. In 88.9% of the cases, all three scores were low or at least acceptable. In 4.8% of assessments, the COMFORTneo was 14 or higher, but none of the NRS was >3. In 3.7 of cases, both COMFORTneo and NRS distress were high, but NRS pain was <3. In 1% of the assessments, all three scores were too high. Of our complete cases of 2,901 assessments, 89.2% included standard pain assessments; in 7.1%, the reason for assessment was suspected pain or distress. 2.8% of assessments were performed after a pain- or distress-reducing intervention. In 0.6% (n = 17), the reason to assess was suspected oversedation. Finally, only 8 assessments were performed after an acute painful procedure. Ninety infants out of the 169 (53.2%) had at least once a COMFORTneo score of 14 or higher.

Possible reasons for high scores were NEC (n = 7), skin related (n = 5), delivery related (n = 3, breech and vacuum extraction), thorax drainage (n = 2), postoperative (n = 2) and others (n = 8).

Discussion

Our analysis revealed that the mean number of painful procedures per patient per day had statistically significantly declined from 14.3 in 2001 to 12.2 in 2009. Studies from NICUs in different countries likewise have shown a similar trend with a range from 6 to 17.3 procedures per

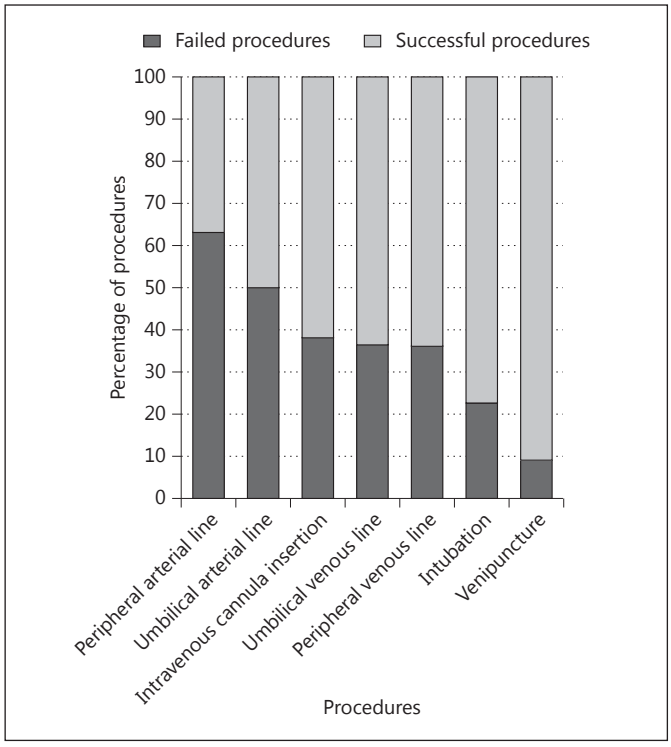


Fig. 1. Percentages of failed and successful procedures.

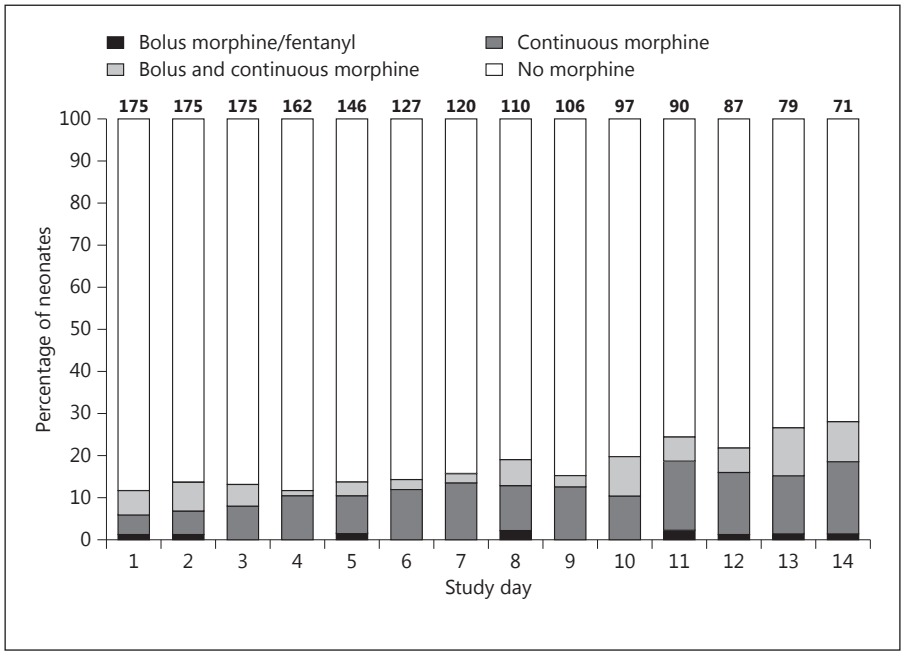


Fig. 2. Pharmacological analgesic treatment. The numbers of neonates are printed in bold.

patient per day [1–3, 19–21]. Suctioning, venous catheter placement and heel lancing are most frequent across all settings. In our NICU, endotracheal suctioning still accounts for 23.0% of all procedures (same in 2001) and is comparable with the 23.3% reported in the EPIPPAIN study, even though we stopped routine suctioning of mechanically ventilated neonates after 2003 [2].

The nasopharyngeal tube insertion rate increased from 2.4 in 2001 to 3.3% in the current study, and the number of intubations dropped from 0.9 (2001) to 0.6%

of all procedures in 2009. This may be due to the introduction of noninvasive ventilation in 2008. Introduction of propofol as premedication for intubation explains the lesser number of failed intubations in 2009. Compared to the 2001 cohort, we included more preterm infants in the current study but the more preterm infants (24–29.6 weeks) unalterably need the highest number of painful procedures due to their unstable condition in the first period of life. It remains a source of concern that adequate care for our patients still involves on average 11 painful events per day.

In 2001, 60.3% of neonates received analgesics, especially opioids, versus 36.6% in 2009. This significant drop is the result of study findings showing that routine administration of morphine in ventilated neonates had no beneficial effects on pain expression and neurologic outcome [22–24]. A follow-up study described negative effects of neonatal morphine administration on cognitive functioning at age 5 years [10]. Preemptive use of opioids in preterm newborns has not been properly studied. Morphine might be beneficial when pain is present, but could be neurotoxic in the absence of pain, as suggested in animal studies [9]. Intravenous paracetamol administration might be an alternative but is used off label and may be unsafe unless future PK/PD studies prove otherwise. In the meantime, we should focus on expanding the range of pharmacological and nonpharmacological pain treatment. As to the latter, we have already experience with sucrose and NIDCAP interventions such as positioning, swaddling, nonnutritive sucking, and kangaroo care. Furthermore, our pain management guidelines enabled caregivers in the current study to respond immediately when painful procedures were carried out or pain was suspected. All above measures together might explain the high percentage (89%) of low COMFORTneo scores (<14). In only 2.4% of the pain assessments was the child perceived to be in pain, attributable to pain conditions such as NEC and severe skin lesions. We have every reason to believe, therefore, that we did not undertreat or misdiagnose neonatal pain.

Two study strengths can be identified. First, the second study was conducted in the same level 3 NICU. Second, nursing and medical staff participated in both studies using the same case record forms.

Strikingly, however, the frequency of failed procedures did not decline over the years. An explanation might be that since 2008 more extremely premature infants (gestational age <27 weeks) were admitted and survived on our ward. Nowadays, the critically ill patients and extremely premature infants stay on our ward and undergo the highest number of painful procedures during the first 14 days of life. The high frequency of failed procedures might also be explained by the reduction of the training period for residents on the NICU, so they have less opportunity to gain experience.

Several limitations of this study should be addressed. First, to compare our results with our former study, we did not distinguish between painful and stressful procedures, like Carbajal et al. [2] did. A further distinction between skin breaking and non-skin-breaking procedures would also have been interesting as the former were recently related to white matter changes and brain development on MRI scans at term-equivalent age of ex-premature neonates [25]. Second, during painful procedures, we used sucrose and containment according to our pain guidelines but no other nonpharmacological interventions such as skin-to-skin care or breastfeeding. Thirdly, we found that routine administration of sucrose was not always documented in the patient's chart. A detailed sucrose prescription is now added in the electronic patient chart safeguarding a more accurate report of the daily used doses of sucrose. Furthermore, this study was a single-center study, and not a multiple-center study like in 2001, which could give limited generalizability of these data. And finally, we cannot exclude that (failed) interventions or administration of analgesics went unrecorded.

Conclusions

Our new pharmacological and nonpharmacological pain management has only minimally but statistically significantly ($p < 0.001$) reduced the number of daily painful procedures. It will be hard to achieve further reduction. The findings from the present study were the reason to change our policy: only experienced senior neonatal nurses, nurse practitioners and neonatologists/fellows are allowed to perform procedures on extremely preterm infants in the first postnatal period. We also set up an intravenous access team, started a training program and introduced new support devices to identify reliable venous and arterial access.

Pain and distress management has become a key issue for the daily care in our NICU. In the future, we should focus on individualized pain management and collect data on pharmacokinetics and pharmacodynamics of analgesics in (extremely) preterm neonates.

Appendix 1

COMFORTneo Scale.

Please tick the appropriate response

Alertness

1 ☐ quiet sleep (eyes closed, no facial movement)
2 ☐ active sleep (eyes closed, facial movement)
3 ☐ quietly awake (eyes open, no facial movement)
4 ☐ actively awake (eyes open, facial movement)
5 ☐ awake and hyperalert

Calmness/agitation

1 ☐ calm (appears lucid and serene)
2 ☐ slightly anxious (shows slight anxiety)
3 ☐ anxious (appears agitated but remains in control)
4 ☐ very anxious (appears very agitated, just able to control)
5 ☐ panicky (severe distress with loss of control)

Respiratory response (only in mechanically ventilated children)

1 ☐ no spontaneous respiration
2 ☐ spontaneous respiration on ventilator
3 ☐ unrest or resistance to ventilator
4 ☐ actively breathes against ventilator or coughs regularly
5 ☐ fights ventilator

Crying (only in spontaneously breathing children)

1 ☐ no crying
2 ☐ faint crying
3 ☐ soft crying or moaning
4 ☐ hard crying
5 ☐ intense crying or screaming

Body movement

1 ☐ no or minimal movement
2 ☐ up to three slight arm and/or leg movements
3 ☐ more than three slight arm and/or leg movements
4 ☐ up to three vigorous arm and/or leg movements
5 ☐ more than three vigorous arm and/or leg movements, or whole body

Facial tension

1 ☐ facial muscles fully relaxed, relaxed open mouth
2 ☐ normal facial tension
3 ☐ intermittent eye squeeze and brow furrow
4 ☐ continuous eye squeeze and brow furrow
5 ☐ facial muscles contorted and grimacing (eye squeeze, brow furrow, open mouth, nasal-labial lines)

(Body) muscle tone (observation only)

1 ☐ muscles fully relaxed (open hands, dribbling, open mouth)
2 ☐ reduced muscle tone; less resistance than normal
3 ☐ normal muscle tone
4 ☐ increased muscle tone (clenched hands and/or clenched, bent toes)
5 ☐ extreme muscle tone (rigidity and flexion of fingers and/or toes)

Total score_____
Details medication/treatment _____
Details child's condition _____
Type of assessment _____

COMFORTneo Scale

Date: _____

Time: _____

Observer: _____

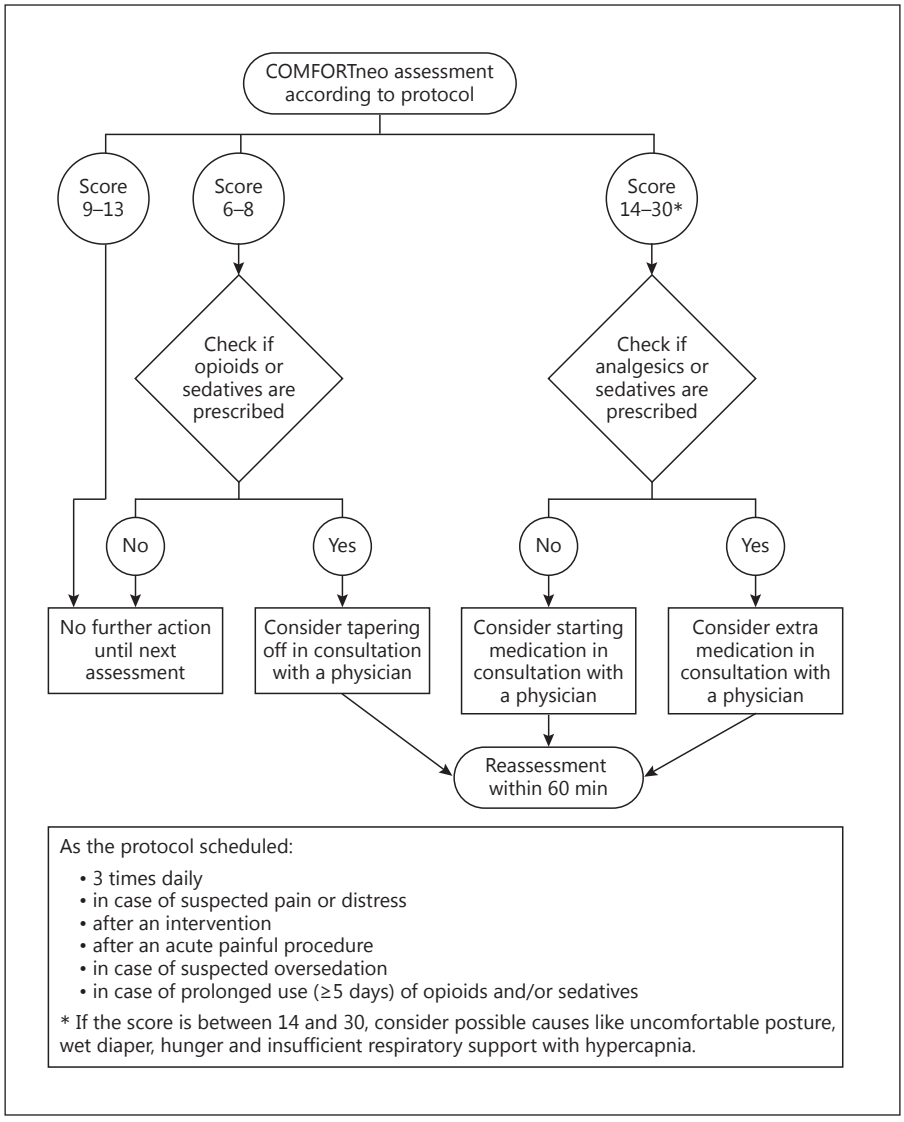
patient sticker

Estimate of pain (0 = no pain to 10 = worst possible pain)	☐
Estimate of distress (0 = no distress to 10 = worst possible distress)	☐

COMFORTneo Scale version 4, April 2005

Appendix 2

Decision tree.



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