Analgesic and sedative pharmacotherapy in asphyxiated neonates treated with therapeutic hypothermia: a cool retrospective study

Abstract

Background: Adequate pain management for asphyxiated neonates treated with therapeutic hypothermia is fundamental to maximise the efficacy of this treatment. Multiple factors contribute to its complexity, including the rapidly maturing physiology of neonates and altered pharmacokinetics during hypothermia, resulting in an increased risk of drug toxicity or therapy failure.

Objective: The aim of this study was to describe and analyse the prescribing behaviour of analgosedative pharmacotherapy by neonatologists in neonates treated with therapeutic hypothermia, to provide a basis for suggesting improvements.

Methods: In this single-centre, retrospective study, all neonates treated with therapeutic hypothermia who were admitted to the neonatal intensive care unit of the Sophia's Children's Hospital, Rotterdam, The Netherlands, between the July 1st, 2017, and October 1st, 2021, were included. Clinical and pharmacological data on morphine, midazolam, fentanyl and acetaminophen were collected from the electronic patient management system for the first seven days of hospital admission, and analysed.

Results: Of the 127 patients included, 126 (99%) received treatment with morphine, 108 (85%) with midazolam, 27 (21%) with fentanyl and 27 (21%) with acetaminophen. Morphine and midazolam loading doses at start of infusion were administered in 63% and 68% of the patients, respectively. Concomitant morphine and midazolam loading doses with dose increases were administered in 45% and 49% of the cases, retrospectively. Cumulative morphine doses were higher during therapeutic hypothermia compared to after therapeutic hypothermia.

Conclusions: This study extensively described and analysed analgosedative pharmacotherapy in neonates treated with therapeutic hypothermia. A suggestion for improving analgosedative therapy may be to consistently administer loading doses when starting or increasing analgosedative therapy, to prevent undertreatment. Further research including drug exposure and effect-measures is needed to develop specific dosing recommendations for this population.

Master's Thesis Farmacie

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1. Introduction

Perinatal asphyxia, severe perinatal oxygen shortage, is one of the major causes of morbidity and mortality for term neonates. A severe hypoxic-ischaemic insult during birth may result in death or hypoxic-ischaemic brain injury, presenting as encephalopathy in the early neonatal period, with a high risk for permanent brain damage. [1–3]

The neonatal intensive care unit (NICU) provides supportive treatment including cardiovascular support, mechanical ventilation and treatment of seizures and infections. Induced moderate hypothermia has been shown to be a neuroprotective strategy for full term asphyxiated neonates by reducing metabolic rate, subsequent oxygen consumption and the release of nitric oxide, improving long term outcome. [2,4,5] Since 2008, therapeutic hypothermia (lowering the core temperature to 33.5°C for 72 hours) has been adopted by all NICUs in the Netherlands as the standard of care for neonates suffering perinatal asphyxia. [2,6]

Neonates treated with therapeutic hypothermia are frequently administered a variety of drugs, including sedatives and analgesics. The induction and maintenance of hypothermia is stressful and potentially painful, which is counterproductive to the neuroprotective effects of hypothermia. [2,7,8] Therefore, maintaining adequate sedation and analgesia during hypothermia is fundamental to maximise the efficacy of therapeutic hypothermia. Routine treatment with morphine has been recommended for all ventilated infants or those showing signs of distress. [6,7] An Italian survey showed that analgosedative medications are nearly always administered during therapeutic hypothermia, with fentanyl being the most used (85.7%) while morphine was used in only 14.3% of the NICUs. [9]

Analgesic and sedative therapy is complex due to multiple reasons, including difficulties in pain assessment [10,11] and the relative rapidly maturing physiology of neonates. [12–15] Furthermore, excretion of these drugs and metabolites can be modified by hypoxic-ischaemic injury of liver and kidneys. [4,16,17] In addition, hypothermia itself can alter pharmacokinetic (PK) and pharmacodynamic (PD) parameters, as many of the enzymes and transporters involved in drug absorption, distribution and metabolism exhibit temperature dependency, and due to potential changes in organ physiology and blood flow during hypothermia. [2,18–21] Population PK models describe a markedly lower morphine clearance in neonates receiving hypothermia compared to reports in normothermic neonates [20,22], and higher and potentially toxic serum morphine concentrations have been found in infants undergoing therapeutic hypothermia compared to normothermic controls. [7] Furthermore, hypothermia has been shown to decrease the systemic clearance of drugs metabolised by cytochrome P450 enzymes between approximately 7% and 22% per degree Celsius below 37°C. [23] A decreased clearance [24] and increased plasma concentration for fentanyl, primarily metabolised by CYP3A4, of 25% during hypothermia have been demonstrated, which remained increased for several hours after rewarming. [25] For the CYP3A substrate midazolam contradictory reports have been published. Two described decreased clearance and increased plasma concentrations when core body temperature was below 35°C compared to normothermia [26,27], however, other papers did not observe an effect of hypothermia on the PK of midazolam. [24,28–30]

These altered PK and PD parameters can result in an increased risk of drug toxicity or therapy failure. Adverse drug effects in critically ill patients receiving therapeutic hypothermia include hypotension, prolonged sedative effects, prolonged cardiovascular support and prolonged respiratory depression, which can potentially diminish the overall efficacy of therapeutic hypothermia. [2,18,29] The prolonged sedative effects caused by toxic analgesic levels additionally can interfere with required clinical neurological evaluations. [2] Besides, long term side effects of overdosing analgesic therapy in neonates have been shown, including lower body weight and head circumference, increased social problems, and poorer executive function. [31,32]

To provide a basis for suggesting improvements for sedative and analgesic pharmacotherapy in neonates admitted to the NICU receiving therapeutic hypothermia, this study aimed to retrospectively describe and analyse the prescribing behaviour of analgosedative treatment by neonatologists in this population.

2. Methods

2.1 Study design and sample

In this single-centre, retrospective study, all neonates treated with therapeutic hypothermia who were admitted to the neonatal intensive care unit of the Erasmus MC – Sophia's Children's Hospital, Rotterdam, The Netherlands, between the July 1st, 2017, and October 1st, 2021, were included. Only patients with parental consent for research purposes were included.

2.2 Data collection

Demographic, clinical and pharmacological data were retrieved from the electronic patient management system HiX (Chipsoft Amsterdam, The Netherlands). The administered doses of the analgesics morphine, fentanyl and acetaminophen and of the sedative midazolam were obtained from ICON. The start of data collection was the date of admission to the Sophia Children's Hospital. The end of data collection was at 23:59h seven days after admission, or earlier if the patient was transferred to the paediatric intensive care unit for treatment with extracorporeal membrane oxygenation (ECMO), or passed away.

2.3 Data handling

Pharmacological data on doses and duration of the analgesics morphine (µg/kg), fentanyl (µg/kg) and acetaminophen (mg/kg) and of the sedative midazolam (µg/kg) were used to calculate each patient's daily cumulative doses, the maximum daily cumulative dose and total cumulative dose. For morphine and midazolam, the maintenance doses of continuous infusion at start (T0) and 12 (T12), 24 (T24) and 48 (T48) hours after start of the infusion were compared to describe the dosage titration within the first 48 hours of treatment. Bolus doses within two hours before or after starting or increasing continuous infusion were determined loading doses. The duration of morphine infusion was determined as the time between initiation and termination in hours for uninterrupted infusions. For interrupted infusions, the duration of interruption was deducted from the time between initiation and termination of the continuous infusion. Ongoing infusions at the end of data collection were considered terminated at that point.

Cumulative doses of morphine therapy during and after therapeutic hypothermia were compared per 24-hour period. The start and end of therapeutic hypothermia were collected from HiX, and the rewarming phase was determined to be 7.5 hours after the end of therapeutic hypothermia, considering the rewarming of 0.4°C per hour until a body temperature of 36.5°C is reached. [6] Incomplete therapeutic hypothermia was determined based on reports in the patients' files stating 'early rewarming' or an equivalent.

2.4 Statistical analyses

Descriptive statistics included median and interquartile ranges (IQR) for continuous variables and frequencies or proportions for categorical variables. The doses of analgesics are presented as medians (IQR). The median doses of analgesics were calculated among patients receiving those analgesics.

Background characteristics and analgesic doses of unpaired samples were compared using Mann-Whitney *U* tests or Kruskall-Wallis tests in case of continuous variables. For continuous variables of paired samples, Wilcoxon Signed-Ranks tests were used. χ^2 tests or Fisher's exact tests were used in case of categorical variables. Pearson correlation tests were used to examine the correlation between two quantitative variables. Analgosedative treatment was compared between the following patient characteristics: gender (male/female), gestational age (<37 weeks, 37-40 weeks, >40 weeks), type of delivery (vaginal birth/Caesarean section) and mechanical ventilation at start of hospital admission (yes/no). Pharmacological treatment with analgesics and sedatives associated to COMFORTneo scores, which are validated pain assessment scores in neonates [33], was visualised for two illustrative patients. Data analyses were conducted using Statistical Package for the Social Sciences SPSS version 28.0.1.0 (IBM Corp., Armonk, New York). All *p*-values <.05 were deemed statistically significant. Figures and graphs were created using Microsoft Excel 2016 (Microsoft Corporation) and Plotly's Python v.5.8.2 (Plotly Technologies Inc.).

3. Results

3.1 Patient population

During the study period, 2645 patients were admitted to the NICU of the Erasmus MC – Sophia's Children's Hospital, of whom 127 received therapeutic hypothermia. Table 1 displays the background and clinical characteristics of the patients treated with therapeutic hypothermia. Some values were missing for various characteristics (supplementary table S1). Thirty-two neonates (25%) died during hospital admission, of whom twenty-nine (23%) within the first seven days of hospital admission. The median (IQR) time to death was 4 (3-6) days. Five patients (4%) were transferred to the paediatric intensive care unit for ECMO treatment within the first seven days of hospital admission.

Table 1: Background and clinical characteristics for n=127 neonates treated with therapeutic hypothermia.

Variable	
Gender	
Male, number (%)	76 (59.8)
Female, number (%)	51 (40.2)
Type of delivery	
Vaginal birth, number (%)	59 (46.5)
Caesarean section, number (%)	68 (53.5)
Location of birth	
Inborn, number (%)	13 (10.2)
Outborn, number (%)	114 (89.8)
Multiple birth, number (%)	3 (2.4)
Birth weight in grams, median (IQR)	3370 (3000-3670)
Gestational age at birth in weeks, median (IQR)*	39.3 (37.4-40.6)
Clinical parameters	
Apgar 5 min, median (IQR)*	3 (1-5)
Apgar 10 min, median (IQR)*	5 (3.25-6)
Thompson score, median (IQR)*	9.5 (8-12)
Umbilical cord pH (arterial blood), median (IQR)*	6.95 (6.90-7.11)
Mechanical ventilation	
Mechanically ventilated at start hospital admission, number (%)	81 (63.8)
(Partially) mechanically ventilated during therapeutic hypothermia, number (%)	104 (81.9)
Length of hospitalisation in days, median (IQR)	6 (4-8)
Therapeutic hypothermia	
Starting therapeutic hypothermia, median hours of life (IQR)	5:26 (4:22-6:00)
Incomplete therapeutic hypothermia, number (%)	27 (21.3)
Mortality	
Mortality within first week of hospital admission, number (%)	29 (22.8)
Mortality during hospital admission, number (%)	32 (25.2)

*Missing values, see Supplementary table S1

3.2 Morphine treatment

The total, daily and maximum daily cumulative doses of the administered analgesics and sedative, split up by route of administration, are shown in table 2. All patients except one were treated with morphine during therapeutic hypothermia. One of these patients also received morphine orally. The median (IQR) daily cumulative dose of intravenous (IV) morphine was 240 (121-290) µg/kg for a median (IQR) of 5 (4-5.75) days, corresponding with a median (IQR) continuous dose of 10 (5-12) µg/kg/h.

Loading doses at start

The median (IQR) morphine dose at T0 was 10 (5-10) µg/kg/h in all subgroups. In 80 patients (63.5%) a loading dose was administered when starting continuous morphine infusion, of which the median (IQR) dose was 100 (52.5-100) µg/kg. Patients who were mechanically ventilated at the start of their hospital admission, were less frequently given a loading dose compared to patients who were not mechanically ventilated (55% versus 78%, $\chi^2(1)=6.82$, $p=.009$). However, if a loading dose was given, this dose was

higher in the mechanically ventilated group (median (IQR) 100 (100-100) µg/kg) compared to the non-ventilated patients (median (IQR) 96.5 (50-100) µg/kg) (U=543, p=.007). Also, in patients delivered by Caesarean section the loading doses were higher (median (IQR) 100 (98.5-100) µg/kg) compared to patients born vaginally (median (IQR) 100 (50-100) µg/kg) (U=601, p=.032). There were no differences in loading doses at start of continuous morphine infusions between the other subgroups (supplementary table S2). The loading doses were administered between 1 hour and 22 minutes before and 1 hour and 24 minutes after start of continuous infusion. As it is remarkable that the loading doses are higher in both the mechanically ventilated patients and patients born by Caesarean section, an association test between these subgroups was performed, revealing a positive association ($\chi^2(1)=7.98$, p=.006).

Maintenance doses

At T12, T24 and T48, the median (IQR) morphine doses were 10 (10-14.6) µg/kg/h (n=122), 10 (10-15) µg/kg/h (n=117) and 10 (10-14.7) µg/kg/h (n=111), respectively. There were no differences in the maintenance doses at these times between any of the subgroups (supplementary table S2).

Infusion duration

The median (IQR) duration of morphine infusion was 98 (87-108) hours in patients with complete follow-up (n=93). Morphine was administered for a longer duration in patients who were mechanically ventilated at start of their hospital admission (median (IQR) 103 (91-22) hours) compared to patients who were not mechanically ventilated (median (IQR) 95 (84-102) hours) (U=749, p=.013). There were no differences in the other subgroups.

Dose increases

In 82 patients (65.1%), morphine dose was increased during the first week of hospital admission. Of the 125 dose increases in these patients, a concomitant loading dose of median (IQR) 94 (50-100) µg/kg was administered in 56 cases (44.8%) between 1 hour and 29 minutes before and 1 hour and 3 minutes after dose increase. There were no differences between any of the subgroups in increasing the maintenance dose or not, or between the loading doses administered with dose increases between any of the subgroups.

In 114 of the patients treated with morphine (90.5%), additional analgosedative drugs were administered during the follow-up period: 73 patients (57.9%) were treated with two, 30 patients (23.8%) with three, and 11 patients (8.7%) with all four analgosedatives.

Table 2: Analgesic and sedative pharmacological treatment.

Analgesics	
Any intravenous analgesic	
Number of patients	126 (99.2)
Morphine intravenous	
Number of patients	126 (99.2)
Total cumulative dose (µg/kg)	1005 (811-1301)
Daily cumulative dose (µg/kg)	240 (121-290)
Maximum daily cumulative dose (µg/kg)	303 (240-380)
Morphine oral	
Number of patients	1 (0.8)
Total cumulative dose (µg/kg)	535*
Daily cumulative dose (µg/kg)	154-380*
Maximum daily cumulative dose (µg/kg)	380*
Fentanyl intravenous	
Number of patients	27 (21.3)
Total cumulative dose (µg/kg)	2.7 (2.0-8.7)
Daily cumulative dose (µg/kg)	2.0 (1.8-4.1)
Maximum daily cumulative dose (µg/kg)	2.0 (1.7-5.9)
Acetaminophen intravenous	27 (21.3)
Number of patients	27 (21.3)
Total cumulative dose (mg/kg)	95 (50-119)
Daily cumulative dose (mg/kg)	30 (20-40)

Maximum daily cumulative dose (mg/kg)	40 (30-41)
Acetaminophen rectal	
Number of patients	5 (3.9)
Total cumulative dose (mg/kg)	30 (22-65)
Daily cumulative dose (mg/kg)	34 (20-51)
Maximum daily cumulative dose (mg/kg)	30 (22-49)
Acetaminophen oral	
Number of patients	1 (0.8)
Total cumulative dose (mg/kg)	26*
Daily cumulative dose (mg/kg)	9-17*
Maximum daily cumulative dose (mg/kg)	17*
Sedative	
Midazolam intravenous	
Number of patients	108 (85.0)
Total cumulative dose (µg/kg)	2526 (1101-5241)
Daily cumulative dose (µg/kg)	896 (463-1350)
Maximum daily cumulative dose (µg/kg)	1200 (674-2045)

Values are expressed as median (IQR) or number (%). *Only one or two values, so no IQR could be calculated.

3.2 Midazolam treatment

108 patients (85%) were treated with IV midazolam, of whom 99 patients received continuous infusion and 9 patients only bolus administrations. The median (IQR) daily cumulative dose of midazolam was 896 (463-1350) µg/kg for a median (IQR) of 3 (2-4) days.

Loading doses at start

The median (IQR) midazolam dose at T0 was 50 (50-100) µg/kg/h. In patients delivered by Caesarean section, this starting dose was higher (median (IQR) 50 (50-100) µg/kg/h) compared to patients born vaginally (median (IQR) 50 (50-51) µg/kg/h) (U=895, p=.018). In all other subgroups, there were no differences (supplementary table S3). In 67 patients (67.7%) a loading dose was administered when starting continuous midazolam infusion, of which the median (IQR) dose was 100 (51-100) µg/kg. There were no differences in these doses between any of the subgroups. Patients who were mechanically ventilated at the start of their hospital admission, were more frequently given a loading dose than patients who were not ventilated (77% versus 48%, $\chi^2(1)=8.34$, p=.004). The loading doses were administered between 1 hour before and 1 hour and 34 minutes after start of continuous infusion. A Pearson's correlation test showed a moderate, positive correlation between the midazolam dose at T0 and the loading dose ($r(65)=.35$, p=.004).

Maintenance doses

At T12, T24 and T48, the median (IQR) midazolam doses were 50 (50-100) µg/kg/h (n=74), 50 (50-100) µg/kg/h (n=60) and 50 (50-101) µg/kg/h (n=41), respectively. At T12, the maintenance dose in patients delivered by Caesarean section was still higher (median (IQR) 50 (50-100) µg/kg/h) compared to patients born vaginally (median (IQR) 50 (50-51) µg/kg/h) (U=407, p=.002), but this was no longer true at T24 and T48. At T24, female patients received a higher maintenance dose (median (IQR) 80 (50-100) µg/kg/h) than male patients (median (IQR) 50 (50-54) µg/kg/h) (U=302, p=.037) (figure 1). No other differences were found between the subgroups (supplementary table S3).

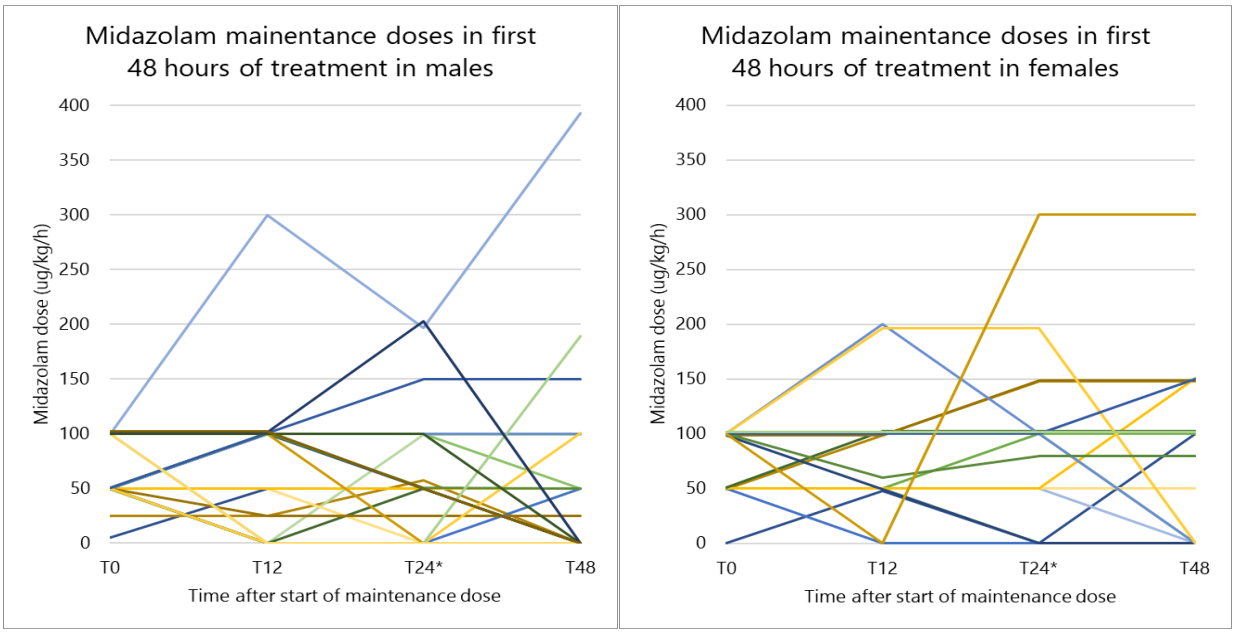

Figure 1: Maintenance doses of midazolam in the first 48 hours of midazolam treatment in males (left, n=50) and females (right, n=36). T0 indicates the start of continuous midazolam infusion and T12, T24 and T48 indicate the time points of 12, 24 and 48 hours after start of continuous midazolam infusion, respectively. *Statistically significant difference indicated by a Mann-Whitney *U* test (p=.037).

Dose increases

In 42 patients (42.4%), midazolam dose was increased during the first week of hospital admission. Of the 78 dose increases in these patients, a concomitant loading dose of median (IQR) 97.8 (100-100) µg/kg was administered in 38 cases (48.7%) between 1 hour and 17 minutes before and 33 minutes after dose increase. There were no differences between any of the subgroups in increasing the midazolam dose or not, or between the loading doses administered with dose increases.

3.3 Fentanyl treatment

27 patients (21.3%) were treated with IV fentanyl. Mainly bolus infusions were administered. The median (IQR) daily cumulative dose of fentanyl was 2.0 (1.8-4.1) µg/kg for a median (IQR) of 1 (1-2) day. 3 patients received continuous infusion of fentanyl for a median (IQR) duration of 0.8 (0.1-9.0) hours with a median (IQR) infusion rate of 2 (1-3) µg/kg/h.

3.4 Acetaminophen treatment

31 patients (24.4%) were administered acetaminophen, of whom 25 only IV, 1 both IV and rectally, 4 only rectally and 1 both IV and orally. The median (IQR) daily cumulative dose of IV acetaminophen was 30 (20-40) mg/kg. A median (IQR) number of 3 (2-4) administrations were given per day for a median (IQR) of 3 (1.5-4) days.

Protocol adherence

Dosage recommendations for morphine, fentanyl and acetaminophen are provided in the local NICU pain guideline [34], however, there are no specific recommendations for neonates treated with therapeutic hypothermia. According to this guideline, for IV acetaminophen a loading dose of 15 mg/kg should precede the maintenance dose of 7.5 mg/kg every 6 hours for neonates with a bodyweight of 1500-3000 grams and 10 mg/kg every 6 hours for neonates with a bodyweight of 3000-5500 grams. Five patients received a single IV administration, and to 19 of the 22 (86.4%) patients receiving multiple IV administrations, a loading dose was administered. 11 loading doses were 15 mg/kg, 1 was 18 mg/kg and 7 were 20 mg/kg. Two of the loading doses were not reduced to the maintenance dose afterwards, resulting in a complete protocol adherence for 10 patients (45.5%). The median (IQR) interval between administrations was 6.0 (5.7-6.5) hours.

3.5 Cumulative IV doses over time

The cumulative doses were calculated per 24-hour period from initiation of therapeutic hypothermia (figure 2). Patients with incomplete follow-up due to ECMO or death (n=34) or incomplete therapeutic hypothermia (n=4) were excluded from this figure and the subsequent analyses. The cumulative dose of morphine during the first 24 hours of therapeutic hypothermia (median 302 µg/kg) was higher than in the second (median 240 µg/kg) and third (median 240 µg/kg) 24-hour periods during therapeutic hypothermia (p<.001). Wilcoxon Signed-Ranks tests indicated that for each period until the sixth (period 5), the cumulative dose of morphine was higher than the subsequent period (supplementary figure S4). The cumulative dose of morphine in the 24-hour periods during therapeutic hypothermia (median (IQR) 240 (240-336) µg/kg) was higher than in the 24-hour periods after therapeutic hypothermia (median (IQR) 116 (85-157) µg/kg) (Z=-8.0, p<.001). Within the first 24 hours after the end of therapeutic hypothermia (period 3), morphine therapy was discontinued in 33 patients. Morphine was more often discontinued in patients who were not mechanically ventilated at the start of their hospital admission ($\chi^2(1)$=7.59, p=.008). In accordance with this, the cumulative morphine dose was lower in this period in these patients (median (IQR) 123 (88-189 µg/kg) compared to the ventilated patients (median (IQR) 190 (121-240) µg/kg) (U=681, p=.017), as was the median and total cumulative dose after therapeutic hypothermia (p=.026 and p=.002).

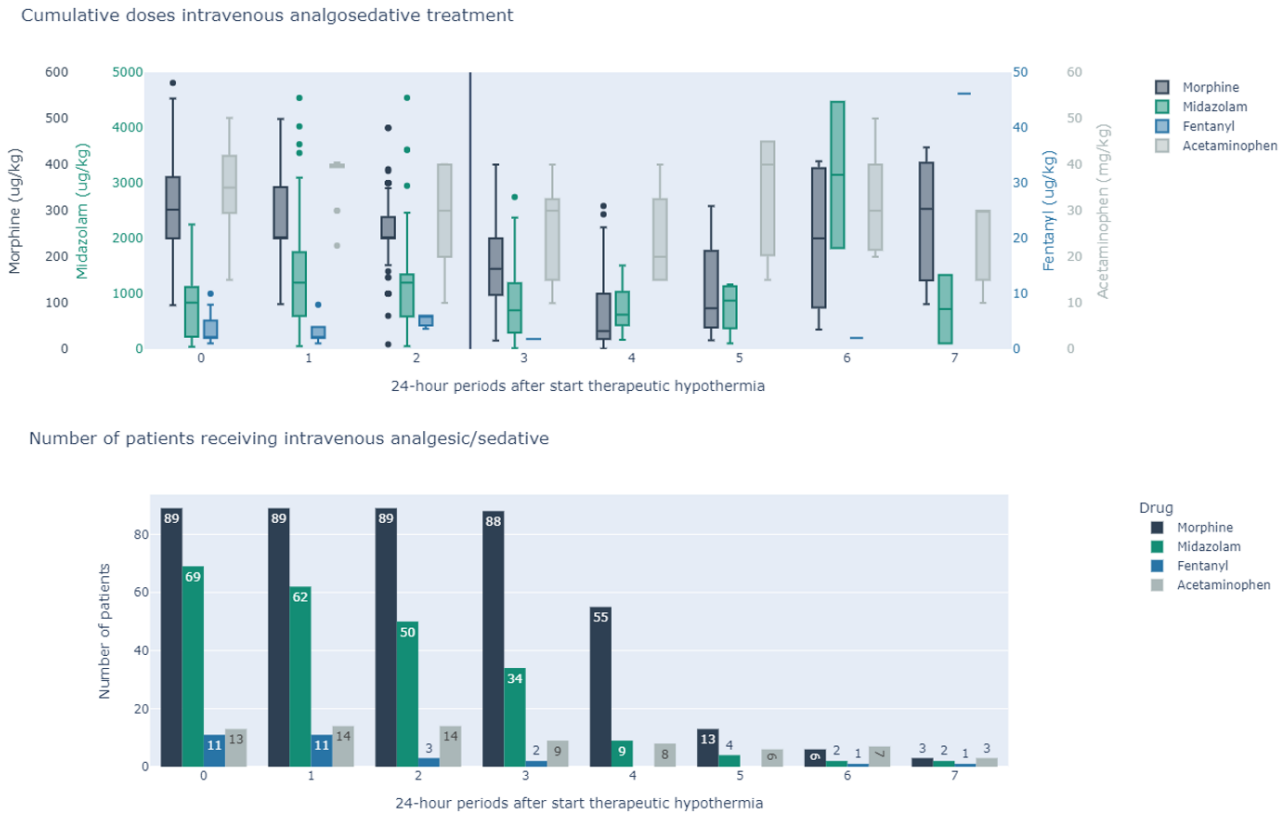

Figure 2: Cumulative doses of IV analgosedatives. In the upper part of the figure, the cumulative doses per drug are shown over 24-hour periods after initiation of therapeutic hypothermia. In the lower part of the figure, the number of patients per boxplot are shown. The total number of patients per 24-hour period from the first to last period are: 89, 89, 89, 89, 57, 19, 10 and 4. Periods 0, 1 and 2 are during therapeutic hypothermia. The vertical line indicates the end of therapeutic hypothermia. Period 3 contains the rewarming phase of 7.5 hours.

For two illustrative patients, one with and one without mechanical ventilation at the start of hospital admission, the pharmacological treatment with analgosedatives and COMFORTneo scores are shown over time (figures 3 and 4). In figure 3, displaying the non-ventilated patient, morphine was discontinued within 24 hours after the end of rewarming. In figure 4, displaying the mechanically ventilated patient, morphine was discontinued almost 60 hours after the end of rewarming, six hours before extubation.

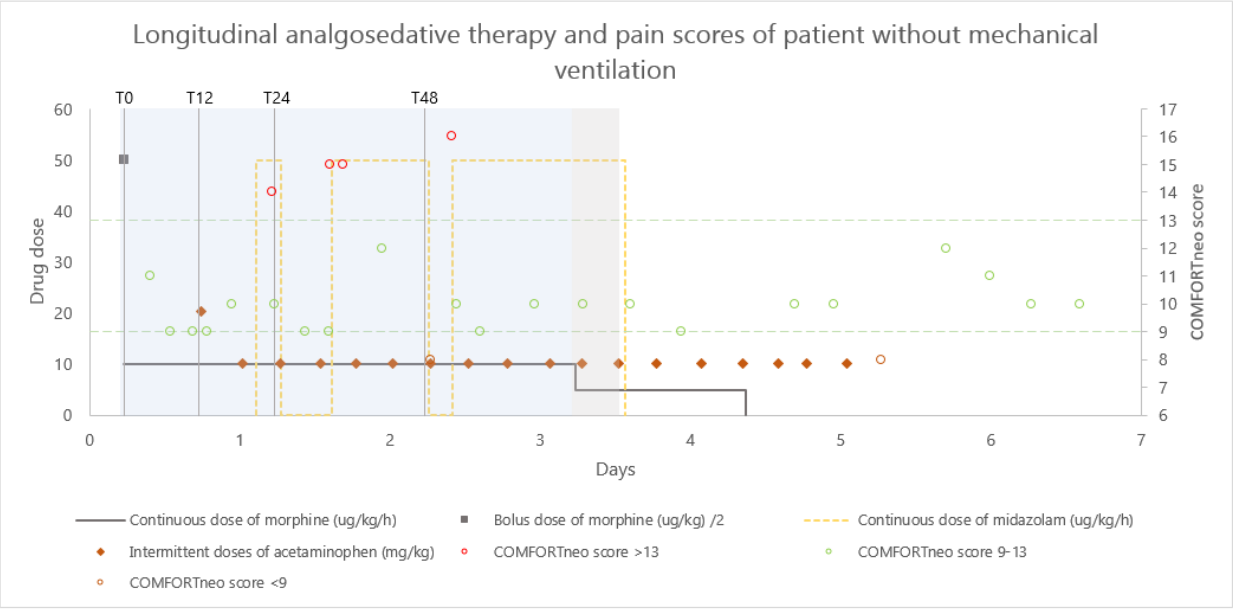

Figure 3: In this figure, dosages of analgesics and COMFORTneo scores of a patient without mechanical ventilation are shown. Drug doses are shown on the left y-axis and COMFORTneo scores are shown on the right y-axis. The COMFORTneo score ranges from 6 to 30; a score of 14 or higher indicates pain and a score of 8 or lower indicates possible analgesic overtreatment. Therapeutic hypothermia is shown in blue, and the rewarming phase is shown in grey. T0 indicates the start of continuous morphine infusion and T12, T24 and T48 indicate the time points of 12, 24 and 48 hours after start of continuous morphine infusion, respectively. At initiation of therapeutic hypothermia, morphine continuous infusion was started and a loading dose was administered, after which adequate COMFORTneo scores were seen. Subsequently, acetaminophen was administered followed by midazolam because of agitation. No loading dose of midazolam was administered. Continuous infusion of midazolam was discontinued twice due to excessive sedation, but restarted due to agitation. At the end of therapeutic hypothermia, morphine dose was lowered. At the end of the rewarming phase, midazolam was discontinued. Morphine was discontinued within 24 hours after the end of the rewarming phase. Finally, acetaminophen was discontinued after a low COMFORTneo score.

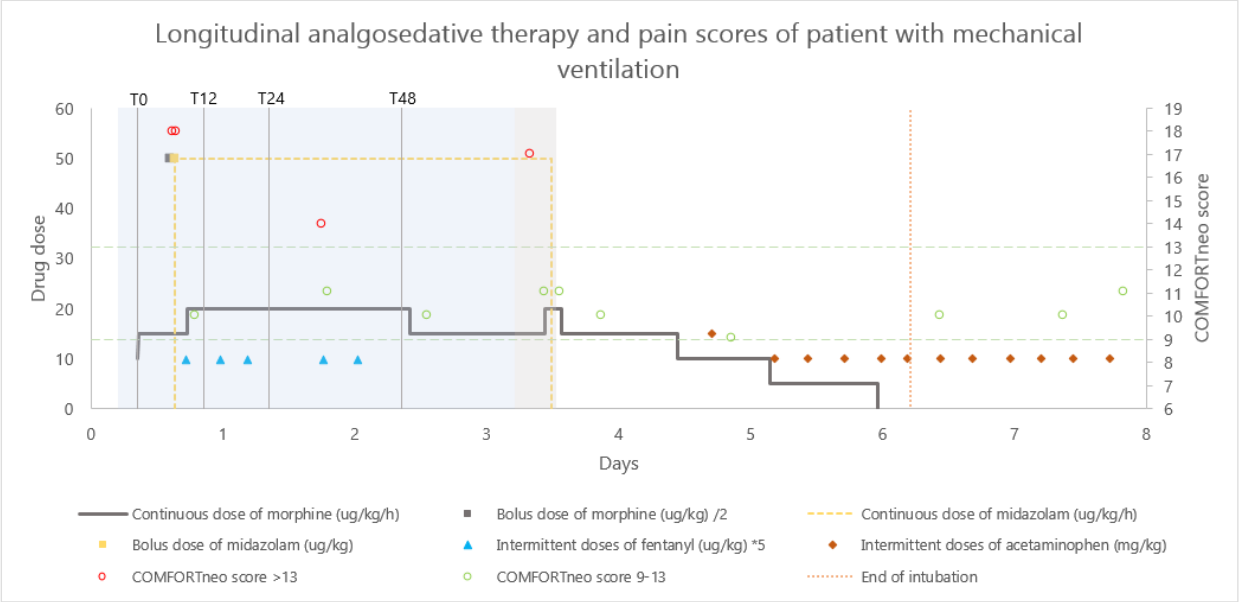

Figure 4: In this figure, analgosedative therapy and pain scores of a patient with mechanical ventilation at the start and during the major part of the hospitalisation are shown. Morphine was initiated a couple of hours after starting therapeutic hypothermia without an initial loading dose. Because of agitation and discomfort, a morphine bolus dose was administered, infusion with midazolam was started along with a loading dose, and the continuous infusion dose of morphine was increased. During nursing, intermittent fentanyl was utilized. During the rewarming phase, morphine dose was increased in response to a high COMFORTneo score, and after adequate effect, midazolam was discontinued at the end of rewarming. After rewarming, morphine dose was gradually lowered until it was discontinued 59 hours later, and acetaminophen was started as maintenance analgesia. The patient was extubated 6 hours after the discontinuation of morphine infusion.

4. Discussion

The aim of this study was to describe and analyse the prescribing behaviour of analgosedative pharmacotherapy by neonatologists in neonates treated with therapeutic hypothermia, to provide a basis for suggesting improvements for analgosedative pharmacotherapy in this population. This study provides an extensive description and analyses of the analgosedative treatment in this population.

4.1 Morphine treatment

In compliance with the recommendations, all patients except one were treated with morphine. This one patient was not treated with morphine or any other analgosedative due to low tension and irresponsiveness to pain, and passed away within 24 hours after birth.

Loading doses in mechanically ventilated patients

Clinicians did not recognise the lower frequency of loading doses of morphine in the mechanically ventilated population and could not explain this prescribing behaviour. However, they did recognise the higher loading doses of morphine in this subpopulation. Clinicians might be more cautious in the non-ventilated patients as they are still breathing on their own. They do not want to give a dose that is too high and might cause the neonate to stop breathing. This caution might also explain the lower frequency of midazolam loading doses in non-ventilated patients compared to ventilated patients. However, not administering a loading dose leads to undertreatment until steady state is reached. Since stress and pain have been shown to be counterproductive to the neuroprotective effects of therapeutic hypothermia [7,8], it is recommended that also in the spontaneously breathing patients, adequate analgesic therapy is provided by administering loading doses.

The higher loading doses in patients delivered by Caesarean section were not recognised by clinicians, but could be explained by the positive association between these two subpopulations, indicating an overlap.

Infusion duration in mechanically ventilated patients

Not only the loading dose of morphine in mechanically ventilated patients was higher, also the duration of morphine treatment was longer than in patients who were not mechanically ventilated at start of their admission. After termination of therapeutic hypothermia, morphine was less often discontinued in this subpopulation in the first 24 hours. This finding was also recognised by clinicians; in addition to preventing discomfort during hypothermia, morphine is prescribed against agitation and counter-breathing during mechanical ventilation. As mechanical ventilation often is continued after therapeutic hypothermia until the MRI scan to facilitate sedation during the scan, also morphine is likely to be continued after therapeutic hypothermia. A second explanation may be that patients who are mechanically ventilated at the start of their hospital admission, are usually more sick. More sick patients might have more pain for a longer time and have a higher risk of receiving medications.

4.2 Midazolam treatment

Midazolam also is a commonly used drug in neonates treated with therapeutic hypothermia. Besides being used as a sedative, it is the second drug in line for treating convulsions (after phenobarbital) [35], which are common among asphyxiated neonates suffering hypoxic-ischaemic encephalopathy [36]. In this study, unfortunately, no distinction between these indications could be made as this data was not available.

Loading and starting doses

A possible explanation for the higher frequency of midazolam loading doses seen in the ventilated patients, has been mentioned above. The duration of midazolam treatment has not been analysed, as midazolam was used more intermittently. The positive correlation between the starting and loading dose is explained by the prescribing behaviour of clinicians; they recognise prescribing a loading dose of 100 ug/kg when the starting dose is 100 ug/kg/h, and a loading dose of 50 ug/kg when the starting dose is 50 ug/kg/h.

Delicate balance

The delicate balance between adequate and excessive sedation is evident in the illustrative patient's profile in figure 3. Midazolam was discontinued twice due to excessive sedation, but also restarted again because of agitation, which can be recognised in the high COMFORTneo scores.

4.3 Fentanyl and acetaminophen treatment

Fentanyl and acetaminophen are not part of the routine treatment for these patients. Fentanyl was mainly administered as bolus infusions during nursing. As the number of patients treated with these drugs were relatively low, no statistical analyses on these treatments were performed.

4.4 Cumulative morphine doses

Patients with incomplete follow-up or incomplete therapeutic hypothermia were excluded from the analyses of the cumulative morphine doses over time, as many of these patients were critically ill and treated with palliative sedation. Including these would result in higher cumulative doses, so to prevent this bias, these patients were excluded.

First 24-hour period

The cumulative doses of morphine decreased over the first six 24-hour periods from initiation of therapeutic hypothermia. The higher cumulative doses in the first 24 hours can be attributed to the loading doses that were administered when starting continuous morphine infusion. A limitation must be stated: loading doses that were administered before the start of therapeutic hypothermia were excluded from the cumulative doses in these analyses, since the initiation of therapeutic hypothermia was taken as the starting point. Sometimes morphine was initiated before start of therapeutic hypothermia. Therefore, some loading doses were missing in these cumulative doses, resulting in a lower cumulative dose.

24-hour periods after therapeutic hypothermia

The rewarming period after therapeutic hypothermia is included in period 3. Lower cumulative morphine doses in this period can be explained by the discontinuation of morphine after rewarming. In 33 patients, the infusion ran only partially during this period, accounting for the lower median cumulative dose. The median cumulative morphine dose increases from period 5 onward, which corresponds to the third 24-hour period after therapeutic hypothermia. As in most patients morphine was discontinued within 48 hours after the end of therapeutic hypothermia, infusions still running in these periods at the end of the week might represent a different clinical indication for continuing morphine.

4.5 Strengths and limitations

A strength of this study is that the analgosedative pharmacotherapy is extensively described and analysed in a substantial cohort of neonates treated with therapeutic hypothermia. This study may provide useful insights for the development of specific treatment guidelines for this population. A limitation of this study is the retrospective nature, which causes the quality of the data to depend on the accuracy and integrity of the documentation by healthcare professionals. Undocumented or incorrectly registered data negatively affect the integrity of these results. Another limitation is that the data only included administered doses but not the actual exposure to drugs or other effect-measures. As the PK and PD in these neonates are complex, drug exposure or other effect-measures could be valuable to assist in drug dosing.

4.6 Conclusion

In conclusion, therapeutic hypothermia is the standard of care for asphyxiated neonates, however, it is a stressful procedure. Discomfort or pain may affect the neuroprotective effects of hypothermia, thus adequate analgosedation is essential and should be further optimised. A suggestion for improving analgosedative treatment during therapeutic hypothermia based on this study, may be to consistently administer loading doses when starting and increasing morphine therapy, to prevent undertreatment.

4.7 Future perspectives

Further research on specific drug dosing in relation to drug exposure and effect-measures in these patients is needed to develop dosing recommendations for analgosedatives for this specific population. Future perspectives might include automated dose adjustments provided by a bedside pain dashboard, integrating a patient's real-time pain level and predicted drug exposure, to optimise pain management.

Abbreviations

NICU, neonatal intensive care unit;
PK, pharmacokinetics;
PD, pharmacodynamics;
ECMO, extracorporeal membrane oxygenation;
IQR, interquartile range;
IV, intravenous.

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Supplementary information

S1. Table with missing values

Table S1: Missing values for table 1

Variable	Number of missing values
Gestational age	1 (term)
Apgar score after 5 minutes	4
Apgar score after 10 minutes	15
Thompson score	9
Umbilical cord pH (arterial blood)	1

S2. Morphine loading and maintenance doses

Table S2: Morphine loading and maintenance doses.

		Gender		**Gestational age**			**Type of delivery**		**Mechanically ventilated at start of hospital admission**	
Morphine	Overall	Male	Female	GA <37 weeks	GA 37-40 weeks*	GA >40 weeks	Vaginal birth	Caesarean section	Yes	No
% loading dose with start continuous infusion	63.5	61.3	66.7	54.5	58.6	73.9	59.7	67.8	55.0^	78.3^
Loading dose with start (µg/kg)	100 (53-100) *n=80*	100 (54-100) *n=46*	100 (52-100) *n=34*	100 (73-100) *n=12*	100 (96-100) *n=34*	100 (50-100) *n=34*	100 (50-100)** *n=40*	100 (98.5 - 100)** *n=40*	100 (100-100)** *n=44*	97 (50-100)** *n=36*
Dose at T0 (µg/kg/h)	10 (5-10) *n=126*	10 (5-10) *n=75*	10 (5-10) *n=51*	10 (5-10) *n=22*	10 (5-10) *n=58*	10 (5-10) *n=46*	10 (5-10) *n=59*	10 (5-10) *n=67*	10 (5-10) *n=80*	10 (5-10) *n=46*
Dose at T12 (µg/kg/h)	10 (10-14.6) *n=122*	10 (10-12.3) *n=72*	10 (10-15) *n=50*	10 (9.9-10) *n=22*	10 (10-10.1) *n=57*	10 (10-15) *n=43*	10 (10-14.9) *n=55*	10 (9.9-10.1) *n=67*	10 (10-12.3) *n=76*	10 (10-14.7) *n=46*
Dose at T24 (µg/kg/h)	10 (10-15) *n=117*	10 (10-15) *n=70*	10 (10-14.7) *n=47*	10 (10-15) *n=19*	10 (10-14.7) *n=57*	10 (10-15) *n=42*	10 (10-15) *n=55*	10 (10-10.1) *n=62*	10 (10-15) *n=71*	10 (10-14.7) *n=46*
Dose at T48 (µg/kg/h)	10 (10-14.7) *n=111*	10 (10-14.9) *n=64*	10 (10-11.1) *n=47*	10 (10-10) *n=17*	10 (10-14.8) *n=52*	10 (10-14.7) *n=42*	10 (10-14.7) *n=53*	10 (10-10.2) *n=58*	10 (10-15) *n=65*	10 (10-10.1) *n=46*

Values are represented as median (IQR) or %. The numbers of patients are displayed per group. GA: Gestational age; *1 missing GA, as a term was mentioned, it was included in this group. ^Statistically significant difference (Chi Square test). **Statistically significant difference (Mann-Whitney *U* test).

S3. Midazolam loading and maintenance doses

Table S3: Midazolam loading and maintenance doses.

		Gender		**Gestational age**			**Type of delivery**		**Mechanically ventilated at start of hospital admission**	
Midazolam	Overall	Male	Female	GA <37 weeks	GA 37-40 weeks*	GA >40 weeks	Vaginal birth	Caesarean section	Yes	No
% loading dose with start continuous infusion	67.7	60.7	76.7	50.0	73.3	66.7	66.7	68.5	77.3^	48.5^
Loading dose with start (µg/kg)	100 (51-100) *n=67*	96 (50-100) *n=34*	100 (52-100) *n=33*	71 (54-100) *n=7*	91 (50-100) *n=36*	100 (100-100) *n=24*	100 (52-100) *n=30*	100 (50-100) *n=37*	100 (51-100) *n=51*	100 (51-100) *n=16*
Dose at T0 (µg/kg/h)	50 (50-100) *n=99*	50 (50-51) *n=56*	50 (50-100) *n=43*	50 (50-50) *n=14*	50 (50-100) *n=49*	50 (50-100) *n=36*	50 (50-51)** *n=45*	50 (50-100)** *n=54*	50 (50-100) *n=66*	50 (50-50) *n=33*
Dose at T12 (µg/kg/h)	50 (50-100) *n=74*	50 (50-100) *n=43*	50 (50-100) *n=31*	50 (49-100) *n=10*	50 (50-100) *n=35*	50 (50-100) *n=29*	50 (50-50)** *n=35*	99 (50-100)** *n=39*	50 (50-100) *n=47*	50 (50-100) *n=27*
Dose at T24 (µg/kg/h)	50 (50-100) *n=60*	50 (50-54)** *n=35*	80 (50-100)** *n=25*	50 (50-75) *n=7*	50 (50-99) *n=27*	50 (50-100) *n=26*	50 (50-54) *n=31*	50 (50-100) *n=29*	50 (50-100) *n=35*	50 (50-99) *n=25*
Dose at T48 (µg/kg/h)	50 (50-101) *n=41*	50 (50-100) *n=22*	80 (50-125) *n=19*	50 (50-50) *n=6*	51 (50-101) *n=15*	50 (50-148) *n=20*	50 (50-100) *n=22*	80 (50-125) *n=19*	51 (50-103) *n=25*	50 (50-99) *n=16*

Values are represented as median (IQR) or %. The numbers of patients are displayed per group. GA: Gestational age; *1 missing GA, as term was mentioned, it was included in this group. ^Statistically significant difference (Chi Square test). **Statistically significant difference (Mann-Whitney *U* test).

S4. Cumulative morphine doses compared per 24-hour period

	Median (IQR) cumulative morphine dose	Period 0	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
Period 0 *n=89*	302 (240-372)								
Period 1 *n=89*	240 (240-348)	<.001							
Period 2 *n=89*	240 (240-285)	<.001	<.001						
Period 3 *n=88*	174 (117-240)	<.001	<.001	<.001					
Period 4 *n=55*	39 (22-120)	<.001	<.001	<.001	<.001				
Period 5 *n=13*	89 (49-204)	<.001	.002	.002	.003	.010			
Period 6 *n=6*	240 (90-392)	.438	.438	.469	.875	.688	.563		
Period 7 *n=3*	304 (201-371)	.750	.500	1	.750	.750	.750	.750	

Figure S4: The median (IQR) cumulative morphine doses per 24-hour period are shown. In the cells intersecting at two periods, *p*-values from Wilcoxon Signed-Ranks tests comparing the paired cumulative doses in those periods are shown. Green cells indicate a statistically significant *p*-value of <.05. The number of patients per period for whom the cumulative doses are compared, is shown below the period on the left.