



## Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004086
Article Type:	Research
Date Submitted by the Author:	20-Sep-2013
Complete List of Authors:	Guedj, Romain; AP-HP - Hôpital Armand Trousseau, Service d'urgences pédiatriques; Inserm U-953, Danan, Claude; Centre Hospitalier Intercommunal de Creteil, Unité de réanimation néonatale Daoud, Patrick; Centre Hospitalier André Grégoire, Réanimation Infantile Zupan, Véronique; AP-HP, Hôpital ANtoine Béclère, Pédiatrie et Réanimation néonatale Renolleau, Sylvain; AP-HP, Hôpital Armand Trousseau, Réanimation Néonatale et Pédiatrique Zana-Taieb, Elodie; Médecine néonatale Port-Royal-Cochin, NICU Aizenfisz, Sophie; AP-HP, Hôpital Robert Debré, Réanimation pédiatrique Lapillonne, Alexandre; Université Paris descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation néonatale de Saint Blanquat, Laure; Hôpital Necker, PICU Granier, Michele; Hôpital sud-francilien, NICU Durand, Philippe; Bicetre Hospital, Paediatric Intensive Care Unit Castela, Florence; Hôpital Poissy, Unité de réanimation néonatale Coursol, Anne; CH René Dubos, NICU Hubert, Philippe; Hopital Necker Paris, intensive care unit Cimerman, Patricia; Hopital Armand Trousseau, Centre National de Ressources de lutte contre la Douleur Anand, Sunny; Le Bonheur Children's Hospital, University of Tennessee Health Science Center Khoshnood, Babak; Hopital Saint Vincent de Paul, INSERM U953 Carbajal, Ricardo; Hôpital Trousseau, Service des Urgences Pédiatriques
<b>Primary Subject Heading</b>:	Paediatrics
Secondary Subject Heading:	Intensive care
Keywords:	NEONATOLOGY, after hour care, painful procedures, Pain

## Neonatal Pain Management is not the same During Days and Nights in Intensive Care

### Units

**Authors** : Romain Guedj<sup>1</sup>, MD, Claude Danan<sup>2</sup>, MD, Patrick Daoud<sup>3</sup>, MD, Véronique Zupan<sup>4</sup>, MD, Sylvain Renolleau<sup>5</sup>, MD, PhD, Elodie Zana<sup>6</sup>, MD, Sophie Aizenfisz<sup>7</sup>, MD, Alexandre Lapillonne<sup>8</sup>, MD, PhD, Laure de Saint Blanquat<sup>9</sup>, MD, Michèle Granier<sup>10</sup>, MD, Philippe Durand<sup>11</sup>, MD, Florence Castela<sup>12</sup>, MD, Anne Coursol<sup>13</sup>, MD, Philippe Hubert<sup>14</sup>, MD, PhD, Patricia Cimerman<sup>15</sup>, Research Nurse, Babak Khoshnood<sup>16</sup>, PhD, KJS Anand<sup>17</sup>, MD, PhD, Ricardo Carbajal<sup>18</sup>, MD, PhD.

<sup>1</sup> Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

M.D.

<sup>2</sup> Centre Hospitalier Intercommunal de Créteil, Unité de réanimation néonatale et soins intensifs, 40 avenue de Verdun 94010 Créteil Cedex, France

M.D.

<sup>3</sup> Centre Hospitalier André Grégoire, Réanimation infantile, 56, bd de la Boissiere 93105 Montreuil-sous-Bois Cedex, France

M.D.

<sup>4</sup> AP-HP, Hôpital Antoine Bécclère, Pédiatrie et Réanimation Néonatale, 157, rue de la Porte de Trivaux 92141 Clamart cedex, France

M.D.

<sup>5</sup> AP-HP, Hôpital Armand-Trousseau, Réanimation Néonatale et Pédiatrique, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

PhD

1  
2  
3 <sup>6</sup> Maternité Port-Royal, Réanimation néonatale, 123 boulevard Port Royal, 75014 Paris,  
4  
5 France

6  
7 M.D.  
8

9  
10 <sup>7</sup> AP-HP, Hôpital Robert Debré, Réanimation et Surveillance continue pédiatrique, 48  
11  
12 boulevard sérurier 75019 Paris, France

13  
14 M.D.  
15

16 <sup>8</sup> Université Paris Descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation  
17  
18 Néonatale, 149 rue de Sèvres 75015 Paris, France

19  
20 Ph.D  
21

22 <sup>9</sup> AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 7149 rue de  
23  
24 Sèvres, 75015 Paris, France

25  
26 M.D.  
27

28  
29 <sup>10</sup> Centre Hospitalier Sud Francilien, Médecine Néonatale, 116 boulevard Jean Jaurès, 91100  
30  
31 Corbeil, France

32  
33 M.D.  
34

35  
36 <sup>11</sup> AP-HP, Hôpital Bicêtre, Réanimation Néonatale et Pédiatrique, 78 rue du général Leclerc,  
37  
38 94275 Kremlin-Bicêtre, France

39  
40 M.D.  
41

42 <sup>12</sup> Centre Hospitalier Intercommunal, Hôpital Poissy, Unité de Réanimation Néonatale, 23  
43  
44 boulevard Gambetta, 78100 Poissy, France

45  
46 M.D.  
47

48  
49 <sup>13</sup> Centre Hospitalier René Dubos, Médecine Néonatale et Réanimation Pédiatrique, 6 avenue  
50  
51 de l'Ile de France, 95303 Pontoise, France

52  
53 M.D.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 <sup>14</sup> AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 149 rue de  
4  
5 Sèvres, 75015 Paris, France

6  
7 PhD

8  
9 <sup>15</sup> AP-HP, Hôpital Armand-Trousseau, Centre Nationale de Ressources de lutte contre la  
10  
11 Douleur 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

12  
13 RN (Research nurse)

14  
15 <sup>16</sup> Inserm U953, Maternité Port-Royal, , 123 boulevard Port Royal, 75014 Paris, France

16  
17 PhD

18  
19 <sup>17</sup> University of Tennessee Health Science Center & Le Bonheur Children's Hospital,  
20  
21 Memphis, TN

22  
23 PhD

24  
25 <sup>18</sup> Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences  
26  
27 pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France; Université  
28  
29 Pierre et Marie Curie, 75006 Paris

30  
31 PhD

32  
33  
34  
35  
36  
37  
38 **Corresponding author** : Romain GUEDJ, Service des urgences pédiatriques, Hôpital  
39  
40 Trousseau, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12

41  
42 Phone: + 33 144 736 487 Fax: +33 144 736 985

43  
44 Email : romainguedj@gmail.com

45  
46  
47  
48  
49  
50  
51  
52 Abbréviations :

53  
54 NICU : Neonatal intensive care unit

55  
56 OR : Odd ratio

1  
2  
3 PICU : Pediatric intensive care unit  
4  
5  
6

7 Key words :  
8

9 Pain ; Neonate ; Neonatology and infant care ; After-hours care ; painful procedures ; pain  
10  
11  
12

13  
14 Word count : 2492 words.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Abstract

**Objective :** To determine whether analgesic use for painful procedures performed in neonates in the Neonatal intensive care unit (NICU) differs during nights and days and during each of the 6-hour period of the day.

**Design :** Conducted as part of the prospective observational EIPPAIN study which was designed to collect in real time and around-the-clock bedside data on all painful or stressful procedures

**Setting :** 13 NICUs and PICUs in the Paris Region, France.

**Participants:** All 430 neonates admitted to the participating units during a 6-week period between September 2005 and January 2006.

**Data collection.** During the first 14 days of admission data were collected on all painful procedures and analgesic therapy. The five most frequent procedures representing 38012 of all 42413 (90%) painful procedures were analyzed.

**Intervention :** Observational study

**Main outcome assesment :** We compared the use of specific analgesia for procedures performed during each of the 6-hour periods of a day: Morning (7:00AM to 12:59PM), Afternoon, Early Night and Late Night, and during Daytime (Morning+Afternoon) and Nighttime (Early Night+Late Night).

**Results:** 7724 out of 38012 (20.3%) painful procedures were carried out with a specific analgesic treatment. For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%. The relative reduction of analgesia was 18.3%,  $p < 0.001$ , between Daytime and Nighttime and 28.8%,  $p < 0.001$ , between Morning and the Rest of the day. Parental presence, nurse 8-hour shifts and written protocols for analgesia were associated with a decrease in this difference.

1  
2  
3 **Conclusion :** The substantial differences in the use of analgesia around-the clock may be  
4  
5 questioned on quality of care grounds.  
6  
7

8  
9 **Article summary :**

10 Article focus : Some epidemiological studies focused on mortality-risk and medical errors  
11  
12 raise concern about the homogeneity of care around the clock. Variation of analgesic use for  
13  
14 painful procedure in neonates in intensive care units during day has never been studied.  
15  
16

17 Key messages : Specific analgesia for painful procedures was more frequent during daytime  
18  
19 than nighttime. It gradually decreased from morning to late night. Pain management  
20  
21 guidelines should include standardization of care across 24 hours.  
22  
23

24 Main strengths and limitations of this study : This is the first prospective multicenter study to  
25  
26 show variations in analgesic practices around-the clock. The around the clock variations in  
27  
28 analgesia use for procedural pain management did not correspond to an isolated practice of a  
29  
30 single center but rather to the practices of a large geographical region.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Patients and their families expect that the same quality of care be provided to patients 24  
4 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Patients and their families expect that the same quality of care be provided to patients 24 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and medical errors have found poorer outcomes for hospital care given during evening or night-time hours<sup>1-7</sup>. Among neonates, one study reported that perinatal mortality rates fluctuated according to the hour of birth with a peak occurring in the evening<sup>3</sup> and another study found a higher mortality for term neonates born in the evenings, nights or weekends<sup>4</sup>. These studies raise concern about the homogeneity of care in settings where patients expect safe and high quality care 24 hour-a-day. Significant practice variability also occurs in many other aspects of care. To our knowledge, the variation of neonatal pain management during day and night shifts has not been studied yet.

Neonatal pain management has received much attention during the last two decades leading professional societies to issue guidelines to improve pain management in this vulnerable population<sup>8,9</sup>. These guidelines highlight the necessity to improve analgesia for invasive procedures, which constitute the main source of pain in sick or premature infants admitted to the neonatal intensive care unit (NICU). However, surveys of clinical practices suggest that many evidence-based interventions have not been applied effectively in NICUs<sup>10</sup> and that wide gaps exist between knowledge and practice<sup>11</sup>. The undertreatment of pain in this population would be aggravated by variations in analgesic use according to the time of the day. Thus, the question about variation of quality of pain management during day and night is of practical relevance.

We designed this study to determine whether analgesic use for painful procedures performed in neonates in the NICU and the Pediatric intensive care unit (PICU) differs during nights and days and during four 6-hour periods of the day. This study was conducted as part of the EIPPAIN study<sup>12</sup>.



## METHODS

### Study centers

The detailed methodology of the EIPPAIN study was published elsewhere<sup>12</sup>. EIPPAIN was a prospective observational study designed to collect 24-hours a day bedside data on all painful or stressful procedures performed in neonates admitted to NICUs and PICUs of a geographically defined region. All 14 tertiary care centers, NICUs and PICUs in the Paris Region were invited to participate and 13 accepted the invitation.

All the participating units had developed their pain management protocols locally. No instructions were given to modify the standard of care for procedural pain management in neonates. The study protocol and the data collection forms were reviewed by the local committee for the protection of human subjects.

### Study population

We included in this study all neonates admitted to the participating units during a 6-week period between September 2005 and January 2006. Inclusion criterion was admitted preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria.

### Data collection

During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Specific pre-procedural analgesia included nonpharmacological (eg, sweet solutions, sucking) or pharmacological treatments (eg, single- or multiple drug doses). Nursing and medical staff at the bedside recorded all procedures on a specific form in real

1  
2  
3 time. Since the EIPPAIN study did not include data about the characteristics of the  
4 participating units, we conducted a phone survey with each head nurse in March 2010. Since  
5 the EIPPAIN study did not include data about the characteristics of the participating units,  
6 we conducted in March 2010 a phone survey with each head nurse present at the time of the  
7 initial study (2005-2006). We inquired about nurse shifts (two or three per day), shift rotation  
8 (between day and night), existence of a pain coordinator, written standardized protocols for  
9 sucrose analgesia, parental presence authorized 24-hours a day, ratios of residents to number  
10 of beds in order to describe the teaching status <sup>13</sup>, and existence of a night head nurse.  
11  
12  
13  
14  
15  
16  
17  
18  
19

### 20 **Painful procedures**

21  
22 The EIPPAIN study collected data on 430 neonates who underwent 60969 procedures.  
23 Because the current international definition of pain <sup>14</sup> does not apply to neonates, we chose a  
24 published empirical approach to define pain. Of these 60969 procedures, 42413 were  
25 considered painful, including 44 different procedures. In order to study the differences in  
26 analgesic management during the 24 hours of the day, we selected the five most frequent  
27 procedures that would both be readily performed at any time in an intensive care unit and also  
28 represent the majority of painful procedures : nasal or tracheal suctioning, heel sticks,  
29 adhesive removals, and vascular punctures (arterial punctures, venipunctures and intravenous  
30 cannulas). As shown in figure 1, these five procedures accounted for 90% of all painful  
31 procedures.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

45 The use of procedural analgesia was defined as the use of specific analgesia given prior to  
46 painful procedures (pharmacological or nonpharmacological therapy).  
47  
48  
49

### 50 **Data analysis**

51  
52 Data were double entered into a relational database (EpiData Entry, version 3·0, Odense,  
53 Denmark) and analyzed with SPSS, v14 for Windows, (SPSS Inc, Chicago, Illinois) and Stata  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 v.10.0 software (Stata Corporation, College Station, TX, USA). Procedures were distributed  
4  
5 according to the time when they were performed, into four 6-hour periods: Morning (from  
6  
7 7:00AM to 12:59PM), Afternoon (from 1:00PM to 6:59PM), Early Night (from 7:00PM to  
8  
9 0:59AM) and Late Night (from 1:00AM to 6:59AM). We also defined Daytime as Morning +  
10  
11 Afternoon and Nighttime as Early Night + Late Night. These timings were chosen because in  
12  
13 France most of the day and night nurse shifts start at 7:00am and 7:00pm, respectively.  
14  
15 Descriptive statistics were used to summarize continuous and categorical variables.  
16

17  
18 We calculated the percentage of use of specific analgesia for each of the 6-hour periods,  
19  
20 Daytime, Nighttime and for the period including Afternoon + Early Night + Late Night. The  
21  
22 use of specific analgesia was compared between periods using Chi2-tests.  
23

24  
25 We included in our model procedures and children characteristics that were found to be  
26  
27 associated with the use of specific analgesia prior to procedures in the EIPPAIN study (Day  
28  
29 of procedure, mechanical ventilation, parental presence, continuous analgesia, surgery, sex,  
30  
31 and gestational age) and variables describing centers (nurse shift, nurse rotation, pain  
32  
33 coordinator, written protocols for sucrose analgesia, policy on parental presence authorized  
34  
35 24-hours, night head nurse and teaching status). In order to investigate factors associated with  
36  
37 differences in analgesia use 24-hours a day, we tested the interactions between analgesia use  
38  
39 and the characteristics of newborns, centers, and procedures. Since data were not independent,  
40  
41 procedures were clustered by child and center. We used a multilevel logistic regression model  
42  
43 with random intercept and slope in order to adjust interactions, to test cross level interactions  
44  
45 and to control for confounding factors<sup>15,16</sup>. In this multilevel analysis, procedure, child and  
46  
47 center were at the lowest, second and highest level, respectively.  
48  
49

50  
51 All the described factors were included in our model and all interactions between time of  
52  
53 procedures (daytime or nighttime) and each covariate were obtained. Results are presented as  
54  
55

1  
2  
3 point estimate odds ratios (ORs) with 2-sided 95% confidence intervals (CI). The threshold  
4  
5 for statistical significance was set up at a probability value of <0.05.  
6  
7  
8  
9

## 10 **RESULTS**

11  
12  
13 From the 430 neonates included in the study, 309 (71.9%) were from NICUs and 121 (28.1%)  
14  
15 from PICUs. The mean (SD) length of stay was 8.4 (4.6) calendar days and the observation  
16  
17 period represented 3598 patient-days. The overall rate of mechanical tracheal ventilation was  
18  
19 70.5%, but it varied from 46.2% to 92% across units. Table 1 lists the demographic  
20  
21 characteristics of the study population and Table 2 lists the characteristics of the participating  
22  
23 centers. Figure 2 shows the distribution of painful procedures by hour of the day.  
24  
25  
26

### 27 **Specific Analgesic treatments**

28  
29 Overall, 7724 out of 38012 (20.3%) painful procedures were carried out with the provision of  
30  
31 a specific analgesic treatment. Regarding heel sticks and vascular punctures, 3696/8396  
32  
33 (44.0%) and 1483/2088 (71.0%), respectively, were performed with specific analgesia.  
34  
35 Analgesic treatment varied widely among centers. Table 3 shows the use of specific  
36  
37 analgesia, by center, for all procedures, heel sticks and vascular punctures.  
38  
39  
40  
41  
42

### 43 **Analgesia use according to time of the day**

44  
45 Figure 3 shows the use of analgesia for each 6-hour period of the day. For all painful  
46  
47 procedures or for skin-breaking procedures, the use of analgesia was higher in the morning,  
48  
49 decreased during the day and was lowest in the late night ( $p<0.001$ ).  
50  
51  
52  
53

54  
55 For all procedures taken together or for skin breaking procedures analyzed separately, the use  
56  
57 of analgesia was significantly higher for procedures performed in the morning versus the rest  
58  
59  
60

1  
2  
3 of the day,  $p < 0.001$ , as well as for procedures performed during the daytime versus the  
4  
5 nighttime,  $p < 0.001$ , Table 4.  
6  
7

### 8 **Clinical Factors associated with Diurnal Variations in Analgesia**

9  
10 Interactions between differences in analgesia use during daytime and nighttime and the  
11  
12 characteristics of children, centers and procedures in univariate analysis are listed in Table 5.

13  
14 We can see for instance that regarding mechanical ventilation the relative reduction in  
15  
16 analgesia use during nighttime compared to daytime was 13.1% in invasively ventilated  
17  
18 infants and 20.8% in spontaneously breathing or non-invasively ventilated infants.  
19

20  
21 The inclusion of all clinical factors in a multilevel analysis, showed that analgesia use was  
22  
23 significantly higher for procedures performed during the daytime versus the nighttime, (OR =  
24  
25 2.11[1.18–3.78],  $p < 0.05$ ). In this multilevel model, day of procedure (related to admission),  
26  
27 mechanical ventilation, parental presence, nurse shift, and written protocol for analgesia  
28  
29 significantly interacted with time of procedure, as shown in table 6.  
30  
31  
32  
33  
34  
35

### 36 **DISCUSSION**

37  
38 This is the first prospective multicenter study to show variations in analgesic practices  
39  
40 around-the clock. The use of specific analgesia for painful procedures was more frequent  
41  
42 during daytime than nighttime. Moreover, we found that specific analgesia for painful  
43  
44 procedures was the highest in the morning and the lowest in the nighttime. In fact, it gradually  
45  
46 decreased from morning to late night.  
47  
48

49  
50 The relative reduction in the use of specific analgesia between daytime and nighttime was  
51  
52 18.3% for all five painful procedures and this difference reached 28.8% between the morning  
53  
54 and the rest of the day. Such substantial differences in the use of analgesia may be questioned  
55  
56 on quality of care grounds. We consider that the lower use of analgesia during those periods  
57  
58  
59  
60

1  
2  
3 represents a marker of poor quality care that needs to be overcome. The differences in  
4 analgesia use between daytime and nighttime that we found in this study were independent of  
5 the type of procedure and whether the procedure was more frequently performed during a  
6 period of the day. In fact, heel sticks were homogeneously distributed around-the clock and  
7 vascular punctures were more frequent during the morning, but the differences in analgesia  
8 use were very similar and consistent (figure 3).  
9  
10  
11  
12  
13  
14  
15  
16  
17

18 The around the clock variations in analgesia use for procedural pain management did not  
19 correspond to an isolated practice of a single center but rather to the practices of a large  
20 geographical region. The participation of all but one center in this region, the uniform data  
21 collection at all centers, and 100% patient inclusion during the study period ensure that the  
22 study cohort was representative of NICU procedural pain management in the Paris region.  
23 Moreover, we feel that these results could be extrapolated to the entire French territory  
24 because this is the most populated region of France and it closely reflects the practices in the  
25 rest of the country.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

39 The variation of quality of neonatal care over the day has been rarely studied directly. Most  
40 studies have used outcomes as a proxy to assess this variation. Some studies reported  
41 increased rates of perinatal death at night<sup>3-5</sup>. Although mortality could be considered as an  
42 important proxy to assess quality of care, it has the disadvantage of being related to only  
43 serious or critical conditions and it is exposed to several confounding factors. Medication  
44 error rate has also been used in a few studies to assess variations in quality of care. It has been  
45 found that errors were higher during nighttime than during daytime(6, 20). However, care  
46 quality cannot be restricted to a safety problem. Optimal care quality implies, among other  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 standards, care without pain. Thus, analgesic use for painful procedure is also a parameter to  
4  
5 measure care quality.  
6  
7

8  
9  
10 In an attempt to explain our findings, we investigated factors associated with differences of  
11  
12 analgesia use around-the-clock. Parental presence, nurse 8-hour shifts and written protocols  
13  
14 for analgesia decreased the difference of analgesia use between day and night. These results  
15  
16 suggest that written protocols or parental presence may limit the reduction of analgesia use  
17  
18 during nighttime. Protocols limit the freedom of health care providers about the management  
19  
20 of pain, making the practice of caregivers more homogeneous. It has been reported that the  
21  
22 presence of protocols, by harmonizing practices, increases the quality of care<sup>10</sup>. Similarly, it  
23  
24 has been reported that the presence of parents influences the practice of caregivers<sup>17</sup>. Our  
25  
26 data also suggest that shorter hour shifts (8-hour) for nurses decrease the difference of  
27  
28 analgesia use between day and night. In other health care areas, it has been shown that 12-  
29  
30 hours shifts negatively influence the behavior of care providers yielding to less efficient  
31  
32 care<sup>18,19</sup>. However, the area of variations in pain management practices is highly complex and  
33  
34 to attempt to explain it by staffing or protocols is probably simplistic. Other factors that we  
35  
36 have not studied could play a role. Contextual factors may influence staff behaviors. Although  
37  
38 number of nurses is homogeneous during daytime and nighttime in French NICUs, more  
39  
40 medical staff is around in the morning and in the afternoon. Interprofessional collaboration  
41  
42 practices<sup>20</sup> and higher access to personnel to care for complex patients<sup>21</sup> may enhance pain  
43  
44 practices. Thus, analgesic use may also be influenced by the total number of staff and not only  
45  
46  
47  
48  
49  
50 nurses.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 We acknowledge two limitations of this study. First, a potential bias would be a difference in  
4  
5 quality of data collection during days and nights. We consider that this is not likely because  
6  
7 we ensured a completeness of reporting by verifying from the patients' charts that all  
8  
9 procedures were documented on the study datasheets. Furthermore, there is no reason that a  
10  
11 nurse recorded a procedure but not the use of analgesia. Second, we collected data about the  
12  
13 characteristics and organization of center in a retrospective manner 5 years after the collection  
14  
15 of clinical data. This might have introduced a bias. However, we feel that this bias was  
16  
17 minimized because we obtained data from the head nurse who usually keeps records of all  
18  
19 organizational details. Since we only had 13 centers, data about organizational characteristics  
20  
21 should be looked upon with caution.  
22  
23  
24  
25  
26  
27

## 28 CONCLUSION

29  
30  
31 Our findings suggest that the constant efforts to improve care quality should also include  
32  
33 standardization of care across 24 hours and pain management guidelines should reinforce this  
34  
35 message. The variation of care quality during the day is certainly a complex phenomenon that  
36  
37 deserves further research. It appears that human factors intervene in the process of care  
38  
39 delivery and we need to better understand them in order to improve care quality. Our results  
40  
41 suggest that the modification of organisational factors such as parental presence and written  
42  
43 protocols may contribute to the homogenization of quality of care around the clock.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

## 54 Acknowledgment

55  
56 We would like to acknowledge l'Académie de Médecine  
57  
58  
59  
60



## REFERENCES

- 1 Duke GJ, Green JV, Briedis JH. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. *Anaesth Intensive Care* 2004;**32**:697–701.
- 2 Laupland KB, Shahpori R, Kirkpatrick AW, *et al.* Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care* 2008;**23**:317–24.
- 3 Paccaud F, Martin-Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. *Lancet* 1988;**1**:340–3.
- 4 Pasupathy D, Wood AM, Pell JP, *et al.* Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ* 2010;**341**:c3498.
- 5 Stephansson O, Dickman PW, Johansson ALV, *et al.* Time of birth and risk of intrapartum and early neonatal death. *Epidemiology* 2003;**14**:218–22.
- 6 Miller AD, Piro CC, Rudisill CN, *et al.* Nighttime and weekend medication error rates in an inpatient pediatric population. *Ann Pharmacother* 2010;**44**:1739–46.
- 7 Hendeby GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. *Academic Emergency Medicine* 2005;**12**:629–34.
- 8 Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;**155**:173–80.
- 9 Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics* 2000;**105**:454–61.
- 10 Sharek PJ, Powers R, Koehn A, *et al.* Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics* 2006;**118 Suppl 2**:S78–86.
- 11 Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. *J Paediatr Child Health* 2011;**47**:92–8.
- 12 Carbajal R, Rousset A, Danan C, *et al.* Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA* 2008;**300**:60–70.
- 13 Aiken LH, Clarke SP, Sloane DM, *et al.* Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002;**288**:1987–93.
- 14 Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;**6**:249.
- 15 Merlo J, Chaix B, Ohlsson H, *et al.* A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;**60**:290–7.

- 1  
2  
3 16 Merlo J, Chaix B, Yang M, *et al.* A brief conceptual tutorial on multilevel analysis in  
4 social epidemiology: interpreting neighbourhood differences and the effect of  
5 neighbourhood characteristics on individual health. *J Epidemiol Community Health*  
6 2005;**59**:1022–8.  
7  
8 17 Johnston C, Barrington KJ, Taddio A, *et al.* Pain in Canadian NICUs: have we improved  
9 over the past 12 years? *Clin J Pain* 2011;**27**:225–32.  
10  
11 18 Borges FN da S, Fischer FM. Twelve-hour night shifts of healthcare workers: a risk to the  
12 patients? *Chronobiol Int* 2003;**20**:351–60.  
13  
14 19 Macias DJ, Hafner J 2nd, Brillman JC, *et al.* Effect of time of day and duration into shift  
15 on hazardous exposures to biological fluids. *Acad Emerg Med* 1996;**3**:605–10.  
16  
17 20 Latimer MA, Johnston CC, Ritchie JA, *et al.* Factors affecting delivery of evidence-based  
18 procedural pain care in hospitalized neonates. *J Obstet Gynecol Neonatal Nurs*  
19 2009;**38**:182–94.  
20  
21 21 Stevens B, Riahi S, Cardoso R, *et al.* The influence of context on pain practices in the  
22 NICU: perceptions of health care professionals. *Qual Health Res* 2011;**21**:757–70.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1. Demographic characteristics of 430 neonates

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
<b>Gestational age group at birth</b>				
24-29 wk	119 (27.7)			
30-32 wk	108 (25.1)			
33-36 wk	84 (19.5)			
37-42 wk	119 (27.7)			
<b>Birth weight (g)</b>		<b>1962 (957)</b>	<b>1743 (1155-2738)</b>	<b>490-4760</b>
<b>Male</b>	<b>237 (55.1)</b>			
<b>Inborn (born at study hospital)</b>	<b>237 (55.1)</b>			
<b>Age at admission (h)</b>			<b>2.5 (0.5 – 24.0)</b>	
<b>Surgery during the study period</b>	<b>30 (7.0)</b>			
<b>Mechanical tracheal ventilation</b>	<b>303 (70.5)</b>			
<b>Duration of participation (d)</b>				
<b>Overall</b>		<b>8.4 (4.6)</b>	<b>8.0 (4.0-14.0)</b>	<b>1-14</b>
<b>24-29 wk</b>		<b>11.6 (3.8)</b>	<b>14.0 (9.0-14.0)</b>	<b>2-14</b>
<b>30-32 wk</b>		<b>8.7 (4.6)</b>	<b>9.0 (4.0-14.0)</b>	<b>1-14</b>
<b>33-36 wk</b>		<b>6.6 (4.0)</b>	<b>6.0 (3.0-9.0)</b>	<b>2-14</b>
<b>37-42 wk</b>		<b>6.0 (3.9)</b>	<b>5.0 (3.0-8.0)</b>	<b>1-14</b>
<b>Hospitalized for more than 14 days</b>	<b>126 (29.3)</b>			
<b>Died during the study period</b>	<b>24(5.6)</b>			

Table 2: Characteristics of centers

	Number of centers n = 13
<b><u>Nurse shift</u></b>	
2 per day	9
3 per day	4
<b><u>Day-night nurse rotation</u></b>	
Yes	7
No	6
<b><u>Pain coordinator</u></b>	
Yes	10
No	3
<b><u>Written standardized protocols for sucrose analgesia</u></b>	
Yes	11
No	2
<b><u>Parental presence authorized 24-hours</u></b>	
Yes	6
No	7
<b><u>Teaching status*</u></b>	
Minor	6
Major	7
<b><u>Night head nurse</u></b>	
Yes	2
No	11

\* postgraduate trainees /bed ratio : minor teaching units if ratios were  $\frac{1}{4}$  or less,  
major teaching units if ratios were higher than  $\frac{1}{4}$

Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 2002 Oct 23-30;288(16):1987-93

Table 3 – Use of specific analgesia for painful procedures by center

Center (n°)	Procedures carried out with specific preprocedural analgesia					
	All 5 painful procedures		Heel sticks		Vascular punctures	
	n/N*	%	n/N*	%	n/N*	%
1	89 / 1 356	6.6	3/ 8	37.5	35/ 67	52.2
2	162 / 4 091	4.0	22/ 926	2.4	114/ 207	55.1
3	1 614/ 3 239	49.8	939/ 1312	71.6	224/ 285	78.6
4	544 / 2 105	25.8	270/ 629	42.9	183/ 199	92.0
5	1 682 / 9 110	18.5	847/ 1 560	54.3	279/ 374	74.6
6	590/ 2 467	23.9	410/ 489	83.8	86/ 105	81.9
7	213 / 2 138	10.0	94/ 633	14.8	55/ 82	67.1
8	711 / 2 309	30.8	394/ 573	68.8	94/ 162	58.0
9	111 / 1 235	9.0	18/ 264	6.8	55/ 106	51.9
10	331 / 1 953	16.9	109/ 360	30.3	53/ 84	63.1
11	237 / 2316	10.2	140/ 643	21.8	43/ 75	57.3
12	200 / 983	20.3	87/ 241	36.1	37/ 60	61.7
13	1 240 / 4710	26.3	363/ 758	47.9	225/ 282	79.8
All centers	7 724/ 38 012	20.3	3 696/ 8 396	44.0	1 483/ 2088	71.0

\*

Number of painful procedures performed with analgesia / total number of that specific procedure

Table 4. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

	Number of procedures	Procedures carried out with specific analgesia		Relative Reduction *	p
	N	n	%		(chi2)
<b>MORNING VS REST OF THE DAY</b>					
<b>5 painful procedures</b>					
Morning	9 861	2 546	25.8%	28.8 %	<0.001
Rest of the day	28 151	5 178	18.4%		
<b>Heel sticks</b>					
Morning	1 860	980	52.7%	21.1 %	<0.001
Rest of the day	6 536	2 716	41.6%		
<b>Vascular punctures</b>					
Morning	955	723	75.7%	11.4 %	<0.001
Rest of the day	1 133	760	67.1%		
<b>DAYTIME VS NIGHTTIME</b>					
<b>5 painful procedures</b>					
Daytime	19 059	4 261	22.5%	18.3 %	<0.001
Nighttime	18 953	3 463	18.3%		
<b>Heel sticks</b>					
Daytime	3 871	1 856	47.9%	15.2 %	<0.001
Nighttime	4 525	1 840	40.7%		
<b>Vascular punctures</b>					
Daytime	1 363	1 003	73.6%	10.0 %	<0.001
Nighttime	725	480	66.2%		

\*Percentage of relative reduction in the use of specific analgesia

Table 5 - Interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in univariate analysis

Factor		UNIVARIATE ANALYSIS						
		Procedures carried out with specific analgesia				Daytime compared to nighttime : Relative reduction <sup>a</sup>	Daytime compared to nighttime : OR	Interaction test (p) <sup>b</sup>
		Daytime		Nighttime				
		n/N	%	n/N	%			
<u>Day of procedure<sup>c</sup></u>	D1	272/ 1 789	15.2	276/ 1 667	16.6	-8.9%	0.90 (0.75 -1.09)	<b>&lt;10-3</b>
	D2-D14	3 989/17 164	23.2	3 187/17 392	18.3	21.2%	1.35 (1.28 -1.42)	
<u>Mechanical ventilation</u>	Yes	1 668/11 908	14.0	1 501/12 327	12.2	13.1%	1.18 (1.09 -1.27)	<b>&lt;10-3</b>
	No	2 593/ 7 045	36.8	1 962/ 6 732	29.1	20.8%	1.42 (1.32 -1.52)	
<u>Parental presence</u>	Yes	331/ 1 488	22.2	131/ 485	27.0	-21.4%	0.77 (0.61 -0.98)	<b>&lt;10-3</b>
	No	3 930/17 465	22.5	3 332/18 574	17.9	21.0%	1.33 (1.26 -1.40)	
<u>Continuous analgesia</u>	Yes	738/ 6 341	11.6	722/ 6 864	10.8	9.6 %	1.12 (1.01 -1.25)	<b>0.005</b>
	No	3 523/12 612	27.9	2 741/12 195	22.5	19.5 %	1.34 (1.26 -1.42)	
<u>Surgery</u>	Yes	337/ 1 576	21.4	300/ 1 714	17.5	18.2%	1.28 (1.08 -1.53)	0.829
	No	3 924/17 377	22.6	3 163/17 345	18.2	19.5%	1.31 (1.24 -1.38)	
<u>Sex</u>	Male	2 363/10 758	22.0	1 877/10 757	17.4	20.9%	1.33 (1.25 -1.43)	0.410
	Female	1 898/ 8 198	23.2	1 586/ 8 302	19.1	17.6%	1.28 (1.18 -138)	
<u>Gestational age</u>	≥ 37 weeks	583/ 3 803	15.3	435/ 3 796	11.5	25.2%	1.40 (1.22 -1.60)	0.295
	< 37 weeks	3 678/15 150	24.3	3 028/15 263	19.8	18.3%	1.30 (1.23 -1.37)	
<u>Nurse shift</u>	3 per day	1 634/ 5 995	27.3	1 276/ 5 907	21.6	20.7%	1.36 (1.25 -1.48)	0.230
	2 per day	2 627/12 958	20.3	2 187/13 152	16.6	18.0%	1.28 (1.20 -1.36)	
<u>Nurse rotation</u>	No	1 853/ 7 507	24.7	1 477/ 7 704	19.2	22.3%	1.38 (1.28 -1.49)	0.068
	Yes	2 408/11 446	21.0	1 986/11 355	17.5	16.9%	1.26 (1.18 -1.34)	
<u>Pain coordinator</u>	No	502/ 2 844	17.7	368/ 2 933	12.5	28.9%	1.49 (1.29 -1.73)	0.053
	Yes	3 759/16 109	23.3	3 095/16 126	19.2	17.8%	1.28 (1.22 -1.35)	
<u>Written protocols for sucrose analgesia</u>	Yes	3 663/15 325	23.9	3 155/15 508	20.3	14.9%	1.23 (1.17 -1.30)	<b>&lt;10-3</b>
	No	598/ 3 628	16.5	308/ 3 551	8.7	47.4%	2.08 (1.80 -2.41)	
<u>Parental presence authorized 24-hours</u>	No	2 510/ 11 949	21.0	2 091/12 023	17.4	17.2%	1.26 (1.18 -1.35)	0.102
	Yes	1 751/ 7 004	25.0	1 372/ 7 036	19.5	22.0%	1.28 (1.27 -1.49)	
<u>Night head nurse</u>	No	2 843/12 348	23.0	2 399/12 889	18.6	19.2%	1.31 (1.23 -1.39)	0.955
	Yes	1 418/ 6 605	21.5	1 064/ 6 170	17.2	19.7%	1.31 (1.20 -1.43)	
<u>Teaching status</u>	Minor	1 798/ 7 222	24.9	1 511/ 7 516	20.1	19.2%	1.32 (1.22 -1.42)	0.864
	Major	2 463/11 731	21.0	1 952/11 543	16.9	19.5%	1.31 (1.22 -1.40)	

<sup>a</sup> If positive, analgesia was higher during daytime  
<sup>c</sup> related to admission

<sup>b</sup> p value < 0.05 indicates that the factor modified the difference in analgesia use between daytime and nighttime in univariate

Table 6 – Significant interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in a multivariate, multilevel analysis<sup>a</sup>

Factor	Interaction test (p-value)	Interaction direction		OR
		Increase difference <sup>c</sup>	Decrease difference <sup>c</sup>	
Day of procedure <sup>b</sup>	<0.001	D2-D14		1.55 (1.23-1.94)
Mechanical ventilation	<0.05	Absence of mechanical ventilation during procedure		1.21 (1.02-1.43)
Parental presence	<0.001		Parents present	0.59 (0.44-0.79)
Nurse shift	<0.01	12 hour nurse shifts		2.25 (1.23-4.12)
Written protocols for sucrose analgesia	<0.001	Absence of written protocols for sucrose analgesia		2.40 (1.74-3.30)

<sup>a</sup> This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model. Only factors that significantly interacted with time of procedure are shown in the table.

<sup>b</sup> related to admission

<sup>c</sup> Refers to the difference in analgesia use during daytime compared to nighttime



1  
2  
3 **Funding source and conflict of interest statement** : This study was supported by grant  
4  
5 funds from the Fondation CNP, and the Fondation de France, France. R Guedj received a  
6  
7 grant from L'Académie de Médecine to work on this study. These funding agencies did not  
8  
9 participate in any of the following: design and conduct of the study; collection, management,  
10  
11 analysis, and interpretation of the data; and preparation, review, or approval of the  
12  
13 manuscript. No financial relationships with any organisations that might have an interest in  
14  
15 the submitted work in the previous 3 years; no other relationships or activities that could  
16  
17 appear to have influenced the submitted work  
18  
19

20  
21  
22  
23 **Data Sharing** : No available data sharing  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Contributor's statement page

1  
2  
3  
4  
5  
6 Romain Guedj : Dr Guedj analysed and interpreted the data. He drafted the initial  
7 manuscript and approved the final manuscript as submitted.  
8

9  
10 Claude Danan : Dr Danan implemented, coordinated and supervised the trial at one of thirteen  
11 participating unit. He reviewed and revised the manuscript, and he approved the final  
12 manuscript as submitted.  
13

14 Patrick Daoud : Dr Daoud implemented, coordinated and supervised the trial at one of thirteen  
15 participating unit. He reviewed and revised the manuscript, and he approved the final  
16 manuscript as submitted.  
17

18 Véronique Zupan : Dr Zupan implemented, coordinated and supervised the trial at one of  
19 thirteen participating unit. She reviewed and revised the manuscript, and she approved the  
20 final manuscript as submitted.  
21

22 Sylvain Renolleau : Pr Renolleau implemented, coordinated and supervised the trial at one of  
23 thirteen participating unit. He reviewed and revised the manuscript, and he approved the final  
24 manuscript as submitted.  
25

26 Elodie Zana : Dr Zana implemented, coordinated and supervised the trial at one of thirteen  
27 participating unit. She reviewed and revised the manuscript, and she approved the final  
28 manuscript as submitted.  
29

30 Sophie Aizenfisz : Dr Aizenfisz implemented, coordinated and supervised the trial at one of  
31 thirteen participating unit. She reviewed and revised the manuscript, and she approved the  
32 final manuscript as submitted.  
33

34 Alexandre Lapillonne : Dr Lapillonne implemented, coordinated and supervised the trial at one  
35 of thirteen participating unit. He reviewed and revised the manuscript, and he approved the  
36 final manuscript as submitted.  
37

38 Laure de Saint Blanquat : Dr de Saint Blanquat implemented, coordinated and supervised the  
39 trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she  
40 approved the final manuscript as submitted.  
41

42 Michèle Granier : Dr Granier implemented, coordinated and supervised the trial at one of  
43 thirteen participating unit. She reviewed and revised the manuscript, and she approved the  
44 final manuscript as submitted.  
45

46 Philippe Durand : Dr Durand implemented, coordinated and supervised the trial at one of  
47 thirteen participating unit. He reviewed and revised the manuscript, and he approved the final  
48 manuscript as submitted.  
49

50 Florence Castela : Dr Castela implemented, coordinated and supervised the trial at one of  
51 thirteen participating unit. She reviewed and revised the manuscript, and she approved the  
52 final manuscript as submitted.  
53

1  
2  
3 Anne Coursol : Dr Coursol implemented, coordinated and supervised the trial at one of thirteen  
4 participating unit. She reviewed and revised the manuscript, and she approved the final  
5 manuscript as submitted.  
6

7 Philippe Hubert : Pr Hubert designed the study. He reviewed and revised the manuscript, and  
8 he approved the final manuscript as submitted.  
9

10 Patricia Cimerman : Mrs Cimerman designed the study. She reviewed and revised the  
11 manuscript, and she approved the final manuscript as submitted.  
12

13 Babak Khoshnood : Pr Khoshnood designed the study and interpreted the data. He reviewed  
14 and revised the manuscript, and he approved the final manuscript as submitted.  
15

16 KJS Anand : Pr Anand designed the study. He reviewed and revised the manuscript, and he  
17 approved the final manuscript as submitted.  
18

19 Ricardo Carbajal : Pr Carbajal designed the study and interpreted the data. He reviewed and  
20 revised the manuscript, and he approved the final manuscript as submitted. He is guarantor  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

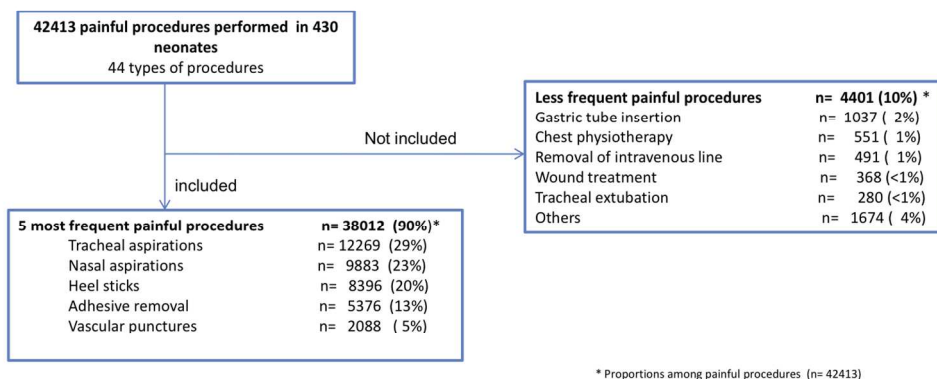


Figure 1 – Distribution of painful procedures analysed in the study

254x190mm (150 x 150 DPI)

Review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

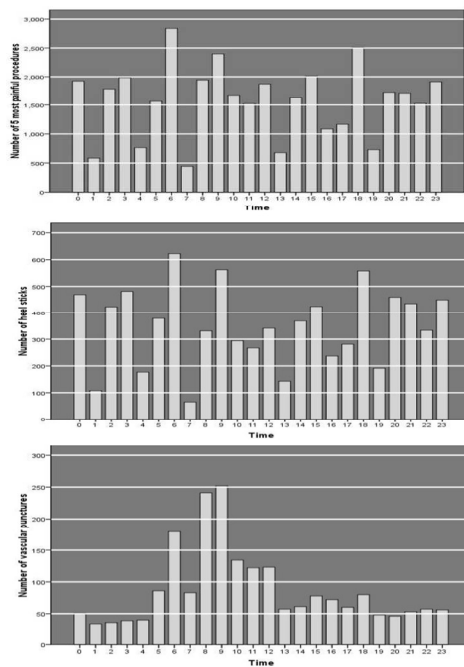
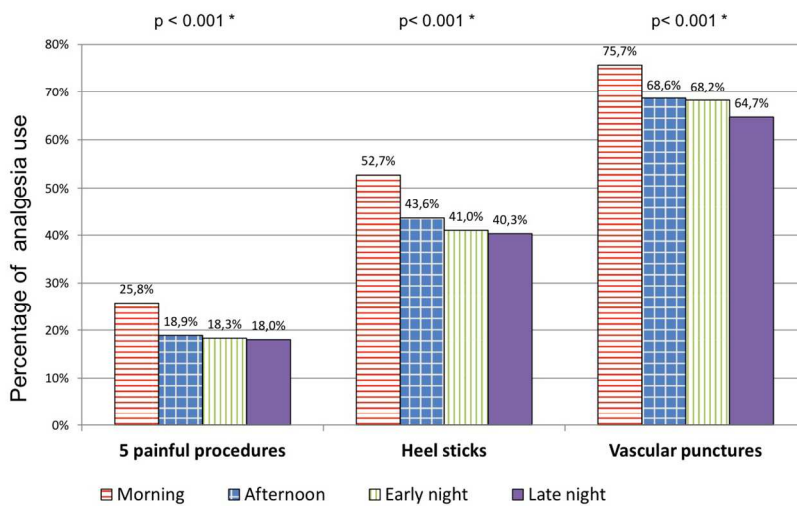


Figure 2 – Distribution of painful procedures by hour of the day  
 (Five most frequent painful procedures, n=38 012 ; Heel sticks, n = 8 396 ; Vascular punctures, n = 2 088)

254x190mm (150 x 150 DPI)

View only



**Figure 3 – Use of analgesia during each of the 6-hour period of the day for all procedures as well as for heel sticks and vascular punctures**

\*Global comparison of all four 6-hour periods  
 For all five painful procedures, heel sticks and vascular punctures, the comparison of morning vs each one of the other 6-hour periods was significant with  $p < 0.001$ .  
 For heel sticks, the comparison of afternoon vs late night showed a p value = 0,032  
 All other pairwise comparisons were not significant

254x190mm (150 x 150 DPI)

View only

1  
2  
3 **Neonatal Pain Management is not the same During Days and Nights in Intensive**  
4 **Care Units: Analysis from the prospective EIPPAIN Study**  
5

6 **Strobe Checklist**  
7

8 **TITLE AND ABSTRACT**  
9

10  
11 **1a/ (a) Indicate the study's design with a commonly used term in the title or the**  
12 **abstract**

13 Done on page 1  
14

15 **1b) Provide in the abstract an informative and balanced summary of what was**  
16 **done and what was found**

17 Done  
18  
19

20  
21 **INTRODUCTION :**  
22

23 **2/ Explain the scientific background and rationale for the investigation being**  
24 **reported**

25 Done in paragraph 1 and 2 (page 2)  
26  
27

28 **3/ State specific objectives, including any prespecified hypotheses**

29 Done in paragraph 3  
30  
31

32 **METHODS :**  
33

34 **4/ Present key elements of study design early in the paper**

35 Done in the first paragraph of the Methods section  
36  
37

38 **5/ Describe the setting, locations, and relevant dates, including periods of**  
39 **recruitment, exposure, follow-up, and data collection.**

40 Setting and locations are described in the paragraph called "study center"

41 Period of recruitment is described in the paragraph called "study population".

42 Dates of exposure and data collection are described in the paragraph called "Data  
43 collection".  
44

45  
46 **6/ Give the eligibility criteria, and the source and methods of selection of**  
47 **participants**

48 This information is given in paragraphs called "study population" and "painful  
49 procedures"  
50

51  
52 **7/ Clearly define all outcomes, exposures, predictors, potential confounders, and**  
53 **effect modifiers.**

54 The outcome (use of analgesia) is defined in paragraph named "painful procedures".

55 Exposures are defined in the paragraph named "data analysis".

56 Predictors and effect modifiers are presented in the "Data analysis" section and in the  
57 "Clinical factors associated with diurnal variations in analgesia"  
58  
59  
60



1  
2  
3  
4 **8/ For each variable of interest, give sources of data and details of methods of**  
5 **assessment.**

6 All patient and procedure variables were collected prospectively and systematically.  
7 Center variables were collected retrospectively. This information is stated in the  
8 Methods section.  
9

10  
11 **9/ Describe any efforts to address potential sources of bias.**

12 We motivated all staff from all participating centers to obtain a 100% inclusion rate so  
13 that data reflect real practices.  
14

15  
16 **10/ Explain how the study size was arrived at**

17 A 6-week data collection period for each unit was considered sufficient to study the  
18 practices of all rotating personnel and to minimize temporal changes in clinical  
19 practices. This is stated in the Method section.  
20

21  
22 **11/ Explain how quantitative variables were handled in the analyses.**

23 Quantitative variables existed only in demographic data and these were described as  
24 mean (SD) and median (interquartile range). There were no other quantitative  
25 variables.  
26

27  
28 **12/ a Describe all statistical methods, including those used to control for**  
29 **confounding**

30 These methods are included in paragraph named "data analysis"  
31

32  
33 **12b/ Describe any methods used to examine subgroups and interactions**

34 These methods are included in paragraph named "data analysis"  
35

36  
37 **12c/ Explain how missing data were addressed**

38 There were no missing data.  
39

40  
41 **RESULTS**

42  
43 **13a/ Report numbers of individual at each stage of study,**

44 **b/ Give reasons for non-participation at each stage**

45 **c/ Consider use of a flow diagram**

46 This information is given in paragraphs called "painful procedures" of methods section  
47 and in figure 1.  
48

49  
50 **14a/ Give characteristics of study population and information on exposures and**  
51 **potential confounders**

52 **b/ Indicate number of participants with missing data for each variable of interest**

53 This information is given in tables 1, 2 and 3 and in the first paragraph of results section.  
54

55  
56 **15/ Reports number of outcome events**

57 This information is given in paragraph named "specific analgesia treatment"  
58  
59  
60

1  
2  
3 **16a/ Give unadjusted estimates and if applicable, confounder-adjusted estimates**  
4 **and their precision. Make clear which confounders were adjusted for and why**  
5 **they were included.**

6 Unadjusted estimates are given in table 4.

7 Confounder-adjusted estimates are given in paragraph named “clinical factors  
8 associated with diurnal variation in analgesia”.

9 **16b and c : not applicable**

10  
11  
12 **17/ Report other analyses done**

13 Analyses of interactions are reported in table 5 and 6

14  
15 **DISCUSSION**

16  
17  
18 **18/ Summarise key results with reference to study objectives**

19 Key results are summarized in the first two paragraphs.

20  
21 **19/ Discuss limitations of the study, taking into account sources of bias or**  
22 **imprecision.**

23 Limitations are discussed in the last paragraph.

24  
25  
26 **20/ Give a cautious overall interpretation of results considering objectives,**  
27 **limitations, multiplicity of analyses, results from similar studies, and other**  
28 **relevant evidence**

29 Done

30  
31 **21/ Discuss the generalisability of the study results**

32 Generalisability is discussed in paragraph 3.

33  
34 **OTHER INFORMATION**

35  
36  
37 **22/ Give the source of funding and the role of the funders for the present study**  
38 **and, if applicable, for the original study on which the present article is based.**

39 The funding agencies of the Epippain study are listed in the manuscript.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004086.R1
Article Type:	Research
Date Submitted by the Author:	03-Dec-2013
Complete List of Authors:	Guedj, Romain; AP-HP - Hôpital Armand Trousseau, Service d'urgences pédiatriques; Inserm U-953, Danan, Claude; Centre Hospitalier Intercommunal de Creteil, Unité de réanimation néonatale Daoud, Patrick; Centre Hospitalier André Grégoire, Réanimation Infantile Zupan, Véronique; AP-HP, Hôpital ANtoine Béclère, Pédiatrie et Réanimation néonatale Renolleau, Sylvain; AP-HP, Hôpital Armand Trousseau, Réanimation Néonatale et Pédiatrique Zana-Taieb, Elodie; Médecine néonatale Port-Royal-Cochin, NICU Aizenfisz, Sophie; AP-HP, Hôpital Robert Debré, Réanimation pédiatrique Lapillonne, Alexandre; Université Paris descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation néonatale de Saint Blanquat, Laure; Hôpital Necker, PICU Granier, Michele; Hôpital sud-francilien, NICU Durand, Philippe; Bicetre Hospital, Paediatric Intensive Care Unit Castela, Florence; Hôpital Poissy, Unité de réanimation néonatale Coursol, Anne; CH René Dubos, NICU Hubert, Philippe; Hopital Necker Paris, intensive care unit Cimerman, Patricia; Hopital Armand Trousseau, Centre National de Ressources de lutte contre la Douleur Anand, Sunny; Le Bonheur Children's Hospital, University of Tennessee Health Science Center Khoshnood, Babak; Hopital Saint Vincent de Paul, INSERM U953 Carbajal, Ricardo; Hôpital Trousseau, Service des Urgences Pédiatriques
<b>Primary Subject Heading</b>:	Paediatrics
Secondary Subject Heading:	Intensive care
Keywords:	NEONATOLOGY, after hour care, painful procedures, Pain

SCHOLARONE™  
Manuscripts

## Neonatal Pain Management is not the same During Days and Nights in Intensive Care

### Units

**Authors** : Romain Guedj<sup>1</sup>, MD, Claude Danan<sup>2</sup>, MD, Patrick Daoud<sup>3</sup>, MD, Véronique Zupan<sup>4</sup>, MD, Sylvain Renolleau<sup>5</sup>, MD, PhD, Elodie Zana<sup>6</sup>, MD, Sophie Aizenfisz<sup>7</sup>, MD, Alexandre Lapillonne<sup>8</sup>, MD, PhD, Laure de Saint Blanquat<sup>9</sup>, MD, Michèle Granier<sup>10</sup>, MD, Philippe Durand<sup>11</sup>, MD, Florence Castela<sup>12</sup>, MD, Anne Coursol<sup>13</sup>, MD, Philippe Hubert<sup>14</sup>, MD, PhD, Patricia Cimerman<sup>15</sup>, Research Nurse, Babak Khoshnood<sup>16</sup>, PhD, KJS Anand<sup>17</sup>, MD, PhD, Ricardo Carbajal<sup>18</sup>, MD, PhD.

<sup>1</sup> Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France  
M.D.

<sup>2</sup> Centre Hospitalier Intercommunal de Créteil, Unité de réanimation néonatale et soins intensifs, 40 avenue de Verdun 94010 Créteil Cedex, France  
M.D.

<sup>3</sup> Centre Hospitalier André Grégoire, Réanimation infantile, 56, bd de la Boissiere 93105 Montreuil-sous-Bois Cedex, France  
M.D.

<sup>4</sup> AP-HP, Hôpital Antoine Bécclère, Pédiatrie et Réanimation Néonatale, 157, rue de la Porte de Trivaux 92141 Clamart cedex, France  
M.D.

<sup>5</sup> AP-HP, Hôpital Armand-Trousseau, Réanimation Néonatale et Pédiatrique, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

1  
2  
3 PhD

4  
5 <sup>6</sup> Maternité Port-Royal, Réanimation néonatale, 123 boulevard Port Royal, 75014 Paris,  
6  
7 France

8  
9 M.D.

10  
11 <sup>7</sup> AP-HP, Hôpital Robert Debré, Réanimation et Surveillance continue pédiatrique, 48  
12  
13 boulevard sérurier 75019 Paris, France

14  
15 M.D.

16  
17 <sup>8</sup> Université Paris Descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation  
18  
19 Néonatale, 149 rue de Sèvres 75015 Paris, France

20  
21 Ph.D

22  
23 <sup>9</sup> AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 7149 rue de  
24  
25 Sèvres, 75015 Paris, France

26  
27 M.D.

28  
29 <sup>10</sup> Centre Hospitalier Sud Francilien, Médecine Néonatale, 116 boulevard Jean Jaurès, 91100  
30  
31 Corbeil, France

32  
33 M.D.

34  
35 <sup>11</sup> AP-HP, Hôpital Bicêtre, Réanimation Néonatale et Pédiatrique, 78 rue du général Leclerc,  
36  
37 94275 Kremlin-Bicêtre, France

38  
39 M.D.

40  
41 <sup>12</sup> Centre Hospitalier Intercommunal, Hôpital Poissy, Unité de Réanimation Néonatale, 23  
42  
43 boulevard Gambetta, 78100 Poissy, France

44  
45 M.D.

46  
47 <sup>13</sup> Centre Hospitalier René Dubos, Médecine Néonatale et Réanimation Pédiatrique, 6 avenue  
48  
49 de l'Ile de France, 95303 Pontoise, France

50  
51 M.D.

1  
2  
3 <sup>14</sup> AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 149 rue de  
4  
5 Sèvres, 75015 Paris, France

6  
7 PhD

8  
9 <sup>15</sup> AP-HP, Hôpital Armand-Trousseau, Centre Nationale de Ressources de lutte contre la  
10  
11 Douleur 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

12  
13 RN (Research nurse)

14  
15 <sup>16</sup> Inserm U953, Maternité Port-Royal, , 123 boulevard Port Royal, 75014 Paris, France

16  
17 PhD

18  
19 <sup>17</sup> University of Tennessee Health Science Center & Le Bonheur Children's Hospital,  
20  
21 Memphis, TN

22  
23 PhD

24  
25 <sup>18</sup> Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences  
26  
27 pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France; Université  
28  
29 Pierre et Marie Curie, 75006 Paris

30  
31 PhD

32  
33  
34  
35  
36  
37  
38 **Corresponding author** : Romain GUEDJ, Service des urgences pédiatriques, Hôpital  
39  
40 Trousseau, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12

41  
42 Phone: + 33 144 736 487 Fax: +33 144 736 985

43  
44 Email : romainguedj@gmail.com

45  
46  
47  
48  
49  
50  
51  
52 Abbréviations :

53  
54 NICU : Neonatal intensive care unit

55  
56 OR : Odd ratio

1  
2  
3 PICU : Pediatric intensive care unit  
4  
5  
6

7 Key words :  
8

9 Pain ; Neonate ; Neonatology and infant care ; After-hours care ; painful procedures ; pain  
10  
11  
12

13  
14 Word count : 2 717 words.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Abstract

**Objective :** To determine whether analgesic use for painful procedures performed in neonates in the Neonatal intensive care unit (NICU) differs during nights and days and during each of the 6-hour period of the day.

**Design :** Conducted as part of the prospective observational EIPPAIN study which was designed to collect in real time and around-the-clock bedside data on all painful or stressful procedures

**Setting :** 13 NICUs and PICUs in the Paris Region, France.

**Participants:** All 430 neonates admitted to the participating units during a 6-week period between September 2005 and January 2006.

**Data collection.** During the first 14 days of admission data were collected on all painful procedures and analgesic therapy. The five most frequent procedures representing 38012 of all 42413 (90%) painful procedures were analyzed.

**Intervention :** Observational study

**Main outcome assesment :** We compared the use of specific analgesia for procedures performed during each of the 6-hour periods of a day: Morning (7:00AM to 12:59PM), Afternoon, Early Night and Late Night, and during Daytime (Morning+Afternoon) and Nighttime (Early Night+Late Night).

**Results:** 7724 out of 38012 (20.3%) painful procedures were carried out with a specific analgesic treatment. For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%. The relative reduction of analgesia was 18.3%,  $p < 0.01$ , between Daytime and Nighttime and 28.8%,  $p < 0.001$ , between Morning and the Rest of the day. Parental presence, nurse 8-hour shifts and written protocols for analgesia were associated with a decrease in this difference.



1  
2  
3 **Conclusion :** The substantial differences in the use of analgesia around-the clock may be  
4  
5 questioned on quality of care grounds.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**Article summary :**

Article focus : Some epidemiological studies focused on mortality-risk and medical errors raise concern about the homogeneity of care around the clock. Variation of analgesic use for painful procedure in neonates in intensive care units during day has never been studied.

Key messages : Specific analgesia for painful procedures was more frequent during daytime than nighttime. It gradually decreased from morning to late night. Pain management guidelines should include standardization of care across 24 hours.

Main strengths and limitations of this study : This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region.

1  
2  
3 Patients and their families expect that the same quality of care be provided to patients 24  
4 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Patients and their families expect that the same quality of care be provided to patients 24 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and medical errors have found poorer outcomes for hospital care given during evening or night-time hours.<sup>1-7</sup> Among neonates, one study reported that perinatal mortality rates fluctuated according to the hour of birth with a peak occurring in the evening<sup>3</sup> and another study found a higher mortality for term neonates born in the evenings, nights or weekends.<sup>4</sup> These studies raise concern about the homogeneity of care in settings where patients expect safe and high quality care 24 hour-a-day. Significant practice variability also occurs in many other aspects of care. To our knowledge, the variation of neonatal pain management during day and night shifts has not been studied yet.

Neonatal pain management has received much attention during the last two decades leading professional societies to issue guidelines to improve pain management in this vulnerable population.<sup>8,9</sup> These guidelines highlight the necessity to improve analgesia for invasive procedures, which constitute the main source of pain in sick or premature infants admitted to the neonatal intensive care unit (NICU). However, surveys of clinical practices suggest that many evidence-based interventions have not been applied effectively in NICUs<sup>10</sup> and that wide gaps exist between knowledge and practice.<sup>11</sup> The undertreatment of pain in this population would be aggravated by variations in analgesic use according to the time of the day. Thus, the question about variation of quality of pain management during day and night is of practical relevance.

We designed this study to determine whether analgesic use for painful procedures performed in neonates in the NICU and the Pediatric intensive care unit (PICU) differs during nights and days and during four 6-hour periods of the day. This study was conducted as part of the EIPPAIN study.<sup>12</sup>

## METHODS

### Study centers

The detailed methodology of the EIPPAIN study was published elsewhere.<sup>12</sup> EIPPAIN was a prospective observational study designed to collect 24-hours a day bedside data on all painful or stressful procedures performed in neonates admitted to NICUs and PICUs of a geographically defined region. All 14 tertiary care centers, NICUs and PICUs in the Paris Region were invited to participate and 13 accepted the invitation.

All the participating units had developed their pain management protocols locally. No instructions were given to modify the standard of care for procedural pain management in neonates. The study protocol and the data collection forms were reviewed by the local committee for the protection of human subjects.

### Study population

We included in this study all neonates admitted to the participating units during a 6-week period between September 2005 and January 2006. Inclusion criterion was admitted preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria.

### Data collection

During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Specific pre-procedural analgesia included nonpharmacological (eg, sweet solutions, sucking) or pharmacological treatments (eg, single- or multiple drug doses). Nursing and medical staff at the bedside recorded all procedures on a specific form in real

1  
2  
3 time. Since the EIPPAIN study did not include data about the characteristics of the  
4 participating units, we conducted in March 2010 a phone survey with each head nurse present  
5 at the time of the initial study (2005-2006). We inquired about nurse shifts (two or three per  
6 day), shift rotation (between day and night), existence of a pain coordinator, written  
7 standardized protocols for sucrose analgesia, parental presence authorized 24-hours a day,  
8 ratios of residents to number of beds in order to describe the teaching status,<sup>13</sup> and existence  
9 of a night head nurse.  
10  
11

### 12 **Painful procedures**

13  
14 The EIPPAIN study collected data on 430 neonates who underwent 60969 procedures.  
15 Because the current international definition of pain<sup>14</sup> does not apply to neonates, we chose a  
16 published empirical approach to define pain. This describes pain as an inherent quality of life  
17 that appears early in ontogeny to serve as a signaling system for tissue damage.<sup>15</sup> Thus, a  
18 procedure was considered painful if it invaded the neonate's bodily integrity, causing skin  
19 injury or mucosal injury from the introduction or removal of foreign material into airway or  
20 digestive or urinary tract. Of these 60969 procedures, 42413 were considered painful,  
21 including 44 different procedures. In order to study the differences in analgesic management  
22 during the 24 hours of the day, we selected the five most frequent procedures that would both  
23 be readily performed at any time in an intensive care unit and also represent the majority of  
24 painful procedures : nasal or tracheal suctioning, heel sticks, adhesive removals, and vascular  
25 punctures (arterial punctures, venipunctures and intravenous cannulas). As shown in figure 1,  
26 these five procedures accounted for 90% of all painful procedures.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

49 The use of procedural analgesia was defined as the use of specific analgesia given prior to  
50 painful procedures (pharmacological or nonpharmacological therapy).  
51  
52  
53  
54  
55

### 56 **Data analysis**

1  
2  
3 Data were double entered into a relational database (EpiData Entry, version 3.0, Odense,  
4 Denmark) and analyzed with SPSS, v14 for Windows, (SPSS Inc, Chicago, Illinois) and Stata  
5 v.10.0 software (Stata Corporation, College Station, TX, USA). Procedures were distributed  
6 according to the time when they were performed, into four 6-hour periods: Morning (from  
7 7:00AM to 12:59PM), Afternoon (from 1:00PM to 6:59PM), Early Night (from 7:00PM to  
8 0:59AM) and Late Night (from 1:00AM to 6:59AM). We also defined Daytime as Morning +  
9 Afternoon and Nighttime as Early Night + Late Night. These timings were chosen because in  
10 France most of the day and night nurse shifts start at 7:00am and 7:00pm, respectively.  
11 Descriptive statistics were used to summarize continuous and categorical variables.  
12

13  
14 The outcome was the use of procedural analgesia. We calculated the percentage of use of  
15 procedural analgesia for each of the 6-hour periods, Daytime, Nighttime and for the period  
16 including Afternoon + Early Night + Late Night. Since data were not independent, procedures  
17 were clustered by child and center. Therefore, the use of procedural analgesia was compared  
18 across periods using a multilevel model with random effect at child and center levels.  
19

20  
21 We assessed changes in the effect of time of day across center by computing specific center  
22 crude OR to test heterogeneity of the ORs across centers. Then, we constructed a model  
23 including procedures and children characteristics that were found to be associated with the  
24 use of specific analgesia prior to procedures in the EIPPAIN study (Day of procedure,  
25 mechanical ventilation, parental presence, continuous analgesia, surgery, sex, and gestational  
26 age) and variables describing centers (nurse shift, nurse rotation, pain coordinator, written  
27 protocols for sucrose analgesia, policy on parental presence authorized 24-hours, night head  
28 nurse and teaching status). In order to investigate factors associated with differences in  
29 analgesia use 24-hours a day, we tested the interactions between analgesia use and the  
30 characteristics of newborns, centers, and procedures.. We used a multilevel logistic regression  
31 model with random intercept and random slope in order to test cross level interactions and to  
32

control for confounding factors.<sup>16,17</sup> In this multilevel analysis, procedure, child and center were at the lowest, second and highest level, respectively.

All the described factors were included in our model and all interactions between time of procedures (daytime or nighttime) and each covariate were obtained. Results are presented as point estimate odds ratios (ORs) with 2-sided 95% confidence intervals (CI). The threshold for statistical significance was set up at a probability value of <0.05.

## RESULTS

From the 430 neonates included in the study, 309 (71.9%) were from NICUs and 121 (28.1%) from PICUs. The mean (SD) length of stay was 8.4 (4.6) calendar days and the observation period represented 3598 patient-days. The overall rate of mechanical tracheal ventilation was 70.5%, but it varied from 46.2% to 92% across units. Table 1 lists the demographic characteristics of the study population and Table 2 lists the characteristics of the participating centers. Appendix 1 shows the distribution of painful procedures by hour of the day. Overall, 7724 out of 38012 (20.3%) painful procedures were carried out with the provision of a specific analgesic treatment. Regarding heel sticks and vascular punctures, 3696/8396 (44.0%) and 1483/2088 (71.0%), respectively, were performed with specific analgesia..

### **Analgesia use according to time of the day**

For Morning, Afternoon, Early Night and Late Night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18% ( $p < 0.001$ ). Figure 2 shows the use of analgesia for each 6-hour period of the day by category of procedures. For all painful procedures taken together or for skin-breaking procedures, the use of analgesia was higher in the morning, decreased during the day and was lowest in the late night.

1  
2  
3 For all procedures taken together or for skin breaking procedures analyzed separately, the use  
4 of analgesia was significantly higher for procedures performed in the morning versus the rest  
5 of the day, ( $p < 0.001$  for all painful procedures,  $p < 0.01$  for heel sticks and vascular punctures),  
6 as well as for all painful procedures ( $p < 0.01$ ) and heel sticks ( $p < 0.05$ ) performed during the  
7 daytime versus the nighttime, Use of analgesia was close to be significantly higher for  
8 vascular punctures performed during daytime versus nighttime ( $p = 0.07$ ). Table 3.  
9  
10  
11  
12  
13  
14  
15  
16

### 17 **Factors associated with Diurnal Variations in Analgesia**

18 Use of analgesia varied widely among centers (from 4.0% to 49.8%) as shown in appendix 2.  
19 Moreover, difference of use analgesia between daytime and nighttime significantly varied  
20 among centers as shown in figure 3.  
21  
22  
23  
24  
25

26 Interactions between differences in analgesia use during daytime and nighttime and the  
27 characteristics of children, centers and procedures in univariate analysis are listed in Table 4.  
28 We can see for instance that regarding mechanical ventilation the relative reduction in  
29 analgesia use during nighttime compared to daytime was 13.1% in invasively ventilated  
30 infants and 20.8% in spontaneously breathing or non-invasively ventilated infants.  
31  
32  
33  
34  
35  
36

37 The inclusion of all clinical factors in a multilevel analysis, showed that analgesia use was  
38 significantly higher for procedures performed during the daytime versus the nighttime, ( $OR =$   
39  $2.25 [1.10-4.60]$ ,  $p < 0.05$ ). In this multilevel model, day of procedure (related to admission),  
40 mechanical ventilation, parental presence, nurse shift, and written protocol for analgesia  
41 significantly interacted with time of procedure, as shown in table 5. (the whole list of ORs  
42 from the model is shown in appendix 3). Presence of parents reversed the difference of use of  
43 analgesia between daytime and nighttime; i.e. analgesia was significantly more frequent in  
44 nighttime than in daytime when parents were presents.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## DISCUSSION

This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The use of specific analgesia for painful procedures was more frequent during daytime than nighttime. Moreover, we found a sharp decrease in use of analgesia from morning to afternoon followed by a gentle decline thereafter.

The relative reduction in the use of specific analgesia between daytime and nighttime was 18.3% for all five painful procedures and this difference reached 28.8% between the morning and the rest of the day. Such substantial differences in the use of analgesia may be questioned on quality of care grounds. We consider that the lower use of analgesia during those periods represents a marker of poor quality care that needs to be overcome. The differences in analgesia use between daytime and nighttime that we found in this study were independent of the type of procedure and whether the procedure was more frequently performed during a period of the day. In fact, heel sticks were homogeneously distributed around-the clock and vascular punctures were more frequent during the morning, but the differences in analgesia use were very similar and consistent (Appendix 1).

The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region. The participation of all but one center in this region, the uniform data collection at all centers, and 100% patient inclusion during the study period ensure that the study cohort was representative of NICU procedural pain management in the Paris region. The extrapolation of these results to the entire French territory may be possible but not totally certain because of conflicting arguments. On one side, (i) the Paris region is the most populated region in France and practices within this area closely may reflect those of the country and (ii) analgesia use was significantly more frequent during daytime than nighttime

1  
2  
3 in eight of thirteen centers but on the other side, the analysis of crude OR by center did not  
4  
5 show homogeneity (figure 3).  
6  
7  
8  
9

10 The variation of quality of neonatal care over the day has been rarely studied directly. Most  
11 studies have used outcomes as a proxy to assess this variation. Some studies reported  
12 increased rates of perinatal death at night.<sup>3-5</sup> Although mortality could be considered as an  
13 important proxy to assess quality of care, it has the disadvantage of being related to only  
14 serious or critical conditions and it is exposed to several confounding factors. Medication  
15 error rate has also been used in a few studies to assess variations in quality of care. It has been  
16 found that errors were higher during nighttime than during daytime.<sup>6,20</sup> However, care quality  
17 cannot be restricted to a safety problem. Optimal care quality implies, among other standards,  
18 care without pain. Thus, analgesic use for painful procedure is also a parameter to measure  
19 care quality.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34

35 In an attempt to explain our findings, we investigated factors associated with differences of  
36 analgesia use around-the-clock. Parental presence, nurse 8-hour shifts and written protocols  
37 for analgesia decreased the difference of analgesia use between day and night. These results  
38 suggest that written protocols or parental presence may limit the reduction of analgesia use  
39 during nighttime. Protocols limit the freedom of health care providers about the management  
40 of pain, making the practice of caregivers more homogeneous. It has been reported that the  
41 presence of protocols, by harmonizing practices, increases the quality of care.<sup>10</sup> Similarly, it  
42 has been reported that the presence of parents influences the practice of caregivers.<sup>18</sup> Our  
43 data also suggest that shorter hour shifts (8-hour) for nurses decrease the difference of  
44 analgesia use between day and night. In other health care areas, it has been shown that 12-  
45 hours shifts negatively influence the behavior of care providers yielding to less efficient  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 care.<sup>19,20</sup> However, the area of variations in pain management practices is highly complex and  
4  
5 to attempt to explain it by staffing or protocols is probably simplistic. Other factors that we  
6  
7 have not studied could play a role. Contextual factors may influence staff behaviors. Although  
8  
9 number of nurses is homogeneous during daytime and nighttime in French NICUs, more  
10  
11 medical staff is around in the morning and in the afternoon. Interprofessional collaboration  
12  
13 practices<sup>21</sup> and higher access to personnel to care for complex patients<sup>22</sup> may enhance pain  
14  
15 practices. Thus, analgesic use may also be influenced by the total number of staff and not only  
16  
17 nurses.  
18  
19

20  
21  
22  
23  
24  
25 We acknowledge two limitations of this study. First, a potential bias would be a difference in  
26  
27 quality of data collection during days and nights. We consider that this is not likely because  
28  
29 we ensured a completeness of reporting by verifying from the patients' charts that all  
30  
31 procedures were documented on the study datasheets. Furthermore, there is no reason that a  
32  
33 nurse recorded a procedure but not the use of analgesia. Second, we collected data about the  
34  
35 characteristics and organization of center in a retrospective manner 5 years after the collection  
36  
37 of clinical data. This might have introduced a bias. However, we feel that this bias was  
38  
39 minimized because we obtained data from the head nurse who usually keeps records of all  
40  
41 organizational details. Since we only had 13 centers, data about organizational characteristics  
42  
43 should be looked upon with caution.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6 CONCLUSION  
7  
8

9 Our findings suggest that the constant efforts to improve care quality should also include  
10 standardization of care across 24 hours and pain management guidelines should reinforce this  
11 message. The variation of care quality during the day is certainly a complex phenomenon that  
12 deserves further research. It appears that human factors intervene in the process of care  
13 delivery and we need to better understand them in order to improve care quality. Our results  
14 suggest that the modification of organisational factors such as parental presence and written  
15 protocols may contribute to the homogenization of quality of care around the clock.  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Aknowledgment

We would like to aknowledge l'Académie de Médecine

## Funding and Competing Interests

This study was supported by grant funds from the Fondation CNP, and the Fondation de France, France. R Guedj received a grant from L'Académie de Médecine to work on this study. These funding agencies did not participate in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. No financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work

## Contributorship Statement

Romain Guedj: Dr Guedj participated in the design of study hypothesis, analysed and interpreted the data. He drafted the initial manuscript and approved the final manuscript as submitted.

Claude Danan: Dr Danan implemeted, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patrick Daoud: Dr Daoud implemeted, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Véronique Zupan: Dr Zupan implemeted, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sylvain Renolleau: Pr Renolleau implemeted, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Elodie Zana: Dr Zana implemeted, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sophie Aizenfisz: Dr Aizenfisz implemeted, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Alexandre Lapillonne: Dr Lapillonne implemeted, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Laure de Saint Blanquat: Dr de Saint Blanquat implemeted, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

1  
2  
3 Michèle Granier: Dr Granier implemented, coordinated and supervised the trial at one of  
4 thirteen participating unit. She reviewed and revised the manuscript, and she approved the  
5 final manuscript as submitted.  
6

7 Philippe Durand: Dr Durand implemented, coordinated and supervised the trial at one of  
8 thirteen participating unit. He reviewed and revised the manuscript, and he approved the final  
9 manuscript as submitted.  
10

11 Florence Castela: Dr Castela implemented, coordinated and supervised the trial at one of  
12 thirteen participating unit. She reviewed and revised the manuscript, and she approved the  
13 final manuscript as submitted.  
14

15 Anne Coursol : Dr Coursol implemented, coordinated and supervised the trial at one of thirteen  
16 participating unit. She reviewed and revised the manuscript, and she approved the final  
17 manuscript as submitted.  
18

19 Philippe Hubert: Pr Hubert participated in the design of the study. He reviewed and revised  
20 the manuscript, and he approved the final manuscript as submitted.  
21

22 Patricia Cimerman Mrs Cimerman participated in the design of the study. She reviewed and  
23 revised the manuscript, and she approved the final manuscript as submitted.  
24

25 Babak Khoshnood: Pr Khoshnood participated in the design of the study and interpreted the  
26 data. He reviewed and revised the manuscript, and he approved the final manuscript as  
27 submitted.  
28

29  
30  
31 KJS Anand: Pr Anand participated in the design of the study. He reviewed and revised the  
32 manuscript, and he approved the final manuscript as submitted.  
33

34 Ricardo Carbajal : Pr Carbajal designed the study and interpreted the data. He reviewed and  
35 revised the manuscript, and he approved the final manuscript as submitted. He is the  
36 guarantor of this study  
37

### 38 **Data Sharing Statement**

39 No available data sharing  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Duke GJ, Green JV, Briedis JH. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. *Anaesth Intensive Care*. oct 2004;32(5):697-701.
2. Laupland KB, Shahpori R, Kirkpatrick AW, et al. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care*. sept 2008;23(3):317-324.
3. Paccaud F, Martin-Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. *Lancet*. 13 févr 1988;1(8581):340-343.
4. Pasupathy D, Wood AM, Pell JP, et al. Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ*. 2010;341:c3498.
5. Stephansson O, Dickman PW, Johansson ALV, et al. Time of birth and risk of intrapartum and early neonatal death. *Epidemiology*. mars 2003;14(2):218-222.
6. Miller AD, Piro CC, Rudisill CN, et al. Nighttime and weekend medication error rates in an inpatient pediatric population. *Ann Pharmacother*. nov 2010;44(11):1739-1746.
7. Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. *Academic Emergency Medicine*. 1 juill 2005;12(7):629-634.
8. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med*. févr 2001;155(2):173-180.
9. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics*. févr 2000;105(2):454-461.
10. Sharek PJ, Powers R, Koehn A, et al. Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics*. nov 2006;118 Suppl 2:S78-86.
11. Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. *J Paediatr Child Health*. mars 2011;47(3):92-98.
12. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2 juill 2008;300(1):60-70.
13. Aiken LH, Clarke SP, Sloane DM, et al. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA*. 23 oct 2002;288(16):1987-1993.
14. Pain terms: a list with definitions and notes on usage. Recommended by the IASP

1  
2  
3 Subcommittee on Taxonomy. *Pain*. juin 1979;6(3):249.

4  
5 15. Anand KJ, Craig KD. New perspectives on the definition of pain. *Pain*. sept  
6 1996;67(1):3-6; discussion 209-211.

7  
8  
9 16. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in  
10 social epidemiology: using measures of clustering in multilevel logistic regression to  
11 investigate contextual phenomena. *J Epidemiol Community Health*. avr 2006;60(4):290-297.

12  
13 17. Merlo J, Chaix B, Yang M, et al. A brief conceptual tutorial on multilevel analysis in  
14 social epidemiology: interpreting neighbourhood differences and the effect of  
15 neighbourhood characteristics on individual health. *J Epidemiol Community Health*. déc  
16 2005;59(12):1022-1028.

17  
18  
19 18. Johnston C, Barrington KJ, Taddio A, et al. Pain in Canadian NICUs: have we improved  
20 over the past 12 years? *Clin J Pain*. avr 2011;27(3):225-232.

21  
22  
23 19. Borges FN da S, Fischer FM. Twelve-hour night shifts of healthcare workers: a risk to  
24 the patients? *Chronobiol Int*. mars 2003;20(2):351-360.

25  
26  
27 20. Macias DJ, Hafner J 2nd, Brillman JC, et al. Effect of time of day and duration into  
28 shift on hazardous exposures to biological fluids. *Acad Emerg Med*. juin 1996;3(6):605-610.

29  
30  
31 21. Latimer MA, Johnston CC, Ritchie JA, et al. Factors affecting delivery of evidence-  
32 based procedural pain care in hospitalized neonates. *J Obstet Gynecol Neonatal Nurs*. avr  
33 2009;38(2):182-194.

34  
35  
36 22. Stevens B, Riahi S, Cardoso R, et al. The influence of context on pain practices in the  
37 NICU: perceptions of health care professionals. *Qual Health Res*. juin 2011;21(6):757-770.



Table 1. Demographic characteristics of 430 neonates

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
<b>Gestational age group at birth</b>				
24-29 wk	119 (27.7)			
30-32 wk	108 (25.1)			
33-36 wk	84 (19.5)			
37-42 wk	119 (27.7)			
<b>Birth weight (g)</b>		<b>1962 (957)</b>	<b>1743 (1155-2738)</b>	<b>490-4760</b>
<b>Male</b>	<b>237 (55.1)</b>			
<b>Inborn (born at study hospital)</b>	<b>237 (55.1)</b>			
<b>Age at admission (h)</b>			<b>2.5 (0.5 – 24.0)</b>	
<b>Surgery during the study period</b>	<b>30 (7.0)</b>			
<b>Mechanical tracheal ventilation</b>	<b>303 (70.5)</b>			
<b>Duration of participation (d)</b>				
Overall		8.4 (4.6)	8.0 (4.0-14.0)	1-14
24-29 wk		11.6 (3.8)	14.0 (9.0-14.0)	2-14
30-32 wk		8.7 (4.6)	9.0 (4.0-14.0)	1-14
33-36 wk		6.6 (4.0)	6.0 (3.0-9.0)	2-14
37-42 wk		6.0 (3.9)	5.0 (3.0-8.0)	1-14
<b>Hospitalized for more than 14 days</b>	<b>126 (29.3)</b>			
<b>Died during the study period</b>	<b>24(5.6)</b>			

Table 2: Characteristics of centers

	Number of centers n = 13
<b><u>Nurse shift</u></b>	
2 per day	9
3 per day	4
<b><u>Day-night nurse rotation</u></b>	
Yes	7
No	6
<b><u>Pain coordinator</u></b>	
Yes	10
No	3
<b><u>Written standardized protocols for sucrose analgesia</u></b>	
Yes	11
No	2
<b><u>Parental presence authorized 24-hours</u></b>	
Yes	6
No	7
<b><u>Teaching status*</u></b>	
Minor	6
Major	7
<b><u>Night head nurse</u></b>	
Yes	2
No	11

\* postgraduate trainees /bed ratio : minor teaching units if ratios were  $\frac{1}{4}$  or less,  
major teaching units if ratios were higher than  $\frac{1}{4}$

Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 2002 Oct 23-30;288(16):1987-93

Table 3. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

	Number of procedures	Procedures carried out with specific analgesia		Relative Reduction *	Univariate analysis p
	N	n	%		
<b>MORNING VS REST OF THE DAY</b>					
<b>5 painful procedures</b>					
Morning	9 861	2 546	25.8%	28.8 %	<b>&lt;0.001</b>
Rest of the day	28 151	5 178	18.4%		
<b>Heel sticks</b>					
Morning	1 860	980	52.7%	21.1 %	<b>&lt;0.01</b>
Rest of the day	6 536	2 716	41.6%		
<b>Vascular punctures</b>					
Morning	955	723	75.7%	11.4 %	<b>&lt;0.01</b>
Rest of the day	1 133	760	67.1%		
<b>DAYTIME VS NIGHTTIME</b>					
<b>5 painful procedures</b>					
Daytime	19 059	4 261	22.5%	18.3 %	<b>&lt;0.01</b>
Nighttime	18 953	3 463	18.3%		
<b>Heel sticks</b>					
Daytime	3 871	1 856	47.9%	15.2 %	<b>&lt;0.05</b>
Nighttime	4 525	1 840	40.7%		
<b>Vascular punctures</b>					
Daytime	1 363	1 003	73.6%	10.0 %	<b>0.07</b>
Nighttime	725	480	66.2%		

\*Percentage of relative reduction in the use of specific analgesia

\*\*These are results from multilevel analysis with time of day as the only explanatory variable. In this multilevel analyses, procedure, child and center were at the lowest, second and highest level, respectively.

Table 4 - Interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in univariate analysis

Factor		UNIVARIATE ANALYSIS						
		Procedures carried out with specific analgesia				Daytime compared to nighttime : Relative reduction <sup>a</sup>	Daytime compared to nighttime : OR	Interaction test (p) <sup>b</sup>
		Daytime		Nighttime				
		n/N	%	n/N	%			
<u>Day of procedure<sup>c</sup></u>	D1	272/ 1 789	15.2	276/ 1 667	16.6	-8.9%	0.90 (0.75 -1.09)	<b>&lt;10-3</b>
	D2-D14	3 989/17 164	23.2	3 187/17 392	18.3	21.2%	1.35 (1.28 -1.42)	
<u>Mechanical ventilation</u>	Yes	1 668/11 908	14.0	1 501/12 327	12.2	13.1%	1.18 (1.09 -1.27)	<b>&lt;10-3</b>
	No	2 593/ 7 045	36.8	1 962/ 6 732	29.1	20.8%	1.42 (1.32 -1.52)	
<u>Parental presence</u>	Yes	331/ 1 488	22.2	131/ 485	27.0	-21.4%	0.77 (0.61 -0.98)	<b>&lt;10-3</b>
	No	3 930/17 465	22.5	3 332/18 574	17.9	21.0%	1.33 (1.26 -1.40)	
<u>Continuous analgesia</u>	Yes	738/ 6 341	11.6	722/ 6 864	10.8	9.6 %	1.12 (1.01 -1.25)	<b>0.005</b>
	No	3 523/12 612	27.9	2 741/12 195	22.5	19.5 %	1.34 (1.26 -1.42)	
<u>Surgery</u>	Yes	337/ 1 576	21.4	300/ 1 714	17.5	18.2%	1.28 (1.08 -1.53)	0.829
	No	3 924/17 377	22.6	3 163/17 345	18.2	19.5%	1.31 (1.24 -1.38)	
<u>Sex</u>	Male	2 363/10 758	22.0	1 877/10 757	17.4	20.9%	1.33 (1.25 -1.43)	0.410
	Female	1 898/ 8 198	23.2	1 586/ 8 302	19.1	17.6%	1.28 (1.18 -138)	
<u>Gestational age</u>	≥ 37 weeks	583/ 3 803	15.3	435/ 3 796	11.5	25.2%	1.40 (1.22 -1.60)	0.295
	< 37 weeks	3 678/15 150	24.3	3 028/15 263	19.8	18.3%	1.30 (1.23 -1.37)	
<u>Nurse shift</u>	3 per day	1 634/ 5 995	27.3	1 276/ 5 907	21.6	20.7%	1.36 (1.25 -1.48)	0.230
	2 per day	2 627/12 958	20.3	2 187/13 152	16.6	18.0%	1.28 (1.20 -1.36)	
<u>Nurse rotation</u>	No	1 853/ 7 507	24.7	1 477/ 7 704	19.2	22.3%	1.38 (1.28 -1.49)	0.068
	Yes	2 408/11 446	21.0	1 986/11 355	17.5	16.9%	1.26 (1.18 -1.34)	
<u>Pain coordinator</u>	No	502/ 2 844	17.7	368/ 2 933	12.5	28.9%	1.49 (1.29 -1.73)	0.053
	Yes	3 759/16 109	23.3	3 095/16 126	19.2	17.8%	1.28 (1.22 -1.35)	
<u>Written protocols for sucrose analgesia</u>	Yes	3 663/15 325	23.9	3 155/15 508	20.3	14.9%	1.23 (1.17 -1.30)	<b>&lt;10-3</b>
	No	598/ 3 628	16.5	308/ 3 551	8.7	47.4%	2.08 (1.80 -2.41)	
<u>Parental presence authorized 24-hours</u>	No	2 510/ 11 949	21.0	2 091/12 023	17.4	17.2%	1.26 (1.18 -1.35)	0.102
	Yes	1 751/ 7 004	25.0	1 372/ 7 036	19.5	22.0%	1.28 (1.27 -1.49)	
<u>Night head nurse</u>	No	2 843/12 348	23.0	2 399/12 889	18.6	19.2%	1.31 (1.23 -1.39)	0.955
	Yes	1 418/ 6 605	21.5	1 064/ 6 170	17.2	19.7%	1.31 (1.20 -1.43)	
<u>Teaching status</u>	Minor	1 798/ 7 222	24.9	1 511/ 7 516	20.1	19.2%	1.32 (1.22 -1.42)	0.864
	Major	2 463/11 731	21.0	1 952/11 543	16.9	19.5%	1.31 (1.22 -1.40)	

<sup>a</sup> If positive, analgesia was higher during daytime<sup>b</sup> p value < 0.05 indicates that the factor modified the difference in analgesia use between daytime and nighttime in univariate<sup>c</sup> related to admission

Table 5– Significant interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in a multivariate, multilevel analysis<sup>a</sup>

Factor	Interaction test (p-value)	Interaction direction		OR
		Increase difference <sup>c</sup>	Decrease difference <sup>c</sup>	
Day of procedure <sup>b</sup>	<0.001	D2-D14		1.56 (1.24-1.95)
Mechanical ventilation	<0.05	Absence of mechanical ventilation during procedure		1.20 (1.02-1.43)
Parental presence	<0.001		Parents present	0.58 (0.44-0.78)
Nurse shift	<0.01	12 hour nurse shifts		1.42 (1.05-5.55)
Written protocols for sucrose analgesia	<0.001	Absence of written protocols for sucrose analgesia		2.44 (1.56-3.70)

<sup>a</sup> This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model. Only factors that significantly interacted with time of procedure are shown in the table.

<sup>b</sup> related to admission

<sup>c</sup> Refers to the difference in analgesia use during daytime compared to nighttime

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## Neonatal Pain Management is not the same During Days and Nights in Intensive Care

### Units

**Authors** : Romain Guedj<sup>1</sup>, MD, Claude Danan<sup>2</sup>, MD, Patrick Daoud<sup>3</sup>, MD, Véronique Zupan<sup>4</sup>, MD, Sylvain Renolleau<sup>5</sup>, MD, PhD, Elodie Zana<sup>6</sup>, MD, Sophie Aizenfisz<sup>7</sup>, MD, Alexandre Lapillonne<sup>8</sup>, MD, PhD, Laure de Saint Blanquat<sup>9</sup>, MD, Michèle Granier<sup>10</sup>, MD, Philippe Durand<sup>11</sup>, MD, Florence Castela<sup>12</sup>, MD, Anne Coursol<sup>13</sup>, MD, Philippe Hubert<sup>14</sup>, MD, PhD, Patricia Cimerman<sup>15</sup>, Research Nurse, Babak Khoshnood<sup>16</sup>, PhD, KJS Anand<sup>17</sup>, MD, PhD, Ricardo Carbajal<sup>18</sup>, MD, PhD.

<sup>1</sup> Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

M.D.

<sup>2</sup> Centre Hospitalier Intercommunal de Créteil, Unité de réanimation néonatale et soins intensifs, 40 avenue de Verdun 94010 Créteil Cedex, France

M.D.

<sup>3</sup> Centre Hospitalier André Grégoire, Réanimation infantile, 56, bd de la Boissiere 93105 Montreuil-sous-Bois Cedex, France

M.D.

<sup>4</sup> AP-HP, Hôpital Antoine Béchère, Pédiatrie et Réanimation Néonatale, 157, rue de la Porte de Trivaux 92141 Clamart cedex, France

M.D.

<sup>5</sup> AP-HP, Hôpital Armand-Trousseau, Réanimation Néonatale et Pédiatrique, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

PhD



1  
2  
3  
4  
5  
6  
7 <sup>6</sup> Maternité Port-Royal, Réanimation néonatale, 123 boulevard Port Royal, 75014 Paris,  
8 France

9  
10 M.D.

11  
12 <sup>7</sup> AP-HP, Hôpital Robert Debré, Réanimation et Surveillance continue pédiatrique, 48  
13 boulevard sérurier 75019 Paris, France

14  
15  
16 M.D.

17  
18 <sup>8</sup> Université Paris Descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation  
19 Néonatale, 149 rue de Sèvres 75015 Paris, France

20  
21 Ph.D

22  
23 <sup>9</sup> AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 7149 rue de  
24 Sèvres, 75015 Paris, France

25  
26  
27 M.D.

28  
29 <sup>10</sup> Centre Hospitalier Sud Francilien, Médecine Néonatale, 116 boulevard Jean Jaurès, 91100  
30 Corbeil, France

31  
32  
33 M.D.

34  
35 <sup>11</sup> AP-HP, Hôpital Bicêtre, Réanimation Néonatale et Pédiatrique, 78 rue du général Leclerc,  
36 94275 Kremlin-Bicêtre, France

37  
38  
39 M.D.

40  
41 <sup>12</sup> Centre Hospitalier Intercommunal, Hôpital Poissy, Unité de Réanimation Néonatale, 23  
42 boulevard Gambetta, 78100 Poissy, France

43  
44  
45 M.D.

46  
47 <sup>13</sup> Centre Hospitalier René Dubos, Médecine Néonatale et Réanimation Pédiatrique, 6 avenue  
48 de l'Île de France, 95303 Pontoise, France

49  
50  
51 M.D.

1  
2  
3  
4  
5  
6  
7 <sup>14</sup> AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 149 rue de  
8  
9 Sèvres, 75015 Paris, France

10 PhD

11  
12 <sup>15</sup> AP-HP, Hôpital Armand-Trousseau, Centre Nationale de Ressources de lutte contre la  
13  
14 Douleur 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

15  
16 RN (Research nurse)

17  
18 <sup>16</sup> Inserm U953, Maternité Port-Royal, , 123 boulevard Port Royal, 75014 Paris, France

19  
20 PhD

21  
22 <sup>17</sup> University of Tennessee Health Science Center & Le Bonheur Children's Hospital,  
23  
24 Memphis, TN

25  
26 PhD

27  
28 <sup>18</sup> Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences  
29  
30 pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France; Université  
31  
32 Pierre et Marie Curie, 75006 Paris

33  
34 PhD

35  
36  
37 **Corresponding author** : Romain GUEDJ, Service des urgences pédiatriques, Hôpital  
38  
39 Trousseau, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12

40  
41 Phone: + 33 144 736 487 Fax: +33 144 736 985

42  
43 Email : romainguedj@gmail.com  
44  
45  
46  
47  
48

49 Abréviations :

50 NICU : Neonatal intensive care unit

51  
52 OR : Odd ratio  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 PICU : Pediatric intensive care unit  
8  
9

10 Key words :

11  
12 Pain ; Neonate ; Neonatology and infant care ; After-hours care ; painful procedures ; pain  
13  
14

15  
16 Word count : 2 ~~717492~~ words.  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### Abstract

**Objective :** To determine whether analgesic use for painful procedures performed in neonates in the Neonatal intensive care unit (NICU) differs during nights and days and during each of the 6-hour period of the day.

**Design :** Conducted as part of the prospective observational EIPPAIN study which was designed to collect in real time and around-the-clock bedside data on all painful or stressful procedures

**Setting :** 13 NICUs and PICUs in the Paris Region, France.

**Participants:** All 430 neonates admitted to the participating units during a 6-week period between September 2005 and January 2006.

**Data collection.** During the first 14 days of admission data were collected on all painful procedures and analgesic therapy. The five most frequent procedures representing 38012 of all 42413 (90%) painful procedures were analyzed.

**Intervention :** Observationnal study

**Main outcome assesment :** We compared the use of specific analgesia for procedures performed during each of the 6-hour periods of a day: Morning (7:00AM to 12:59PM), Afternoon, Early Night and Late Night, and during Daytime (Morning+Afternoon) and Nighttime (Early Night+Late Night).

**Results:** 7724 out of 38012 (20.3%) painful procedures were carried out with a specific analgesic treatment. For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%. The relative reduction of analgesia was 18.3%,  $p<0.01$ , between Daytime and Nighttime and 28.8%,  $p<0.001$ , between Morning and the Rest of the day. Parental presence, nurse 8-hour shifts and written protocols for analgesia were associated with a decrease in this difference.

1  
2  
3  
4  
5  
6  
7 **Conclusion** : The substantial differences in the use of analgesia around-the clock may be  
8 questioned on quality of care grounds.  
9

10  
11  
12 **Article summary** :

13  
14 Article focus : Some epidemiological studies focused on mortality-risk and medical errors  
15 raise concern about the homogeneity of care around the clock. Variation of analgesic use for  
16 painful procedure in neonates in intensive care units during day has never been studied.  
17  
18

19  
20 Key messages : Specific analgesia for painful procedures was more frequent during daytime  
21 than nighttime. It gradually decreased from morning to late night. Pain management  
22 guidelines should include standardization of care across 24 hours.  
23

24  
25  
26 Main strengths and limitations of this study : This is the first prospective multicenter study to  
27 show variations in analgesic practices around-the clock. The around the clock variations in  
28 analgesia use for procedural pain management did not correspond to an isolated practice of a  
29 single center but rather to the practices of a large geographical region.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 Patients and their families expect that the same quality of care be provided to patients 24  
8 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and  
9 medical errors have found poorer outcomes for hospital care given during evening or night-  
10 time hours.<sup>1-7</sup> Among neonates, one study reported that perinatal mortality rates fluctuated  
11 according to the hour of birth with a peak occurring in the evening<sup>3</sup> and another study found  
12 a higher mortality for term neonates born in the evenings, nights or weekends.<sup>4</sup> These  
13 studies raise concern about the homogeneity of care in settings where patients expect safe and  
14 high quality care 24 hour-a-day. Significant practice variability also occurs in many other  
15 aspects of care. To our knowledge, the variation of neonatal pain management during day and  
16 night shifts has not been studied yet.

17  
18 Neonatal pain management has received much attention during the last two decades leading  
19 professional societies to issue guidelines to improve pain management in this vulnerable  
20 population.<sup>8,9</sup> These guidelines highlight the necessity to improve analgesia for invasive  
21 procedures, which constitute the main source of pain in sick or premature infants admitted to  
22 the neonatal intensive care unit (NICU). However, surveys of clinical practices suggest that  
23 many evidence-based interventions have not been applied effectively in NICUs<sup>10</sup> and that  
24 wide gaps exist between knowledge and practice.<sup>11</sup> The undertreatment of pain in this  
25 population would be aggravated by variations in analgesic use according to the time of the  
26 day. Thus, the question about variation of quality of pain management during day and night  
27 is of practical relevance.

28  
29 We designed this study to determine whether analgesic use for painful procedures performed  
30 in neonates in the NICU and the Pediatric intensive care unit (PICU) differs during nights and  
31 days and during four 6-hour periods of the day. This study was conducted as part of the  
32 EIPPAIN study.<sup>12</sup>

## METHODS

### Study centers

The detailed methodology of the EIPPAIN study was published elsewhere.<sup>12</sup> EIPPAIN was a prospective observational study designed to collect 24-hours a day bedside data on all painful or stressful procedures performed in neonates admitted to NICUs and PICUs of a geographically defined region. All 14 tertiary care centers, NICUs and PICUs in the Paris Region were invited to participate and 13 accepted the invitation.

All the participating units had developed their pain management protocols locally. No instructions were given to modify the standard of care for procedural pain management in neonates. The study protocol and the data collection forms were reviewed by the local committee for the protection of human subjects.

### Study population

We included in this study all neonates admitted to the participating units during a 6-week period between September 2005 and January 2006. Inclusion criterion was admitted preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria.

### Data collection

During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Specific pre-procedural analgesia included nonpharmacological (eg, sweet solutions, sucking) or pharmacological treatments (eg, single- or multiple drug doses). Nursing and medical staff at the bedside recorded all procedures on a specific form in real

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

time. ~~Since the EIPPAIN study did not include data about the characteristics of the participating units, we conducted a phone survey with each head nurse in March 2010.~~ Since the EIPPAIN study did not include data about the characteristics of the participating units, we conducted in March 2010 a phone survey with each head nurse present at the time of the initial study (2005-2006). We inquired about nurse shifts (two or three per day), shift rotation (between day and night), existence of a pain coordinator, written standardized protocols for sucrose analgesia, parental presence authorized 24-hours a day, ratios of residents to number of beds in order to describe the teaching status,<sup>13,13</sup> and existence of a night head nurse.

### **Painful procedures**

The EIPPAIN study collected data on 430 neonates who underwent 60969 procedures.

Because the current international definition of pain<sup>14,14</sup> does not apply to neonates, we chose a published empirical approach to define pain. This describes pain as an inherent quality of life that appears early in ontogeny to serve as a signaling system for tissue damage.<sup>15</sup> Thus, a procedure was considered painful if it invaded the neonate's bodily integrity, causing skin injury or mucosal injury from the introduction or removal of foreign material into airway or digestive or urinary tract. Of these 60969 procedures, 42413 were considered painful, including 44 different procedures. In order to study the differences in analgesic management during the 24 hours of the day, we selected the five most frequent procedures that would both be readily performed at any time in an intensive care unit and also represent the majority of painful procedures : nasal or tracheal suctioning, heel sticks, adhesive removals, and vascular punctures (arterial punctures, venipunctures and intravenous cannulas). As shown in figure 1, these five procedures accounted for 90% of all painful procedures.

The use of procedural analgesia was defined as the use of specific analgesia given prior to painful procedures (pharmacological or nonpharmacological therapy).



## Data analysis

Data were double entered into a relational database (EpiData Entry, version 3.0, Odense, Denmark) and analyzed with SPSS, v14 for Windows, (SPSS Inc, Chicago, Illinois) and Stata v.10.0 software (Stata Corporation, College Station, TX, USA). Procedures were distributed according to the time when they were performed, into four 6-hour periods: Morning (from 7:00AM to 12:59PM), Afternoon (from 1:00PM to 6:59PM), Early Night (from 7:00PM to 0:59AM) and Late Night (from 1:00AM to 6:59AM). We also defined Daytime as Morning + Afternoon and Nighttime as Early Night + Late Night. These timings were chosen because in France most of the day and night nurse shifts start at 7:00am and 7:00pm, respectively. Descriptive statistics were used to summarize continuous and categorical variables.

The outcome was the use of procedural analgesia. We calculated the percentage of use of ~~specific-procedural~~ analgesia for each of the 6-hour periods, Daytime, Nighttime and for the period including Afternoon + Early Night + Late Night. Since data were not independent, procedures were clustered by child and center. Therefore, the use of ~~specific-procedural~~ analgesia was compared ~~between-across~~ periods using ~~Chi2-tests a multilevel model with random effect at child and center levels.~~

We assessed changes in the effect of time of day across center by computing specific center crude OR to test heterogeneity of the ORs across centers. Then, we ~~We constructed a model including~~ ~~included in our model~~ procedures and children characteristics that were found to be associated with the use of specific analgesia prior to procedures in the EPIPAIN study (Day of procedure, mechanical ventilation, parental presence, continuous analgesia, surgery, sex, and gestational age) and variables describing centers (nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, policy on parental presence authorized 24-hours, night head nurse and teaching status). In order to investigate factors associated with differences in analgesia use 24-hours a day, we tested the interactions between analgesia use

1  
2  
3  
4  
5  
6  
7 and the characteristics of newborns, centers, and procedures. ~~Since data were not independent,~~  
8 ~~procedures were clustered by child and center.~~ We used a multilevel logistic regression model  
9  
10 with random intercept and random slope in order ~~to adjust interactions,~~ to test cross level  
11 interactions and to control for confounding factors.<sup>16,17</sup> ~~15,16.~~ In this multilevel analysis,  
12  
13 procedure, child and center were at the lowest, second and highest level, respectively.  
14  
15

16 All the described factors were included in our model and all interactions between time of  
17 procedures (daytime or nighttime) and each covariate were obtained. Results are presented as  
18 point estimate odds ratios (ORs) with 2-sided 95% confidence intervals (CI). The threshold  
19 for statistical significance was set up at a probability value of <0.05.  
20  
21  
22  
23  
24  
25

## 26 RESULTS

27  
28  
29 From the 430 neonates included in the study, 309 (71.9%) were from NICUs and 121 (28.1%)  
30 from PICUs. The mean (SD) length of stay was 8.4 (4.6) calendar days and the observation  
31 period represented 3598 patient-days. The overall rate of mechanical tracheal ventilation was  
32 70.5%, but it varied from 46.2% to 92% across units. Table 1 lists the demographic  
33 characteristics of the study population and Table 2 lists the characteristics of the participating  
34 centers. [Appendix 1](#) [Figure 2](#) shows the distribution of painful procedures by hour of the day.  
35  
36  
37  
38

### 39 Specific Analgesic treatments

40  
41  
42 Overall, 7724 out of 38012 (20.3%) painful procedures were carried out with the provision of  
43 a specific analgesic treatment. Regarding heel sticks and vascular punctures, 3696/8396  
44 (44.0%) and 1483/2088 (71.0%), respectively, were performed with specific analgesia.  
45  
46  
47

48 ~~Analgesic treatment varied widely among centers. Table 3 shows the use of specific~~  
49 ~~analgesia, by center, for all procedures, heel sticks and vascular punctures.~~  
50  
51  
52  
53  
54  
55

### Analgesia use according to time of the day

For Morning, Afternoon, Early Night and Late Night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18% (p< 0.001). Figure 23 shows the use of analgesia for each 6-hour period of the day by category of procedures. For all painful procedures taken together or for skin-breaking procedures, the use of analgesia was higher in the morning, decreased during the day and was lowest in the late night. ~~(p<0.001). For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%~~

For all procedures taken together or for skin breaking procedures analyzed separately, the use of analgesia was significantly higher for procedures performed in the morning versus the rest of the day, (p<0.001 for all painful procedures, p<0.01 for heel sticks and vascular punctures), as well as for all painful procedures (p<0.01) and heel sticks (p<0.05) performed during the daytime versus the nighttime. ~~p<0.001,~~ Use of analgesia was close to be significantly higher for vascular punctures performed during daytime versus nighttime (p = 0.07). -Table 34.

### ~~Clinical~~ Factors associated with Diurnal Variations in Analgesia

Use of analgesia varied widely among centers (from 4.0% to 49.8%) as shown in appendix 2. Moreover, difference of use analgesia between daytime and nighttime significantly varied among centers as shown in figure 3.

Interactions between differences in analgesia use during daytime and nighttime and the characteristics of children, centers and procedures in univariate analysis are listed in Table 45. We can see for instance that regarding mechanical ventilation the relative reduction in analgesia use during nighttime compared to daytime was 13.1% in invasively ventilated infants and 20.8% in spontaneously breathing or non-invasively ventilated infants.

The inclusion of all clinical factors in a multilevel analysis, showed that analgesia use was significantly higher for procedures performed during the daytime versus the nighttime, (OR =

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

2.25 ~~4~~[1.108–4.603.78],  $p < 0.05$ ). In this multilevel model, day of procedure (related to admission), mechanical ventilation, parental presence, nurse shift, and written protocol for analgesia significantly interacted with time of procedure, as shown in table [56](#). (the whole list of ORs from the model is shown in appendix 3). Presence of parents reversed the difference of use of analgesia between daytime and nighttime; i.e. analgesia was significantly more frequent in nighttime than in daytime when parents were presents.

## DISCUSSION

This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The use of specific analgesia for painful procedures was more frequent during daytime than nighttime. Moreover, we found a sharp decrease in use of analgesia from morning to afternoon followed by a gentle decline thereafter. ~~that specific analgesia for painful procedures was the highest in the morning and the lowest in the nighttime. In fact, it gradually decreased from morning to late night.~~

The relative reduction in the use of specific analgesia between daytime and nighttime was 18.3% for all five painful procedures and this difference reached 28.8% between the morning and the rest of the day. Such substantial differences in the use of analgesia may be questioned on quality of care grounds. We consider that the lower use of analgesia during those periods represents a marker of poor quality care that needs to be overcome. The differences in analgesia use between daytime and nighttime that we found in this study were independent of the type of procedure and whether the procedure was more frequently performed during a period of the day. In fact, heel sticks were homogeneously distributed around-the clock and vascular punctures were more frequent during the morning, but the differences in analgesia use were very similar and consistent ([Appendix 1 figure 3](#)).

1  
2  
3  
4  
5  
6  
7  
8  
9 The around the clock variations in analgesia use for procedural pain management did not  
10 correspond to an isolated practice of a single center but rather to the practices of a large  
11 geographical region. The participation of all but one center in this region, the uniform data  
12 collection at all centers, and 100% patient inclusion during the study period ensure that the  
13 study cohort was representative of NICU procedural pain management in the Paris region.

14  
15  
16  
17  
18 ~~Moreover, we feel that these results could be extrapolated to the entire French territory~~  
19 ~~because this is the most populated region of France and it closely reflects the practices in the~~  
20 ~~rest of the country.~~The extrapolation of these results to the entire French territory may be  
21 possible but not totally certain because of conflicting arguments. On one side, (i) the Paris  
22 region is the most populated region in France and practices within this area closely may  
23 reflect those of the country and (ii) analgesia use was significantly more frequent during  
24 daytime than nighttime in eight of thirteen centers but on the other side, the analysis of crude  
25 OR by center did not show homogeneity (figure 3).

26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36 The variation of quality of neonatal care over the day has been rarely studied directly. Most  
37 studies have used outcomes as a proxy to assess this variation. Some studies reported  
38 increased rates of perinatal death at night<sup>3-5, 3-5</sup>. Although mortality could be considered as an  
39 important proxy to assess quality of care, it has the disadvantage of being related to only  
40 serious or critical conditions and it is exposed to several confounding factors. Medication  
41 error rate has also been used in a few studies to assess variations in quality of care. It has been  
42 found that errors were higher during nighttime than during daytime.<sup>(6, 20)</sup> However, care  
43 quality cannot be restricted to a safety problem. Optimal care quality implies, among other  
44 standards, care without pain. Thus, analgesic use for painful procedure is also a parameter to  
45 measure care quality.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

In an attempt to explain our findings, we investigated factors associated with differences of analgesia use around-the-clock. Parental presence, nurse 8-hour shifts and written protocols for analgesia decreased the difference of analgesia use between day and night. These results suggest that written protocols or parental presence may limit the reduction of analgesia use during nighttime. Protocols limit the freedom of health care providers about the management of pain, making the practice of caregivers more homogeneous. It has been reported that the presence of protocols, by harmonizing practices, increases the quality of care.<sup>10,10</sup> Similarly, it has been reported that the presence of parents influences the practice of caregivers.<sup>18,17</sup> Our data also suggest that shorter hour shifts (8-hour) for nurses decrease the difference of analgesia use between day and night. In other health care areas, it has been shown that 12-hours shifts negatively influence the behavior of care providers yielding to less efficient care.<sup>19,20,18,19</sup> However, the area of variations in pain management practices is highly complex and to attempt to explain it by staffing or protocols is probably simplistic. Other factors that we have not studied could play a role. Contextual factors may influence staff behaviors. Although number of nurses is homogeneous during daytime and nighttime in French NICUs, more medical staff is around in the morning and in the afternoon. Interprofessional collaboration practices<sup>21,20</sup> and higher access to personnel to care for complex patients<sup>22,21</sup> may enhance pain practices. Thus, analgesic use may also be influenced by the total number of staff and not only nurses.

We acknowledge two limitations of this study. First, a potential bias would be a difference in quality of data collection during days and nights. We consider that this is not likely because we ensured a completeness of reporting by verifying from the patients' charts that all

1  
2  
3  
4  
5  
6  
7 procedures were documented on the study datasheets. Furthermore, there is no reason that a  
8 nurse recorded a procedure but not the use of analgesia. Second, we collected data about the  
9 characteristics and organization of center in a retrospective manner 5 years after the collection  
10 of clinical data. This might have introduced a bias. However, we feel that this bias was  
11 minimized because we obtained data from the head nurse who usually keeps records of all  
12 organizational details. Since we only had 13 centers, data about organizational characteristics  
13 should be looked upon with caution.  
14  
15  
16  
17  
18  
19  
20  
21

## 22 CONCLUSION

23  
24  
25 Our findings suggest that the constant efforts to improve care quality should also include  
26 standardization of care across 24 hours and pain management guidelines should reinforce this  
27 message. The variation of care quality during the day is certainly a complex phenomenon that  
28 deserves further research. It appears that human factors intervene in the process of care  
29 delivery and we need to better understand them in order to improve care quality. Our results  
30 suggest that the modification of organisational factors such as parental presence and written  
31 protocols may contribute to the homogenization of quality of care around the clock.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

## 45 Acknowledgment

46  
47 We would like to acknowledge l'Académie de Médecine  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

- 1 Duke GJ, Green JV, Briedis JH. Night shift discharge from intensive care unit increases the mortality risk of ICU survivors. *Anaesth Intensive Care* 2004;**32**:697-701.
- 2 Laupland KB, Shahpori R, Kirkpatrick AW, *et al*. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care* 2008;**23**:317-24.
- 3 Paccaud F, Martin Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. *Lancet* 1988;**1**:340-3.
- 4 Pasupathy D, Wood AM, Pell JP, *et al*. Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ* 2010;**341**:e3498.
- 5 Stephansson O, Dickman PW, Johansson ALV, *et al*. Time of birth and risk of intrapartum and early neonatal death. *Epidemiology* 2003;**14**:218-22.
- 6 Miller AD, Piro CC, Rudisill CN, *et al*. Nighttime and weekend medication error rates in an inpatient pediatric population. *Ann Pharmacother* 2010;**44**:1739-46.
- 7 Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. *Academic Emergency Medicine* 2005;**12**:629-34.
- 8 Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;**155**:173-80.
- 9 Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics* 2000;**105**:454-61.
- 10 Sharek PJ, Powers R, Koehn A, *et al*. Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics* 2006;**118** Suppl 2:S78-86.
- 11 Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. *J Paediatr Child Health* 2011;**47**:92-8.
- 12 Carbajal R, Rousset A, Danan C, *et al*. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA* 2008;**300**:60-70.
- 13 Aiken LH, Clarke SP, Sloane DM, *et al*. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002;**288**:1987-93.
- 14 Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;**6**:249.
- 15 Merlo J, Chaix B, Ohlsson H, *et al*. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;**60**:290-7.



- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- ~~16 Merlo J, Chaix B, Yang M, et al. A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. *J Epidemiol Community Health* 2005;**59**:1022–8.~~
- ~~17 Johnston C, Barrington KJ, Taddio A, et al. Pain in Canadian NICUs: have we improved over the past 12 years? *Clin J Pain* 2011;**27**:225–32.~~
- ~~18 Borges FN da S, Fischer FM. Twelve hour night shifts of healthcare workers: a risk to the patients? *Chronobiol Int* 2003;**20**:351–60.~~
- ~~19 Macias DJ, Hafner J 2nd, Brillman JC, et al. Effect of time of day and duration into shift on hazardous exposures to biological fluids. *Acad Emerg Med* 1996;**3**:605–10.~~
- ~~20 Latimer MA, Johnston CC, Ritchie JA, et al. Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. *J Obstet Gynecol Neonatal Nurs* 2009;**38**:182–94.~~
- ~~21 Stevens B, Riahi S, Cardoso R, et al. The influence of context on pain practices in the NICU: perceptions of health care professionals. *Qual Health Res* 2011;**21**:757–70.~~
1. Duke GJ, Green JV, Briedis JH. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. *Anaesth Intensive Care*. oct 2004;**32**(5):697–701.
2. Laupland KB, Shahpori R, Kirkpatrick AW, Stelfox HT. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care*. sept 2008;**23**(3):317–324.
3. Paccaud F, Martin-Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. *Lancet*. 13 févr 1988;**1**(8581):340–343.
4. Pasupathy D, Wood AM, Pell JP, Fleming M, Smith GCS. Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ*. 2010;**341**:c3498.
5. Stephansson O, Dickman PW, Johansson ALV, Kieler H, Cnattingius S. Time of birth and risk of intrapartum and early neonatal death. *Epidemiology*. mars 2003;**14**(2):218–222.
6. Miller AD, Piro CC, Rudisill CN, Bookstaver PB, Bair JD, Bennett CL. Nighttime and weekend medication error rates in an inpatient pediatric population. *Ann Pharmacother*. nov 2010;**44**(11):1739–1746.
7. Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. *Academic Emergency Medicine*. 1 juill 2005;**12**(7):629–634.
8. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med*. févr 2001;**155**(2):173–180.
9. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. Pediatrics. févr 2000;105(2):454-461.

10. Sharek PJ, Powers R, Koehn A, Anand KJS. Evaluation and development of potentially better practices to improve pain management of neonates. Pediatrics. nov 2006;118 Suppl 2:S78-86.

11. Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. J Paediatr Child Health. mars 2011;47(3):92-98.

12. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA. 2 juill 2008;300(1):60-70.

13. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 23 oct 2002;288(16):1987-1993.

14. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain. juin 1979;6(3):249.

15. Anand KJ, Craig KD. New perspectives on the definition of pain. Pain. sept 1996;67(1):3-6; discussion 209-211.

16. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. avr 2006;60(4):290-297.

17. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. J Epidemiol Community Health. déc 2005;59(12):1022-1028.

18. Johnston C, Barrington KJ, Taddio A, Carbajal R, Filion F. Pain in Canadian NICUs: have we improved over the past 12 years? Clin J Pain. avr 2011;27(3):225-232.

19. Borges FN da S, Fischer FM. Twelve-hour night shifts of healthcare workers: a risk to the patients? Chronobiol Int. mars 2003;20(2):351-360.

20. Macias DJ, Hafner J 2nd, Brillman JC, Tandberg D. Effect of time of day and duration into shift on hazardous exposures to biological fluids. Acad Emerg Med. juin 1996;3(6):605-610.

21. Latimer MA, Johnston CC, Ritchie JA, Clarke SP, Gilin D. Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. J Obstet Gynecol Neonatal

1  
2  
3  
4  
5  
6  
7 [Nurs. avr 2009;38\(2\):182-194.](#)

8 [22. Stevens B, Riahi S, Cardoso R, Ballantyne M, Yamada J, Beyene J, et al. The influence](#)  
9 [of context on pain practices in the NICU: perceptions of health care professionals. Qual](#)  
10 [Health Res. juin 2011;21\(6\):757-770.](#)  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1. Demographic characteristics of 430 neonates

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
<b>Gestational age group at birth</b>	<b>119 (27.7)</b>			
24-29 wk	108 (25.1)			
30-32 wk	84 (19.5)			
33-36 wk	119 (27.7)			
37-42 wk				
<b>Birth weight (g)</b>		<b>1962 (957)</b>	<b>1743 (1155-2738)</b>	<b>490-4760</b>
<b>Male</b>	<b>237 (55.1)</b>			
<b>Inborn (born at study hospital)</b>	<b>237 (55.1)</b>			
<b>Age at admission (h)</b>			<b>2.5 (0.5 – 24.0)</b>	
<b>Surgery during the study period</b>	<b>30 (7.0)</b>			
<b>Mechanical tracheal ventilation</b>	<b>303 (70.5)</b>			
<b>Duration of participation (d)</b>				
<b>Overall</b>		<b>8.4 (4.6)</b>	<b>8.0 (4.0-14.0)</b>	<b>1-14</b>
<b>24-29 wk</b>		<b>11.6 (3.8)</b>	<b>14.0 (9.0-14.0)</b>	<b>2-14</b>
<b>30-32 wk</b>		<b>8.7 (4.6)</b>	<b>9.0 (4.0-14.0)</b>	<b>1-14</b>
<b>33-36 wk</b>		<b>6.6 (4.0)</b>	<b>6.0 (3.0-9.0)</b>	<b>2-14</b>
<b>37-42 wk</b>		<b>6.0 (3.9)</b>	<b>5.0 (3.0-8.0)</b>	<b>1-14</b>
<b>Hospitalized for more than 14 days</b>	<b>126 (29.3)</b>			
<b>Died during the study period</b>	<b>24(5.6)</b>			

Table 2: Characteristics of centers

	Number of centers n = 13
<b><u>Nurse shift</u></b>	
2 per day	9
3 per day	4
<b><u>Day-night nurse rotation</u></b>	
Yes	7
No	6
<b><u>Pain coordinator</u></b>	
Yes	10
No	3
<b><u>Written standardized protocols for sucrose analgesia</u></b>	
Yes	11
No	2
<b><u>Parental presence authorized 24-hours</u></b>	
Yes	6
No	7
<b><u>Teaching status*</u></b>	
Minor	6
Major	7
<b><u>Night head nurse</u></b>	
Yes	2
No	11

\* postgraduate trainees /bed ratio : minor teaching units if ratios were  $\frac{1}{4}$  or less,

major teaching units if ratios were higher than  $\frac{1}{4}$

Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality , nurse burnout, and job dissatisfaction. JAMA. 2002 Oct 23-30;288(16):1987-93

Table 3. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

Table 3 — Use of specific analgesia for painful procedures by center

Center (n°)	Procedures carried out with specific preprocedural analgesia					
	All 5 painful procedures		Heel sticks		Vascular punctures	
	n/N*	%	n/N*	%	n/N*	%
1	89/1356	6.6	3/8	37.5	35/67	52.2
2	162/4091	4.0	22/926	2.4	114/207	55.1
3	1614/3239	49.8	939/1312	71.6	224/285	78.6
4	544/2105	25.8	270/629	42.9	183/199	92.0
5	1682/9110	18.5	847/1560	54.3	279/374	74.6
6	590/2467	23.9	410/489	83.8	86/105	81.9
7	213/2138	10.0	94/633	14.8	55/82	67.1
8	711/2309	30.8	394/573	68.8	94/162	58.0
9	111/1235	9.0	18/264	6.8	55/106	51.9
10	331/1953	16.9	109/360	30.3	53/84	63.1
11	237/2316	10.2	140/643	21.8	43/75	57.3
12	200/983	20.3	87/241	36.1	37/60	61.7
13	1240/4710	26.3	363/758	47.9	225/282	79.8
All-centers	7724/38012	20.3	3696/8396	44.0	1483/2088	71.0

	Number of procedures N	Procedures carried out with specific analgesia n %	Relative Reduction *	Univariate analysis P
<b>MORNING VS REST OF THE DAY</b>				
<b>5 painful procedures</b>				
Morning	9861	2546 25.8%		
Rest of the day	28151	5178 18.4%	28.8%	<0.001
<b>Heel sticks</b>				

<u>Morning</u>	<u>1 860</u>	<u>980</u> 52.7%		
<u>Rest of the day</u>	<u>6 536</u>	<u>2 716</u> 41.6%	<u>21.1 %</u>	<u>&lt;0.01</u>
<b><u>Vascular punctures</u></b>				
<u>Morning</u>	<u>955</u>	<u>723</u> 75.7%		
<u>Rest of the day</u>	<u>1 133</u>	<u>760</u> 67.1%	<u>11.4 %</u>	<u>&lt;0.01</u>
<b><u>DAYTIME VS NIGHTTIME</u></b>				
<b><u>5 painful procedures</u></b>				
<u>Daytime</u>	<u>19 059</u>	<u>4 261</u> 22.5%		
<u>Nighttime</u>	<u>18 953</u>	<u>3 463</u> 18.3%	<u>18.3 %</u>	<u>&lt;0.01</u>
<b><u>Heel sticks</u></b>				
<u>Daytime</u>	<u>3 871</u>	<u>1 856</u> 47.9%		
<u>Nighttime</u>	<u>4 525</u>	<u>1 840</u> 40.7%	<u>15.2 %</u>	<u>&lt;0.05</u>
<b><u>Vascular punctures</u></b>				
<u>Daytime</u>	<u>1 363</u>	<u>1 003</u> 73.6%		
<u>Nighttime</u>	<u>725</u>	<u>480</u> 66.2%	<u>10.0 %</u>	<u>0.07</u>

\* Number of painful procedures performed with analgesia / total number of that specific procedure

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

|

For peer review only

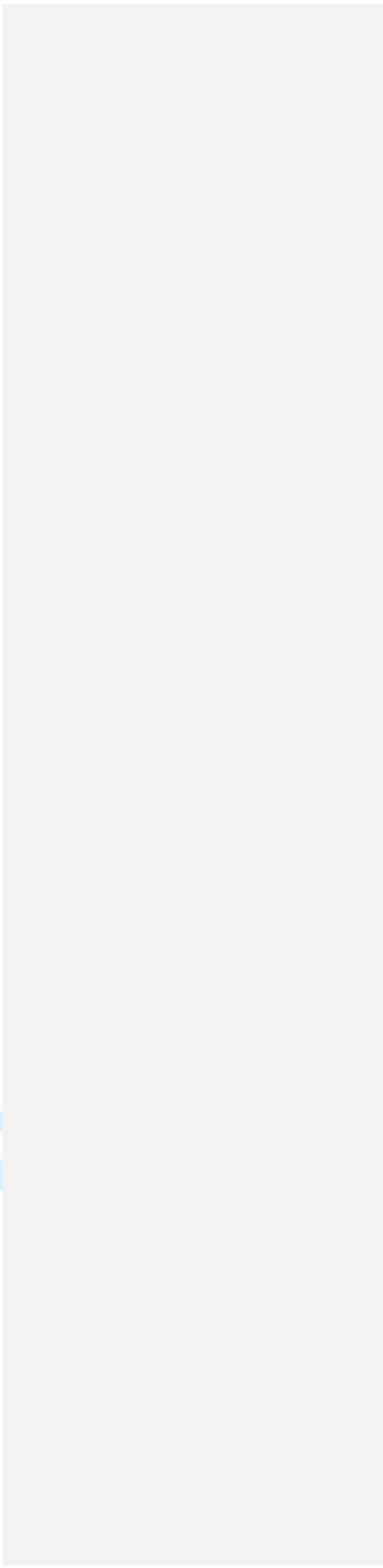




Table 4. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

	Number of procedures	Procedures carried out with specific analgesia	Relative Reduction $\pm$	p
	N	n—%		(chi2)
<b>MORNING VS REST OF THE DAY</b>				
<b>5 painful procedures</b>				
-Morning	9 861	2 546—25.8%		
-Rest of the day	28 151	5 178—18.4%	28.8%	<0.001
<b>Heel sticks</b>				
-Morning	1 860	980—52.7%		
-Rest of the day	6 536	2 716—41.6%	21.1%	<0.001
<b>Vascular punctures</b>				
-Morning	955	723—75.7%		
-Rest of the day	1 133	760—67.1%	11.4%	<0.001
<b>DAYTIME VS NIGHTTIME</b>				
<b>5 painful procedures</b>				
-Daytime	19 059	4 261—22.5%		
-Nighttime	18 953	3 463—18.3%	18.3%	<0.001
<b>Heel sticks</b>				
-Daytime	3 871	1 856—47.9%		
-Nighttime	4 525	1 840—40.7%	15.2%	<0.001
<b>Vascular punctures</b>				
-Daytime	1 363	1 003—73.6%		
-Nighttime	725	480—66.2%	10.0%	<0.001

\*Percentage of relative reduction in the use of specific analgesia

\*\*These are results from multilevel analysis with time of day as the only explanatory variable. In this multilevel analyses, procedure, child and center were at the lowest, second and highest level, respectively.

Table 45 - Interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in univariate analysis

Factor	UNIVARIATE ANALYSIS							
	Procedures carried out with specific analgesia				Daytime compared to nighttime : Relative reduction <sup>a</sup>	Daytime compared to nighttime : OR	Interaction test (p) <sup>b</sup>	
	Daytime		Nighttime					
	n/N	%	n/N	%				
<u>Day of procedure<sup>c</sup></u>	D1	272/ 1 789	15.2	276/ 1 667	16.6	-8.9%	0.90 (0.75 -1.09)	<b>&lt;10.3</b>
	D2-D14	3 989/17 164	23.2	3 187/17 392	18.3	21.2%	1.35 (1.28 -1.42)	
<u>Mechanical ventilation</u>	Yes	1 668/11 908	14.0	1 501/12 327	12.2	13.1%	1.18 (1.09 -1.27)	<b>&lt;10-3</b>
	No	2 593/ 7 045	36.8	1 962/ 6 732	29.1	20.8%	1.42 (1.32 -1.52)	
<u>Parental presence</u>	Yes	331/ 1 488	22.2	131/ 485	27.0	-21.4%	0.77 (0.61 -0.98)	<b>&lt;10-3</b>
	No	3 930/17 465	22.5	3 332/18 574	17.9	21.0%	1.33 (1.26 -1.40)	
<u>Continuous analgesia</u>	Yes	738/ 6 341	11.6	722/ 6 864	10.8	9.6 %	1.12 (1.01 -1.25)	<b>0.005</b>
	No	3 523/12 612	27.9	2 741/12 195	22.5	19.5 %	1.34 (1.26 -1.42)	
<u>Surgery</u>	Yes	337/ 1 576	21.4	300/ 1 714	17.5	18.2%	1.28 (1.08 -1.53)	0.829
	No	3 924/17 377	22.6	3 163/17 345	18.2	19.5%	1.31 (1.24 -1.38)	
<u>Sex</u>	Male	2 363/10 758	22.0	1 877/10 757	17.4	20.9%	1.33 (1.25 -1.43)	0.410
	Female	1 898/ 8 198	23.2	1 586/ 8 302	19.1	17.6%	1.28 (1.18 -138)	
<u>Gestational age</u>	≥ 37 weeks	583/ 3 803	15.3	435/ 3 796	11.5	25.2%	1.40 (1.22 -1.60)	0.295
	< 37 weeks	3 678/15 150	24.3	3 028/15 263	19.8	18.3%	1.30 (1.23 -1.37)	
<u>Nurse shift</u>	3 per day	1 634/ 5 995	27.3	1 276/ 5 907	21.6	20.7%	1.36 (1.25 -1.48)	0.230
	2 per day	2 627/12 958	20.3	2 187/13 152	16.6	18.0%	1.28 (1.20 -1.36)	
<u>Nurse rotation</u>	No	1 853/ 7 507	24.7	1 477/ 7 704	19.2	22.3%	1.38 (1.28 -1.49)	0.068
	Yes	2 408/11 446	21.0	1 986/11 355	17.5	16.9%	1.26 (1.18 -1.34)	
<u>Pain coordinator</u>	No	502/ 2 844	17.7	368/ 2 933	12.5	28.9%	1.49 (1.29 -1.73)	0.053
	Yes	3 759/16 109	23.3	3 095/16 126	19.2	17.8%	1.28 (1.22 -1.35)	
<u>Written protocols for sucrose analgesia</u>	Yes	3 663/15 325	23.9	3 155/15 508	20.3	14.9%	1.23 (1.17 -1.30)	<b>&lt;10-3</b>
	No	598/ 3 628	16.5	308/ 3 551	8.7	47.4%	2.08 (1.80 -2.41)	
<u>Parental presence authorized 24-hours</u>	No	2 510/ 11 949	21.0	2 091/12 023	17.4	17.2%	1.26 (1.18 -1.35)	0.102
	Yes	1 751/ 7 004	25.0	1 372/ 7 036	19.5	22.0%	1.28 (1.27 -1.49)	
<u>Night head nurse</u>	No	2 843/12 348	23.0	2 399/12 889	18.6	19.2%	1.31 (1.23 -1.39)	0.955
	Yes	1 418/ 6 605	21.5	1 064/ 6 170	17.2	19.7%	1.31 (1.20 -1.43)	
<u>Teaching status</u>	Minor	1 798/ 7 222	24.9	1 511/ 7516	20.1	19.2%	1.32 (1.22 -1.42)	0.864
	Major	2 463/11 731	21.0	1 952/11 543	16.9	19.5%	1.31 (1.22 -1.40)	

<sup>a</sup> If positive, analgesia was higher during daytime related to admission

<sup>b</sup> p value < 0.05 indicates that the factor modified the difference in analgesia use between daytime and nighttime in univariate

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 65— Significant interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in a multivariate, multilevel analysis<sup>a</sup>

Factor	Interaction test (p-value)	Interaction direction		OR
		Increase difference <sup>c</sup>	Decrease difference <sup>c</sup>	
Day of procedure <sup>b</sup>	<0.001	D2-D14		1.565 (1.243-1.954)
Mechanical ventilation	<0.05	Absence of mechanical ventilation during procedure		1.204 (1.02-1.43)
Parental presence	<0.001		Parents present	0.589 (0.44-0.789)
Nurse shift	<0.01	12 hour nurse shifts		1.422-25 (1.0523-5.554-12)
Written protocols for sucrose analgesia	<0.001	Absence of written protocols for sucrose analgesia		2.440 (1.5674-3.7030)

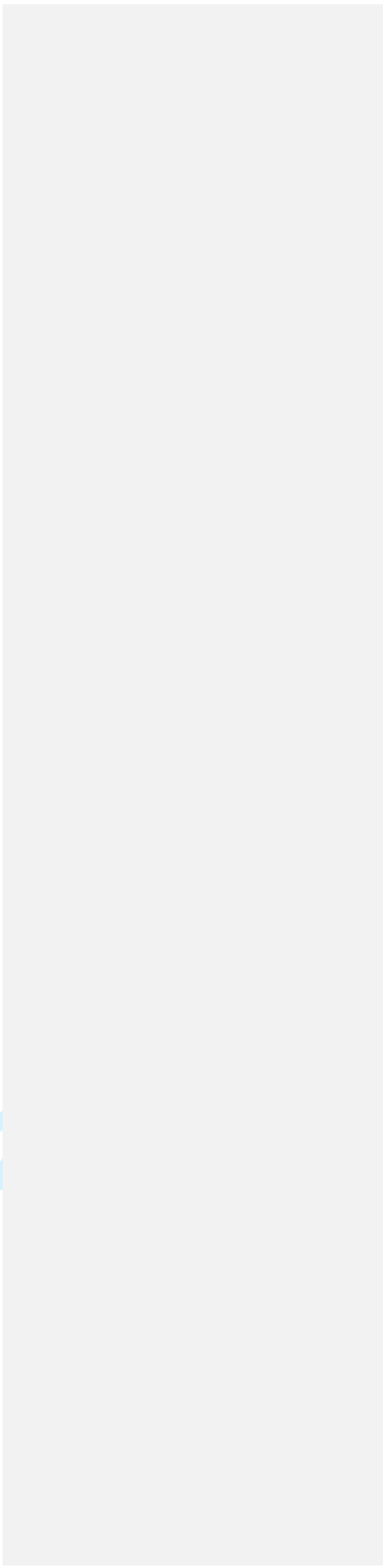
<sup>a</sup> This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model. Only factors that significantly interacted with time of procedure are shown in the table.

<sup>b</sup> related to admission

<sup>c</sup> Refers to the difference in analgesia use during daytime compared to nighttime

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



1  
2  
3  
4  
5  
6  
7 **Funding source and conflict of interest statement** : This study was supported by grant  
8 funds from the Fondation CNP, and the Fondation de France, France. R Guedj received a  
9 grant from L'Académie de Médecine to work on this study. These funding agencies did not  
10 participate in any of the following: design and conduct of the study; collection, management,  
11 analysis, and interpretation of the data; and preparation, review, or approval of the  
12 manuscript. No financial relationships with any organisations that might have an interest in  
13 the submitted work in the previous 3 years; no other relationships or activities that could  
14 appear to have influenced the submitted work  
15  
16  
17  
18  
19  
20  
21  
22  
23

24 **Data Sharing** : No available data sharing  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Contributor's statement page

Romain Guedj : Dr Guedj analysed and interpreted the data. He drafted the initial manuscript and approved the final manuscript as submitted.

Claude Danan : Dr Danan implemented, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patrick Daoud : Dr Daoud implemented, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Véronique Zupan : Dr Zupan implemented, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sylvain Renolleau : Pr Renolleau implemented, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Elodie Zana : Dr Zana implemented, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sophie Aizenfisz : Dr Aizenfisz implemented, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Alexandre Lapillonne : Dr Lapillonne implemented, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Laure de Saint Blanquat : Dr de Saint Blanquat implemented, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Michèle Granier : Dr Granier implemented, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Durand : Dr Durand implemented, coordinated and supervised the trial at one of thirteen participating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Florence Castela : Dr Castela implemented, coordinated and supervised the trial at one of thirteen participating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

1  
2  
3  
4  
5  
6  
7 Anne Coursol : Dr Coursol implemeted, coordinated and supervised the trial at one of thirteen  
8 participating unit. She reviewed and revised the manuscript, and she approved the final  
9 manuscript as submitted.

10 Philippe Hubert : Pr Hubert designed the study. He reviewed and revised the manuscript, and  
11 he approved the final manuscript as submitted.  
12

13 Patricia Cimerman : Mrs Cimerman designed the study. She reviewed and revised the  
14 manuscript, and she approved the final manuscript as submitted.  
15

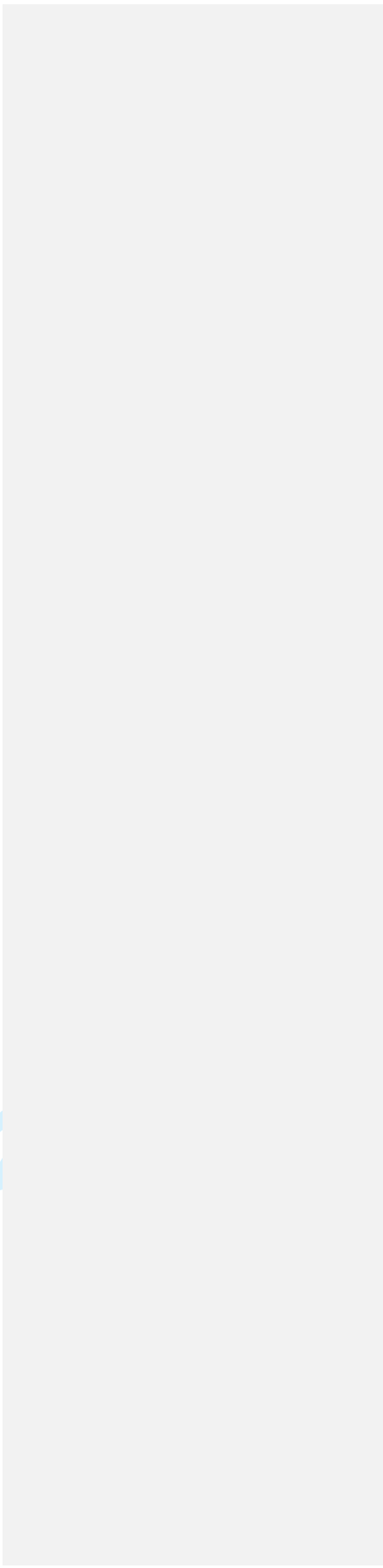
16 Babak Khoshnood : Pr Khoshnood designed the study and interpreted the data. He reviewed  
17 and revised the manuscript, and he approved the final manuscript as submitted.  
18

19 KJS Anand : Pr Anand designed the study. He reviewed and revised the manuscript, and he  
20 approved the final manuscript as submitted.  
21

22 Ricardo Carbajal : Pr Carbajal designed the study and interpreted the data. He reviewed and  
23 revised the manuscript, and he approved the final manuscript as submitted. He is guarantor  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only





1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

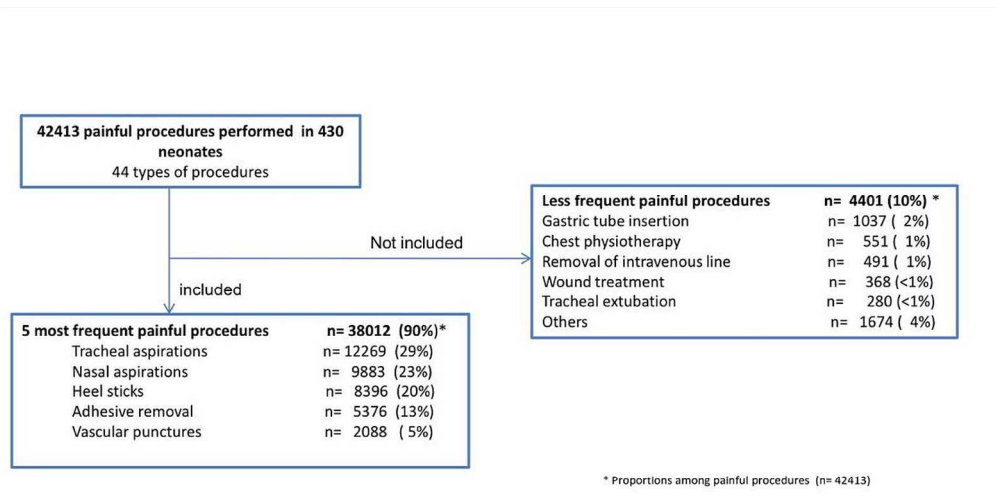
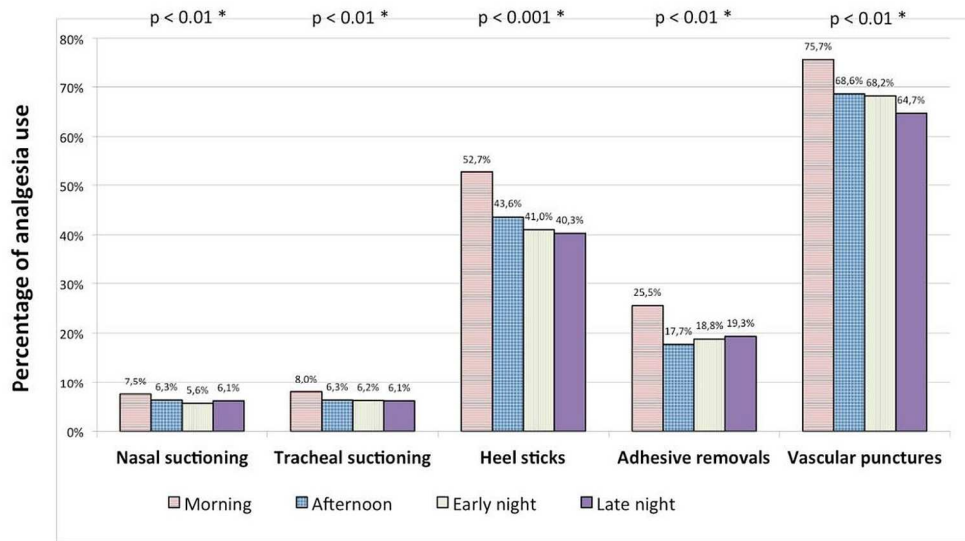


Figure 1 – Distribution of painful procedures analysed in the study

119x90mm (300 x 300 DPI)

Review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



\*Global comparison of all four 6-hour periods

Figure 2 – Use of analgesia during each of the 6-hour period of the day by category of procedure

120x90mm (300 x 300 DPI)

Review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

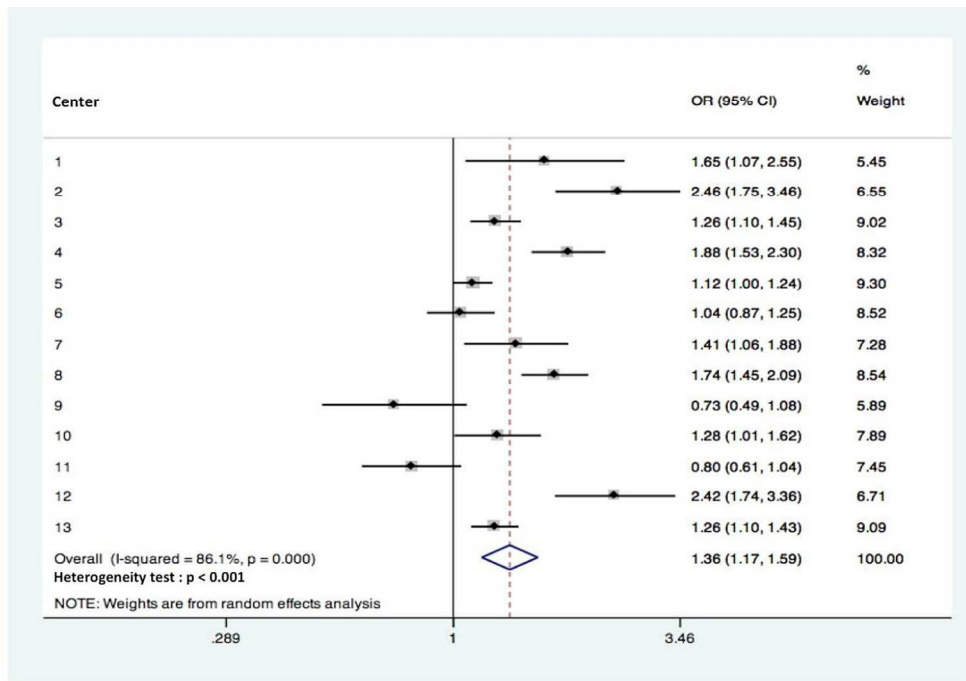
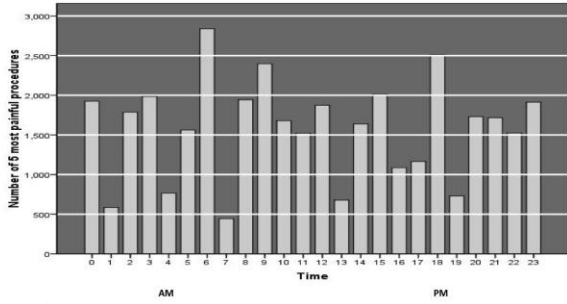


Figure 3 Use of analgesia for procedures performed in daytime versus nighttime by centers; Test of heterogeneity – p<0.001.

119x90mm (300 x 300 DPI)

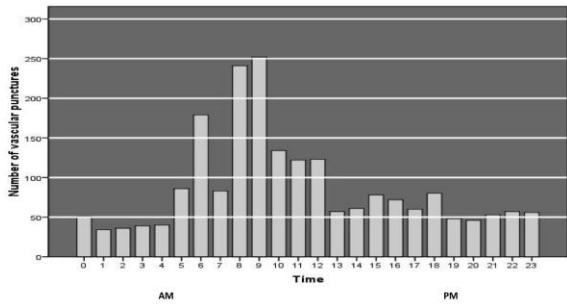
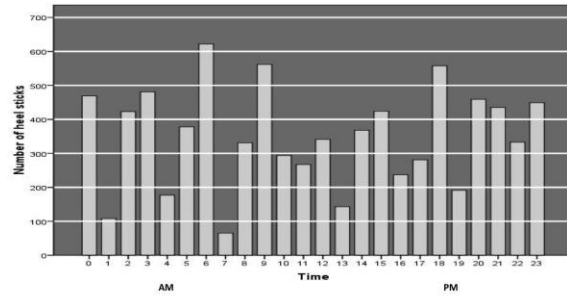
Review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Appendix 1 – Distribution of painful procedures by hour the day

(Five most frequent painful procedures, n=38 012  
Heel sticks, n = 8 396  
Vascular punctures, n = 2 088)



view only

Appendix 2- Use of specific analgesia for painful procedures by center and by time of day

Center	Procedures carried out with specific preprocedural analgesia					
	All 5 painful procedures n/N* (%)		Heel sticks n/N* (%)		Vascular puncture n/N* (%)	
	By time of day D- Daytime N-Nighttime		By time of day D- Daytime N-Nighttime		By time of day D- Daytime N-Nighttime	
1	89 / 1 356 (6.6)	D - 51/ 619 (8.2) N - 38/ 737 (5.2)	3/ 8 (37.5)	D - 1/ 2 (50.0) N - 2/ 6 (33.3)	35/ 67 (52.2)	D - 28/47 (59.6) N - 7/20 (35.0)
2	162 / 4 091 (4.0)	D - 113/2 015 (5.6) N - 49/2 076 (2.4)	22/ 926 (2.4)	D - 16/397 (4.0) N - 6/529 (1.1)	114/ 207 (55.1)	D - 79/149 (53.0) N - 35/ 58 (60.3)
3	1 614/ 3 239 (49.8)	D - 882/1 676 (52.6) N - 732/1 563 ( 5,2)	939/ 1312 (71.6)	D - 457/600 (76.2) N - 482/712 (67.7)	224/ 285 (78.6)	D - 154/183 (84.2) N - 70/102 (68.6)
4	544 / 2 105 (25.8)	D - 349/1 111 (31.4) N - 195/ 994 (19.6)	270/ 629 (42.9)	D - 151/315 (47.9) N - 119/314 (37.9)	183/ 199 (92.0)	D - 142/153 (92.8) N - 41/ 46 (89.1)
5	1 682 / 9 110 (18.5)	D - 905/4 700 (19.3) N - 777/4 410 (17.6)	847/ 1 560 (54.3)	D - 424/742 (57.1) N - 423/818 (51.7)	279/ 374 (74.6)	D - 141/193 (73.1) N - 138/181 (76.2)
6	590/ 2 467 (23.9)	D - 290/1 193 (24.3) N - 300/1 274 (23.5)	410/ 489 (83.8)	D - 176/221 (79.6) N - 234/268 (87.3)	86/ 105 (81.9)	D - 65/ 79 (82.3) N - 21/ 26 (80.8)
7	213 / 2 138 (10.0)	D - 117/1 009 (11.6) N - 96/1 129 ( 8.5)	94/ 633 (14.8)	D - 48/292 (16.4) N - 46/341 (13.5)	55/ 82 (67.1)	D - 47/ 66 (71.2) N - 8/ 16 (50.0)
8	711 / 2 309 (30.8)	D - 462/1 286 (35.9) N - 249/1 023 (24.3)	394/ 573 (68.8)	D - 266/367 (72.5) N - 128/206 (62.1)	94/ 162 (58.0)	D - 76/116 (65.5) N - 18/ 46 (39.1)
9	111 / 1 235 ( 9.0)	D - 46/ 601 ( 7.7) N - 65/ 634 (10.3)	18/ 264 (6.8)	D - 11/131 ( 8.4) N - 7/133 ( 5.3)	55/ 106 (51.9)	D - 16/ 42 (38.1) N - 39/ 64 (60.9)
10	331 / 1 953 (16.9)	D - 168/ 893 (18.8) N - 163/1 060 (15.4)	109/ 360 (30.3)	D - 57/135 (42.2) N - 52/225 (23.1)	53/ 84 (63.1)	D - 37/ 55 (67.3) N - 16/ 29 (55.2)
11	237 / 2316 (10.2)	D - 102/1 114 ( 9.2) N - 135/1 202 (11.2)	140/ 643 (21.8)	D - 53/288 (18.4) N - 87/355 (24.5)	43/ 75 (57.3)	D - 21/ 33 (63.6) N - 22/ 42 (52.4)
12	200 / 983 (20.3)	D - 136/ 502 (27.1) N - 64/ 48 (13.3)	87/ 241 (36.1)	D - 42/106 (39.6) N - 45/135 (33.3)	37/ 60 (61.7)	D - 28/ 41 (68.3) N - 9/ 19 (47.4)
13	1 240 / 4710 (26.3)	D - 640/2 234 (28.6) N - 600/2 476 (24.2)	363/ 758 (47.9)	D - 154/275 (56.0) N - 209/483 (43.3)	225/ 282 (79.8)	D - 169/206 (82.0) N - 56/ 76 (73.7)

\* Number of painful procedures performed with analgesia / total number of that specific procedure

Appendix 3 : Factors Associated With the Use of Analgesia during the 5 most frequent painful procedures in neonates and interaction between time of day and the other factors.

Factors		OR	Interaction with time of the day OR
<u>Time of the day</u>	Night	1	
	Day	<b>2.25 [1.10-4.60]</b>	
<u>Day of procedure<sup>c</sup></u>	D1	1	1
	D2-D14	<b>1.24 [1.05-1.45]</b>	1.56 [1.24-1.95]
<u>Mechanical ventilation</u>	No	1	1
	Yes	0.49 [0.43-0.56]	0.83 [0.70-0.98]
<u>Parental presence</u>	No	1	1
	Yes	<b>1.56 [1.22-2.00]</b>	0.58 [0.44-0.78]
<u>Continuous analgesia</u>	No	1	1
	Yes	<b>0.51 [0.44-0.60]</b>	0.93 [0.76-1.14]
<u>Surgery</u>	No	1	1
	Yes	1.49 [0.92-2.42]	1.01 [0.69-1.47]
<u>Sex</u>	Male	1	1
	Female	0.94 [0.75-1.17]	1.07 [0.90-1.29]
<u>Gestational age</u>	≥ 37 weeks	1	1
	< 37 weeks	1.19 [0.91-1.56]	0.84 [0.67-1.06]
<u>Nurse shift</u>	2 per day	1	1
	3 per day	<b>12.78 [1.73-94.42]</b>	0.41 [0.18-0.95]
<u>Nurse rotation</u>	No	1	1
	Yes	2.02 [0.64-6.37]	0.74 [0.47-1.20]
<u>Pain coordinator</u>	No	1	1
	Yes	1.29 [0.50-3.33]	1.26 [0.86-1.86]
<u>Written protocols for sucrose analgesia</u>	No	1	1
	Yes	<b>3.50 [1.23-9.95]</b>	0.41 [0.27-0.64]
<u>Parental presence authorized 24-hours</u>	No	1	1
	Yes	0.37 [0.07-2.05]	1.92 [0.92-4.00]
<u>Night head nurse</u>	No	1	1
	Yes	0.91 [0.31-2.72]	1.51 [0.96-2.37]
<u>Teaching status</u>	Minor	1	1
	Major	0.59 [0.24-1.47]	0.81 [0.56-1.18]

This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model.