

ORIGINAL ARTICLE

Urinary markers of pain in children in neonatal intensive care units: a cross-section study

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Abstract

Introduction: Repetitive exposition to pain negatively affects newborns development. Procedural pain in newborn in Neonatal Intensive Care Unit (NICU) triggers a series of physiological, behavioral and hormonal disorders that may set off the impairment of the neurological development in preterm infants, who undergo long periods of hospitalization at a moment of physiological immaturity and fast brain development.

Objective: This study aimed not only to observe the pain score in newborns and infants when undergoing painful procedures in neonatal intensive care units but also to analyse urinary IL-8 and cortisol levels at such stressful moments.

Methods: Patients were submitted to venipuncture and to other methods of blood collection. Cortisol and IL-8 levels were measured by immunometric assay and chemiluminescence detection. For the collection of data regarding observation of neonatal pain, the Neonatal Infant Pain Scale was used with immediate results. To describe the qualitative variables, absolute and relative frequencies were used. For the quantitative variables with normal distribution, mean, standard deviation, minimum and maximum were used.

Results: A total of 81 patients were included: 47 were submitted to venipuncture and 36 to other methods of blood collection. Significance for cortisol can be seen ($p=0.04$); however, IL-8 levels, when associated with the pain scale, were not sensitive enough ($p=0.11$).

Conclusion: The results showed that cortisol is a better marker for pain than IL-8, and its accumulation in urine may help the detection and interpretation of pain. Conclusion: Based on this information, nurses can step in to reduce the discomfort brought by painful procedures, and thus highlight humanistic practices in nursing assistance.

Keywords: Neonatal, ICU, pain, IL-8, cortisol, urine

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Authors summary

Why was this study done?

Procedural pain in newborn in Neonatal Intensive Care Unit (NICU) triggers a series of physiological, behavioral and hormonal disorders that may set off the impairment of the neurological development in preterm infants. The aim of this study was to compare through the NIPS score the level of pain in newborns undergoing painful or pain-free procedures and associate these procedures with cortisol and IL-8 levels in urine with the purpose of monitoring stress in infants admitted to intensive care units.

What did the researchers do and find?

This is a cross-sectional study that aimed to investigate urinary markers of pain in children admitted to the neonatal intensive care unit (NICU). The current study compared the effectiveness of the use of the NIPS score and cortisol and IL-8 measurements in newborns' urine whenever they were submitted to blood collection procedures in the neonatal ward. The results here found showed that cortisol had a better discriminatory power than IL-8 when assessed by the NIPS.

What do these findings mean?

In neonatal intensive care units, routine measure of urinary cortisol could be a useful stress marker for baby in pain.

Highlights

Urinary cortisol could be a useful stress marker for baby in pain.

Despite the immaturity of this system, newborns feel pain.

Cortisol is a better marker for pain than IL-8 and its accumulation in urine may help the detection and interpretation of pain.

INTRODUCTION

Pain is a subjective experience and the inability to communicate it verbally does not mean the patient is not experiencing an episode of pain¹. Considered by the North American Nursing Diagnosis Association (NANDA) as a nursing diagnosis, pain is defined as an unpleasant sensory and emotional experience that is usually related to concrete or imminent tissue damage^{2,3}. Repetitive pain that is not relieved may lead to grave adverse consequences to newborn related to an increase in intracranial pressure, which consequently increases the risk factor for intraventricular hemorrhage in preterm infants. Pain and stress can also depress the immune system and contribute to the susceptibility of the newborn to infections².

Procedural pain in newborn in Neonatal Intensive Care Unit (NICU) triggers a series of physiological, behavioral and hormonal disorders that may set off the impairment of the neurological development in preterm infants, who undergo long periods of hospitalization at a moment of physiological immaturity and fast brain development. Children below 3 months of age may have an increase in cortisol levels as a response to the many painful care procedures they are submitted to^{3,4}.

Some studies reveal that the exposition to stress related to pain contributes to the programming of an altered hypothalamus-pituitary-adrenal (HPA) axis reactivity to socio-emotional stress in 3-month-old infants, even in the absence of major perinatal complications¹. When an infant goes through a stressful situation, the developing HPA axis is activated. The adrenal cortex secretes glucocorticoids like cortisol (a stress indicator) and their plasma levels will be high as a result of the physiological and physical response to stress. In the long run, the collateral effects of high concentrations of cortisol may bring about insulin resistance, hyperlipidemia, immune deficiencies and hippocampal destructive injuries/lesions⁵.

Recent works in the literature show that interleukin-8 (IL-8) is associated with inflammatory diseases, persistent inflammatory pain and a persistent mechanical nociceptor hypersensitivity state⁶. Interleukin-8 belongs to a family of chemokines and it stimulates the migration of neutrophils, monocytes and macrophages to the inflammation sites⁷.

Among the many scales developed to evaluate acute pain in preterm newborns, very few were properly validated. The Neonatal Infant Pain Scale (NIPS) is one of the validated instruments^{3,8} utilized for gauging pain in newborns^{8,9}. Numerous studies have been conducted to assess the effectiveness and applications of the Neonatal Infant Pain Scale (NIPS) in various clinical scenarios. For instance, a study⁸⁻¹⁰ specifically examined the inter-rater reliability of NIPS and COMFORT-B, evaluating the proficiency of NICU staff in utilizing these pain assessment tools. The NIPS is employed to evaluate pain levels when a newborn undergoes a stressful moment during a painful procedure. Validated for its inclusion of both physiological and behavioral aspects of newborns in pain, it is easily applied and fulfills all proposed objectives^{9,10}.

The scale assesses five behavioral pain parameters (facial expression, cry, arms, legs and state of arousal) and one physiological (breathing pattern). Each parameter contains two items to which scores of 0 or 1 are assigned (except for the crying factor, which comprises three items and is scored on a scale from 0 to 2). Besides, each item also contains a brief operational definition. The scale yields a total score that ranges from 0 to 7, where scores higher than 3 are indicative of pain^{11,12}.

The aim of this study was to compare through the NIPS score the level of pain in newborns undergoing painful or pain-free procedures and associate these procedures with cortisol and IL-8 levels in urine with the purpose of monitoring stress in infants admitted to intensive care units.

METHODS

Design

This is a cross-sectional study that aimed to investigate urinary markers of pain in children admitted to the neonatal intensive care unit (NICU)^{8,9,13}. The study was conducted from January 2017 to March 2018 at a university hospital in the ABC region of São Paulo, Brazil. The study included full-term and preterm newborns of both genders who were admitted to the NICU within their first hour of life with various diagnostic hypotheses (table 1).

Samples

Urine samples were collected from both groups simultaneously, considering the routine schedule for biological material collection and the resting period of infants who had not undergone painful procedures. The parameters evaluated in the present study were gender, type of puncture, suctioning, urinary cortisol, urinary IL-8, age of the mother, gestation period and days of life.

Inclusion and exclusion criteria

The study included all babies admitted to the intensive care unit, without excluding any specific causes of hospitalization. Babies under analgesia or intubated were excluded from the study. The recruitment strategy for case inclusion in this study involved a convenience approach. The study team actively approached eligible individuals or their legal guardians and provided them with detailed information about the study, its purpose, procedures, and potential benefits.

NIPS application

The NIPS evaluates five behavioral components (facial expression, cry, arms, legs, and state of arousal) and one physiological aspect (breathing patterns). Each component includes two criteria, with scores of 0 or 1 assigned to each (except for the crying component, which consists of three criteria and is rated on a 0 to 2 scale). Additionally, each criterion is accompanied by a brief operational definition. The cumulative score on the scale ranges from 0 to 7, with scores exceeding 3 indicating the presence of pain. The NIPS is user-friendly, easily comprehensible, and serves as a valuable tool for healthcare professionals dealing with newborns exposed to painful stimuli. This method has been validated and adapted for use in Brazil and was applied by the nurses on duty in the neonatology department of the hospital¹¹.

For the collection of data regarding observation of neonatal pain, the Neonatal Infant Pain Scale (NIPS) was used with immediate results. Additionally, urine samples (2 mL) were obtained from each infant up to a maximum period of three hours from the moment the painful procedure was conducted so that the association between the release of biochemical mediators (cortisol and IL-8) and the procedure could be evaluated.

Biochemical analysis

For the correct collection of urine samples, the newborns in diapers were placed in supine position. After the proper aseptic procedures were carried out, urine collector bags were used in the genital area (from the perineum toward the symphysis pubis). A syringe was used to aspirate the urine, and after the collection, comfort measures were provided to the newborns. The urine samples were then taken to the laboratory of clinical analysis of the Centro Universitário FMABC on the same day. Cortisol and IL-8 levels were measured by immunometric assay and chemiluminescence detection using the commercial kit Immulite® (Siemens) according to the manufacturer's directions. Samples were run in duplicate as directed by good laboratory practice. All urinary cortisol readings were in µg/24hs and in pg/mL

for urinary IL-8.

Ethical approval

This study was approved by the Clinical Research Ethics Committee of Centro Universitário FMABC under the approval number 3.031.567. All legal guardians of the minors signed the informed assent and consent form.

Statistical analysis

In this study, was conducted a comprehensive statistical analysis to assess significant relationships and differences within the collected data. The datasets included both absolute and relative values, providing a detailed insight into the phenomena under investigation. We calculated fundamental descriptive measures to characterize the central tendency and dispersion of the data.

Means were used as indicators of centrality, while standard deviations (SD) provided insights into the variability of the data. We also presented maximum and minimum values to highlight the overall range of results. To assess potential differences between independent groups, we employed the Mann-Whitney test. This non-parametric test is suitable for non-normally distributed data, allowing us to identify statistically significant variations between the samples. To investigate linear relationships between continuous variables, we conducted Pearson correlation analysis. This method enabled us to explore positive, negative, or the absence of correlation between the parameters under study.

RESULTS

In this work, 91 infants were investigated, of which 8 (8,8%) infants were excluded from the analysis as they did not meet all the inclusion criteria of this study.

Demographic and clinical characteristics of the study population are presented in table 1. A total of 83 participants were included in the analysis. Regarding gender, 60.2% (n=50) were male, while 39.8% (n=33) were female. The distribution of types of punctures showed that 43.4% (n=36) of the participants had no puncture, 50.6% (n=42) had peripheral puncture, and 6.0% (n=5) had arterial puncture. In terms of suctioning, 80.7% (n=67) of the participants did not undergo suctioning, while 19.3% (n=16) had suctioning performed.

Urinary cortisol levels were analyzed, and it was found that 90.2% (n=74) of the participants had normal levels, while 9.8% (n=8) had altered levels. Similarly, urinary IL-8 levels were assessed, and 89.2% (n=74) of the participants had normal levels, while 10.8% (n=8) had altered levels.

The mean (standard deviation) values and ranges for maternal age, gestation period, and days of life are provided in table 1. The mean age of the mothers was 27.2 (6.5) years, ranging from 17.0 to 44.0 years. The average gestation period was 35.6 (4.0) weeks, with a range of 18.0 to 40.0 weeks. The mean number of days of life for the participants was 13.3 (10.7) days, ranging from 1.0 to 57.0 days.

These results provide a comprehensive overview

of the demographic and clinical characteristics of the study population, including gender distribution, types of punctures, suctioning, urinary cortisol and IL-8 levels, as well as maternal age, gestation period, and days of life. In table 2, the association between the NIPS score and the biochemical markers can be observed. Significance for cortisol can be seen ($p=0.04$); however, IL-8 levels, when associated with the pain scale, were not sensitive enough ($p=0.11$). The confidence interval of both biochemical markers can be seen in figure 1 (a and b). Urinary cortisol showed a higher diagnostic capacity when compared with urinary IL-8, which reveals that a painful procedure occurred.

Upon using the ROC curve, it was possible to observe that cortisol had a higher discriminatory power regarding the babies under stress due to pain (area under the curve of 0.666) when compared with IL-8 (area of 0.580). When the sensitivity versus specificity plot was analysed, the analysis revealed that cortisol showed higher accuracy compared to the other biomarkers to identify positive cases. On the other hand, IL-8 was not a valid indicator since the values found in this study did not only show good sensitivity but also had low specificity.

DISCUSSION

In this study, a higher prevalence of male infants was observed in the Intensive Care Unit. There is no causal relationship regarding this data, as there is random variation in the number of births between females and males. Therefore, it is not possible to infer that the higher number of male infants is a predominant factor in the observed data.

Table 1: Descriptive table of demographic data of the evaluated infants. Type of puncture, suction, urinary cortisol, urinary IL-8, mother's age, gestational period, and days of life of the baby during the evaluation period

Variables	n	%
Gender		
Male	50	60.2
Female	33	39.8
Type of puncture		
No puncture	36	43.4
Peripheral puncture	42	50.6
Arterial puncture	5	6.0
Suctioning		
No	67	80.7
Yes	16	19.3
Urinary Cortisol		
Normal	74	90.2
Altered	8	9.8
Urinary IL 8		
Normal	74	89.2
Altered	8	10.8
	Mean (SD)	Min-Max
Age of the mother	27.2 (6.5)	17.0 - 44.0
Gestation period	35.6 (4.0)	18.0 - 40.0
Days of life	13.3 (10.7)	1.0 - 57.0

SD: standard deviation.

Table 2: Association between the NIPS score and the biochemical markers of the sample

Variables	NIPS score		p*
	not submitted to painful stimuli	submitted to painful stimuli	
	Median (p25; p75)		
Urinary Cortisol	1.7 (1.0; 3.4)	3.1 (1.1; 7.6)	0.04
Urinary IL-8	15.6 (15.6; 21.24)	15.6 (15.6; 31.64)	0.11

*Mann-Whitney test

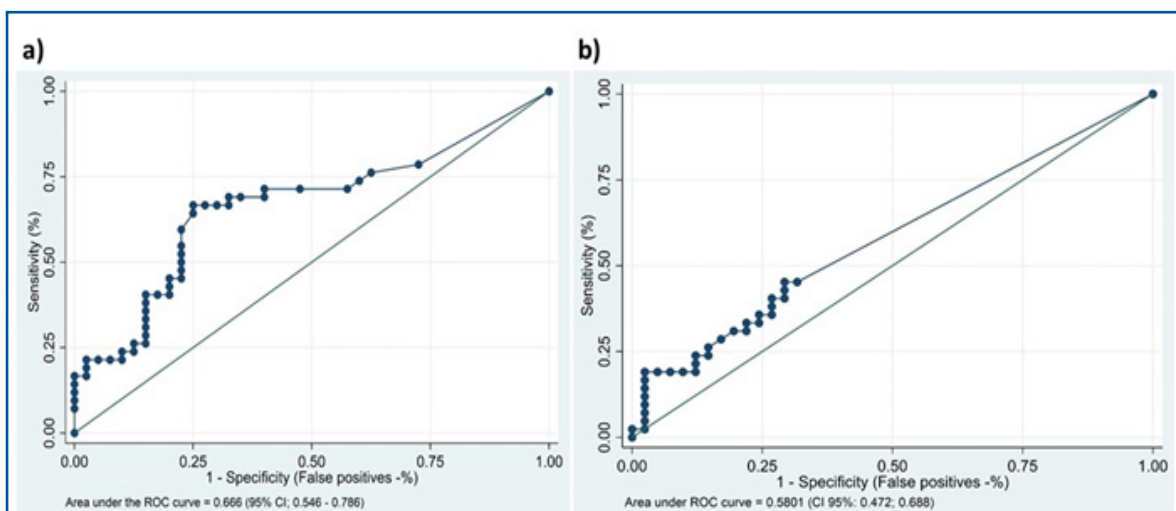


Figure 1: Diagnostic capacity of urinary cortisol (a) and IL-8 (b) to indicate pain. Pearson correlation test

Among the studied infants, it was found that more than 60% of those subjected to painful stimuli exhibited alteration in urinary cortisol levels.

Upon admitting that newborn babies and infants are likely to feel pain during unavoidable procedures in neonatal intensive care units, it is of utmost importance that methods could efficiently characterize this stressful condition so that the assisting team can be better prepared to identify and provide a more humanized care under these circumstances. Additionally, these methods would enable these professionals to perform the clinical and laboratory monitoring of the physiological response of stress caused by pain.

Nevertheless, it is not always that the immediate effect of stress caused by pain can be effectively evaluated just by behavioral patterns measured according to scales or physiological responses monitored by apparatuses. Therefore, researchers are constantly in search of other non-subjective ways to verify the presence of stress¹¹.

The current study compared the effectiveness of the use of the NIPS score and cortisol and IL-8 measurements in newborns' urine whenever they were submitted to blood collection procedures in the neonatal ward. The results here found showed that cortisol had a better discriminatory power than IL-8 when assessed by the NIPS. In order to analyse these parameters, the ROC curve was applied^{12,14} which revealed urinary cortisol as a better marker for the stress of the baby in pain according to its optimal cutoff point and based on the specificity and sensitivity of the test.

Upon considering the way cortisol secretion is activated by the HPA axis as a neurophysiologic response to pain as well as the release of IL-8, which also depends on cellular activation, the cortisol secretion mechanisms may have been fundamental in this study.

Some studies show that there is a direct correlation between plasma cortisol and its detection in babies' urine¹⁵ just like the correlation between plasma cortisol (invasive detection) and saliva (non-invasive detection). Invasive detections for stress are faster, whereas through urine, the presence of cortisol is detected after its long-time accumulation, which may be beneficial for the evaluation of a stress physiological response in newborns in 24 hours.

Still, alternations in periodicity (day/night) regarding to cortisol secretion can be observed in newborns. According to the authors, the pattern in the circadian rhythm in neonates is directly related to the time of birth and the circadian rhythm of the mother. These aspects should be considered relevant according to the targeted aim¹⁶. The detection of cortisol secretion may be masked due to the time of the collection and the methodology applied. Some studies show that not always is there a direct correlation between cortisol detection and the newborn's behavior analyzed by scales¹⁷.

The presented data suggests that cortisol was more effective in assessing painful stimuli effects in newborns compared to IL8 marker. Therefore, cortisol quantification in this patient group can infer pain in a less invasive manner, as the biological matrix used for this quantification was urine, an easily collectible and less invasive material. It is important to point out that according to the methodology

here applied, the collection time of the samples was always the same, which followed the protocols established by the hospitalization department for neonates.

Okamura *et al.* (2017)¹⁸ observed in their studies that the cortisol detection in saliva is not a reliable tool since in their previous studies the success rate of this method was of 46% of all analyzed neonates. Contrarily, when the urine detection of cortisol was applied, this rate rose to 96%. Thus, the detection of cortisol in urine samples, regardless of the NIPS score or the stress moment (detectable in saliva), allows for the identification of pain in newborns, which may facilitate the understanding of how stressful and painful factors can be present despite the newborn's behavior or the scheduled time intervals for assistance¹⁵.

A recent study conducted by Dionysakopoulou *et al.* (2023)¹⁹ investigated a total of 54 full-term neonates and evaluated the nociceptive mediators Substance P, neurokinin A, neuropeptide Y, and cortisol levels, along with the Neonatal Infant Pain Scale (NIPS) for pain assessment. The results revealed a statistically significant decrease in NPY and NKA levels, as well as a significant increase in the NIPS scale. Positive correlations were observed between cortisol and SubP, NKA and NPY, as well as between NIPS. These data corroborate with the findings of the present study, despite not having shown a direct correlation between cortisol and NIPS, but rather the use of NIPS and other nociceptive mediators.

In this study, it was possible to identify some probable cutoff points in the cortisol detection in urine, which enables the use of this method and suggests that a clinical laboratory monitoring may shed some light on the assistance provided to these patients who are constantly under stress due to pain. However, we emphasize that, although interesting, the data represent the results obtained in the analysis of samples collected in a single maternity hospital. This maternity hospital is considered a reference and is located in a large urban center. Still, more studies with data from other maternity hospitals should be conducted to validate the results here described. As limiting factors of this study, we identified difficulties with the sample size, likely reflecting parental insecurity regarding the collection and management of their infants in the Intensive Care Unit.

■ CONCLUSION

Thus, urinary cortisol levels can be used as a complementary tool for assess pain in newborns, despite de NIPS score. Considering that it is an easy measure to be carried out, it can be a very useful tool for the team of health professionals who provide assistance to these patients.

Author Contributions

All authors contributed to the manuscript.

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Conflicts of Interest

The authors report no conflict of interest.

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Resumo

Introdução: a exposição repetitiva à dor afeta negativamente o desenvolvimento de recém-nascidos. A dor procedimental em recém-nascidos na Unidade de Terapia Intensiva Neonatal (UTIN) desencadeia uma série de distúrbios fisiológicos, comportamentais e hormonais que podem resultar no comprometimento do desenvolvimento neurológico em bebês prematuros, que passam por longos períodos de hospitalização em um momento de imaturidade fisiológica e rápido desenvolvimento cerebral.

Objetivo: este estudo teve como objetivo não apenas observar a pontuação de dor em recém-nascidos e lactentes ao passarem por procedimentos dolorosos em unidades de terapia intensiva neonatais, mas também analisar os níveis de IL-8 e cortisol urinário nesses momentos estressantes.

Método: os pacientes foram submetidos à punção venosa e a outros métodos de coleta de sangue. Os níveis de cortisol e IL-8 foram medidos por ensaio imunométrico e detecção por quimiluminescência. Para a coleta de dados sobre a observação da dor neonatal, foi utilizada a Escala de Dor Infantil Neonatal com resultados imediatos. Para descrever as variáveis qualitativas, foram utilizadas frequências absolutas e relativas. Para as variáveis quantitativas com distribuição normal, foram utilizadas média, desvio padrão, mínimo e máximo.

Resultados: um total de 81 pacientes foi incluído: 47 foram submetidos à punção venosa e 36 a outros métodos de coleta de sangue. A significância para o cortisol pode ser observada ($p=0,04$); no entanto, os níveis de IL-8, quando associados à escala de dor, não foram sensíveis o suficiente ($p=0,11$).

Conclusão: os resultados mostraram que o cortisol é um marcador melhor para a dor do que a IL-8, e seu acúmulo na urina pode ajudar na detecção e interpretação da dor. Com base nessas informações, os enfermeiros podem intervir para reduzir o desconforto causado por procedimentos dolorosos, destacando práticas humanísticas na assistência de enfermagem.

Palavras-chave: Neonatal, UTI, dor, IL-8, cortisol, urina

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