Published online 2016 July 18.

Research Article

# Cumulative Stressors in Preterm Infants Hospitalized in Neonatal Intensive Care Units

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Received 2015 August 09; Revised 2016 April 13; Accepted 2016 April 13.

#### **Abstract**

**Background:** Infants' exposure to stressors in neonatal intensive care unit (NICU) and its outcomes is a new issue since previous studies have only focused on painful stimuli. Taking into account frequency and severity of the stressors on each infant, short and long-term outcome of these stressors can be improved.

Objectives: This study aimed to evaluate the cumulative stressors in premature infants hospitalized in a NICU.

**Methods:** In this descriptive study, 197 hospitalized preterm infants between 28 to 30 weeks of gestation were studied in terms of cumulative stressors during 10 days at the NICU of Tabriz Alzahra hospital. Consecutive sampling method was used. Demographic questionnaire and neonatal infant stressor scale were used. Descriptive statistics, repeated measures analysis and Pearson's correlation coefficient tests were used to analyze the data.

**Results:** The total mean of stress scores during 10 days was 99.44  $\pm$  17.37. "Multiple attempts to insert intravenous and intra-arterial catheters and "intubation" were the most frequent procedures in the "extremely stressful" category among four categories of stressors. The highest scores of acute and chronic stress were related to the tenth and third day of hospitalization, respectively. There was no significant difference between infants' characteristics and total mean stress scores. Repeated measures analysis showed that the mean acute stress scores were significantly different among the 10 subsequent days (P < 0.05).

**Conclusions:** The results of this study demonstrated the frequent occurrence of various procedures in preterm infants hospitalized at the NICU. Although these procedures were done with the purpose of improving infants' health, they can lead to problems and complications, which might postpone the infants' recovery process.

Keywords: Preterm Infant, Stress, NICU, Cumulative Stressors

## 1. Background

It is reported that 9.6% of births around the world are preterm and 13 million preterm births occur annually worldwide (1). Prematurity is the most important cause of admission in neonatal intensive care units (2). Preterm infants lack capability to survive outside the uterus due to their physiological and developmental immaturity. These infants usually need intensive care in specialized units (3). For example, one of the most common reasons of preterm infants' hospitalization in NICUs is respiratory distress syndrome, the treatment of which requires invasive and stressful interventions such as intubation (4). Furthermore, NICUs technological setting is usually full of various stimulators that are distressing for premature infants (5, 6) and might affect their development (7-9). A study reported that more than 700 procedures might be performed on a preterm infant during hospitalization (10). Some studies have also reported that preterm infants experience about sixteen stressors daily, among which, ten procedures are

painful (11-13). These frequent medical and nursing procedures are distressing and intolerable for a premature infant because their physiological and hormonal responses to the stimuli and stressors are often undeveloped and unorganized (14-16).

Stressors are defined as physical, mental and social events that violate the dynamic balance between the organism and its environment (17). They occur when the demand of a situation is greater than a person's capability to cope with (18). A set of large and small stresses, which occur in sequence and during time, is called cumulative stresses and can affect the premature infant's development (19). When constant stresses occur in long-term intervals, the person cannot achieve physiological balance, which might lead to physical burn-out or allostatic load. This condition might not only postpone the improvement of an immature infant, but also accelerate the process of the illness (5, 11).

In addition to painful medical and nursing procedures, which are always stressful, painless experiences

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cause imbalance in premature infants as well (5). A study showed that painless sensory stimuli in preterm infants can cause physiological responses equal to or greater than painful stimuli (20). However, in most studies, only the infants' painful stimuli and the ways to decrease the pain have been evaluated (16, 21, 22) and other sources of infants' stress, such as painless stimuli, have been overlooked (5).

#### 2. Objectives

This study aimed to evaluate the cumulative stressors in premature infants hospitalized in a neonatal intensive care unit (NICU) in Alzahra hospital, Tabriz, Iran.

#### 3. Methods

### 3.1. Design and Samples

In this descriptive study, the infants of 28 to 30 weeks of gestation, who were hospitalized in the NICU of Tabriz Alzahra hospital in 2013, were studied. Sample size was calculated after a pilot study on 30 infants, in which the mean and standard deviation of the stress score were 84.25 and 28.17, respectively. Then, considering type I error probability as 0.05,  $\sigma$  = 28.17 and d = 0.05 of stress scores mean (=4.22), 179 samples were estimated to be needed in this study. However, 197 samples were recruited into the study to increase the validity of the results and compensate the possible dropouts.

A consecutive method was used to recruit infants matching the inclusion criteria. Inclusion criteria included lack of any congenital anomalies or any problems in the central nervous system (i.e. asphyxia, intra ventricular hemorrhage). Exclusion criteria were discharge from NICU or being referred to other centers before the study was completed.

#### 3.2. Data Collection Instruments

A two-part instrument was used. The first part included questions addressing the infants characteristics including the type of delivery, gender, multiple pregnancy, mother's and infant's gestational age (week), birth weight (g), height and head circumference at birth (cm), first minute and fifth minute Apgar. These data were extracted from the infants' hospital records.

A modified version of the neonatal infant stressor scale (NISS) (5) was used as the second part of the instrument to evaluate infants' stressors. To adapt the content of NISS to the common procedures in the study setting, the scale was modified according to the ideas of employed nursing experts of the NICU. The modified NISS assesses 35 acute and 19 chronic stress experiences and both groups include

painful and painless stressors. Acute stressors are classified to four categories, including "extremely stressful = 5" (such as multiple attempts to insert a catheter (i.e intravenous (IV) and intra-arterial (IA) catheters, umbilical venous catheter (UVC), umbilical arterial catheter (UAC) and intubation), "very stressful = 4" (i.e. endotracheal tube (ETT) insertion and nose/mouth suctioning), "moderately stressful = 3" (i.e. nappy and position changes), and "a little stressful = 2" (i.e. mouth care and eye care). Chronic stressors are also classified to three categories, including "very stressful = 4" (i.e. having a systemic infection), "moderately stressful = 3" (i.e. nursed in a radiant warmer) and "a little stressful = 2" (i.e. nursed in an incubator).

Content validity of the scale was determined by ten professors in the Nursing and midwifery faculty of Tabriz University of Medical Science. Moreover, the reliability of the scale was confirmed by a Cronbach's alpha of 0.87.

#### 3.3. The Procedures

Infants were evaluated on a daily basis to calculate the cumulative stressors during a ten-day period. To achieve this goal, a checklist was located in infants' overhead chart and all NICU nurses were educated to mark it after performing each procedure. On a daily basis, the completed scales were crosschecked with clinical notes and the infants' electronic chart (in the hospital information system) by the corresponding author and then the daily cumulative stress score was calculated. The score of each procedure was multiplied by its frequency and the scores achieved in each category were summed at the end of every 24 hours.

#### 3.4. Ethical Considerations

The study was approved by the ethics committee of Tabriz University of Medical Sciences (No. 5.4.11380). The aims of the study were explained to the parents of all qualified infants and they signed a written informed consent before participating in the study.

## 3.5. Data Analysis

The data was analyzed using SPSS Ver.13 and descriptive statistics (frequency, percentage, mean and standard deviation). The Kolmogorov-Smirnov test was used to assess normality of the data. Repeated measures analysis of variance was used to compare the infants mean stress scores during the 10 consecutive days. Pearson's correlation coefficient was used to determine the correlation between characteristics of infants (such as gestational age, body weight, the first and the fifth minute Apgar scores) with stress scores. P values of < 0.05 were considered significant in all tests.

#### 4. Results

Of the 197 preterm infants, 58.5% were boys, and 24.4% and 75.6% were born via normal vaginal delivery and cesarean section, respectively. Of all infants, 81.4% were born single, 9.3% were twins and 9.3% were triplets.

The overall mean stress score during the ten days was 107.81  $\pm$  13.29. The mean acute and chronic stress scores were also 99.44  $\pm$  17.37 and 11.78  $\pm$  1.43, respectively. There was no significant correlation between infants' characteristics and the total mean stress scores (Table 1). The greatest portion of recorded scores on the first hospitalization day was related to "extremely stressful" and "very stressful" acute categories.

Repeated measures analysis showed that the mean acute stress scores were significantly different among the ten subsequent days (P < 0.01). Also, the mean chronic stress scores were significantly different among the ten subsequent days (P < 0.01) (Table 2). However, no significant difference was observed between the ten subsequent days, when sum of the acute and chronic stress scores were considered (P = 0.06) (Table 3). As Table 2 shows, acute and chronic stress scores during monitoring days did not follow a certain trend. The highest scores of acute and chronic stress were related to the tenth and third day of hospitalization, respectively.

Each infant experienced painful and painless procedures with mean of 358  $\pm$  50.78 during the study. The most frequent procedures classified in the "extremely stressful" category were multiple IV insertion and intubation attempts. Overall, 153 infants experienced IV insertion attempts more than twice during the study; amongst whom 72 infants experienced these procedures more than three times. Suctioning of nose/mouth and IV insertion, that all infants in the study experienced, were among procedures classified in the "very stressful" category (Table 4). Insertion of chest tube and lumber puncture were among the less frequent procedures. Generally, 70689 procedures were recorded during the study.

Having Nasogastric tubes in situ, phototherapy, IVs in situ, regular fluids and IV drugs administrations were among chronic procedures, which all of the infants experienced during the study. Being nursed in a radiant warmer and ventilation without sedative were done in 98.5% and 87.3% of infants, respectively. Table 5 shows the duration that infants experienced chronic stressors.

### 5. Discussion

In the present study, no correlation was found between infants' characteristics and the total stress score. This is probably due to the fact that most of the procedures, such

as insertion of IV catheters, position changes and nappy changes are commonly performed for all infants admitted to the NICU. Although the mean stress scores were different in various days, however, no specific trend was observed during the study.

Most of the procedures in the first hospitalization day were of the "extremely stressful" and "very stressful" acute category stressors. Similar patterns in number and types of procedures were reported in an earlier cohort study, in which neonatal intensive care unit stress was evaluated in preterm infants. The study also showed that daily exposure to stressors was greater during the first 14 days of life (11).

In the present study every infant experienced on average 385 painful and painless procedures during in the first 10 days of hospitalization. In an earlier study, neonates in intensive care units experienced about 115 procedures during the first six weeks of life, of which 10 daily procedures were painful (12).

The most frequent painful procedures recorded in the present study were IV insertion, intubation, suctioning of nose and mouth, heel pricks, and arterial and venous blood sampling. In a study by Carbajal et al. (12), suctioning of nose, heel pricks, removing plaster from infants' body, arterial and venous blood sampling and IV insertion were the most common procedures, respectively. In general, distribution of painful procedures in both studies was similar and a difference was seen in the order of procedures' frequency. For example, in our study, IV insertion was the most frequent painful procedure while in Carbajal's study it was the eighth most frequent painful procedure. Also in a study by Jeong et al. (13), which was done at two intensive care units in Korea, the most frequent painful procedures were suctioning of mouth, suctioning of ETT, heel pricks, removing plaster from infant's body, venous sampling and IV insertion, respectively and intubation was the 14th procedure. The difference between the present study and the two mentioned studies might be related to the duration of the studies and infants' condition, since all of the infants in our study were preterm and had respiratory distress syndrome, while in both above-mentioned studies, a combination of term and preterm infants with different conditions were studied. Performing frequent nursing and medical procedures in preterm infants, regardless of their painfulness, can disrupt their physiologic equilibrium and make them stressed and imbalanced. Most of the previous studies only focused on painful stressors. However, in the present study, all of the infants' acute and chronic stressors, including painful and painless procedures were stud-

In this study we only assessed the infants for 10 days. However, we suggest further studies with longer periods of time to be done. It is also recommended that, in future

Table 1. Characteristics of Infants and Their Correlation With Total Mean of Stress Scores at the Intensive Care Unit of Tabriz Alzahra Hospital, 2013

Variable	Means $\pm$ SD	Lowes	Highest	r <sup>a</sup>	P Value
Gestational age, w	$28.62\pm1.22$	28	30	-0.10	0.14
Weight of first day, g	$1133.05 \pm 238.55$	640	1700	0.08	0.25
Height of first day, cm	$\textbf{35.8} \pm \textbf{3.12}$	30	44	0.04	0.62
Head circumference of first day, cm	$26.45\pm1.98$	20	30	-0.15	0.10
First minute Apgar	$6.37 \pm 1.69$	2	9	0.04	0.50
Fifth minute Apgar	$7.86\pm1.43$	4	10	0.11	0.11

<sup>&</sup>lt;sup>a</sup>Pearson test.

Table 2. Acute and Chronic Cumulative Stress Scores in Preterm Hospitalized Infants for Monitoring Days, Tabriz Alzahra Hospital, 2013

Variable/Days of Measurement	Means $\pm$ SD	Range
Acute cumulative stress scores		
First	$95.63 \pm 24.570$	55 - 195
Second	$83.53 \pm 17.697$	46 - 171
Third	$91.54 \pm 18.043$	61 - 138
Fourth	$95.13 \pm 19.397$	58 - 135
Fifth	$95.97 \pm 19.198$	62 - 151
Sixth	$96.64 \pm 23.972$	62 - 200
Seventh	$98.18 \pm 22.959$	55 - 147
Eighth	$101.18 \pm 23.339$	52 - 174
Ninth	$100.01 \pm 21.467$	41 - 135
Tenth	$102.28 \pm 23.665$	39 - 160
Chronic cumulative stress scores		
First	$11.76 \pm 1.436$	9 - 18
Second	$12.54 \pm 2.110$	8 - 19
Third	$13.59 \pm 1.881$	9 - 19
Fourth	$12.76 \pm 1.938$	8 - 15
Fifth	$12.49 \pm 2.226$	9 - 18
Sixth	$11.83 \pm 2.530$	4 - 17
Seventh	$10.89 \pm 2.689$	0 - 16
Eighth	$11.19 \pm 2.593$	6 - 18
Ninth	$10.55 \pm 2.749$	4 - 17
Tenth	$10.25 \pm 3.269$	0 - 17

studies, measuring blood pressure and removing plaster from infants' body be added to the list of NISS.

The results of this study demonstrated the frequent occurrence of various procedures in preterm infants hospi-

talized in NICU. Although these procedures were done with the purpose of improving infants' health, they can lead to problems and complications, which might postpone the infants' recovery process. Therefore, taking into account

 Table 3. Result of Repeated Measure Analysis of Variance (ANOVA) of Chronic and Acute Cumulative Stress Scores in Infants During the Study Period, Tabriz Alzahra Hospital,

 2013

Cumulative Stress Score	Sum of Squares	Mean of Squares	df	f	P Value
Acute	48998	5444.22	9	16.73	< 0.001
Chronic	1969	218.77	9	53.93	< 0.001
Acute + Chronic	38232	5425.45	9	13.19	0.06

Table 4. The Number and Mean of Performed Acute Procedures in the First Ten Days of Hospitalization in Preterm Infants, Tabriz Alzahra Hospital, 2013

Level of stress	Procedures	Number of infants (%)	Mean $\pm$ SD of Procedures' in 10 Days	Range
Extremely stressful (score 5)				
	Multiple attempts inserting IV/IA/UAC/UVC	153 (77.7)	$3.40\pm3.11$	1 - 17
	Intubation	125 (63.5)	$1.66\pm1.09$	1-7
Very Stressful (score 4)				
	Suctioning of nose and mouth	197 (100)	$16.13\pm9.69$	1-40
	Insertion of IV/IA/UAC/UVC	197 (100)	$7.50\pm2.85$	3 - 13
	Heel pricks	188 (95.5)	$17.38\pm8.27$	2-36
	Insertion nasal CPAP	181 (91.9)	$\textbf{1.62} \pm \textbf{0.89}$	1-5
	Removing infant from incubator/bed (unwrapped)	107 (54.3)	$1.33\pm0.57$	1-3
	Suctioning of ETT tube	47 (23.9)	$12.45 \pm 7.18$	3 - 27
Moderately stressful (score 3)				
	Nappy changes	197 (100)	$39.17\pm1.91$	27 - 40
	Position changes	197 (100)	$37.55\pm5.83$	6-40
	X-ray	197 (100)	$2.78\pm2.29$	1-15
	Gavage feeding	179 (90.9)	$43.20\pm25.13$	1-90
A little Stressful (score 2)				
	IV Flushing (to ensure patency of IV)	197 (100)	$70.48\pm15.05$	8 - 93
	Attachment of monitor sensors	197 (100)	$26.37 \pm 15.40$	1-40
	Stomach aspiration via NGT	194 (98.5)	$41.35 \pm 26.44$	1-92
	Sampling e.g. blood gases	193 (98.5)	$15.15 \pm 8.02$	3-40

cumulative stressors in preterm infants is a very important issue and NISS is a useful scale to assess it. By using NISS and calculating the score of stress, nurses would be able to estimate the rate of stress received by infants and in case of greater stress, they would postpone stressful procedures to prevent cumulative effects of stressors in preterm infants.

## Acknowledgments

Hereby, we thank the administrative and NICU staff of Alzahra hospital as well as the parents of infants, who participated in the study.

#### **Footnotes**

**Authors' Contribution:** Mahni Rahkar Farshi and Mahnaz Jabraeili contributed to the initial design of the research, Fatemeh Ghorbani and Roya Sabouhi participated in the data collection. Data analysis and drafting of the manuscript were performed by Mahni Rahkar Farshi and Fatemeh Ghorbani, respectively. All authors approved the final manuscript.

**Financial Disclosure:** There is no financial disclosure.

**Funding/Support:** This study was financially supported by the research deputy of Tabriz University of Medical Sciences (Project No 5.55.970), Tabriz, Iran.

Table 5. The Number and Mean of Performed Chronic Procedures in the First Ten Days of Hospitalization in Preterm Infants, Tabriz Alzahra Hospital, 2013

Categories	Procedures	Number of infants (%)	Mean $\pm$ SD of days	Range
Very stressful (score 4)				
	Having non-systemic infection	14 (7.1)	$2.14\pm1.87$	1-5
Moderately stressful (score 3)				
	Nursed in radiant warmer	194 (98.5)	$7.82 \pm 2.65$	1-10
	Pneumothorax chest drain	6(3)	$5.50\pm1.64$	4-7
	Ventilation without sedation	172 (87.3)	$3.10\pm2.20$	1-10
A little stressful (score 2)				
	Nursing in incubator	95 (48.2)	$4.09 \pm 2.37$	1-9
	IV fluids	197 (100)	$9.83 \pm 0.46$	8 - 10
	IV/IA/UAC/UVC in situ	197 (100)	$9.77 \pm 0.63$	7-10
	Ventilation with sedation	143 (72.6)	$3.09 \pm 1.97$	1-8
	Head box oxygen	112 (56.9)	$2.03\pm1.72$	1-8
	Nasogastric tube in situ	197 (100)	$9.02\pm1.66$	2-10
	Phototherapy	197 (100)	$6.37\pm1.92$	2 - 10

#### References

- Liaw JJ, Yang L, Katherine Wang KW, Chen CM, Chang YC, Yin T. Non-nutritive sucking and facilitated tucking relieve preterm infant pain during heel-stick procedures: a prospective, randomised controlled crossover trial. *Int J Nurs Stud.* 2012;49(3):300–9. doi: 10.1016/j.ijnurstu.2011.09.017. [PubMed: 22001561].
- Ghorbani F, Asadollahi M, Valizadeh S. Comparison the effect of Sleep Positioning on Cardiorespiratory Rate in Noninvasive Ventilated Premature Infants. Nurs Midwifery Stud. 2013;2(2):182-7. [PubMed: 25414856].
- Peng NH, Bachman J, Chen CH, Huang LC, Lin HC, Li TC. Energy expenditure in preterm infants during periods of environmental stress in the neonatal intensive care unit. *Jpn J Nurs Sci.* 2014;11(4):241–7. doi: 10.1111/jjns.12025. [PubMed: 25306928].
- Khalili Z, Kavemanesh Z, Amirsalari S, Afsharpeyman SH, Torkaman M, Dastamooz A. Causes and Outcome of Neonatal Respiratory Distress Syndromes in NICU of Baqiyatallah Hospital. *Trauma Mon.* 2005;10(02):143-8.
- Newnham CA, Inder TE, Milgrom J. Measuring preterm cumulative stressors within the NICU: the Neonatal Infant Stressor Scale. Early Hum Dev. 2009;85(9):549–55. doi: 10.1016/j.earlhumdev.2009.05.002. [PubMed: 19520525].
- Grunau RE, Holsti L, Peters JWB. Long-term consequences of pain in human neonates. Seminars in Fetal and Neonatal Medicine. Elsevier; 2006. pp. 268-75.
- Robertson CM, Watt MJ, Dinu IA. Outcomes for the extremely premature infant: what is new? And where are we going?. *Pediatr Neurol.* 2009;40(3):189–96. doi: 10.1016/j.pediatrneurol.2008.09.017. [PubMed: 19218032].
- Peng NH, Bachman J, Jenkins R, Chen CH, Chang YC, Chang YS, et al. Relationships between environmental stressors and stress biobehavioral responses of preterm infants in NICU. *J Perinat Neonatal Nurs*. 2009;23(4):363-71. doi: 10.1097/JPN.0b013e3181bdd3fd. [PubMed: 19915421].
- 9. Verklan MT, Walden M. Core curriculum for neonatal intensive care nursing. Elsevier Health Sciences; 2014.

- Porter FL, Wolf CM, Miller JP. Procedural pain in newborn infants: the influence of intensity and development. *Pediatrics*. 1999;104(1):e13. [PubMed: 10390299].
- Smith GC, Gutovich J, Smyser C, Pineda R, Newnham C, Tjoeng TH, et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol*. 2011;**70**(4):541–9. doi: 10.1002/ana.22545. [PubMed: 21976396].
- 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*. 2008;300(1):60-70. doi: 10.1001/jama.300.1.60. [PubMed: 18594041].
- Jeong IS, Park SM, Lee JM, Choi YJ, Lee J. The frequency of painful procedures in neonatal intensive care units in South Korea. *Int J Nurs Pract*. 2014;20(4):398–407. doi: 10.1111/ijn.12202. [PubMed: 24118662].
- Rohan AJ. Pain-associated stressor exposure and neuroendocrine values for premature infants in neonatal intensive care. *Dev Psychobiol.* 2016;58(1):60-70. doi: 10.1002/dev.21346. [PubMed: 26290118].
- Vinall J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. *Pediatr Res.* 2014;75(5):584–7. doi: 10.1038/pr.2014.16. [PubMed: 24500615].
- Lucas-Thompson R, Townsend EL, Gunnar MR, Georgieff MK, Guiang SF, Ciffuentes RF, et al. Developmental changes in the responses of preterm infants to a painful stressor. *Infant Behav Dev.* 2008;31(4):614– 23. doi: 10.1016/j.infbeh.2008.07.004. [PubMed: 18778857].
- Peng NH, Chen CH, Bachman J, Lin HC, Wang TM, Chang YC, et al. To explore relationships between physiological stress signals and stress behaviors in preterm infants during periods of exposure to environmental stress in the hospital. *Biol Res Nurs.* 2011;13(4):357-63. doi: 10.1177/1099800410392020. [PubMed: 21196425].
- Washington TD. Psychological stress and anxiety in middle to late childhood and early adolescence: manifestations and management. J Pediatr Nurs. 2009;24(4):302-13. doi: 10.1016/j.pedn.2008.04.011. [PubMed: 19632507].
- Gunnar M, Quevedo K. The neurobiology of stress and development. *Annu Rev Psychol.* 2007;58:145-73. doi: 10.1146/annurev.psych.58.110405.085605. [PubMed: 16903808].
- Hellerud BC, Storm H. Skin conductance and behaviour during sensory stimulation of preterm and term infants. Early Hum Dev. 2002;70(1-2):35-46. [PubMed: 12441203].

- 21. Provenzi L, Fumagalli M, Sirgiovanni I, Giorda R, Pozzoli U, Morandi F, et al. Pain-related stress during the Neonatal Intensive Care Unit stay and SLC6A4 methylation in very preterm infants. Front Behav Neurosci. 2015;9:99. doi: 10.3389/fnbeh.2015.00099. [PubMed: 25941480].
- 22. Ahn Y, Jun Y. Measurement of pain-like response to various NICU stimulants for high-risk infants. *Early Hum Dev.* 2007;**83**(4):255–62. doi: 10.1016/j.earlhumdev.2006.05.022. [PubMed: 16854537].