

# Analgesia and sedation during placement of peripherally inserted central catheters in neonates

ANALGESIA E SEDAÇÃO DURANTE A INSTALAÇÃO DO CATETER CENTRAL DE INSERÇÃO PERIFÉRICA EM NEONATOS

ANALGESIA Y SEDACIÓN DURANTE LA INSTALACIÓN DEL CATÉTER VENOSO CENTRAL DE INSERCIÓN PERIFÉRICA EN NEONATOS

Priscila Costa<sup>1</sup>, Mariana Bueno<sup>2</sup>, Cintia Luiza Oliva<sup>3</sup>, Talita Elci de Castro<sup>4</sup>, Patrícia Ponce de Camargo<sup>5</sup>, Amélia Fumiko Kimura<sup>6</sup>

## ABSTRACT

This study aimed to characterize the analgesia and sedation strategies in neonates having a peripherally inserted central catheter (PICC) placed, and to relate it to the number of venipunctures, duration of procedure and catheter tip position. This was a cross-sectional study with prospective data collection, conducted in a neonatal intensive care unit of a private hospital in the city of São Paulo, during the period from August 31, 2010 to July 1, 2011, which evaluated 254 PICC insertions. The adoption of analgesic or sedative strategies occurred in 88 (34.6%) catheter placements and was not related to the number of venipunctures, duration of procedure or catheter tip position. Intravenous administration of midazolam, in 47 (18.5%), and fentanyl, in 19 (7.3%), catheter insertions were the most frequent strategies. Wider adoption of analgesic strategies is recommended before, during and after the procedure.

## DESCRIPTORS

Analgesia  
Infant, newborn  
Pain  
Catheterization, central venous  
Neonatal nursing

## RESUMO

Objetivou-se caracterizar as estratégias de analgesia e sedação em neonatos submetidos à instalação do cateter central de inserção periférica (CCIP) e relacioná-las ao número de punções venosas, duração do procedimento e posicionamento da ponta do cateter. Estudo transversal com coleta prospectiva de dados, realizado em uma unidade de cuidados intensivos neonatais de um hospital privado na cidade de São Paulo, no período de 31 de agosto de 2010 a 01 de julho de 2011, em que foram avaliadas 254 inserções do CCIP. A adoção de estratégias analgésicas ou sedativas ocorreu em 88 (34,6%) instalações do cateter e não esteve relacionada ao número de punções venosas, duração do procedimento ou posicionamento da ponta do cateter. As estratégias mais frequentes foram a administração endovenosa de midazolam em 47 (18,5%) e fentanil em 19 (7,3%) inserções do cateter. Recomenda-se maior adoção de estratégias analgésicas antes, durante e após o procedimento.

## DESCRIPTORIOS

Analgesia  
Recém-nascido  
Dor  
Cateterismo venoso central  
Enfermagem neonatal

## RESUMEN

El objetivo fue caracterizar las estrategias de analgesia y sedación en neonatos sometidos a la instalación del catéter venoso central de inserción periférica (CCIP) y relacionarlas con el número de punciones venosas, duración del procedimiento y la posición de la punta del catéter. Estudio transversal con recolección prospectiva de datos conducido en unidad de cuidados intensivos neonatal de un hospital privado en la ciudad de Sao Paulo; realizado en el periodo del 31 de agosto de 2010 al 01 de julio de 2011 donde fueron evaluadas 254 instalaciones del CCIP. La adopción de estrategias analgésicas o sedación ocurrió en 88 (34,6%) instalaciones de catéter y no estuvo relacionada con el número de punciones venosas, duración del procedimiento o la posición de la punta del catéter. Las estrategias más utilizadas fueron la administración intravenosa de Midazolam en 47 (18,5%) y Fentanil en 19 (7,3%) respectivamente. Se recomienda una mayor adopción de estrategias analgésicas antes, durante y después del procedimiento.

## DESCRIPTORIOS

Analgesia  
Recién nacido  
Dolor  
Cateterismo venoso central  
Enfermería neonatal

<sup>1</sup>Nurse. Master of Science in Health. Specialist in Teaching Laboratory of the Department of Maternal-Child and Psychiatric Nursing, in the School of Nursing of the Universidade de São Paulo (University of São Paulo), São Paulo, SP, Brazil. priscila2.costa@usp.br <sup>2</sup>Nurse. Professor, Doctorate, School of Nursing of the Universidade Federal de Minas Gerais (Federal University of Minas Gerais). Belo Horizonte, MG, Brazil. maribueno@hotmail.com <sup>3</sup>Nurse. Master's student of the Graduate Program of Health Sciences, School of Nursing of the Universidade de São Paulo. São Paulo, SP, Brazil. cintiaoliva@usp.br <sup>4</sup>Nurse. Master's student of the Graduate Program of Health Sciences, School of Nursing of the Universidade de São Paulo. Nurse, Hospital e Maternidade São Luiz. São Paulo, SP, Brazil. telci@saoluiz.com.br <sup>5</sup>Nurse. Doctorate student of the Graduate Program of Health Sciences, School of Nursing of the Universidade de São Paulo. Nurse, Berçário Anexo à Maternidade do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. São Paulo, SP, Brazil. patricia.camargo@jcr.usp.br <sup>6</sup>Nurse. Professor, Doctorate, Department of Maternal-Child and Psychiatric Nursing, in the School of Nursing of the Universidade de São Paulo. São Paulo, SP, Brazil. fumiko@usp.br

## INTRODUCTION

Technological advances in neonatology and development of neonatal intensive care units have contributed significantly to the increased survival of critically ill newborns. However it has exposed them to more stressful and painful therapeutic and diagnostic procedures. This cumulative exposure to pain can result in early and long-term pain process changes in the response system to stress and child development<sup>(1)</sup>.

During the period of hospitalization in the Neonatal Intensive Care Unit (NICU), neonates are exposed to numerous stressors, including painful stimuli, sleep disruption, excessive noise, high light levels, frequent handling associated with nursing procedures and maternal separation<sup>(2)</sup>. On average, they are subjected to 16 painful procedures per day, the majority of which occur without analgesia<sup>(3)</sup>, which highlights the need for changes in the practice of care to reduce stress and pain and to promote improved clinical and adequate neurobehavioral development for the neonates.

Among the common procedures in neonatal care, we highlight the insertion of vascular devices. The need for a safe venous access for infusion of hyperosmolar, irritating or vesicant solutions is a common care demand for newborns in the NICU. For this reason, the peripherally inserted central catheter (PICC) or epicutaneous catheter, has been used extensively in neonates<sup>(4)</sup>, especially in pre-term infants who require medium and long term hospitalization in the NICU.

The insertion of this device involves a puncture of a peripheral vessel and intravenous progression of the catheter until its tip reaches the central venous system. Since this is an invasive procedure, the PICC insertion results in a pain response of moderate to severe intensity<sup>(5)</sup>. However, measures for the relief of pain caused by the procedure are uncommon in neonatal care.

If not treated, pain can compromise the resolution of processes underlying disease, delay surgical recovery, and increase the costs of health care<sup>(6)</sup>. In addition, multiple painful and stressful events experienced by hospitalized infants induce acute physiological changes, as well as permanent structural and functional changes in the central nervous system. This can have long-term consequences, including chronic pain and altered neurobehavioral responses to pain<sup>(7)</sup>. Appropriate use of environmental, behavioral and pharmacological interventions may prevent, reduce or eliminate the pain associated with procedures in neonates.

The use of non-nutritive sucking with sucrose or human milk, and application of the mixture of prilocaine and 5% lidocaine (EMLA), is recommended in infants for PICC insertion. In some situations, the use of systemic

opioid analgesics in bolus, especially for mechanically ventilated newborns<sup>(8)</sup>.

However, studies about strategies for pain management related to PICC insertion are scarce and few reports on the analgesic strategies adopted are available. There is a need for further investigations to describe the phenomenon. The results of a study about pharmacological and non-pharmacological pain relief strategies during PICC insertion in neonates showed only the use of sedatives, which only help in reducing the agitation of the individual<sup>(9)</sup>.

Given that nurses play a central role in the insertion, maintenance and removal of the epicutaneous catheter, as well as ensuring assessment, prevention and treatment of pain resulting from the procedure of inserting the device, it was justified to conduct this study, which aimed to: characterize sedative and analgesic strategies in neonates during PICC insertion and relate them to the frequency of venipunctures, duration of the procedure, and catheter tip position.

## METHOD

Appropriate use of environmental, behavioral and pharmacological interventions may prevent, reduce or eliminate the pain associated with procedures in neonates.

This was a cross-sectional study with prospective data collection, conducted in a NICU of a large private hospital in the city of São Paulo. The NICU had 60 beds and the nursing team was composed of 24 nurses, 18 of whom are skilled in insertion, maintenance and removal of the PICC.

In accordance with Resolution 196/96 of the National Health Council, the research project was approved by the Ethics Committee of the hospital where the study was conducted, and approval was obtained for data collection (Process No. 238/2010).

The PICC management in this institution follows the guidelines of a protocol developed by nurses of the study group on venous catheters, based on norms established by professional societies that empower Brazilian nurses for the management of the PICC.

In the institution where data were collected, the indication for insertion and removal of PICC is a medical attribution. The installation of the catheter is an aseptic procedure conducted at the bedside by trained nurses, after an appraisal of the clinical conditions and venous system. The types of catheters used in the institution were: double lumen polyurethane 2 Frenchs (*Fr*), indicated for infusion of total parenteral nutrition (TPN) and antibiotics or other drugs, and single lumen silicone PICC, 1.9 *Fr*, indicated for neonates with prescription of a single kind of intravenous solution.

Participants were selected from a control diary made by NICU nurses about the type of installed vascular device on every neonate admitted during the period from August

31, 2010, to July 1, 2011, according to the period of data collection approved by the Ethics in Research Committee of the institution.

The eligibility criteria were: neonates without congenital anomalies, born in the maternity unit of the hospital and having a device inserted during the NICU stay. Newborns without notation in the medical record of analgesic or sedative measures employed in the catheter insertion procedure were excluded, and also those with an unsuccessful placement.

Data were extracted from medical records and from the institutional record, called the PICC Control Form, in which the nursing staff recorded information related to insertion, maintenance and removal of the device.

To record the data a proper form was used containing the variables of interest in the study: clinical diagnosis, classification of weight of the newborn in relation to gestational age, gender, postnatal age, gestational age and weight at the time of the procedure, frequency of venipunctures, interval of time between the first venipuncture and the end of the procedure, catheter tip position (central or non-central), analgesic and sedative measures prescribed in order to insert the catheter, as well as intravenous analgesics and sedatives prescribed because of the clinical condition of the neonate.

The analgesic and sedative prescriptions for the epicutaneous catheter insertion procedure included pharmacological and nonpharmacological measures: fentanyl or tramadol intravenous *bolus* administration, intravenous or intranasal midazolam, oral chloral hydrate, 25% sucrose solution via oral route, facilitated containment (delicate motor restraint of arms and legs in flexion, directed to the midline, near the trunk and face, in lateral or supine positions) and non-nutritive sucking (pacifier sucking or gloved finger of caregiver for newborns). The continuous intravenous administration of fentanyl or midazolam was considered as an analgesic or sedative strategy adopted because of the clinical condition of the neonate.

The collected data were stored in a Microsoft Office Excel 2007 spreadsheet and analyzed using the SAS System for Windows 9.0. The continuous variables were analyzed with descriptive statistics, and categorical variables through absolute and relative frequency. For categorical variables, the existence of differences between the groups with and without sedation or analgesia was determined by the Chi-square or Fisher's exact test. For continuous variables, we used the *Student t-test*. The level of statistical significance adopted was  $p < 0.05$  with 95% confidence interval.

## RESULTS

During the study period, 262 PICC insertion attempts occurred in neonates who were assessed for eligibility criteria. After exclusion of two insertions without hospital records and

six due to failure of insertion of the catheter, 254 catheter placements remained for analysis (Table 1). No sedative or analgesic strategy was used for prevention or treatment of pain in the unsuccessful attempts to insert the catheter.

**Table 1** – Demographic and clinical characteristics of neonates having a PICC insertion - São Paulo, 2010-2011.

Demographic and clinical characteristics	N	%
Male sex	150	59.1
Newborn appropriate for gestational age	204	81.3
Diagnostics		
Prematurity	200	78.8
Respiratory distress syndrome	170	66.9
Twin birth	58	22.8
Heart disease	43	17.6
Disorders of the gastrointestinal tract	36	14.8
	<b>Mean</b>	<b>SD</b>
Corrected gestational age at the time of PICC insertion (weeks)	34.1	4.09
Postnatal age (days)	10.6	18.7
Weight at the time of PICC insertion (grams)	1091.5	860.7

The 254 epicutaneous catheters were inserted in 211 newborns, with the majority of neonates having only one catheter (178 / 84.4%). The remaining (33 / 15.6%) received two to four catheters during their hospitalization.

It was observed that in most neonates having PICC insertions, 166 (65.4%), analgesic or sedative strategies were not used. In 88 (34.6%) strategies of analgesia or sedation were adopted (Table 2). It is noteworthy that in 72 (28.3%) insertions, the analgesic or sedative measure was used because of the PICC insertion procedure, and in the rest of the occasions (16 / 6.3%), pharmacological treatment was adopted as a result of the clinical condition of the newborn.

**Table 2** – Measures of pain control in neonates having a PICC insertion - São Paulo, 2010-2011.

Measures of pain control	N	%
No	166	65.4
Yes	88	34.6
Pharmacological		
Midazolam	47	18.5
Fentanyl	19	7.5
Midazolam + Fentanyl	9	3.5
Chloral hydrate	5	2.0
<i>Tramadol</i> hydrochloride	2	0.8
Non- pharmacological		
Sucrose solution	5	2.0
Sucrose solution + non-nutritive sucking	1	0.4

Exclusively analgesic strategies were recommended due to the procedure in 19 (7.5%) of the PICC insertions.

Intravenous administration of fentanyl, followed by oral sucrose solution were the most frequently used strategies.

**Table 3** – Distribution of mean venipunctures, time spent to insert the catheter and the frequency of catheter tip position according to the use of sedative or analgesic strategy. São Paulo, 2010-2011.

Variables	Use of analgesic or sedative strategy				P value
	Yes (n=88)		No (n=166)		
	Mean	SD	Mean	SD	
Frequency of venipunctures	2.9	2.1	2.5	1.6	0.08
Time spent in the insertion of the PICC in minutes	40.2	28.6	36.2	26.7	0.27
<b>Catheter tip position</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	
Central	77	87.5	143	86.1	0.76
Non-central	11	12.5	23	13.9	

It was observed that, for all catheters inserted, the mean venipunctures needed for a successful catheter insertion was 2.7, and the mean time spent to insert the catheter was 37.6 minutes. There was no statistically significant difference between the group of neonates who received and did not receive any strategy for sedation or pain relief regarding the number of venipunctures, time spent in catheter insertion, and catheter tip position.

## DISCUSSION

Pain as a phenomenon that also affects newborns has become a focus of concern and research for health professionals and researchers for nearly two decades<sup>(10)</sup>. However, the use of pharmacological, behavioral and environmental analgesic strategies is still inconsistent in the scenario of care.

The PICC insertion in neonates has gained popularity due to ease of insertion, and studies suggest that between 8.3 to 33% of patients admitted to the NICU use this device for infusion of intravenous therapy<sup>(11)</sup>.

However, it is a painful event, as noted in descriptive study with a sample of 28 neonates who had a PICC insertion, admitted to the NICU of a large teaching hospital in the city of São Paulo. The results showed that 71.4% of infants had PIPP (*Premature Infant Pain Profile*) pain assessment scores indicating moderate to severe pain response to venipuncture, and with less intensity during the progression of the catheter tip<sup>(5)</sup>.

The results of this study show that the care practices of analgesia and sedation during the PICC insertion procedure occurred in only 34.6% of the insertions in neonates. The most used strategies were the intravenous administration of midazolam (47 / 18.5%) and fentanyl (19 / 7.3%). The use of analgesic strategies was less frequent in relation to sedatives.

Consistent with these observed results, an exploratory descriptive study, that evaluated 43 neonates in the neonatal unit of a hospital in the city of São Paulo, indicated

that 86.1% of PICC insertions were not accompanied by analgesia, and in 13.9% of cases, sedatives were used. Non-pharmacologic methods of pain relief and stress were not used<sup>(9)</sup>. Therefore, a high frequency of sedatives was noted during PICC insertion in neonates.

Midazolam is a benzodiazepine with short and limited analgesic effect, commonly used in the NICU to produce sedation and muscle relaxation<sup>(12)</sup>. A systematic review published by the Cochrane Library concluded that there was insufficient data to encourage the intravenous administration of midazolam in neonates in intensive care. Furthermore, it noted

that further research on the effectiveness and safety of midazolam was needed<sup>(13)</sup>.

Chloral hydrate is used for sedation, particularly when numbness is necessary without analgesia. An increased incidence of apnea and oxygen desaturation in term neonates less than one month of age and preterm infants less than 60 weeks of postnatal age, who received this barbiturate to perform magnetic resonance imaging, was identified<sup>(12)</sup>.

Regarding analgesia, the intravenous use of fentanyl and tramadol was observed, along with non-pharmacological measures, such as offering oral glucose solution and non-nutritive sucking. Fentanyl is an opioid analgesic 50-100 times more potent than morphine, often used due to its ability to provide fast analgesia<sup>(12)</sup>.

A randomized clinical trial (RCT) with a sample of 54 neonates, with a mean gestational age of 28 weeks and birth weight of 1,126 grams, evaluated the analgesic effect of remifentanyl on the insertion of monolumen polyurethane PICC lines. The results showed that pain scores were lower in the group that received remifentanyl 0.03 mcg/kg/min and 0.3 mL of 12% sucrose orally and non-nutritive sucking in comparison with the control group, which received only 0.3 mL of 12% sucrose orally and non-nutritive sucking two minutes before the procedure

during skin preparation. It was concluded that low-dose remifentanyl (0.03 mcg/kg/min) has a measurable, synergic analgesic effect in combination with 12% sucrose and non-nutritive sucking in preterm newborns, but does not make PICC insertion easier or quicker<sup>(14)</sup>.

The effectiveness of intravenous morphine and 4% tetracaine gel for the relief of pain in PICC insertion was evaluated in an RCT. A total of 107 preterm infants on mechanical ventilation, with mean gestational age of 30.6 weeks composed the study sample. The results showed that the administration of morphine, alone or in combination with 4% tetracaine gel, was more effective than the tetracaine gel alone, when the procedure was considered in its totality, but not when only venipuncture was evaluated. It is noteworthy that adverse reactions were observed, such as respiratory depression in neonates receiving morphine and erythema in those receiving 4% tetracaine gel topically<sup>(15)</sup>.

Tramadol was administered in only two (0.8%) investigated procedures. It is an analgesic with therapeutic effects via activation of opioid receptors and elevation of the plasma levels of serotonin and norepinephrine<sup>(16)</sup>. However, its use is not recommended since there is no scientific evidence regarding its effectiveness and safety in children<sup>(17)</sup>.

The non-pharmacological strategies have been proven to be effective methods in the control of neonatal pain. Low cost, ease of administration and almost immediate analgesic effect may be cited as its main advantages. However, it is noteworthy that depending on the clinical condition and inserted devices in neonates, these measures are not likely to be implemented, as in cases of intubated neonates and/or those with a restriction in oral intake.

A RCT was conducted in a tertiary level NICU in the city of Belo Horizonte with 30 preterm infants, with a gestational age between 28 and 37 weeks, having a PICC inserted during the first week of life. The infants were divided into three groups and received one of the following interventions: (i) EMLA and 2 mL of distilled water with non-nutritive sucking, (ii) 2 mL of oral glucose with non-nutritive sucking and the application of a topical placebo cream, or (iii) EMLA and oral glucose with non-nutritive sucking. The pain response was assessed using the *Neonatal Infant Pain Scale* (NIPS). The results showed no statistically significant difference among the three groups in terms of maximum heart rate, mean arterial pressure, oxygen saturation drops, and a difference of more than two points in NIPS. The NIPS score indicated moderate pain response, regardless of the treatment employed<sup>(18)</sup>.

Another RCT conducted in a NICU of a tertiary hospital in France aimed to compare the efficacy and safety of pain relief during the PICC insertion in 59 newborns with a gestational age between 28 and 41 weeks, and mechanical ventilation or continuous positive airway pressure. The objective was to compare the efficacy and safety of sevoflurane deep sedation with 0.2 mL of 30% oral glucose and non-nutritive sucking. In addition to the two interventions tested, all newborns

received local anesthesia with EMLA cream 45 minutes before the procedure. The results showed no difference between groups in procedural duration, number of puncture attempts, ease of performing the procedure or success rate. Sevoflurane administration was associated with fewer episodes of increased blood pressure, tachycardia, and bradycardia. The group that received sweetened solution and non-nutritive sucking showed greater desaturation four hours after the procedure. It was concluded that sevoflurane inhalation does not make the PICC insertion easier in neonates, but prevents symptoms related to pain<sup>(19)</sup>.

The explanation for the mechanisms involved in the reduction of pain reactivity resulting from use of sweetened solutions is still controversial. It is assumed that other mechanisms besides the endogenous opioid system may be related to its analgesic effect<sup>(20)</sup>.

Non-nutritive sucking is a valuable tool to assist the newborn to deal with the painful stimulus. For minor procedures, the combination of sweet solutions and non-nutritive sucking should be sufficient. For major procedures, although the non-pharmacological strategies are still applicable, systemic opioid analgesia is usually required<sup>(3)</sup>.

The data from the current study showed no difference between the number of attempted punctures, duration of procedure and catheter tip position between neonates that received or did not receive analgesic or sedation. These results corroborate previous studies that evaluated interventions for sedation and analgesia during PICC insertion in neonates<sup>(7,14-15,19)</sup>. There are probably other factors in addition to movement of the extremities, such as the conditions of the venous system and professional experience, which have some relation to the degree of ease of performing the procedure and the duration of procedure.

Nursing professionals play a privileged role regarding the assessment and treatment of pain during PICC insertion. Observing the signals emitted from the neonate is essential, since the absence of tears and other behavioral responses is not necessarily indicative of a lack of pain<sup>(21)</sup>. Therefore, the nurse should consider and encourage the use of all analgesic and anesthetic methods available before every painful procedure in neonates. This includes adopting behavioral, pharmacological and developmental measures to prevent and reduce pain and discomfort created by procedures for the PICC insertion.

A variety of other strategies that include the inclusion of parents in the procedure, gentle manipulation of the newborn, as well as the decrease of sounds that are not appropriate, can be adopted in the prevention of pain occurring during the PICC insertion. Other non-pharmacological strategies such as offering oral human milk or sweet solution associated with non-nutritive sucking and the use of distraction techniques with soft music can also be used during the procedure. The opioid drugs and EMLA are also options to treat pain.

In order to promote the stabilization of the neonate after the procedure, strategies to facilitate his reorganization, such as nesting, skin to skin contact and facilitated restraint can be used<sup>(8,22)</sup>.

It is necessary to point out the study limitations, such as its unicenter character and data collection based on medical records, which may allow data loss due to lack of information of some study variables. Thus, the results should be treated with caution and without generalization, although our data corroborate the results within the literature.

## CONCLUSION

The adoption of sedation and analgesia measures for PICC insertion was uncommon in newborns. The

most used strategies included the use of sedatives and analgesic opioids. Further studies are needed to evaluate the effectiveness of some pharmacological and non-pharmacological strategies for pain relief during PICC insertion in neonates.

The findings allow us to analyze the treatment of acute pain resulting from invasive procedures conducted in neonates and indicate the need to improve the skills of health professionals who attend to neonates and their families.

It is worth mentioning the need to implement protocols and guidelines in health institutions for the proper management of pain in neonates, especially those admitted to NICU who are subjected to frequent painful and stressful procedures.

## REFERENCES

- Holsti L, Grunau R, Shany E. Assessing pain in preterm infants in the neonatal intensive care unit: moving to a 'brain-oriented' approach. *Pain Manag.* 2011;1(2):171-9.
- Montirosso R, Prete AD, Bellù R, Tronick E, Borgatti. Level of NICU quality of developmental care and neurobehavioral performance in very preterm infants. *Pediatrics.* 2012;129(5):e1129-37.
- 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.
- Uygun I, Okur HM, Otcu S, Ozturk H. Peripherally inserted central catheters in the neonatal period. *Acta Cirur Bras.* 2011;26(5):404-10.
- Costa P, Camargo PP, Bueno M, Kimura AF. Dimensionamento da dor na inserção do PICC em neonatos. *Acta Paul Enferm.* 2009;22(6):35-40.
- Sharek PJ, Powers R, Koehn M, Anand KJS. Evaluation and development of potentially better practices to improve pain management in neonates. *Pediatrics.* 2006; 118:S78-S86.
- Lemyre B, Sherlock R, Hogan D, Gabory I, Blanchard C, Moher D. How effective is tetracaine 4% gel, before a peripherally inserted central catheter, in reducing procedural pain in infants: a randomized double-blind placebo controlled trial. *BMC Med.* 2006;4(11):1741-50.
- Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirrelli A, et al. Guideline for procedural pain in the newborn. *Acta Paediatr.* 2009;98(6):932-9.
- Oliveira MBP, Oliveira DP, Leventhal LC. Intervenções farmacológicas e não farmacológicas utilizadas na passagem do cateter central de inserção periférica por enfermeiros em unidade neonatal. *Rev Dor.* 2009;10(3):241-5.
- Simons SHP, Tibboel D. Pain perception development and maturation. *Semin Fetal Neonatal Med.* 2006;11(4):227-31.
- Hoang V, Sills J, Chandler M, Busalani E, Clifton-Koeppel R, Mosanlou HD. Percutaneously inserted central catheter for total parenteral nutrition in neonates: complications rates related to upper versus lower extremity insertion. *Pediatrics.* 2008;121(5):1151-9.
- Hall RW. Anesthesia and analgesia in the NICU. *Clin Perinatol.* 2012;39(1):239-54.
- Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev.* 2012;(6):CD002052.
- Lago P, Tiozzo C, Bocuzzo G, Allegro A, Zacchello F. Remifentanyl for percutaneous intravenous central catheter placement in preterm infant: a randomized controlled trial. *Paediatr Anesth.* 2008;18(8):736-44.
- Taddio A, Lee C, Yip A, Parvez B, MacNamara PJ, Shah V. Intravenous morphine and topical tetracaine for treatment of pain in preterm neonates undergoing central line placement. *JAMA.* 2006;295(7):793-800.
- Barber J. Examining the use of tramadol hydrochloride as an antidepressant. *Exp Clin Psychopharmacol.* 2011;19(2):123-30.
- World Health Organization (WHO). Persisting pain in children [Internet]. Geneva; 2012 [cited 2012 Mar 19]. Available from: [http://whqlibdoc.who.int/publications/2012/9789241548120\\_%20Policy%20Brochure.pdf](http://whqlibdoc.who.int/publications/2012/9789241548120_%20Policy%20Brochure.pdf)
- Marcatto JO, Vasconcelos PCB, Araújo CM. EMLA versus glucose for PICC insertion: a randomised triple-masked controlled study. *Arch Dis Child Fetal Neonatal.* 2011;96(6):F467-8.

19. Michel F, Vialet R, Hassid S, Nicaise C, Garbi A, Thomachot L, et al. Sevoflurane for central catheter placement in neonatal intensive care: a randomized Trial. *Pediatr Anesth*. 2010;20(8):712-9.
20. Gradin M, Schollin J. The role of endogenous opioids in mediating pain reduction by orally administered glucose among newborns. *Pediatrics*. 2005;115(4):1004-7.
21. Rolim KMC, Cardoso MVLMM. A interação enfermeira-recém-nascido durante a prática de aspiração orotraqueal e coleta de sangue. *Rev Esc Enf USP*. 2006;40(4):515-23.
22. Brasil. Ministério da Saúde; Secretaria de Políticas de Saúde. Área da Saúde da Criança. Atenção humanizada ao recém-nascido de baixo peso: método canguru. Brasília; 2011.