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PHARMACOLOGICAL ANALGESIA IN NEONATES UNDERGOING CARDIAC SURGERY

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The objectives of this study were to verify the frequency of pharmacological analgesia and the occurrence of postoperative pain in neonates undergoing cardiac surgery. Methods: This is a cross-sectional study and data were collected from 30 medical charts of neonates who underwent cardiac surgery in a private hospital in the city of São Paulo. Results: The majority (96.6%) of neonates received analgesia: 18 (60.0%) received continuous analgesics, five (16.7%) received intermittent drugs, and six (20.0%) received a combination of continuous and intermittent analgesics. Fentanyl citrate was continuously administered to 24 (80.0%) neonates. Intermittent dipyrone and morphine was administered to ten (33.3%) and one (3.3%) neonates, respectively. Pain registers were observed in 17 (56.7%) medical charts and the occurrence of pain among neonates who received analgesics was 53.4%. Conclusion: There was no efficacy in pharmacological postoperative pain control in the neonates included in this study.

DESCRIPTORS: newborn; pain; analgesia; congenital heart disease

USO DE FÁRMACOS ANALGÉSICOS EN POSTOPERATORIO DE CIRUGÍA CARDÍACA NEONATAL

Los objetivos de este estudio fueron verificar la frecuencia de cobertura analgésica farmacológica y la aparición de dolor postoperatorio en neonatos sometidos a la cirugía cardíaca. Método: se trata de un estudio transversal con recolección de datos de Historias Clínicas de 30 neonatos sometidos a cirugía cardíaca en un hospital privado de la ciudad de San Pablo. Resultados: La frecuencia de cobertura analgésica fue de 96,6%, 18(60,0%) recibieron analgesia continua, cinco (16,7%) intermitente y seis (20,0%) intermitente y continua. El citrato de fentanil fue administrado continuamente a 24 (80,0%) neonatos. Dipirone y morfina fueron administradas en dosis intermitentes a diez (33,3%) y a un (3,3%) neonatos, respectivamente. Fueron identificados registros de ocurrencia de dolor en 17 (56,7%) Historias Clínicas. La ocurrencia de dolor postoperatorio en recién nacidos con cobertura analgésica fue 53,4 %. Conclusión: los datos apuntan que el abordaje analgésico adoptado se mostró ineficaz para controlar el dolor postoperatorio en los neonatos estudiados.

DESCRIPTORES: recién nacido; dolor; analgesia; cardiopatías congénitas

USO DE FÁRMACOS ANALGÉSICOS EM PÓS-OPERATÓRIO DE CIRURGIA CARDÍACA NEONATAL

Os objetivos deste estudo foram verificar frequência de cobertura analgésica farmacológica e ocorrência de dor pós-operatória em neonatos submetidos à cirurgia cardíaca. Método: estudo transversal com coleta de dados de prontuários de 30 neonatos submetidos à cirurgia cardíaca em um hospital privado da cidade de São Paulo. Resultados: a frequência de cobertura analgésica foi de 96,6%, 18(60%) receberam analgesia contínua, cinco (16,7%) intermitente e seis (20%) intermitente e contínua. O citrato de fentanil foi administrado continuamente a 24 (80%) neonatos. Dipirone e morfina foram administradas em doses intermitentes a dez (33,3%) e um (3,3%) neonato, respectivamente. Foram identificados registros de ocorrência de dor em 17 (56,7%) prontuários. A ocorrência de dor pós-operatória em recém-nascidos com cobertura analgésica foi 53,4%. Conclusão: os dados apontam que a abordagem analgésica adotada mostrou-se ineficaz para controlar a dor pós-operatória nos neonatos estudados.

DESCRIPTORES: recém-nascido; dor; analgesia; cardiopatias congênitas

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INTRODUCTION

Neonatal period is a phase of intense adjustment and change in organs and systems, especially in the circulatory and respiratory system due to the adjustment to the extrauterine environment. The occurrence of cardiac malformations makes these adjustments harder, in addition to contributing to increase in morbidity and mortality of neonates. According to the type of abnormality, neonates may possibly require surgical intervention in the first days of life to survive.

Surgical procedures to correct cardiac abnormalities may be complex and lead to severe postoperative (PO) pain, due to surgical incision and the extensive maneuver of organs and tissues. In turn, in the PO period, newborns (NB) undergo several other invasive and painful procedures such as venous and artery puncture to collect blood samples, frequent tracheal aspiration, as well as the devices maintained such as tracheal canula, drains, vascular catheters, tenckoff catheter, among others⁽¹⁾, which contributes to the occurrence of pain.

For these newborns, pain may lead to tachycardia, resulting in hemodynamic compromising, supraventricular tachyarrhythmias, and hypertension, that may cause a critical and intolerable increase in the ventricular post load⁽²⁾. It is also known that pain in the neonatal period may bring future results in motor, cognitive and affective response and it can cause changes in the pain threshold and in local sensibility⁽³⁾.

Circuits responsible for inhibition and pain modulation are still immature in NB⁽⁴⁾, justifying the importance of adopting measures to control pain, especially in the PO period.

Prescribing analgesics is a medical attribution, however, nurses must offer NB proper control of pain, which includes not only assessing the pain, but also assessing the effectiveness of pharmacological analgesia prescribed and administered. Thus, to know the types of analgesic employed, the dose, time of action, metabolism and excretion, the route of administration, the possible drug interactions, the adverse effects of analgesic and other medications adopted by the medical team is a necessary measure.

However, the literature points out that the prescription of analgesic medication to neonates is still parsimonious. In a study reviewing charts, it was

assessed that 70.0% of adults received PO analgesia, and only 30.0% of children (from one day of life to 14 years old) received pharmacological analgesia⁽⁵⁾.

Assessment of children's charts (between zero and 10 years old) showed that only 2.0% of patients received all doses prescribed of analgesics during PO⁽⁶⁾. Analysis performed in 933 charts of neonates undergoing surgical procedures showed the absence of assessment records of pain and analgesia in 86.0 %⁽⁷⁾.

PO analgesia is extremely important to assist surgical patients⁽⁸⁾, including neonates; however, studies show poor analgesia in the pediatric age group. Clinical experience with NB undergoing cardiac surgeries shows that even under the use of pharmacological analgesia and sedatives given in PO, signs indicating pain continued.

Such observation encouraged us to make the present study, whose objectives were: assess frequency of NB receiving analgesics, identify the analgesic approach, and check the frequency of painful response in neonates between the 24th and 47th complete hours of PO of cardiac surgery.

MATERIALS AND METHODS

Cross-sectional study with retrospective data collection, performed in a private medium-size hospital, located in the West side of the city of São Paulo (SP), and that is a reference in neonatal cardiac surgery. Data were collected as of the records in charts of neonates undergoing cardiac surgery from July 2001 to December 2005. Collection and data analysis were performed from October and December 2005.

Charts of neonates undergoing cardiac surgery and with gestational age ≥ 35 weeks at birth were included in the study. We have excluded deaths in the first 48 hours, and NB with diagnoses of other malformations besides the cardiac one.

Variables studied were: type of pharmacological analgesia administered, dose (in mcg/kg/h or mg/kg/h) administered type of infusion (continuous or intermittent), assessment of pain, and diagnoses of pain. Records made between the 24th and the 47th PO hour were assessed. Records of the first 24 PO hours have been excluded because of residual effects of anesthesia used in the surgery.

Data collection was performed as of the medical prescription and nursing records (prints on

vital data control and nursing notes). Regarding the assessment of pain, this process was inserted, in a systematized fashion, on the Neonatal Intensive Care Unit of NB in November, 2003. Before that, there was no standardization regarding assessment of pain in NB, and the clinical nurse was in charge of prescribing methods and intervals between pain assessments. The way records were made was the responsibility of the nursing team (generally, notes considered some specific signs as pain indicators, for example crying, agitation, tight facial muscles, increase in heart rate, fall in saturation). As of November, 2003, Neonatal Infant Pain Scale – NIPS⁽⁹⁾ started being used for pain assessment. This is a scale validated in 1993 that considers the following parameters in the assessment of pain: facial expression, cry, breathing patterns, arms, legs, and state of arousal of NB; its score ranges from 0 to 7 and pain is considered when scores are higher than 3⁽⁹⁾. Additionally, we have adopted specific paper to record pain and the relief methods employed. With this, assessment methods have been standardized, however, intervals between pain assessments continue to be prescribed according to the need checked by the clinical nurse.

Later, data was transcribed to the tool developed for the study, stored in a Microsoft Excel spreadsheet and assessed by the program Epi-Info, version 6.4.

Data collection was started after assessment and approval by the Ethical Research Committee of the Hospital where the study was conducted.

RESULTS

Forty-two charts from neonates undergoing cardiac surgery have been identified, 30 of them met the eligibility criteria of the study. The group studied presented mean gestational age at birth of 37.64 weeks, with a ± 1.15 standard deviation, and mean weight at birth was 2885.5 grams, ± 573.9 grams. The majority of neonates (70.0%) underwent surgical procedure in the first week of life and in 73.3% sternal surgical incision was performed.

Of the 30 neonates, 29 (96.7%) received some type of pharmacological analgesia in the period studied. The use and the way of administering pharmacological analgesia are presented on Table 1 below.

Table 1 – Forms of administering analgesics prescribed on the 1st PO. São Paulo, 2001 to 2005

Use and form of administration of analgesics	N	%
Yes	29	96.7%
Continuous		
Fentanyl citrate	18	60.0
Intermittent		
Dipyrone	5	16.7
Continuous and intermittent		
Fentanyl citrate and dipyrone	5	16.7
Fentanyl citrate and morphine	1	3.3
No	1	3.3%

It is seen that the use of continuous analgesia prevailed among NB with pharmacologic analgesia, totaling 24 (80.0%). In the interval from the 24th and 30th hour, 24 (80.0%) neonates received continuous analgesia; at the end of the period studied, at the 47th hour, frequency decreased to 20 neonates (66.6%).

Constant doses of fentanyl were administered to 8 neonates (26.7%), during the period studied; on the other hand, there was a large variation on the doses used in 16 neonates (53.3%) during the period studied, as presented by Figure 1.

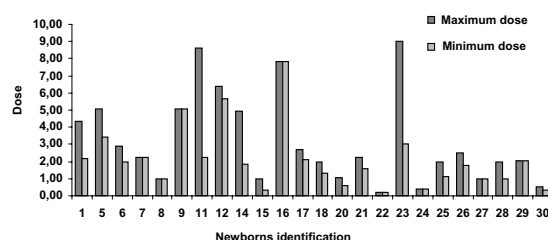


Figure 1 – Maximum and minimal doses of fentanyl citrate in mcg/kg/h, administered in continuous infusion. São Paulo, 2001 - 2005

Table 2 presents descriptive statistical analysis of data referring to minimum and maximum dose of continuous fentanyl citrate.

Table 2 – Descriptive statistics referring to maximum and minimum dose of Fentanyl citrate in mcg/Kg/h, continuously administered. São Paulo, 2001 to 2005.

Doses	Mean	Median	Mode	Maximum	Minimum	Standard-Deviation
Maximum	3.205	2.260	1.0	9.0	0.180	2.610
Minimum	2.093	1.830	1.0	7.8	0.180	1.832

Administration of intermittent medication was seen in 11 NB (36.6%). Ten neonates (33.3%) received dipyrone and 1 (3.3%) received morphine, totaling 28 doses of drugs administered intermittently. Table 3 shows distribution of doses of intermittent drugs administered to neonates studied.

Table 3 – Distribution of doses of intermittent drugs administered to neonates, according to intervals, on the 1st PO. São Paulo, 2001 – 2005

Interval Post-operative	Doses of intermittent drugs			
	Dipyrone		Morphine	
	N	%	N	%
24 th to 29 th hour	6	20.0	-	-
30 th to 35 th hour	6	20.0	1	3.3
36 th to 41 st hour	5	16.7	1	3.3
42 nd to 47 th hour	8	26.7	1	3.3

Doses of dipyrone administered were, on average, of 24.436 mg/kg, with median of 21.730 and standard deviation of 13.920. Minimum dose administered was 15.620 and maximum dose was 89.280mg/kg. morphine doses administered were constant, 0.08 mg/Kg/dose.

It is important to stress that among NB receiving analgesia, 21 (70.0%) also received sedatives, among them, 21 (70.0%) received continuous and/or intermittent midazolam, one (3.3%) received continuous cisatracurium besylate, one (3.3%) received continuous *chlorpromazine* hydrochloride, and one (3.3%) received intermittent propofol.

Presence of PO pain was assessed using behavior and physiological indicators and NIPS scale, alone or together. Table 4 presents distribution of neonates according to the occurrence of pain and use of pharmacological analgesia.

Table 4 – Distribution of newborns according to the occurrence of pain and administration of pharmacological analgesia. São Paulo, 2001 - 2005

Occurrence of pain	Use of analgesic				Total	
	Yes		No			
	N	%	N	%	N	%
Yes	16	53.4	1	3.3	17	56.7
No	7	23.3	-	-	7	23.3
No record	6	20.0	-	-	6	20.0
Total	29	96.7	1	3.3	30	100

It is noticed that only 7 NB (23.3%) did not present pain in the assessment using the scale. One NB (3.3%) did not receive either continuous or intermittent analgesia although it presented record of pain.

DISCUSSION

Because of the several deleterious effects resulting from pain, its treatment during PO of neonatal cardiac surgery presents extreme clinical relevance. Adequate control of pain during PO can reduce morbidity and mortality of neonates undergoing neonatal cardiac surgeries⁽¹⁰⁾.

Treatment with medication must be based on doses adjusted according to body weight, maturation, physiological development, and clinical condition of neonates⁽¹¹⁾. Drugs may be continuous or intermittently administered. Continuous administration of opioids seems preferred over in bolus administration, since it reduces variation of serum concentration of the drug, thus decreasing toxicity associated with peaks of concentration⁽¹¹⁾.

Most of the 24 (80.8%) neonates studied received continuous pharmacological analgesia during PO periods and, among them, 20 NB (66.6%) received continuous drugs during the period studied (up to the 47th PO hour). As previously described, PO analgesia is essential, however, recommendations regarding its duration in newborns have not been found. The use of opioids is recommended in neonates in intensive care undergoing large surgeries, mechanical pulmonary ventilation, placement of drains or venous catheters, and in diseases leading to pain, such as necrotizing enterocolitis⁽¹⁰⁾. However, must be carefully used and followed-up by continuous monitoring of vital data⁽¹¹⁾ in an intensive care environment.

Fentanyl citrate was administered to all 24 newborns receiving continuous medication. This is a synthesized phenylpiperidine derivative opioid, 80 to 100 times more powerful than morphine⁽¹¹⁾. It leads to analgesia by the link with μ receptors that are specific and are located in brain and spinal regions involved in the modulation and transmission of pain; it is extremely fat-soluble and spreads quickly to tissue making it easier for it to pass through the blood-brain barrier⁽¹²⁾. It presents quick onset, reaching peak between 5 to 15 minutes, and short half life, between 1 and 2 hours⁽¹¹⁾.

It is the opioid of choice in pediatrics due to its large safety margin and the benefits on hemodynamic stability⁽¹³⁾. For this reason, administration to hemodynamically unstable patients is suggested⁽¹¹⁾.

Recommended doses range from 0.5 to 2mcg/kg/h continuous fentanyl citrate for neonates in UTIN^(1,11). Especially for PO of neonatal cardiac surgery, doses between 1 and 3 mcg/kg/h are suggested⁽¹⁰⁾. Data presented on Picture 1 show that 6 NB (20.0%) received minimum doses of fentanyl citrate between 0.18 and 1 mcg/kg/h, and 5 (16.6%) maximum doses between 0.18 and 1mcg/kg/h, lower than those recommended by the literature.

Treatment with fentanyl citrate, however, has side effects, and among them the following are highlighted: seizures, difficulty breathing, thoracic rigidity, hypotension and bradycardia, nausea and vomiting, decrease in intestinal motility, constipation and urinary retention^(1,11-12). There may also be physical dependency and neonatal abstinence syndrome resulting from continuous infusion of the medication: the employment of fentanyl citrate for over three days requires gradual decrease of doses until it is suspended, and the administration of methadone, a synthesized opioid with properties similar to those of morphine, which is recommended if abstinence syndrome occurs.

Intermittent analgesics were administered in 11 neonates (36.6%). The use of dipyrone, intermittent drug used in 10 (91.0%) of the 11 NB, is not recommended by the Food and Drug Administration since 1998*. Clinical studies recommending the administration of dipyrone and specific doses for neonate have not been found.

Morphine, described in the literature as the most commonly used opioid in clinical practice, probably because it is more familiar to professionals⁽¹¹⁾, was administered only to one of the neonates studied. This opioid also provides analgesia through the link with μ receptors. It also presents quick onset, around 5 minutes, and the peak is reached in 10 to 30 minutes; its half-life ranges from 3 to 8 hours⁽¹¹⁾. Recommended doses for administration of intermittent morphine in neonates ranges from 0.05 and 0.1mg/kg⁽¹⁾. Following recommendations, the neonates of the present study received intermittent doses of morphine of 0.08mg/kg.

Adverse effects resulting from the administration of morphine are: difficulty breathing,

central nervous system depression, increase in intracranial pressure, bradycardia, arrhythmias, peripheral vasodilation, hypotension, decrease in gastrointestinal tract motility, constipation, nausea, vomiting, biliary tract spasms, release of anti-diuretic hormone, urinary retention, histamine release, physical dependency^(1,11).

Randomized clinical trials recently published⁽¹⁴⁻¹⁵⁾ also point out the impairments on neurological development in preterm newborns receiving continuous morphine, compared to placebo or to those receiving it intermittently, results should be pointed out and show the need for further studies on the use of morphine in NB.

Although drugs have been administered in 29 NB, 17 (56.7%) of them were in pain. The absence of protocols and standardization regarding PO analgesia is evidenced by the several analgesic schemes adopted, as well as the doses inferior to those recommended by other studies with neonates, which can have contributed to the high incidence of pain despite the use of drugs.

Eight NB (26.7%) received only analgesics, either continuously or intermittently; the remaining 21 neonates (70.0%) received sedatives associated with analgesics. Administration of sedatives is effective as an adjuvant treatment in PO analgesia, and it should not be replaceable⁽¹⁰⁾. None of the neonates received only sedatives, and the administration of sedatives can reduce behavioral responses resulting from pain which may have influenced on the assessment of pain performed.

One neonate (3.3%) did not receive any kind of pharmacological analgesia during PO, not following formal guidelines⁽¹⁾ that recommend the use of opioids, especially, morphine and fentanyl citrate.

CONCLUSION

Frequency of the use of analgesics on the 1st PO was 96.7%. Fentanyl citrate was the most frequently continuously administered analgesic, and 8 (26.7%) neonates received constant doses during the 1st PO. Sixteen (53.4%) received doses that

*Since 1998, "Food and Drug Administration" has published through the "Department of Health and Human Services" a relation of drugs that must be withdrawn from the market due to safety and efficacy issues. Dipyrone is included at this list due to risks of fatal agranulocytosis. Available at: <<http://www.fda.gov/cder/fdama/10898.pdf>>.

ranged from 0.18mcg/kg/h to 9mcg/kg/h. Intermittent dipyrone was administered to 10 neonates (33.3%) in doses ranging from 5.62mg/kg to 89.28mg/kg. Only one NB (3.3%) received intermittent morphine at the 0.08mg/kg dose. Despite the administration of analgesics, most neonates (56.7%) presented PO pain.

There was no consensus on the medications administered, as well as the associations and doses administered at PO of neonatal cardiac surgery.

FINAL CONSIDERATIONS

Fentanyl citrate and morphine are indicated for analgesia in neonates. Their beneficial effects have

been proved, as well as their short-terms adverse effects. However, long-term adverse effects from their use have not been proven yet.

Even though pain causes several deleterious effects in NB, we must consider the occurrence of side effects from the medication administered. The impact of these drugs on several organs and systems of neonates must be also considered, since they are still being formed, especially the central nervous system.

Treatment of PO pain in neonates undergoing cardiac surgery must occur after specific assessment to check the presence of pain. Specific instruments (such as NIPS scale, used in the service studied), physiological and behavior changes that can be related to pain are important tools for assessment.

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