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Research Article

Arnica D30 – an alternative for managing procedural pain in full-term neonates

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Abstract

Background: Despite scientific advances, the management of procedural pain in neonates remains suboptimal. Applying adequate therapy to control pain during the neonatal period is a moral and ethical act. In recent decades, ample evidence has accumulated regarding the risks, associated with both untreated pain and the use of more aggressive analgesic therapy. Thus, the emphasis in neonatal clinical practice is on non-aggressive pain management techniques, including non-pharmacological methods, such as glucose and homeopathic agents. The efficacy and safety of homeopathic agents for reducing procedural pain in neonates is the subject of the present study.

Materials and methods: Healthy full-term newborn babies with an average age of 72–84 hours were included. They were divided into three study groups: group (A) – without analgesia, (n = 67), group (B) – analgesic with Arnica D30 (n = 57) and group (C) – analgesic with Sol.Glucose 25% (n = 40). The severity of the pain was assessed using the multimodal - Neonatal Infant Pain Scale (NIPS) and the unimodal - Neonatal Facial Coding System (NFCS) scale. Assessments were done 30s before, 30 seconds after, and 5 minutes after the painful stimulus caused by the heel prick. Heart rate, transcutaneous oxygen saturation, respiratory rate and blood pressure were examined at the same intervals. The results obtained were processed statistically by descriptive analysis and ANOVA at a significance level of $p < 0.05$.

Results: Five minutes after heel prick both scales showed a score near 3, i.e. no significant pain, and statistically significant lower score in those given Arnica D30, compared to those who received Sol.Glucose 25% ($p < 0.05$). When monitoring the physiological indicators, we found a significant increase in the heart rate 30 seconds after the procedure between group B and C. Five minutes after the heel prick we recorded significantly values of respiratory rate and systolic blood pressure in all three groups compared to accounted for pre-procedural values.

Conclusion: Arnica D30 has better analgesic effects compared to Sol.Glucose 25% for newborn babies after heel prick tests.

Keywords

homeopathy, newborn, non-pharmacological methods, procedural pain

Introduction

In recent years, much has been discussed around the diagnosis and methods to control pain in newborn babies. The daily care of newborns, as well as diagnostic and treatment activities, are the cause of discomfort, stress and pain to varying degrees. Heel pricking is considered to be the third most intensive pain procedure in intensive care units and represents 79.2% of all painful manipulations performed without analgesia (Shen and Chaar 2015). Procedural pain occurs when the integrity of the skin or tissue is damaged by diagnostic or therapeutic manipulations (Anand 2017). Most common in the neonatal period are venipuncture, muscle injections, endotracheal intubation, eye examination, lumbar puncture, blood collection from the heel and others. Prevention and treatment of pain in neonates are important because exposure to repeated painful stimuli early in life has immediate short-term and long-term adverse effects, including irritability, disturbed sleep-wake state, ventilation-perfusion mismatch, increased oxygen consumption and impaired nutritional intake (Hall and Anand 2014).

Numerous studies have documented neonatal responses to pain, which include autonomic (eg, increases in heart rate, blood pressure), hormonal (eg, cortisol and catecholamine responses), and behavioral changes (eg, facial grimace). These responses form the basis of the many pain assessment tools used to evaluate acute pain in the neonate. Physiologic parameters include changes in heart rate, respiratory rate, blood pressure, vagal tone, heart rate variability, breathing pattern, oxygen saturation, in-tracranial pressure, palmar sweating, skin color, or pupillary size. Behavioral responses include crying patterns, acoustic features of infant crying, facial expressions, hand and body movements, muscle tone, sleep patterns, behavioral state changes, and consolability (Roué 2024). Sol.Glucose 25% has been established as a non-pharmacological method of analgesia in many studies.

The use of homeopathic remedies with *Arnica montana* and *Hypericum perforatum* in women in labor and newborns after traumatic childbirth, burns or other injuries (venipuncture) with varying degrees of pain gave us the idea that their use as non-pharmacological agent for procedural pain could be relevant, as there was data that it improved the physical and mental recovery of the body (Jones and Kassityn 2001; Burgari 2002). The use of Arnica Montana is based on its composition: lactones (analgesic, anti-inflammatory, antiecchymotic effect), phenols (antibacterial action), flavanoids (venous tropism) (Burgari 2002). The basis of the homeopathic product Arnica D30 is Arnica Montana, so that Arnica D30's ability to manage procedural pain in neonates could be a new alternative for pain relief in clinical practice. In vitro studies show that the most active components of Arnica, as well as other preparations from the Asteraceae family, are helenalin and the secuterpene lactones - 11a,13-dihydrohelenalin and hamisonolide (Iannitti et al. 2016). First Lyss et al. found that helenalin inhibits the transcription nuclear factor, factor kappa B (NF-kB) by altering and stabi-lizing the NF-kB/inhibitor of kappa B (I kappa B) complex in T cells, B cells and epithe-lial cells and abolishes kappa gene expression. This is one of the earliest pieces of evidence of Arnica's anti-inflammatory properties. A later study showed that helenalin could inhibit human neutrophil migration, chemotaxis, 5-lipoxygenase activity, and leukotriene C4 synthetase. It leads to reduced expression of the cell surface receptors CD25, CD28, CD27 and CD120b, which play a key role in the activation of NF-kB in T cells. This supports the mechanism proposed by Lyss in 1997 (Iannitti et al. 2016; Olioso et al. 2016). NF-kB activation is associated with the induction of pain and inflammation, characterized by the release of proinflammatory cytokines (tumor necrosis factor-alpha [TNF-a] and interleu-kin-1beta [IL-1b] and local leukocyte recruitment (Kawakami et al. 2011). the analgesic effect of Arnica D30(Petleshkova et al. 2019) We decided to compare the analgesic effect of Arnica D30(Petleshkova et al. 2019) with the proven non-pharmacological method for the treatment of neonatal pain Sol.Glucose 25%.

The aim of the study is to determine and compare the analgesic effect of both agents Arnica D30 and Sol.Glucose 25% on procedural pain induced by heel prick, evaluating by the Neonatal Infant Pain Scale (NIPS) and the Neonatal Facial Coding System (NFCS) and dynamic changes of physiological indicators - pain markers.

Materials and methods

A prospective study on healthy, full-term newborns (n = 164) in the Obstetrics and Gynecology Clinic, Neonatology Department of the "St. Georgi" - the city of Plovdiv for the period from 07.10.2016 to 15.04.2017, at an average age of 72–84 hours. Our study was based on CONSORT guideline. The full-term newborns were divided into three groups: control group A - without analgesia (n = 67), B receiving Arnica D30 (n = 57), and C with Sol.Glucose 25% (n = 40). The study group had birth weight 3261.60 g ± 205.35, and no evidence of perinatal asphyxia. 68 (41.47%) of the study group had a normal birth, 91 (55.49%) by caesarean section, 4 (2.44%) by vacuum extractor and 1 (0.60%) using forceps. Procedural pain was induced in each newborn during the national neonatal screening for phenylketonuria, congenital hypothyroidism and congenital adrenal hyperplasia between the 72nd and 84th hour after birth by a single puncture of the heel on the latero- or postero-medial surface with a medical needle №20. The procedure is carried out when the baby is calm and about 40 minutes after feeding. The severity of the procedural pain was assessed by Neonatal Infant Pain

Scale (NIPS) and the Neonatal Facial Coding System (NFCS) using video surveillance before, during and after the procedure. Analysis of the videos was performed by two independent neonatologist surveyors, trained to use the relevant pain assessment scales. In cases of discrepancy in the values of the evaluation score up to 2, arbitration was carried out by a third neonatologist - an expert on the indicated scales, and his assessment was accepted as final. Patients with a difference of more than 2 points were excluded from the study. Heart rate, respiratory rate, arterial blood pressure and transcutaneous saturation ($tSpO_2$) were also monitored with a Biocare iM/2014 monitor. Results were taken 30 seconds before the heal prick test, 30 seconds and 5 min after, as well as in the interval 12–24 h after procedural pain. In Group B neonates, Arnica D30 is administered orally as an individual solution of three pills in sterile water for analgesia. Each intake was 1 ml. The first reception is 2 hours before, the second immediately after the prick test, and the third in the interval 12–24 hours after the procedure, i.e. - a total of 3 × 1 ml per os. For newborns of group C, the analgesia was performed by Sol.Glucose 25% 2 ml per os 2 min before the heel prick.

According to the international consensus for the assessment of neonatal pain, two of the most frequently applied scales in term and preterm newborns are: Neonatal Infant Pain Scale (NIPS) and Neonatal Facial Coding System (NFCS). The multimodal NIPS is used to assess pain in preterm and term neonates (Lawrence et al. 1993). It includes one physiological/breathing pattern/ and five behavioral reactions: facial expression; cry; arms; legs; and state of arousal (da Paixão Freitas et al. 2018). The items are rated 0 or 1. Only the crying factor is rated 0, 1 or 2. The sum of the items is referred to as an evaluation score and gives a quantitative assessment of the presence and severity of pain. The inventors of the scale and other authors accept the presence of pain at a score ≥ 4 (de Cassia Pinheiro da Motta et al. 2015; Bernardo et al. 2019). Independently, the minimum score is 0 points, and the maximum is 7 points.

The unimodal NFCS was created in 1987 by Grunau et al. and has later undergone various modifications (Grunau and Craig 1987). Mimic changes for pain assessment in full-term and premature newborns in the original scale are as follows: 1. Brow bulge; 2. Eyes squeeze; 3. Nasolabial furrow; 4. Open lips; 5. Taut tongue; 6. Tongue sticking out; 7. Chin quiver; 8. Stretched mouth: 8.1 Horizontal mouth, 8.2 Vertical mouth, 8.3 Oo-shaped mouth. The evaluation is rated 0 or 1 according to the presence or absence of the corresponding indicator. When using the NFCS an optimal score of 8 is accepted, and pain is reported at ≥ 3 (Grunau and Craig 1990; Hardeep and Gaurav 2019).

Based on literature data, we accepted the following: absent pain when score is less than 4 according to NIPS or less than 3 according to NFCS; pain when NIPS score was ≥ 4, and NFCS score was ≥3; and very severe pain - when score is above 6 in NIPS and above 7 in NFCS , with a maximum score 7 in the NIPS, and 8 in the NFCS (Sposito 2017; da Paixão Freitas et al. 2018; Roué et al. 2018; Hardeep and Gaurav 2019).

Inclusion and exclusion criteria for participants in the study

Inclusion criteria: full-term newborns – 37–41 GA with + 6 days (chronological gestational age); without primary resuscitation (optimal Apgar score at the 1st and 5th minute of birth); normal postpartum adaptation; no abnormalities in muscle tone, reflexes, and motor activity assessed by clinical examination prior to initiation of screening; no drug therapy; written informed consent from the mother for participation in the study.

Exclusion criteria: abnormal body temperature measured axillary for 5 min /normal for the newborn: 36.1–37.5 °C (Rennie and Kendall 2013); respiratory failure - rhythmic breathing disorders, apnea > 20 sec.; cardiocirculatory disorders – bradycardia, tachycardia, rhythm changes, episodes of oxygen de-saturation, heart failure; early jaundice until the 24th hour; hepatosplenomegaly – liver size > 1.5–2 cm and spleen > 0.5 cm, palpated below the edge of the costal arch; omphalitis; impaired enteral tole-rance; hemorrhagic syndrome – hematemesis, rectal bleeding, melena, bleeding from the navel and puncture sites; skin changes – pustular rash, petechiae; fever capillary refill time > 3s.; abnormal values from the reference ranges of paraclinical parameters (Rennie and Kendall 2013); seizures or seizure equivalent; microbiological isolates from ear discharge and stomach aspirate, examined up to the 6th hour after birth; crying and increased motor activity of the newborn before starting the procedure; technical problems while shooting a video clip; difference (over 2 points) in the pain score between surveyors assessing the pain.

Statistical methods

Results are presented as the mean value, standard deviation, and standard error for continuous variables while for categorical variables as the whole numbers (N). An Analysis of Variance (ANOVA) test was used to determine whether there was a statistically significant difference between the means of three independent groups. To find out exactly which groups differed from each other, a **post hoc test** (also known as a multiple comparison test) was also conducted, which allowed us to examine the difference between means. Data were statistically analyzed using IBM SPSS software, version 27.0. Statistical significance was set at $p < 0.05$.

This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. The study was approved by the Scientific Ethics Committee of Medical University-Plovdiv – No P-7326/ 5.10.2016 year.

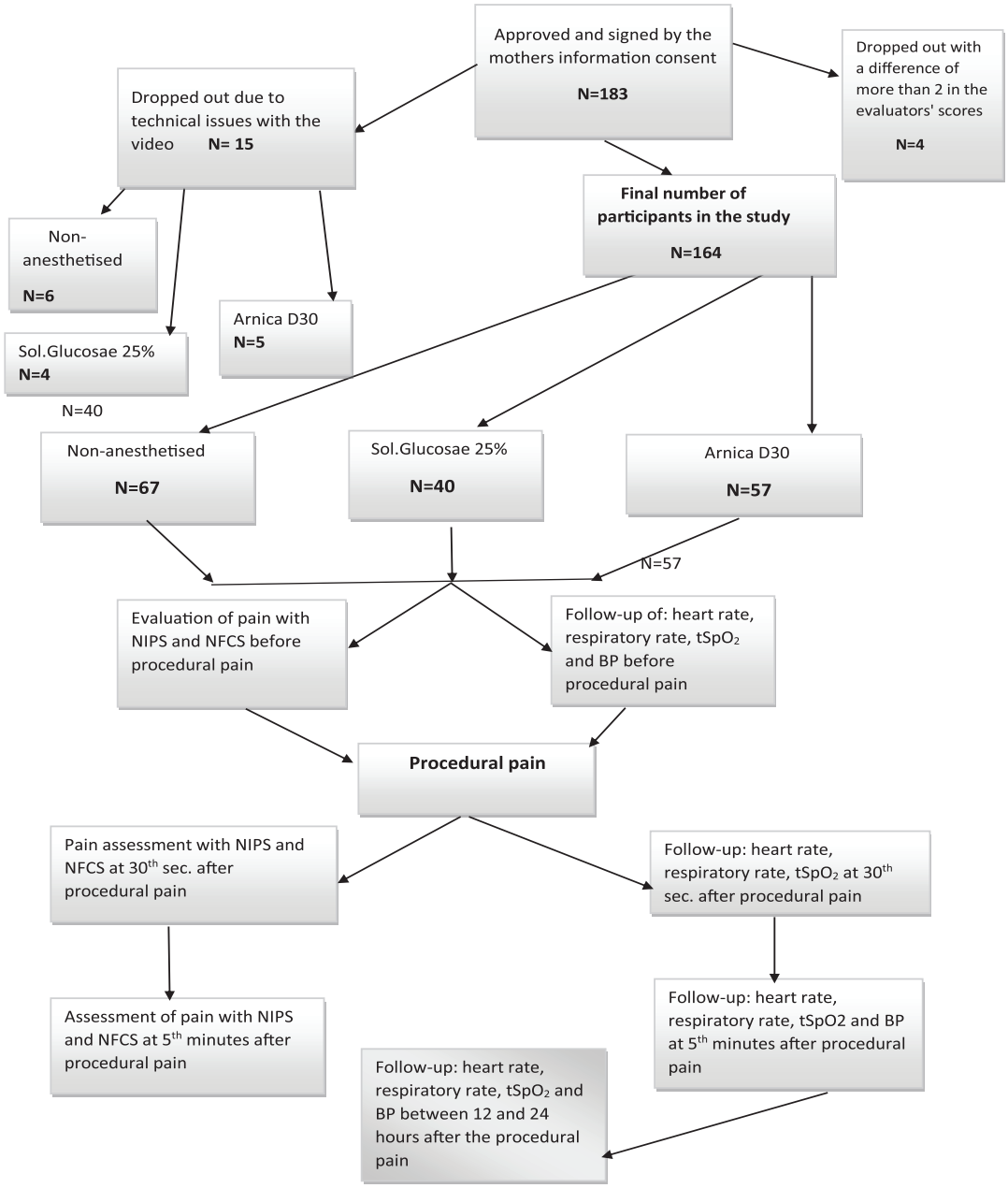

Figure 1. Study design.

Results

Before the procedure there were no statistically significant differences between the groups, assessed with both scales (Table 1). All infants demonstrated pain at the 30th sec following the procedure without any significant differences between three groups.

At the 5th minute, a lower score of both scales was reported in the newborns with Arnica D30 compared to those who received Sol.Glucose 25%. In both groups, the overall score corresponded to no pain. Statistically significant differences in total evaluations of NIPS and NFCS were registered (Tables 2, 3).

Table 1. General assessment on the pain scales before and after the 30th sec. after the procedure.

Pain rating scales	Groups	before the procedure	SD	F	Sig. level	at the 30th sec.	SD	F	p-value
NIPS – Overall Assessment	Without anesthesia -/A/	1.79±0.18	1.46	1.227	0.296	6.73±0.11	0.898	1.702	0.186
	Arnica D30-/B/	1.35±0.22	1.65			6.89±0.09	0.673		
	Sol.Glucosae 25%- /C/	1.50±0.28	1.70			6.98±0.03	0.158		
NFCS – Overall Assessment	Without anesthesia -/A/	1.24±0.15	1.24	0.408	0.666	6.85±0.09	0.751	2.499	0.085
	Arnica D30–/B/	1.04±0.18	1.04			6.28±0.10	0.959		
	Sol.Glucosae 25%- /C/	1.24±0.20	1.24			6.88±0.05	0.335		

Table 2. Evaluation of observed NIPS scale at 5 minutes after depending on analgesia method.

NIPS -5th min	Groups	N	Mean	Std. Deviation	F	p-value
Overall Assessment	without analgesia	67	4.46	2.127	8.989	**0.000*****
	Arnica D30	57	3.00	2.699		
	Sol. Glucose 25%	40	3.28	2.552		

The results are significant at *p < 0.05; **p < 0.01; ***p < 0.001.

Table 3. Evaluation of observed NFCS scale at 5 minutes depending on analgesia method.

NFCS-5th min.	Groups	N	Mean	Std. Deviation	F	p-value
Overall Assessment	without analgesia	67	3.85	2.502	5.273	**0.006****
	Arnica D30	57	2.35	2.443		
	Sol. Glucose 25%	40	2.95	2.469		

The results are significant at *p < 0.05; **p < 0.01.

Table 4. Post Hoc Tests.

NIPS -5th min	Groups	Groups	Mean Difference	p-value
Overall Assessment	Arnica D30	Sol.Glucose 25%	-1.181*	**0.037**
	Sol. Glucose 25%	Arnica D30	1.181*	**0.037**

* The mean difference is significant at the 0.05 level.

Table 5. Post Hoc Test.

Groups	Groups	Mean Difference	p-value
Arnica D30	Sol.Glucose 25%	-1.234*	**0.041**
Sol. Glucose 25%	Arnica D30	1.234*	**0.041**

* The mean difference is significant at the 0.05 level.

When applying Post Hoc Tests a significant difference was registered between groups B and C in overall assessment (p = 0.037) (Table 4).

In **NFCS** at the 5th minute after heel prick, we established significant differences in the overall assessment (p = 0.006) (Table 3).

When applying Post Hoc Tests, a significant difference was registered between groups B and C at overall assessment (p = 0.041) (Table 5).

We tracked the dynamics of physiological indicators - markers of pain. Tracking at 30th sec and the 5th min. reported statistical significance in heart rate (p = 0.012), respiratory rate (p = 0.007) and systolic blood pressure (p = 0.000) (Table 6).

Using analysis Post Hoc Tests confirmed significant differences between groups B and C (Table 7). We found significantly slowed respiratory rate before the procedure and higher heart rate at the 30th sec in those who have received glucose solution. We also reported higher systolic blood pressure (regardless of the reference limits for this age) in neonates who had received Sol.Glucose 25% before the procedure and at the 5th min after the procedural pain (Table 7).

Table 6. Dynamics of physiological indicators in the groups at the 30th sec. and on the 5th min after the procedure.

Indicators	Groups	at the 30th sec.	Std. Deviation	F	p-value	on the 5th min.	Std. Deviation	F	p-value
Heart rate	no analgesia/A/	158.07±3.49	28.557	4.569	**.012***	143.99±3.67	30.017	1.358	0.26
	ArnicaD30 /B/	162.37±3.21	27.369			141.35±3.57	23.579		
	Sol.Glucose 25%/C/	170.70±4.01	25.341			137.18±4.89	30.937		
Oxygen saturation	no analgesia	88.13±1.09	8.881	1.777	0.173	94.12±1.08	8.845	2.675	0.072
	Arnica D30	89.93±0.81	5.812			97.00±0.50	4.767		
	Sol.Glucose 25%	86.08±1.75	10.781			93.08±1.09	6.776		
Respiratory rate	no analgesia	30.47±1.19	9.67	0.256	0.774	45.34±1.68	13.749	5.143	**.007****
	Arnica D30	29.61±2.09	15.391			40.13±1.81	13.433		
	Sol.Glucose 25%	31.54±2.17	13.553			35.03±3.58	22.668		
Systolic blood pressure	no analgesia	-	-			93.16±1.98	14.68	8.503	**.000*****
	Arnica D30	-	-			86.35±2.38	17.013		
	Sol.Glucose 25%	-	-			101.10±2.64	14.211		
Diastolic blood pressure	no analgesia	-	-			53.45±1.89	14.004	0.941	0.393
	ArnicaD30	-	-			53.75±1.88	13.409		
	Sol.Glucose 25%	-	-			57.62±2.82	15.197		

The results are significant at **p < 0.01; ***p < 0.001.

Table 7. Post Hoc Tests.

Physiological markers	Groups	Groups	Mean Difference	p-value
Respiratory rate - before the procedure	Arnica D30/B/	Sol. Glucose 25%	12.305*	**0.000**
	Sol. Glucose 25%/C/	Arnica D30	-12.305*	**0.000**
Systolic blood pressure - before the procedure	Arnica D30	Sol. Glucose 25%	-8.590*	**0.043**
	Sol. Glucose 25%	Arnica D30	8.590*	**0.043**
Heart rate - at the 30th sec.	Arnica D30	Sol. Glucose 25%	-16.682*	**0.010**
	Sol. Glucose 25%	Arnica D30	16.682*	**0.010**
Systolic blood pressure-at the 5th min.	Arnica D30	Sol. Glucose 25%	-14.751*	**0.000**
	Sol. Glucose 25%	Arnica D30	14.751*	**0.000**

* The mean difference is significant at the 0.05 level.

Discussion

Over the past two decades, analgesia with sweet solution has been extensively studied in neonates undergoing painful procedures. Sweet taste is thought to trigger the release of endogenous opioids. The analgesic effectiveness of the solution may depend on its degree of sweetness, arranged in the following order according to the degree of manifestation: sucrose, fructose, glucose and lactose (Bueno et al. 2013). Many studies have shown that oral sucrose is safe and effective in reducing nociception in single and short-term procedures, and as a result it has been proposed as the standard treatment for procedural pain (Liu et al. 2017). This study also confirmed its analgesic effect at the 5th min after the procedure / the total score of NIPS and NFCS showed no pain in the group receiving glucose. It has been suggested that the greatest analgesic effect is achieved when the sweet solution is given approximately two minutes before the start of the painful procedure, and we followed this method. According to one hypothesis, this interval coincides with the endogenous release of opioids, but the mechanism of its analgesic action is still incompletely understood and partly controversial (Messerer et al. 2014).

As the most common painful procedure, heel prick tests were investigated in 38 studies (Stevens et al. 2016). Most of the studies prove the analgesic effect of sweet solutions, but some of them do not register it for procedural pain (Bonetto et al. 2008; Slater, R. et al. 2010; Stevens et al. 2016). Therefore 25% glucose solution can be used as an alternative to sucrose to reduce procedural pain in healthy term and preterm neonates. There is evidence that sucrose and glucose (20% to 50%) significantly reduce NIPS values in the heel prick (Ahn et al. 2006; Tutag Lehr et al. 2015; Kumari et al. 2017; Stevens et al. 2016).

Comparing the glucose group with the NIPS control group in the present study found that the patients who had received non-pharmacological agents had a significantly lower score compared to the 5th min control group with no analgesia ($p = 0.000$). The results showed a reduction in pain intensity and duration after administration of 25% glucose solution, which confirmed the analgesic effect of glucose in procedural pain caused by a heel prick test and supported the other authors' data (Liu et al. 2010; Suhrabi et al. 2014).

According to the literature data, facial manifestations of procedural pain were detected in 99% of newborns within 6 seconds after a heel prick test, and are thought to be very sensitive indicators of infant pain (Gray et al. 2015). According to our results of NFCS score there is a tendency towards a lower score at the 5th minute, below 3 (2.95), which is minimal for pain ($p = 0.006$). Similar data were reported by Ogawa et al. (2005), Okan F et al. (2007) and Gaspardo et al. (2008).

In their study, Asmerom et al. (2013) reported that a single dose of sucrose reduced behavioral indicators of pain by heel prick tests in preterm infants, but increased the physiological markers of oxidative stress and heart rate. These results coincide with ours: the application of Sol. Glucose 25% recorded the highest values of heart rate at the 30th second, as well as lower oxygen saturation and slower breathing even before the procedural pain. These statistically significant pre-screening differences in respiratory rate, oxygen saturation, and systolic and diastolic blood pressure, are assumed to be the result of the action of the applied oral intake of Sol.Glucose 25% associated with intracellular oxidative stress as well as sympathetic activation (Bueno et al. 2013). Published studies also found increases in heart rate, decreases in oxygen saturation, and lower respiratory rates, but without statistically significant results (Giraldo Montoya et al. 2009; Milazzo et al. 2011).

In the present study, at the 30th second the higher heart rate in the newborns with analgesia is striking ($p = 0.012$), which is probably related to the described supposed influence of the sweet solution (Steven et al. 2016). At the 5th minute after the procedure, we report significant differences in the values of the indicators: respiratory rate lower ($p = 0.007$) and systolic pressure higher ($p = 0.000$), which we associate with the continued effect of the glucose solution. Our results match with those of Liaw et al. (2011), where, after application of Hbvax under analgesia with glucose solution a higher value of heart rate and a decrease in respiratory rate, as well as their significant stabilization, was reported. Jatana et al. (2003) also reported a significant increase in heart rate, and a decrease in crying time and oxygen saturation under glucose analgesia following blood collection from the heel.

In the interval 12–24 hours we found no deviations from the reference range of the monitored physiological indicators - heart rate, respiratory rate, transcutaneous saturation and arterial pressure after analgesia with Sol.Glucosae 25%.

Homeopathic remedies can be used for certain conditions in the neonatologist's clinical practice (Jones and Kassityn 2001; Martin 2009; Baltacis 2017; Lennihan 2017). Homeopathic remedies/ Aconitum napellus C 200, Opium C 200, Phosphorus C 200/are used in the course of resuscitation and in the treatment of premature and sick newborns, which confirms their effectiveness and safety (Allen 1998). There is some research on homeopathic remedies for pregnant women, but little research about the neonatal population in the United States; however, one can certainly ascertain many potential uses. One must keep in mind that "all homeopathic remedies given to the mother during pregnancy and childbirth will also benefit the fetus, and any that are given to the mother after childbirth will also be given to the newborn if breast-fed." The use of *Arnica montana* before and after surgery has been documented to reduce hematoma, swelling, tenderness, and pain. It is the basis of homeopathic products. The effect is related to variations in the efficacy (potency) and frequency of dosing of the homeopathic product. Different potencies – D3, D6, D30, 30C and different application schedules are recommended commensurate with the reason for administering the product (Morrison 1993; Allen 1998; Martin 2009). The anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory activities of the chemical compounds in Arnica have been investigated in different models (Smith et al. 2021). It is preferred as a non-pharmacological

alternative, due to the proven effect in clinical neonatological and pediatric practice in the treatment of trauma with hematomas, fractures, cephalhematomas and other conditions accompanied by varying degrees of pain (Burgari 2002; Martin 2009; Taneva et al. 2021). It is especially preferred in the healing of wounds of different origins (Castro et al. 2012). Homeopathic remedies such as Arnica, as well as Staphysagria and Calendula, can be used to help baby boys heal from the physical and psychological trauma of a circumcision. Additionally, Arnica administered orally in homeopathic dilutions has shown positive clinical effects in reducing postoperative pain, edema, and ecchymosis. Topical application of Arnica combined with oral homeopathic dilutions has been found to have a synergistic effect in reducing postoperative pain (Iannitti et al. 2016).

In recent years, progress has been made in understanding the mechanisms of biological action of homeopathic medicines at the molecular level (Marzotto et al. 2020). A modulating action of gene expression has been detected in cell cultures of macrophages, neurocytes, epithelial cells, embryonic kidney, and even plant cells. In microbiological models, Arnica 30c modified the expression of specific genes that are the targets of ultraviolet irradiation injury (Saha et al. 2012). The changes in gene expression induced by Arnica m. They are particularly low, ranging from 20 to 30% of basal expression. However, even a small increase in macrophage activity in the production of key proteins can have a decisive positive effect on tissue healing and repair. A study by Marzotto et al. (2020) found FN1 (fibronectin 1) to be the main gene whose expression is stimulated by *Arnica montana*, which affects a network of biological functions, including inflammation and regulation of the extracellular matrix. These and other findings, reviewed elsewhere (Dei and Bernardini 2015; Bell 2019), support the hypothesis that highly diluted homeopathic medicines are able to turn some important genes on or off, initiating a cascade of gene actions to correct the gene expression changes that produced the disorder or disease. These scientifically proven facts give reason to expand our understanding of the possibilities of homeopathy in clinical practice.

Comparing the newborns without analgesia with those who received Arnica D30 and Sol.Glucose25% showed a lower rating on both pain scales for the newborns who had received analgesia before, and at 5 minutes after, the procedure. The effect was most pronounced in those who received ArnicaD30 at the 5th minute - a score was achieved showing the absence of pain in this group, which means that the pain sensation is the shortest. Furthermore, using the NFCS at 30 seconds after the heel prick, the lowest total score was recorded in the group receiving arnica. The lack of significant difference may speculate that the severity of procedural pain was lowest in this group immediately after the heel stick. More newborns need to be investigated to draw a firm conclusion.When monitoring changes in heart rate during the observed intervals, no significant difference was found. The present study found that transcutaneous oxygen saturation after administration of Arnica D30 was higher and systolic pressure was lower at the 5th minute compared to those without analgesia and those, who received Sol.Glucosae 25%. It is noteworthy that when taking Arnica D30, the smallest dynamics are recorded in the respiratory and heart rate values before and at the 5th minute after the heel prick. This once again confirms the analgetic effect (reducing the duration and severity of pain) of the preparation Arnica D30.

In the interval 12–24 h we did not find deviations from the norm for the age of the monitored physiological indicators - heart rate, respiratory rate, oxygen saturation and arterial pressure after analgesia with Arnica D30.

In our available literature, no data were found on the use of Arnica D30 in the neonatal period and childhood for the treatment of procedural pain, which did not allow us to compare our results with similar studies. To confirm the effect of Arnica Montana, future studies are needed in three areas: inflammatory processes, pain management, and postoperative conditions, necessitating new meta-analyses in a large number of patients (Iannitti et al. 2016). This will help to validate complementary medicine as part of the therapeutic approach in a wide range of areas.

Conclusions

Arnica D30 could be used as an alternative method for relieving pain in neonates. It has at least a similar analgesic effect as Sol.Glucose 25% for procedural pain induced by heel prick tests in term neonates, even better especially for the duration of procedural pain. Unlike Sol.Glucose 25%, Arnica D30 did not change physiological parameters: respiratory rate, oxygen saturation and sistolic blood pressure, and no adverse reactions regarding vital parameters were registered.

Because of limited data in the literature about the analgesic effect of Arnica D30 and the limitation of our study, which includes only full-term babies and investigation of procedural pain, further studies are needed to make recommendations for use of this product for pain relief in neonatal clinical practice.

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