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RESEARCH ARTICLE

COMPARISON OF PARENTERAL NUTRITION CYCLED AND CONTINUOUS IN THE PRESENTATION OF CHOLESTASIS IN PRETERM INFANTS

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ABSTRACT

Introduction: Prematurity is one of the pathologies that lead to greater morbidity and mortality, being the first cause of death in newborn patients (up to 28 days of life) and the second cause in children under 5 years of age. One of the most used strategies to improve the general conditions of the preterm patient is the early initiation of total parenteral nutrition (TPN) to ensure an adequate caloric protein intake, avoid malnutrition and improve nutritional reserves. There are different modes of administration of parenteral nutrition.

Material and methods: Two groups of premature patients who received TPN in continuous modality or cycled for at least 7 days were formed, all newborns under 37 weeks of gestation that met the selection criteria were chosen. Laboratory controls were taken at the beginning of the TPN (day 0) and on days 7, 14, 21 and 28 of its use, the values of bilirubins, AST, ALT, GGT, alkaline phosphatase were compared and the presence or absence was compared of cholestasis at any time of the use of TPN between both groups.

Results: A prevalence of cholestasis of 19.4% was reported in all patients admitted to the NICU, with 24% in whom it was infused in continuous mode and 18.6% in those who received the nutrition in cycle mode, Wald prediction analysis was performed observing that patients with continuous TPN have a 7.6 times higher risk of presenting cholestasis than those who were infused with the cycled method (Stanford University method).

INTRODUCTION

Prematurity is the leading cause of death in the neonatal period (during the first four weeks of life) and the second cause of death in children under five years of age, after pneumonia, according to the World Health Organization (Blecowe *et al*., 2012). Every year around 15 million premature babies are born in the world (less than 37 weeks of gestation). In Mexico, more than 120,000 premature babies are born annually. There are three groups of preterm infants: extreme preterm (<28 weeks of gestation [SDG]), moderate preterm (29 to 32 SDG) and preterm infants (33 to 36 SDG), each group with different associated complications (Blecowe *et al*., 2012). The birth of a premature newborn carries an important impact on the family, both in the psychosocial, quality of life and monetary aspects, as well as the high cost of attention to health systems (Scribner *et al*., 2012). The improvement of neonatal resuscitation techniques, technological advances, drugs and advanced therapies, invasive mechanical ventilation and parenteral nutritional therapies have influenced the increase in survival of premature patients, with a lower gestational age at birth, higher incidence of complications in the newborn with these characteristics (Scribner *et al*., 2012). These complications can occur in different organs and systems, the most frequent being neurological, metabolic, gastronomic, renal, pulmonary and cardiovascular (Scribner *et al*., 2012, Coller *et al*., 1994). One of the most frequently used techniques in preterm patients is the administration of Total Parenteral Nutrition (TPN) early (in the first seven days of life), which is very helpful because it provides macro and micronutrients for proper development, as well as contributions of liquids, vitamins, trace elements and substrates necessary for the correct anabolism and catabolism of the different body systems. (Coller *et al*., 1994, Cotogni *et al*., 2007, Izquierdo *et al*., 2016, Ertugrul *et al*., 2016). Despite the advantages offered by this technique, it is common to find complications inherent to TPN or the process of administration of the same (incorrect patient administration, by an incorrect route (central or peripheral route), wrong infusion rate, as well as alteration at the biliary level, infections associated with the infusion site, etc. (Ertugrul *et al*., 2016), The cholestatic disease associated with TPN was described since 1970, since then it has gone through a significant decrease in its incidence in the subsequent decades, being an important cause of morbidity and mortality (Peden *et al*., 1971).

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The causes are multiple, having as one of the associated factors the time of use of the TPN, being from 17 to 35% in the first 14 to 28 days of beginning of the management, with a mortality of 3 to 17% (Kubota *et al*., 2000). From the beginning of the description of this complication, the "cycling" of TPN was described as a technique proposed in adults to improve the lifestyle of patients who require TPN (Scribner *et al*., 2012) demonstrating safety in children (one month to 20 years of age) and adults, being an adequate nutritional support strategy and with better control of conjugated and unconjugated bilirubins (Byrne *et al*., 1977). Recently, the safety and incidence of cholestasis in neonates receiving TPN has been investigated. The prevalence is 4.5 to 20% of patients receiving TPN, finding as risk factors the prematurity, birth weight, male sex and duration in days of the TPN (Yan *et al*., 2017). The objective of this study was to compare the presentation of cholestasis between two groups, one that received the TPN in continuous modality and another that received it in cycled mode.

MATERIAL AND METHODS

Non-randomized ambispective clinical trial, where all patients less than 37 weeks of gestation who received parenteral nutrition for at least seven days were taken, in a tertiary level hospital, between January 2014 and September 2017, patients with surgical pathology at the time of birth, who presented liver abnormalities at birth, were diagnosed metabolic alterations and those who did not complete the seven days with parenteral nutritionwere excluded from the study.

After the patient's admission to intensive neonatal therapy, informed consent was obtained and parenteral nutrition was started before the first seven days of life. Hepatic function tests were taken before the start of parenteral nutrition, repeating the tests every seven days. Statistical analysis was carried out using the statistical package SPSS 22.

RESULTS

98 patients divided into 44 girls (44.9%) and 54 boys (55.1%) were included in the analysis with an average Capurro of 32.0 +/- 2.4 (range 26-36) weeks and a weight of 1338.3 +/- 337.0 (range 650-2250) grams. Apgar at one minute ranged from 2 to 8 with an average of 5.8 +/- 1.6 and by five minutes was between 4-9 with an average of 8.1 +/- 1.0 points. The basal values of bilirubins and liver functioning enzymes are shown in Table 1. The children remained interned 37.9 +/- 26.9 (range 10-128) days. With the international cut-off point of direct bilirubin> 2.0, the prevalence rate of cholestasis was 19.4%. Regarding the compared outcomes (table 2), the relative risk of cholestasis was 1.58 times (IC95% 0.7-3.5) higher for the TPN continues but the difference was not significant (p = 0.21); there were also no significant differences in the average days of stay (p = 0.72) and days of TPN (p = 0.86). See the evolution of BD according to the type of TPN and the presence or absence of cholestasis (Table 3). In both types of TPN it is evident that BD increases significantly as the measurement time passes in children with cholestasis and stays more or less stable in the group without cholestasis, however, it is clear that the levels of increase are higher in the cases treated with TPN continues especially to the fourth and fifth measurement; according to the Hotelling Trace statistic, there is a significant interaction between BD evolution, cholestasis and TPN mode, which indicates that long BD levels increase more in those treated with continuous vs. cycled mode (p. = 0.02); adjustment with basal alkaline phosphatase by analysis of covariance did not modify the interaction.

Table 1. Basal values of bilirubins and liver functioning enzymes of premature infants with total parenteral nutrition

	Min	Max	Med	Desv. tip.
ConjugatedBilirrubin	.1	.9	.368	.2049
UnconjugatedBilirrubin	.4	6.5	2.427	1.4344
AST	14.0	65.3	38.089	12.8354
ALT	15.6	160.5	42.196	19.6246
GGT	12.0	118.0	41.485	17.1177
Alcalinephosphatase	29.4	211.0	106.198	37.2477

Table 2. Outcomes of the treatment groups of total parenteral nutrition cycled versus continuous of premature infants

Outcome variables	TPN		p	Applied test
	Cicled (n = 38)	Continue (n = 60)		
Cholestasis	5 (13.2%)	14 (23.3%)	0.21	Chi square
TPN days	17.7 +/- 11.9	17.0 +/- 11.1	0.86	U of Mann-Whitney
Days of stay	38.8 +/- 27.5	37.4 +/- 26.7	0.72	U of Mann-Whitney

Table 3. Evolution of direct bilirubin (BD) according to the presence or absence of cholestasis and type of TPN in premature children

Measurement	Cicled(Colestasis)			Continue (Colestasis)		
	SI	NO	P	SI	NO	p
1	0.46 (0,08)	0.29 (0.05)	0.11	0.46 (0.05)	0.37 (0.04)	0.22
2	0.86 (0.18)	0.52 (0.10)	0.12	1.00 (0.11)	0.49 (0.09)	0.0001
3	2.64 (0.50)	0.49 (0.29)	0.001	2.11 (0.30)	0.51 (0.26)	0.0001
4	3.68 (0.62)	0.39 (0.35)	0.0001	4.24 (0.37)	0.31 (0.32)	0.0001
5	4.14 (0.42)	0.42 (0.26)	0.0001	5.24 (0.27)	0.30 (0.24)	0.0001

Finally, the prediction of cholestasis by logistic regression applying the Wald step method backwards, from the prognostic factors indicated in table 2 and including the NPT administration mode, gave the following results (Table 4): Note that in the fourth step of the regression two adjusted

Table 4. Logistic regression model to predict the presence or absence of cholestasis in preterm infants treated with TPN

		B	E.T.	Wald	Sig.	Exp(B)	I.C. 95.0% para EXP(B)	
Step1(a)	APGAR1	-.439	.406	1.170	.279	.645	.291	1.428
	APGAR5	-.320	.542	.348	.555	.726	.251	2.102
	CAPURRO	.496	.460	1.165	.281	1.643	.667	4.045
	WEIGHT	-.002	.004	.225	.635	.998	.991	1.006
	TPN.DAYS	.273	.087	9.924	.002	1.314	1.109	1.558
	TPN.MODE	1.946	.968	4.046	.044	7.002	1.051	46.654
	Constant	-17.038	12.201	1.950	.163	.000		
Step2(a)	APGAR1	-.421	.394	1.140	.286	.657	.303	1.421
	APGAR5	-.374	.522	.514	.473	.688	.248	1.912
	CAPURRO	.337	.309	1.185	.276	1.401	.764	2.569
	TPN.DAYS	.281	.088	10.203	.001	1.324	1.115	1.573
	TPN.MODE	1.944	.968	4.034	.045	6.986	1.048	46.569
	Constant	-14.161	10.575	1.793	.181	.000		
Paso 3(a)	APGAR1	-.631	.275	5.265	.022	.532	.310	.912
	CAPURRO	.260	.284	.842	.359	1.297	.744	2.262
	TPN.DAYS	.278	.086	10.428	.001	1.320	1.115	1.563
	TPN.MODE	1.900	.940	4.087	.043	6.683	1.060	42.141
	Constant	-13.478	10.234	1.734	.188	.000		
Paso 4(a)	APGAR1	-.648	.277	5.483	.019	.523	.304	.900
	TPN.DAYS	.231	.059	15.119	.000	1.259	1.121	1.415
	TPN.MODE	2.034	.928	4.809	.028	7.644	1.241	47.083
	Constant	-4.444	1.912	5.402	.020	.012		

Variables entered in step 1: APGAR1, APGAR5, CAPURRO, WEIGHT, DAYS.,TPN, MODE.TPN.

variables turn out to be the best predictors of the presence or absence of cholestasis: the days of TPN and the TPN mode; In fact, for each day of TPN the risk of cholestasis increases 1.25 times more (IC95% 1.12-1.41, p = 0.0001), and patients treated with continuous TPN have 7.6 times (IC 95% 1.24-47.08, p = 0.02)) more likelihood of cholestasis compared to those of cycled TPN.

DISCUSSION

The results of our study showed that the incidence of cholestasis in our Neonatal Intensive Care Unit (19.4%) resembles that reported in the international literature of 20% (Yan *et al*., 2017). It was described that patients who presented cholestasis have a common antecedent in Apgar and a birth weight lower than those who did not present it, which may be associated with these conditions as risk factors (Yan *et al*., 2017). Patients with continuous TPN presented cholestasis in 24%, while those who started cycled TPN presented it in 18.7%, which did not present statistical significance. When performing the risk analysis by linear regression and analysis of independent samples, the TPN in continuous mode represented a 7.6 times more risk of presenting cholestasis than the cycled modality, increasing according to the time of use. Likewise, the male sex corresponds as a risk factor. As a result, it was found that the patients with the highest levels of alkaline phosphatase at the time of baseline measurement were significantly related to the presence of cholestasis at the end of follow-up.

Conclusion

In all premature patients with inability to enter the enteral route, parenteral nutrition should be started in the first 24 hours of life. The liver function tests will be analyzed systematically, as well as assessing the risk factors that the patient presents. In extreme premature infants it is recommended to use TPN in cycled mode using the Lucyle Packard Children Hospital method to reduce the risk of presenting cholestasis, since they are the ones who use this nutritional strategy for a longer time.

In moderate preterm and late patients assess the start of cycling since almost all these patients will have prolonged use of PN more than 21 days. This study provides the basis for the study of the complications of total parenteral nutrition, a nutritional strategy widely used in all age groups, for new studies can be taken as a reference in terms of the methodology of cycling use according to the University of Stanford, which began to be used when the study began. Another important recommendation is the comparison of two randomized groups in a prospective way, controlling all the variables of nutritional contributions, since the contributions of lipids are correlated with the presentation of metabolic complications. This follow-up will also be useful to keep track of growth and be able to add variables, such as caloric intake, protein caloric ratio, non-protein caloric ratio to be able to relate the appropriate contributions with the growth of the premature.

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