DOI: 10.1590/0100-6991e-20202353

Metabolic and Inflammatory Benefits of Reducing Preoperative Fasting Time in Pediatric Surgery

Benefícios Metabólicos e Inflamatórios da Abreviação do Jejum Pré-operatório em Cirurgia Pediátrica

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A B S T R A C T

Objective: To investigate the metabolic/inflammatory impact of reducing the preoperative fasting time in preschool children. **Methods:** Forty children were randomly assigned to a fasting group (absolute fasting after 00:00) and a carbohydrate (CHO) group (allowed to ingest, two hours before surgery, a carbohydrate-rich beverage). Blood samples were collected right before and after surgery to quantify the levels of albumin, interleukin-6, glucose, insulin, C-reactive protein and to calculate insulin resistance by the HOMA-IR index. **Results:** Preoperative fasting time in the CHO group were shorter than in the fasting group (2.49h vs. 11.24h, p <0.001). Pre- and post-surgical CRP levels were significantly lower in the CHO group (p = 0.05 and p = 0.02, respectively). The preoperative CRP/albumin ratios in the CHO group were lower than in the fasting group (p = 0.03). Four patients (21%) in the fasting group but none in the CHO group were hyperglycemic before surgery (p = 0.04). The two groups had similar levels of albumin, interleukin-6, insulin and HOMA index. There were no adverse events. **Conclusion:** Reducing the preoperative fasting time with carbohydrate-rich beverages improves the perioperative metabolic and inflammatory responses of preschool children undergoing inguinal hernia surgery.

Keywords: Fasting. Carbohydrates. Preoperative Care. Pediatrics.

INTRODUCTION

Fasting before surgical/anesthetic procedures was instituted to reduce gastric content at the time of anesthetic induction, reducing severe consequences associated with the risk of vomiting and bronchoaspiration. The American Anesthesiology Society (ASA) published its first preoperative fasting *guideline* at the end of the 90s, and since then, it allows the use of clear or without residues liquids up to two hours before procedures that require general and local anesthesia or sedation[1]. Other prestigious Anesthesiology Societies also authorize the use of these liquids as a way to shorten the preoperative fasting time[2,3].

However, current studies show that these *guidelines* have not been performed routinely in pediatric surgical hospitals, and several publications highlight a long time of fasting in pediatric patients[4-6]. This long period of preoperative fasting has clinical and metabolic consequences for these patients. Children undergoing prolonged fasting have higher rates of hunger and thirst, irritability, anxiety, discomfort, malaise, dehydration (which can hinder venous access), headache and delayed surgical recovery[7-9]. Also, these patients present depletion of glycogen stores and increased gluconeogenesis, as well as worsening of catabolism with higher plasma levels of ketone bodies and fatty acids, risk of hyperglycemia and insulin resistance in the postoperative period[10,11].

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Absolute fasting from 00:00, on the night before the procedure, is the most common prescription by surgeons. This is an easy-to-follow recommendation, widely accepted, that does not require calculations of any kind and can be easily explained to patients and their families. However, this prescription does not specify the fasting time required for each type of food, does not consider the scheduled time for the surgical procedure the next day and does not take into account the constant delays regarding the operating room agenda. In addition, prolonged fasting times do not promote an additional reduction of gastric residual volumes or increase the safety of the procedure.

Consuming carbohydrate-rich beverages, which can be used up to two hours before the surgical procedure, reduces the preoperative fasting time. Studies enrolling adults have described the benefits of this protocol, as it leads to much better wellbeing, better glycemic metabolism (with decreased postoperative insulin resistance up to 50%) and a reduction of lean body mass loss, leading to better surgical recovery[12-14]. Some of these benefits in children have also been published, such as lower insulin concentrations and lower insulin resistance in patients undergoing reduced fasting times[15,16].

However, the reduction of the preoperative fasting time in children, with the intake of carbohydrate-rich beverages, is a topic that still needs more research. There is no extensive literature investigation about the acute inflammatory phase response associated with this protocol in pediatric patients. Our research group has previously studied the safety of reducing the preoperative fasting time using a drink with maltodextrin during a national task force of pediatric surgery, obtaining good results[17]. The ACERTO[18] Project has encouraged these paradigm changes in Brazil, but once again, there is no study regarding children. Thus, this work aims to evaluate the metabolic and inflammatory effects of reducing the preoperative fasting, using carbohydrate-rich beverages, in preschool children undergoing inguinal herniorrhaphy.

METHODS

This is a prospective, randomized-controlled study performed at Santa Casa de Misericórdia Hospital in Cuiabá, MT. It included children from the Pediatric Surgery Center, aged 2 to 6 years, and with ASA I or II anesthetic risk. They underwent elective unilateral or bilateral inguinal herniorrhaphy. The sample size was determined based on a pilot study by measuring PCR, and with a power of 80% and an alpha error of 5%, an adequate sample of 17 patients in each group was determined (stoa.usp.br/edsonzm/files/2423/15156/Calculadora.xls). Randomization was performed at the time of hospitalization, using Graphpad *@software*. Patients were randomized into two groups: fasting group (absolute fasting from midnight was prescribed), and carbohydrate group (CHO), [fasting solids from midnight was prescribed and a carbohydrate-rich beverage (12.5% maltodextrin diluted in 150 mL of water] was offered approximately two hours before the operation. Anesthetic induction was performed with a mask and inhalation anesthetic (Sevorane®) in all children. After the patient's sedation, venous access in the upper limb was performed with Abocath®, in order to collect a blood sample regarded as "preoperative" (this access was kept salinized and exclusive for extraction of blood samples).

Another venous access in the contralateral upper limb was also performed to provide venous hydration and anesthetic medications. Immediately after the end of the operation and before the patient awoke from anesthesia, a blood sample named "postoperative" was collected (using the exclusive access for blood sampling). Blood samples were sent to the laboratory for quantification of albumin, interleukin 6 (IL-6), blood glucose, insulin and C-reactive protein (PCR). Insulin resistance was calculated using the HOMA-IR Index, by the formula: [Fasting glucose (mg / dl) x 0.0555 x Insulin (uU / ml)] / 22.5.

The anesthesiologist chose the type of anesthesia, the fluid infusion in the intraoperative period and the vomiting prophylaxis. All patients underwent inguinal herniorrhaphy by inguinotomy, with ligation of the hernia sac with an absorbable wire of 3-0 or 4-0 polyglycolic acid. Patients were discharged on the same day of the operation.

This research project was carried out following the Declaration of Helsinki by the World Medical Association and was approved by the Research Ethics Committee under protocol no 51932515400005541. All parents or guardians signed the informed consent form (ICF).

Data were analyzed using the statistical program Statistical Package for the Social Sciences (SPSS) version 22. The results were presented as the median and interquartile range (IIQ) or mean and standard deviation (SD) measures. Fisher's test or chi-square test was used for categorical variables. For continuous data, the Mann-Whitney test or Student's t-test was used. The follow up of laboratory measurements was analyzed using the ANOVA test of repeated measures. The $p \leq 0,05$ was considered statistically significant.

RESULTS

Between February 2016 and October 2017, 54 children were eligible to enter the study. Subsequently, 14 children were excluded for several reasons: parents did not accept the participation in the study; the operation was cancelled due to respiratory symptoms; failure to collect blood specimen; other concomitant surgical diseases or violation of the perioperative protocol (non-ingestion of the carbohydrate-rich beverage). 21 patients in the intervention group and 19 in the fasting group, as shown in figure 1, were then included. The same surgeon operated all the children. Initially, patients received inhalation anesthesia and 20 (50%) underwent spinal anesthesia, 7 (17.5%) peri-dural and 13 (32.5%) ilioinguinal block, with no difference between the two groups ($p = 0.85$). The hydration used during the procedure was 0.9% saline (mean: 0.43, ranging from 0.05 to 1.44 mL/kg/min). Vomiting prophylaxis was performed with ondansetron (0.1 mg/kg), but 15 children, in both groups, also received dexamethasone (0.1 mg/kg) during the operation (fasting group 15/19 vs. CH 15/21, $p=0.58$). There were no cases of perioperative complications (including vomiting or bronchoaspiration during the anesthetic induction) or death. The distribution of patients according to sex, age, weight, diagnosis, anesthetic risk and preoperative hemoglobin was similar between the groups. The operative time varied between 15 and 55 minutes, and was similar between groups (fasting: 32 min ± 11 x CHO: 30 min ± 7, $p=0.65$), as shown in table 1.

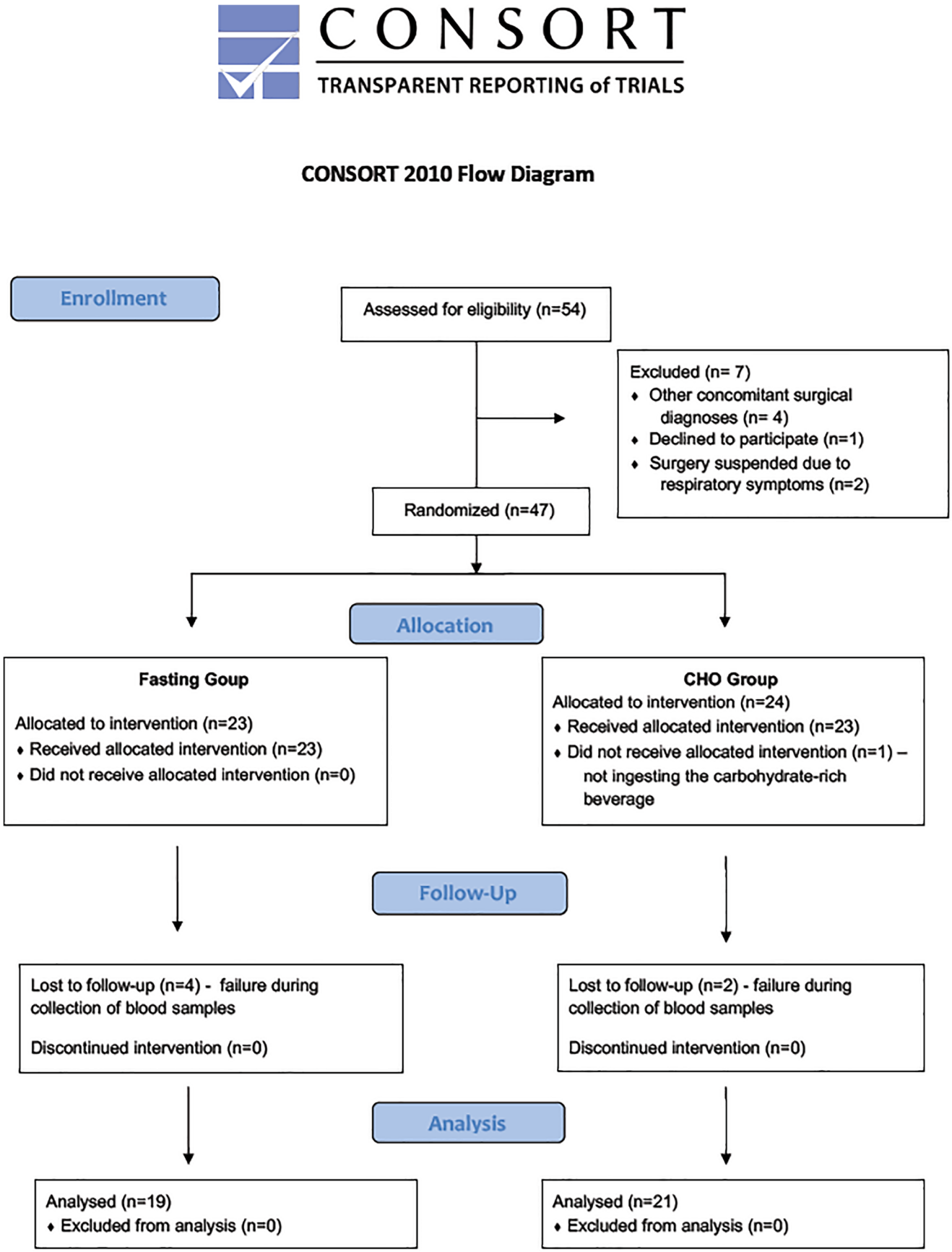

Figure 1. *Consolidated Standards of Reporting Trials (Consort) Flow Diagram.*

Table 1. *Clinical and demographic comparison of patients.*

	Fasting Group	CHO Group	P
Sex (n,%)			
Male	15 (78.9)	14 (66.7)	
Female	4 (21.1)	7 (33.3)	0.3 8
Age (mean/years)	3.42 ± 1.0 1	4.10 ± 1.3 7	0.0 8
Weight (mean/Kg)	16.7 ± 3.0 6	18.6 ± 5.2 8	0.1 7
Diagnosis (n,%)			
Right inguinal hernia	12 (63.2)	10 (47.6)	
Left Inguinal hernia	2 (10.5)	4 (19)	
Bilateral inguinal hernia	5 (26.3)	7 (33.3)	0.5 8
Anesthetic risk (n,%)			
ASA I	18 (94.7)	21 (100)	
ASA II	1 (5.3)	0	0.2 8
Preoperative hemoglobin (g / dL)	12.5 ± 1.2 8	12.7 ± 0.7 9	0.5 1
Prothrombin activity time (%)	92.5 ± 9.1 5	91.4 ± 9.6 4	0.7 3
Operative time (minutes)	32 ± 1 1	30 ± 7	0.6 5

The preoperative fasting time was significantly shorter in the CHO group compared to the fasting group (2: 49h vs. 11: 24h, p <0.001), as shown in figure 2.

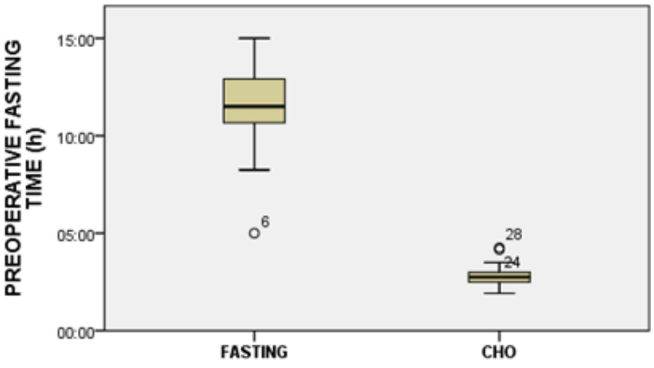

Figure 2. *Preoperative fasting time for liquids between groups (p <0.001).*

The CRP values were significantly lower in the CHO group, both preoperatively (fasting group: 3.60 ± 7.60 mg/L vs CHO group: 0.53 ± 0.59 mg/L; p = 0, 05) and postoperative period (fasting group: 3.53 ± 7.75 mg/L vs CHO group: 0.49 ± 0.53 mg/L, p = 0.02), as shown in Figure 3.

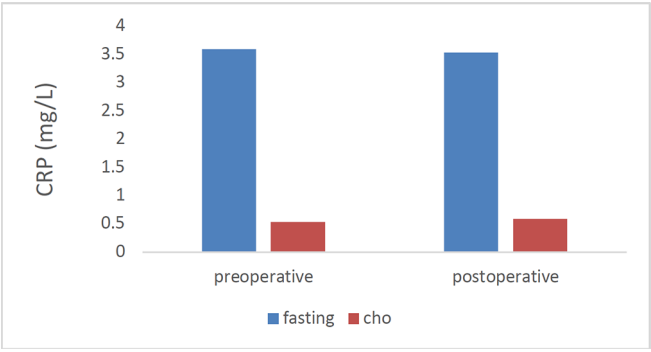

Figure 3. *Comparison of PCR values pre and postoperative between groups.*

In the follow up of laboratory data (ANOVA test), there was a significant reduction in CRP values only in the CHO group (p = 0.01).

The PCR/albumin ratio was also significantly lower in the CHO group in the preoperative period (0.89 ± 1.86 vs 0.13 ± 0.15, p = 0.03). In the postoperative period, there was a tendency towards lower values in the CHO group (0.91 ± 1.97 vs. 0.13 ± 0.15, p = 0.08), as shown in figure 4. Analyzing the follow up of PCR/albumin ratio (ANOVA test), there was a marginally lower value in the CHO group (p = 0.07).

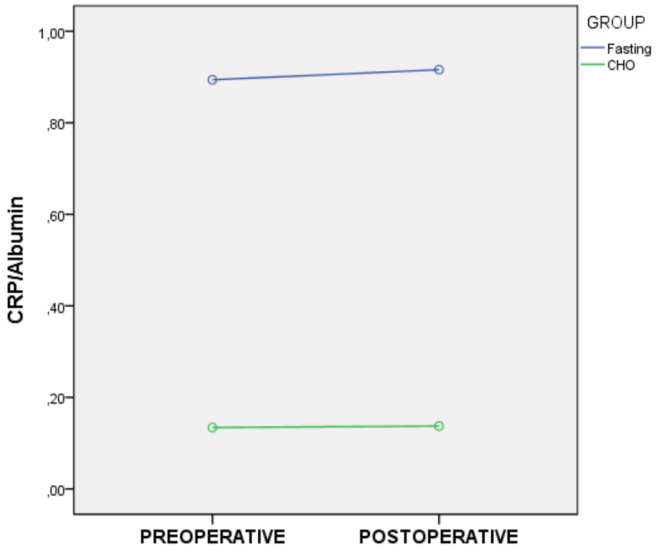

Figure 4. *Comparison of pre and postoperative PCR/Albumin ratio values between groups.*

There was no statistical difference between groups regarding blood glucose in the preoperative period (fasting: 88 ± 16 mg/dL vs CHO: 86 ± 9 mg/dL, p=0.32) or in the postoperative period (fasting: 91 ± 34 mg/dL vs CHO: 93 ± 24 mg/dL, p = 0.60). However, four (21%) patients in the fasting group became hyperglycemic in the preoperative period, presenting glycaemia higher than 99 mg/dL. No (0%) patient was hyperglycemic in the CHO group (p = 0.04). Normoglycemia was considered when the values were below 99 mg/dL, according to the Brazilian Diabetes Society Guideline[19]. There was no difference between the groups for albumin, Interleukin-6, Insulin and HOMA- IR Index data, both before and after the operation, as shown in Table 2.

DISCUSSION

The results of this study indicate that the reduction of preoperative fasting in healthy children, with the use of carbohydrate-rich beverages, decreases the inflammatory response related to the surgical trauma in the pre and postoperative periods. This was evidenced by the lower CRP values and the CRP/albumin ratio when comparing the two groups. CRP is an acute-phase protein that, under stress/inflammation response, has its levels increase. In contrast, albumin is an acute phase protein with a negative response, which is inversely associated with the inflammatory response. Another potential metabolic benefit is the blood glucose level in the perioperative period. The results showed that the administration of a carbohydrate-rich beverage, two hours before the operation, did not increase blood glucose in any of the 21 patients, in contrast to the elevation of blood glucose in 1/5 of the patients who remained under traditional fasting. Simple and straightforward extrapolation is that prolonged fasting turns healthy children into patients with type II diabetes mellitus, even before the surgical trauma, which can predispose to perioperative complications. Also, an association between morbidity and high levels of intraoperative glucose (> 150mg/dL) in pediatric patients undergoing cardiac surgery has been reported[20].

Table 2. *Laboratory results in the pre and postoperative period.*

	Preoperative			Postoperative		
	Fasting Group	**CHO Group**	**p**	**Fasting Group**	**CHO Group**	**p**
Albumin	4.08 ± 0.39	4.12 ± 0.29	0.94	3.82 ± 0.48	3.77 ± 0.29	0.53
IL-6	1.5 ± 2.6	2.0 ± 1.3	0.98	2.0 ± 2.3	1.5 ± 2.0	0.41
Glycemia	88 ± 16	86 ± 9	0.32	91 ± 34	93 ± 24	0.60
Insulin	3.09 ± 6.34	2.53 ± 1.80	0.69	4.90 ± 4.52	4.55 ± 3.43	0.78
HOMA-IR	0.86 ± 2.05	0.54 ± 0.40	0.49	1.57 ± 1.86	1.13 ± 1.05	0.37

The results of the current study, both metabolic and inflammatory, are relevant and suggest that the reduction of fasting time with carbohydrate-rich beverages up to two hours before anesthetic induction in children undergoing elective procedures is seen.

Our results showed similar values of insulin resistance between the groups during the perioperative period, measured by the HOMA-IR index. This index may not correspond to the exact value of insulin resistance, as reported by several authors who criticize this method. The euglycemic-hyperinsulinemic clamp is the gold standard method for this assessment, according to the literature[21]. However, this test was not available to be carried out in the current study.

Several other authors have supported the benefits of reduced fasting by using clear liquids enriched with carbohydrates before the operation, in adults. Dock-Nascimento et al. consistently showed benefits of the reduction of fasting time, from a metabolic and inflammatory point of view and even anti-oxidative stress[22]. Pexe-Machado et al. also showed a reduction PCR/albumin ratio in patients undergoing resections of gastrointestinal cancer, and having reduced fasting times with drinks containing carbohydrates[23]. It was not observed an increase in serum CRP, mostly because it usually reaches a peak 24-72 hours after tissue injury, and its collection was performed less than 1 hour after the beginning of the surgical trauma. However, the CRP values differed at both times and between the groups, suggesting that the consumption of carbohydrate-rich beverages can decrease the inflammation of the acute phase, induced by prolonged fasting times.

Using a population of only 40 patients can be a limitation, considering that with a higher number of cases, we could probably find more considerable differences in different variables, such as blood glucose, insulin and insulin resistance. Furthermore, the blood collection in the postoperative period was right at the end of the surgical procedure (for ethical reasons, before the removal of the venous access). We could have found a more significant difference between the groups if the collection was performed a few hours after the end of the operation, due to the maximum serum peak reached by cytokine IL-6 six hours after the procedure[24]. In addition, we chose inguinal herniorrhaphy as the surgical procedure, which is a minor trauma procedure and represents a short surgical time, with rapid patient recovery. We did not assess differences in clinical parameters between groups, which we consider a potential area for future studies. The use of dexamethasone to prevent postoperative nausea and vomiting may interfere with blood sample data. However, there were no statistical differences in the use of this medication between the groups. We highlight the need for complementary studies in patients undergoing major operations so that we can state that reducing fasting times together with the use of carbohydrate-rich beverages has significant effects in attenuating the metabolic and inflammatory response to trauma.

In this research, we chose to study the reduction of fasting periods in children, a protocol that has been advocated by the ACERTO Project for many years. We believe that this study is relevant for pediatric patients due to the lack of data. This study opens an opportunity for other researchers in Pediatric Surgery to be able to reproduce the model. The consistency of other future results will serve to support this protocol in Pediatric Surgery. The Brazilian Association of Pediatric Surgery - CIPE has approved the support of the ACERTO Project guidelines for the pediatric population in a meeting held in 2015[25].

The sample size was not calculated to assess the risk of bronchoaspiration. There was no case of perioperative complications that could be associated with reduced fasting time, such as vomiting during the anesthetic induction or pulmonary bronchoaspiration. Although this trial encompasses a small sample of patients, this is an important outcome and showed that the use of this beverage was safe, corroborating the literature that has reported the safety of using liquids without residues that have a rapid gastric emptying[26-28].

In summary, the analysis of the results allows researchers to continue studying the changes in the preoperative fasting time recommended for children. An overview of the results indicates that the protocol is safe and adds benefits to infant patients. For future research, it would be interesting to study this protocol in patients undergoing major operations, with new markers and potential clinical variables like irritability, nausea, vomiting, and parental anxiety.

CONCLUSION

The reduction of preoperative fasting time, using carbohydrate-rich beverages up to two hours before the operation, improves the metabolic and inflammatory responses in preschool children undergoing elective inguinal herniorrhaphy.

R E S U M O

Objetivo: *Avaliar os efeitos metabólicos e inflamatórios da abreviação do jejum pré-operatório em crianças pré-escolares.* **Métodos:** *Quarenta crianças foram prospectivamente randomizadas em um grupo chamado jejum (jejum absoluto a partir de 00:00h) e outro chamado de carboidrato (CHO - em que as crianças eram autorizadas a ingerir uma bebida contendo carboidrato duas horas antes da operação). Foram colhidas amostras sanguíneas no pré e pós-operatório imediatos, para dosagens de albumina, interleucina 6, glicemia, insulina, proteína C reativa, e calculada resistência a insulina pelo índice de HOMA-IR.* **Resultados:** *O tempo de jejum pré-operatório foi significativamente menor no grupo submetido a abreviação do jejum (11:24h vs 2:49h, p<0,001). Os valores da PCR foram significativamente menores no grupo CHO, tanto no pré quanto no pós-operatório (p=0,05 e p=0,02, respectivamente). Os valores da razão PCR/ Albumina foram significativamente menores no grupo CHO no período pré-operatório (p=0,03). Quatro pacientes (21%) do grupo jejum tornaram-se hiperglicêmicos no pré-operatório, enquanto nenhum teve hiperglicemia no grupo CHO (p=0,04). Não houveram diferenças estatisticamente significativas nos valores de albumina, interleucina-6, insulina e índice de HOMA entre os grupos. Não houve nenhum evento adverso no trabalho.* **Conclusão:** *A abreviação do jejum pré-operatório através do uso de bebidas contendo carboidratos melhora a resposta metabólica e inflamatória no peri-operatório de crianças pré-escolares submetidas a cirurgia eletiva de herniorrafia inguinal.*

DESCRITORES: *Jejum. Carboidratos. Cuidados Pré-Operatórios. Pediatria.*

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Received in: 09/17/2019
Accepted for publication: 11/20/2019
Conflict of interest: None.
Financing source: None.

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