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RAPID COMMUNICATION

Hyperglycemia and postoperative outcomes in pediatric neurosurgery

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INTRODUCTION

Recent studies in adults have demonstrated the deleterious effects of hyperglycemia in intensive care patients and its substantial impact on crucial outcomes such as mortality. As a result, there is an increasing interest in the impact of this complication on the outcomes of critical illness in children.[1]

Hyperglycemia is prevalent among critically ill children and may be associated with poor outcomes and higher morbidity during hospitalization.[2] Few prospective studies have analyzed the occurrence of hyperglycemia and the use of intensive insulin therapy in critically ill children. A recent single-center trial demonstrated the efficacy and safety of an insulin therapy protocol. The trial results indicated improved survival rates among the patients who received the treatment.[3]

A clear association between hyperglycemia and poorer outcomes has been demonstrated in some specific clinical situations, such as septic shock, cardiac surgery, and traumatic brain injury.[4-7] However, hyperglycemia has yet to be fully studied in the context of pediatric surgery, and no pediatric neurosurgical studies have analyzed the association between hyperglycemia, morbidity, and mortality.

This study evaluated the postoperative glucose levels of children who underwent neurosurgeries for different indications and analyzed the association of these levels with lengths of mechanical ventilation, intensive care, and hospital stay.

MATERIAL AND METHODS

The study was conducted in the Pediatric Intensive Care Unit (PICU) of Santa Catarina Hospital, Sao Paulo, Brazil, a tertiary multidisciplinary hospital with 16 PICU beds. This retrospective cohort study evaluated all patients admitted to the PICU who underwent neurosurgical procedures from May 2004 to May 2009. Both plasma and capillary blood glucose values were collected from patients during their stay in the PICU and during their stay in the pediatric ward after transfer from the PICU. Hyperglycemia was defined as a blood glucose level $\geq$150 mg/dL. The three outcomes evaluated in the study were the durations of mechanical ventilation, PICU, and hospital stay. Hyperglycemia was studied along with other likely risk factors in these patients, such as fever, laryngitis, infection, hypothermia, packed red blood cells, and hormonal disorders. First, a univariate analysis was performed to identify the main risk factors associated with the three outcomes, and the statistically relevant risk factors were separated and analyzed in a multivariate analysis. The level of significance was set at 5%. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 18.0 (Chicago, Illinois). The study was approved by the Ethics in Research Committee of the institution where it was conducted.

RESULTS

The charts of 198 patients were analyzed during the study. The most frequent surgeries were brain tumor resection (37.4%), craniosynostosis (31.3%), ventriculoperitoneal shunting (16.7%), craniotomy for craniofacial dysostosis (4.5%), spinal arthrodesis (4%), epilepsy surgery (2%), and brain revascularization for Moyamoya disease (1.5%).

A total of 139 glucose measurements were recorded for the patients included in the study. Hyperglycemia was diagnosed in 62.6% of the patients. The patient glucose level upon admission to the PICU and the highest glucose level noted in the first 24 hours post-admission were recorded. The mean glucose level was recorded following the 24-hour measurement. The results of the glucose measurements according to surgical diagnosis are listed in Table 1.

A univariate analysis identified a positive association between hyperglycemia and a prolonged duration of PICU stay (3.88 days *vs*. 2.46 days, $p = 0.042$). However, hyperglycemia was not associated with prolonged hospitalization or the duration of mechanical ventilation required (Table 2). The multivariate analysis did not identify any positive associations between hyperglycemia and any of the three outcomes studied (Table 3).

Table 1 - Glucose levels according to surgical diagnosis.

Diagnosis	Glucose level at admission *	Highest glucose level in 24 hours *	Mean glucose level *
Ventriculoperitoneal shunting	135.4±66.5	133.6±38.5	117.9±23.6
Craniostenosis	159.2±69.9	150.4±64.2	118±39.9
Supratentorial brain tumors	160.5±83.3	163.3±47.9	131±31.9
Infratentorial brain tumor	131.2±30.8	151±44.7	126.1±36.9
Craniotomy for craniofacial dysostosis	161.8±39.2	152.7±14.2	155.1±42.3
Spinal arthrodesis	149.8±61.8	238±172.5	112.2±13.1
Epilepsy surgery	154.3±41.1	138±9.9	110.9±11.9
Brain revascularization for arteriopathy	148±28.3	N/E	N/E
Spinal cord tumors	128.3±30.1	N/E	N/E

*Mean ± Standard Deviation (mg/dL).
N/E – Blood glucose measurement not evaluated due to the small number of samples.

DISCUSSION

To the best of our knowledge, the present study is the first to analyze the effects and the incidence of hyperglycemia in a pediatric neurosurgery environment. The highest glucose levels were found in patients that underwent surgery for craniosynostosis, supratentorial tumor resection, and craniotomies; these procedures are more likely to involve longer surgical times and higher incidence of complications, such as bleeding and infection. These higher incidences of complications increase the risk of hyperglycemia. Univariate analysis indicated an association between hyperglycemia and prolonged duration of stay in the PICU. However, no association was found between hyperglycemia and the total duration of hospital stay or the length of mechanical ventilation time required. Multivariate analysis indicated no statistically relevant associations between hyperglycemia and any of the outcomes. The occurrence of severe hyperglycemia (above 300 mg/dL) was rare.

Hyperglycemia is common in critical illness as a consequence of organic stress and counter-regulatory hormones and is typically interpreted as a secondary event in critical care. Several studies have tried to identify an association between hyperglycemia and a worse prognosis in children, but their findings should be interpreted as markers of severe illness. As the patient's condition improves, it is likely that their glucose levels will revert to the normal range. As a secondary event, patients with other complications that may affect glucose levels, either directly or indirectly, such as fever, infection or bleeding, are more likely to develop hyperglycemia and, consequently, worse outcomes such as a prolonged ICU stay. Such factors may explain why hyperglycemia was found to be associated with a prolonged stay in the PICU in the univariate but not in the multivariate analysis.

Up to 50% of pediatric patients who undergo neurosurgeries may develop several postoperative complications,[8] and hyperglycemia is an important event that may impact on their clinical course. Stress hyperglycemia is associated with insulin resistance and frequently affects adults and children. Some of the factors that may contribute to stress hyperglycemia are high glucose infusion rates, the increase in the production of endogenous glucose due to action of the counter-regulatory hormones (cortisol, glucagon, and catecholamine), and changes in glucose transport.[9]

Changes in insulin counter-regulatory hormones due to surgical stress have not been clearly defined; therefore, the highest glucose level within the first 24 hours following surgery was analyzed separately from the glucose level at admission. There was a progressive reduction in glucose levels in all surgical groups during the course of hospitalization. Mild hyperglycemia was identified and its rapid progression to normal levels may be explained by the low preoperative morbidity of the population studied, as most procedures were elective and performed in patients with a low anesthetic risk. According to this hypothesis, the patients were more likely not to present the main consequences of severe hyperglycemia, such as osmotic diuresis, dehydration, and metabolic disorders. When considering the results of the entire study population, hyperglycemia was not severe enough in this scenario to cause adverse effects and outcomes related to this metabolic disorder.

It was not possible to evaluate the correlation between hyperglycemia and mortality because only two deaths occurred during the study. Nearly 59% of the patients received one or more doses of systemic corticosteroids during surgery or their ICU stay, while 93% of the patients who underwent brain tumor surgeries received them. There are no current recommendations regarding the routine postoperative use of corticosteroids, which are administered with the aim of reducing the brain edema associated with resection. Nevertheless, corticosteroids are well known to increase glucose levels, which may have contributed to our findings.

We did not identify a significant association between hyperglycemia and the three outcomes examined, which may be explained by the small sample size and the relatively few glucose measurements taken in the study population. As hyperglycemia was common in this group, special attention should be paid to it to prevent adverse events, especially because other studies with larger series of patients found a significant association between hyperglycemia and worse outcomes in surgical patients.

There were a few limitations associated with this study, particularly due to the retrospective analytical design and consequent lack of a previous protocol of glucose measurement. Moreover, some of the surgery subgroups contained few patients, which made it difficult to establish an association between glucose levels and outcomes.

The treatment of hyperglycemia in pediatric intensive care must be further analyzed, as there is no consensus on the benefits of several procedures, such as insulin therapy and strict glycemic control in these situations. In children, organic components such as beta cells, liver, kidneys, and muscles have not been exposed to oxidative, lipotoxic or

Table 2 - Results of univariate analysis.

Outcome	Risk Factor	Median	SD	N	*p*-value
	Fever				
PICU LOS	No	2.7	1.9	138	**0.006**
	Yes	5.08	8.11	60	
Hosp. LOS	No	5.96	4.61	138	**0.001**
	Yes	9.9	10.97	60	
MV time	No	5.83	8.49	138	**<0.001**
	Yes	8.48	11.57	60	
	Use of PRBC				
PICU LOS	No	3.13	2.94	102	0.468
	Yes	3.73	6.26	96	
Hosp. LOS	No	7.23	6.79	102	0.623
	Yes	7.08	7.95	96	
MV time	No	5.54	5.55	102	**0.017**
	Yes	7.8	12.43	96	
	Laryngitis				
PICU LOS	No	2.9	2.29	168	**0.027**
	Yes	6.33	10.89	30	
Hosp. LOS	No	6.6	5.66	168	0.059
	Yes	10.3	13.06	30	
MV time	No	6.21	8.83	168	**0.036**
	Yes	9.02	12.91	30	
	Coag. Disorders				
PICU LOS	No	3.32	4.82	189	**0.065**
	Yes	5.44	5.05	9	
Hosp. LOS	No	7.08	7.4	189	0.247
	Yes	8.78	6.4	9	
MV time	No	5.92	6.58	189	**0.006**
	Yes	21.72	31.15	9	
	Inappropriate ADH Syndrome				
PICU LOS	No	3.4	4.87	195	**0.037**
	Yes	4.67	1.15	3	
Hosp. LOS	No	7.4	7.41	195	0.214
	Yes	6.3	0.58	3	
MV time	No	6.61	9.64	195	**0.022**
	Yes	8.33	1.15	3	
	Seizures				
PICU LOS	No	3.03	2.62	190	**0.003**
	Yes	12.63	19.33	8	
Hosp. LOS	No	6.65	5.79	190	**<0.001**
	Yes	19.25	21.07	8	
MV time	No	6.56	9.75	190	**0.002**
	Yes	8.5	3.02	8	
	Hyperglycemia				
PICU LOS	No	2.46	1.43	52	**0.042**
	Yes	3.88	3.76	87	
Hosp. LOS	No	5.15	2.02	52	0.073
	yes	8.46	7.49	87	
MV time	No	5.27	1.71	52	0.078
	yes	9.74	15.6	87	
	CSF Leakage				
PICU LOS	No	3.24	4.72	192	**0.001**
	yes	9.17	5.6	6	
Hosp. LOS	No	6.7	6.75	192	**<0.001**
	yes	21.67	11.47	6	
MV time	No	6.32	8.49	192	0.152
	yes	16.83	27.05	6	
	ICH				
PICU LOS	No	2.97	2.54	189	**<0.001**
	yes	12.78	17.95	9	
Hosp. LOS	No	6.72	5.78	189	**0.011**
	yes	16.33	21.14	9	
MV time	No	6.49	9.67	189	**0.039**
	Yes	9.67	6.96	9	
	Infection				
PICU LOS	No	3.17	4.7	189	**<0.001**
	Yes	8.56	5.22	9	
Hosp. LOS	No	6.58	6.74	189	**<0.001**
	Yes	19.33	9.46	9	

Table 2 Cont.

Outcome	Risk Factor	Median	SD	N	*p*-value
MV time	No	6.18	8.8	189	**0.001**
	Yes	16.17	18.15	9	
	Hypothermia				
PICU LOS	No	3.5	5.14	166	0.65
	Yes	3	2.86	32	
Hosp. LOS	No	7.37	7.8	166	0.365
	Yes	6.06	4.28	32	
MV time	No	7.05	10.38	166	**0.038**
	Yes	4.47	1.88	32	

Legend – PICU LOS – Pediatric Intensive Care Unit Length of stay, SD – standard deviation, MV – mechanical ventilation, PRBC – packed red blood cells, CSF – cerebrospinal fluid, ICH – intracranial hypertension, ADH – antidiuretic hormone.

hyperglycemic stress for extended periods, and the effects of hyperglycemia on these patients may differ from those seen in adult populations.[10-12] Therefore, changes in glucose levels that develop after neurosurgery should be better studied to outline preventive measures, such as determination of glucose infusion rates, prevention of unnecessary use of systemic corticosteroids, and early diagnosis of infection.

CONCLUSIONS

Hyperglycemia is frequent in children following neurosurgery and was not found to be associated with the durations of mechanical ventilation, PICU stay, or hospital stay in this sample of pediatric patients. In pediatric patients, glucose levels should be carefully and accurately controlled after surgery, as this may reduce morbidity and hospitalization time. Further studies are necessary to elucidate the role of hyperglycemia in pediatric neurosurgical patients.

Table 3 - Results of multivariate analysis.

Outcome	Risk Factor	Regression Analysis (Wald Test)	*p*-value
PICU LOS	Fever	7.72	**<0.001**
	Laryngitis	9.13	**0.003**
	Hyperglycemia	3.2	0.062
	Coagulation disorders	0.23	0.63
	Infection	4.1	**0.043**
	Use of steroids	2.96	**0.085**
Hospital LOS	Fever	7.54	**0.006**
	Laryngitis	3.39	0.066
	Coagulation disorders	0.31	0.576
	Infection	8.99	**0.003**
	Use of steroids	0.02	0.894
MV time	Fever	3.88	**0.049**
	Laryngitis	4.29	**0.038**
	Use of PRBC	5.27	**0.022**
	Coagulation disorders	14.11	**<0.001**
	Infection	2.36	0.125
	Use of steroids	48.24	**<0.001**

REFERENCES

1. Preissig CM, Rigby MR. Pediatric critical illness hyperglycemia: risk factors associated with development and severity of hyperglycemia in critically ill children. J Pediatr. 2009;155:734-9, doi: 10.1016/j.jpeds.2009.05.007.
2. Hirshberg E, Larsen G, Van Duker HV. Alterations in glucose homeostasis in the pediatric intensive care unit: hyperglycemia and glucose variability are associated with increased mortality and morbidity. Pediatr Crit Care Med. 2008;9:361-6, doi: 10.1097/PCC.0b013e318172d401.
3. Verhoeven JJ, Brand JB, van de Polder MM, Joosten KFM. Management of hyperglycemia in the pediatric intensive care unit; implementation of a glucose control protocol. Pediatr Crit Care Med. 2009;10:648-52, doi: 10.1097/PCC.0b013e3181ae787b.
4. Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC. Glucose level and risk of mortality in pediatric septic shock. Pediatr Crit Care Med. 2005;6:470-2, doi: 10.1097/01.PCC.0000161284.96739.3A.
5. Yates AR, Dyke PC 2nd, Taeed R, Hoffman TM, Hayes J, Feltes JF, et al. Hyperglycemia is a marker for poor outcome in the postoperative pediatric cardiac patient. Pediatr Crit Care Med. 2006;7:351-5, doi: 10.1097/01.PCC.0000227755.96700.98.
6. Chiaretti A, Piastra M, Pulitano S, Pietrini D, De Rosa G, Barbaro G, et al. Prognostic factors and outcome of children with severe head injury: an 8-year experience. Childs Nerv Syst. 2002;18:129-36, doi: 10.1007/s00381-002-0558-3.
7. Smith RL, Lin JC, Adelson PD, Kochanek PM, Fink EL, Wisniewski S, et al. Relationship between hyperglycemia and outcome in children with severe traumatic brain injury. Pediatr Crit Care Med. 2012;13 (in press).
8. Fernández de Sevilla Estrach M, Cambra Lasaosa FJ, Segura Matute S, Guillén Quesada A, Palomeque Rico A. Postoperatorio de tumores cerebrales en la unidad de cuidados intensivos pediátricos. An Pediatr (Barc). 2009;70:282-6, doi: 10.1016/j.anpedi.2008.10.015.
9. Ognibene KL, Vawdrey DK, Biagas KV. The association of age, illness severity, and glycemic status in a pediatric intensive care unit. Pediatr Crit Care Med. 2012;13 (in press).
10. Kyle UG, Bu JAC, Kennedy CE, Jefferson LS. Organ dysfunction is associated with hyperglycemia in critically ill children. Intensive Care Med. 2010;36:312-20, doi: 10.1007/s00134-009-1703-1.
11. Klein GW, Hojsak JM, Rapaport R. Hyperglycemia in the pediatric intensive care unit. Curr Opin Clin Nutr Metab Care. 2007;10:187-92, doi: 10.1097/MCO.0b013e3280147d3e.
12. Rosenbaum M, Nonas C, Horlick M, Fennov I, Vargas I, Schachner H, et al. Beta-cell function and insulin sensitivity in early adolescence: association with body fatness and family history of type 2 diabetes mellitus. J Clin Endocrinol Metab. 2004;98:5469-76, doi: 10.1210/jc.2004-0971.