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Original Research Paper

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HYPERGLYCEMIA AND LEUCOCYTOSIS -PREDICTORS OF OUTCOME IN PEDIATRIC SEVERE HEAD INJURY PATIENTS

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ABSTRACT

Aim & Objective: To study the relationship between hyperglycemia and leucocytosis and the outcome in pediatric severe head injury patients,thereby prevention and early recognition of these complications in treatment of children with severe traumatic brain injury. **Design:** Retrospective review of collected data in Pediatic Head injury registry. **Materials and Methods:** Data of 124 Pediatric patients admitted in SMS Trauma centre in Neurosurgery department between January 2020 to December 2021 with severe Traumatic Brain Injury (GCS ≤ 8) are taken and analyzed systematically. The age group included pediatric patients from infancy to 14 years. Blood Glucose and Total Leucocyte count was collected at the time of admission and assessed again at 48 hours(Early) after admission, 3rd day to 7th day after admission was collected and assessed. Glasgow outcome scores (GOS) were assessed at 3 months and these patients were categorized into Favourable (GOS = 1-2) and Unfavourable (GOS = 3-5). Blood glucose level < 150mg/dl are labeled normal group,150-200 mg/dl are labeled mild hyperglycemia group >200 mg/dl are labeled severe hyperglycemia group. Leucocyte count of more than 11,000 are considered as leucocytosis. **Results:** Blood glucose values which were noted on the 3 mentioned time intervals, at the time of admission,3rd day,7th day in the patient's file were taken over the research period, which included the enrollment of 124 children. There was no correlation between result and peak serum concentrations in the Early period (p = 0.09, percent positive outcome: NG – 26 percent; MHG – 26 percent; SHG – 72 percent).Children in the late MHG and late SHG had a lower GOS scores in the follow up period (percent good outcome: NG – 41 percent, MHG– 50 percent, SHG– 33 percent; p = 0.005 and P = 0.0001 respectively. 30 patients (24.2%) had normal white blood cells (WBC) count, whereas 94 patients(75.8%) had increased WBC counts. The is a marked difference in the outcome scores, the table no 7 analyses that the leucocytosis has significant effect on outcome scores, with p value 0.0001 **Conclusion:** For children with severe TBI, we discovered that prolonged hyperglycemia-either as a daily average or during specified episodes is related by poor neurological outcomes. Children who have suffered severe TBI should have their blood sugar levels monitored at regular intervals for prolonged duration and the risk of hyperglycemia cannot be excluded in the patients who had normoglycemia in the initial 48 hours. It is as well important to determine the best method for managing their blood sugar for longer periods as this has profound impact on long-term outcomes.

KEYWORDS : Hyperglycemia, Leucocytosis, Pediatric ,Traumatic Brain Injury.

INTRODUCTION

There has not been any study in the recent times after the improvement of care in medical standards in the recent years regarding the effects of Hyperglycemia in head injury patients and the paucity of studies in the past 10 years,based on metabolic disturbances in pediatric head injury patients led to this study .There has been a lot of debate and inquiry on the effects of hyperglycemia and the best ways to regulate glucose in pediatric critical care medicine (1-6). Many studies have examined the association between hyperglycemia and prognosis in TBI, but few have examined the ideal method of administering glucose to babies and children who have had a TBI (7-12). Some studies show that severe illness-induced hypoglycemia may have detrimental consequences on health by altering immunity and increasing infections (13-15) and by altering inflammation (16) and endothelial integrity(17) and affecting mitochondrial activity (18). Even after a brain injury (TBI), glycemic management or nutritional assistance is highly debated since CNS and systemic metabolic needs are interconnected and complicated. Many studies show that hyperglycemia is detrimental immediately following or shortly,exhibiting significantly worsening oxidative stress-induced brain damage (19). There is a positive correlation between a good result in experimental TBI with fasting for 48 hours, which reduces the risk of post-TBI hyperglycemia (20). The availability of ketonesin various experimental studies has shown to recreate this effect, indicating that other fuel sources are accessible and are utilized as a source of energy in the initial 48 hours of TBI.

As a result of a variety of causes, including mitochondrial failure (21), hyperglycolysis due to glutamate absorption (22), hypoperfusion and/or ischemia-associated increases in glycolysis (23), and increased brain tissue lactate levels (24), glucose consumption is substantially changed during the initial 48 hours after TBI (24). Serum/blood glucose concentrations have been employed as a surrogate marker in the majority of clinical studies seeking to correlate glucose metabolism with neurological outcomes after TBI. Hyperglycemia at the time of admission has been linked to poor outcomes in adult TBI patients (25-28), with the stress response and catecholamine release being proposed as the fundamental reason (26). Patients with TBI may benefit from strict glucose management with rigorous insulin treatment to avoid hyperglycemia, which may minimize the requirement for vasopressors to maintain CPP, reduce seizure frequency, and even prevent diabetes insipidus (29). On the other hand,a study by Vespa et al shown that strict glucose management in individuals with severe TBI was linked to increase in lactate/pyruvate levels and reduction in brain interstitial glucose levels leading to metabolic crisis (30). There is a paucity of research on the link between hyperglycemia and

health outcomes in children with severe TBI. In a small sample of children (n = 36), Parish found no link between poor outcome and entrance hyperglycemia (blood glucose concentration 270 mg/dL) (31). Another group of researchers has shown an association between early hyperglycemia and injury severity (7-10). Furthermore, these studies had two major flaws: no protocolized glucose delivery and insufficient data on the timing of hyperglycemic episodes.

Serum glucose levels and neurological outcomes after severe TBI in children were examined in this study. A consistent method to care for pediatric patients with severe TBI was established in our institute ,as a protocol, there was no exogenous administration of glucose until 48 hours after TBI to prevent early hyperglycemia, which may be fatal, until and unless the child is in hypoglycemia (blood glucose concentration ≤ 70 mg/dL). A frequent strategy in facilities caring for adults with TBI is to minimize glucose delivery early after the injury, which may be less prevalent in pediatric hospitals. Using this method, we investigated whether or not the amount of hyperglycemia specified a priorly had any effect on the outcome of severe TBI in babies and children.

Following head traumas, the release of catecholamines may cause hypokalemia and leucocytosis (33). Patients with moderate and severe head injuries whose WBC counts were higher had a worse prognosis. The stimulation of the transmembrane sodium potassium pump by the 2 adrenergic receptors may be the cause of hypokalemia in TBI patients. This causes hypokalemia by shifting potassium from the intravascular spaces into the cells. Neurological outcomes may be improved by timely identification and adequate treatment

MATERIALS AND METHODS

All children with severe TBI were given a detailed treatment plan to prevent further damage. It was a requirement of this strategy that exogenous administration of glucose until 48 hours after TBI to prevent early hyperglycemia until blood glucose levels remain below 70 gm/dl for at least 48 hours after TBI. The age group included pediatric patients from infancy to 14 years. Glucose tests, which were done on a regular basis twice in the day. For this study purpose blood sugar values that are collected on specified timings as mentioned before were taken into consideration. For management of intracranial hypertension and general clinical care, a protocol based on the Guidelines for Medical Management of Severe TBI in Children were all used as part of a multi-tiered strategy to treating intracranial hypertension. Intravenous fluids containing 5% dextrose were begun 48 hours after the injury as per the daily requirement. The clinical team assessed the best method of nutritional assistance, whether it be parenteral or enteral, and started it on day 3 for most patients. There was no use of protocolized insulin treatment throughout this trial, and insulin was delivered at a clinician's discretion. In certain instances of intractable intracranial hypertension, additional techniques such as rescue treatment with decompressive craniectomy were used to treat the condition.

Obtaining and Analyzing Information

The study used blood glucose levels taken at the patient's bedside and in the laboratory, both of which were documented in the patient's medical file. Insulin exposure was considered as a categorical variable for the sake of all analyses in this work. At three months, the Glasgow outcome scale (GOS) scores were categorized into positive (GOS = 1-2) and unfavourable (GOS = 3-5) categories.

Prior to doing statistical analysis, two time periods were established: Early(until 48 hours) and Late (49 – 168 hours after injury). This stratification was necessary to account for the possibility that variations in glucose concentrations across time may represent distinct pathophysiological processes. Serum glucose levels were examined twice, each time independently. Each patient's blood glucose concentrations for each time were determined . The peak blood glucose levels of each child were determined and they were categorized into 3 glycemic groups based upon their peak blood glucose [normal (NG) – peak glucose < 150 mg/dL; mild hyperglycemia (MHG) – peak glucose ≤ 200 mg/dL; severe hyperglycemia (SHG) – peak glucose > 200 mg/dL].In table no 3, A multivariable regression analysis was used to investigate any possible confounding variables with a p 0.1. Using SAS, we carried out all of our analysis (SAS Institute; Cary, NC). By using a p-value of less than 0.05, we determined statistical significance.

Similarly when the WBC count exceeded 11000 cells/cc, Leucocytosis was considered. Before being admitted to the ward and ICU, all patients blood samples were submitted to the Emergency Department for testing.

Microsoft Excel was used to input all of the data that had been obtained in a proforma. Data were presented in terms of percentages and frequencies for the research variables.

RESULTS :

A totals of 3864(average of 20 samples per patient) blood glucoses measures which were noted in the patient's file were taken over the research period, which included the enrollment of 124 children. 62 percent of the patients were male patients, 38 percent were female paatients the average stay was 10.2 days, and 82.6 percent of the patients were able to be discharged from the hospital (Table 1). The analysis from tables 4 to table 7 shows that although increased mean blood glucose concentrations were associated with poor outcomes in the Late period as indicated by P 0.005 and P 0.0001 respectively with MHG and SHG groups, this was not the case in the Early phase. In the early stages of the study, univariate analysis indicated age, ISS, and insulin exposure as possible confounds. In the result groups, there were no changes in glucose levels once these variables were taken into account (p = 0.72). Similarly, univariate studies in the Late Period showed that insulin consumption was a possible confounder (Table 2). The difference in mean glucose levels across the groups remained significant after adjusting for this variable (p = 0.03). When it came to table 4 and table 5, there was no correlation between result and peak serum concentrations in the Early period (p = 0.09, percent positive outcome: NG – 26 percent; MHG – 26 percent; SHG – 72 percent). Even yet, children in the late MHG and late SHG had a lower GOS scores in the follow up period (percent good outcome: NG – 41 percent, MHG– 50 percent, SHG– 33 percent; p = 0.005 and P = 0.0001 respectively. This is in contrast to other glycemic groups. During the Late period, only insulin exposure differed between the glycemic groups (p = 0.003) in Analysis 2 (Table 3). There was no difference in the confounding factors across the groups in the early period (Table 3). MHG and SHG had statistically significant influence on outcome as compared to NG after accounting for insulin usage (p = 0.323 and 0.272, respectively).

30 patients (24.2%) had normal white bloodcells (WBC) count (4000-11000/cc), whereas 94 patients(75.8%) had increased WBC counts. The is a marked difference in the outcome scores, the table no 7 analyses that the leucocytosis has significant effect on outcome scores, with p value 0.0001

DISCUSSION

In children with severe TBI, prolonged hyperglycemia beyond 48 hours is linked with a poor prognosis. We found a correlation between mean blood glucose concentrations and the frequency of episodes of hyperglycemia. Hyperglycemia and TBI outcomes may be linked, according to our study.But,

only a prospective research will be able to tell us whether or not adjusting blood glucose concentrations after a pediatric patient suffers a TBI improves their prognosis.

Early Hyperglycemia

Treatment for Traumatic Brain Injury may result in early hyperglycemia. For a long time, researchers have looked at serum glucose as a potential prognostic indicator following a traumatic brain injury. Serum glucose levels upon admission were shown to be a risk factor for poor outcomes in a number of retrospective studies (25-28, 36-37). At the 18-day, 3-month, and 1-year follow-ups of 59 persons with TBI, Young and colleagues found a link between admission hyperglycemia 200 mg/dl and poor outcomes (25). In 169 people with severe TBI, Lam and colleagues found a correlation between admission hyperglycemia and both outcomes and baseline GCS (36). While Yang found a correlation between high glucose levels early in the disease and a bad prognosis, he also found a link between elevated levels of the stress hormone catecholamines and a worse GCS score (26). Children who died from traumatic brain injury (TBI) were found to have higher admission glucose concentrations (267 mg/dl vs. 135 mg/dl) than those who survived (10). However, neither the mean nor the peak glucose concentrations allowed us to validate the link between early hyperglycemia and outcome. This finding might have been caused by a variety of factors relating to our patients and the treatment they get.In light of this, and in accordance with our strict methodology for withholding exogenous glucose, we decided to divide our epochs into early (the first 48 hours) and late (the 49th–169th hours). Although Young and others have shown a link between peak glucose concentrations at 24 hours and outcome, we have found no such link thus far (25). No correlation was seen between mean glucose concentrations and peak glucose concentrations in the early time period. Marton found a strong correlation between poor outcome and hyperglycemia in babies (under 12 months of age) during the first 24 hours after a traumatic brain injury (TBI) (12). According to our research, this is the first time a strategy of limiting or eliminating glucose delivery during the first two days following injury has been evaluated. For this lack of correlation between glucose and prognosis after TBI, additional research is clearly required.

Delayed hyperglycemia

In contrast to what we found in the first 48 hours after a TBI, we found that later hyperglycemia was linked to a bad outcome in children. These results are in line with previous research on adults (28). Patients with traumatic brain injury (TBI) who had hyperglycemia on days 3–5 had a worse prognosis than those who did not have it, according to Jeremitsky and colleagues (28). In a large cohort of TBI patients, Salim and colleagues found that chronic hyperglycemia (average daily blood glucose > 150 mg/dl) was linked with death with an OR of 4.91 [2.88 – 8.56](38). Chiaretti and colleagues found a link between hyperglycemia and worse outcomes in children with milder traumatic brain injury (OR = 1.55 [1.01 – 2.33]). (7). After 48 hours, we found a link high blood glucose (mean and peak) had an undesirable result in terms of outcome. This might have a number of therapeutic applications. After 48 hours of strict glucose administration control in our study and most others, we took a more relaxed approach. Improvements in glucose management and potential reductions in mortality and morbidity may result from a more precisely titrated glucose (and total nutrition) dosing routine.

Because of this, a precise glucose goal for individuals with TBI, including children, is still debatable. In our retrospective investigation, we were unable to address the critical issue of whether strict glucose management may enhance the outcomes of children who have had TBI. In light of these considerations, a well-designed experiment investigating precision glucose delivery and management for children with TBI is necessary in order to optimize neurological prognosis while limiting potentially crucial secondary effects. Our results are subject to a number of limitations. First and foremost, we did not apply a conventional methodology to regulate glucose or provide insulin beyond the first 48 hours, despite using a prospectively applied glucose regimen and a stringent treatment plan for elevated ICP. This retrospective evaluation could only identify whether exposure to insulin had an effect on outcomes, despite our attempts to obtain accurate temporal data about insulin treatment and glucose levels on all patients in this trial. Unfortunately, we can't tell whether insulin usage influenced our findings,since the study is aretrospective review, timing of insulin administration was not possible. Therefore, for all of the analyses of insulin within this paper, exposure to insulin during the study period was treated as a categorical variable.But we feel that further studies should be conducted to firmly address this issue and incorporate regular glucose testing protocols, as well as point-of-care testing and other approaches, in order to provide a clearer picture.

Leucocytosis

The cause for leucocytosis may be due to role of catecholamines and steroids. Catecholamines increase the leukocyte count by release of the marginated cells into the circulating pool whereas corticosteroids increase the neutrophil count by releasing the cells from the storage pool in the bone marrow into the blood and by preventing regress from the circulation into these tissues. In our study 30 patients (24.2%) had normal white blood cells (WBC) count (4000-11000/cc), whereas 94 patients (75.8%) had increased WBC counts. There was favourable outcome in patients with normal leucocyte count This reveals strong association with traumatic brain injury in our study. Yet the confounding factors such as lacerations and immunocompromise disease states were not taken into consideration as retrospectively the progress of other injuries could not be evaluated and further studies are required to make leucocytosis as a strong predictive factor.

CONCLUSION

For children with severe TBI, we discovered that prolonged hyperglycemia or late hyperglycemia - either as a daily average or during specified episodes is related by poor neurological outcomes. Children who have suffered severe TBI should have their blood sugar levels monitored not only for the first 48 hours but strict glucose monitoring is required to determine the best course of action for managing their glucose and nutrients, as well as long-term outcomes. In pediatric patients with head injury nearly 2/3rd of them have leucocytosis which is a predictive factor for poor outcome, early and prompt focus should be kept on leucocyte count and managed accordingly to make a good impact on pediatric patients with severe traumatic brain injuries.

RESULTS

S.No	Demographics	Value
1	Mean Age in years	6.9
2	Male	68 %
3	Female	32 %
4	Admission GCS, median (range)	6 (3, 8)
5	Admission ISS, median (range)	26 (10, 43)
6	Length of Stay (d), mean ± SEM)	12.5±1.8
7	GOS	2.25
8	Mortality (%)	18.4 %

Table 1: Patient demographic characteristics, GCS-Glasgow Coma Scale, ISS – Injury Severity Score, GOS-Glasgow Outcome Scale, SEM-Standard Error of Mean

Early period	Mean Glucose (mg/dl)	P Value
Gender		0.31
Female	139.7±39	
Male	131±27	
Insulin		0.07

Yes	143.4±31.7	
No	128±31.8	
Late period	Mean Glucose (mg/dl)	P Value
Gender		0.92
Female	123.8±32.9	
Male	123.1±22.9	
Insulin		0.01
No	114.4±17	

Table 2: Glucose and outcome when analyzed for mean concentrations in both time periods (Early – first 48 h; Late 49-168 h

EARLY	NG	MHG	SHG	P Value
	N=26	N=26	N=72	
Female (%)	8 (31 %)	10 (38 %)	22(31 %)	0.140
Male (%)	18 (69 %)	16 (62 %)	50(69 %)	0.165
Age (mean in years)	6.35	8.32	6.44	0.158
ISS	22.10	27.45	25.71	0.151
GCS (mean)	6.27	5.82	6.14	0.748
Insulin (%)	18.18	36.36	48.57	0.296
GOS	2.01	2.35	2.4	0.09
LATE	NG	MHG	SHG	P Value
	N=41	N=50	N=33	
Female (%)	17 (41.7 %)	13 (26.2%)	10 (30 %)	0.505
Male (%)	24 (59.3 %)	37 (74.8%)	23 (70 %)	0.550
Age (mean years)	5.57	7.32	7.96	0.232
ISS	24.71	26.38	26.19	0.660
GCS (mean)	6.52	5.94	5.71	0.201
Insulin (%)	14.29	47.37	68.75	0.003

Table 3: Univariate analysis of potential confounding variables between glucose and outcome (% with favorable outcome) when children were categorized into glycemic groups (Early – first 48 h; Late 49 – 168 h; normal (NG) – peak glucose < 150 mg/dl; mild hyperglycemia (MHG) – peak glucose ≤ 200 mg/dl; severe hyperglycemia (SHG) – peak glucose > 200 mg/dl). GCS-Glassgow Coma Scale,ISS – Injury Severity Score.

Variables	No of Patients	Mean GOS	P value
NG	26	2.0	0.0542
SHG	72	2.4	

Table 4 : Analysis of impact of Early SHG on Mean GOS as compared to Early NG, the P value calculation was done using Student t test

Variables	No of Patients	Mean GOS	P value
NG	26	2.0	0.116
MHG	26	2.3	

Table 5 : Analysis of impact of Early MHG on Mean GOS as compared to Early NG, the P value calculation was done using Student t test

Variables	No of Patients	Mean GOS	P value
NG	41	1.7	0.0001
SHG	33	3.1	

Table 6 : Analysis of impact of Late SHG on Mean GOS as compared to Late NG, the P value calculation was done using Student t test.

Variables	No of Patients	Mean GOS	P value
NG	41	1.7	0.005
MHG	50	2.0	

Table 7 : Analysis of impact of Late MHG on Mean GOS as compared to Late NG, the P value calculation was done using Student t test.

Variables	No of Patients	Mean GOS	P value
NG	30	1.7	0.0001
MHG	94	2.8	

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