Relationship between serum and csf glucose in subarachnoid hemorrhage

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ABSTRACT

Introduction: There has been considerable controversy regarding the effect of serum and cerebrospinal fluid (csf) glucose levels in the prognosis of aneurysmal subarachnoid hemorrhage (aSAH) patients.

Objective: We have explored the relationship between serum and csf glucose serum glucose levels in such patients and have also explored the levels of serum and csf glucose required to maintain a good outcome.

Methods: Retrospective review of 2000 aSAH patients, from a prospectively collected database of Thomas Jefferson University Hospital, was done. The Hunt-Hess (H-H) grade of the SAH, cerebral and serum glucose on admission, serum glucose on the day of surgery and 14 days post the surgery as well as the GOS-E score at discharge was noted. Parameters were analyzed individually for significance via contingency tables and significant parameters (p < 0.05) were further examined. Relationship between serum and csf glucose is established via Spearman's rank correlation coefficient.

Result: Correlation between csf and serum glucose at admission was found to be 0.52, it increased from HH grade 1-4 and then became negative but more tightly bound at HH5. Serum glucose higher than 151.58 mg/dl (95% confidence interval, 141.36- 160.63) and csf glucose higher than 77.83 mg/dl (95% confidence interval, 75.05- 80.61) was found to be associated with worse outcome. 95.57% of the patients, who had even a single event of hypoglycemia, have had a previous episode of hyperglycemia and fared badly. Csf glucose < 38 mg/dl also led to more deaths.

Conclusion: Serum and csf glucose bear a linear relationship in mild to moderate SAH. Incidences of hypoglycemia in aSAH patients are mainly due to the intensive insulin therapy to combat a hyperglycemic episode and results in worse outcome. Hence, serum glucose level of 80-140 mg/dl and csf glucose level of 38-75 mg/dl should be maintained in all aSAH patients.

Keywords: Aneurysmal subarachnoid hemorrhage, serum glucose, cerebral glucose, correlation, extended Glasgow outcome score.

Introduction

Every year approximately 30 000 people develop aneurysmal subarachnoid hemorrhage (aSAH), accounting for up to 3% of all strokes [1]. About 51% of the affected persons die in the first 30 days and one third of the survivors require lifelong care [2]. Hyperglycemia is a common problem in aSAH being reported since 1925 [3], and occurs in 70% to 90% of the patients [4]. Thus, treatment of persistent hyperglycemia has become an attractive management strategy to improve outcomes in patients with aSAH.

There is commendable volume of literature showing a significant association between persistent hyperglycemia and poor outcomes in different acute medical and surgical conditions [5-6]. In aSAH, hyperglycemia has been linked to development of clinical vasospasm [4], increased neurologic deficits [7], poor functional outcome and increased hospital stay [8]; while intensive insulin therapy has been shown to improve outcome [9-11]. But there has been little knowledge regarding the relationship between serum and csf glucose in such patients and the ideal range of these two that should be maintained in aSAH patients, surviving in the neuro-critical care unit, for a better functional outcome.

We have studied the relationship between serum and cerebrospinal fluid (csf) glucose on the day of admission in aSAH patients. We have also investigated ideal range of serum and csf glucose to be maintained in such patients by studying the effect of mean serum glucose levels on the day of admission and on the 14 days post the surgery on their outcome. We have also calibrated the effect of the degree of the SAH on the glycemic status of such patients.

Material and Method

We have retrospectively reviewed a prospectively collected database of SAH patients, to identify 2000 patients who were admitted in our institution from January 2006 to April 2010. The diagnosis of aSAH was established on the basis of conventional CT or CT/MR angiography. Patients who were admitted >72 hours after the onset of SAH were excluded from the study. The SAH grade at admission, the admission csf and serum glucose levels, serum glucose on the day of surgery and on 14 days following surgery as well as the GOS-E score at discharge were documented. Approval for the collection and review of data was obtained from the Institutional Review Board at the Thomas Jefferson University.

The severity of SAH was assessed by the Hunt-Hess (H-H) grade of the SAH. H-H grade ≤ 3 is considered as better and ≥ 4 as worse. The functional outcome of the patients was determined by the GOS-E score at discharge. GOS-E score ≥ 7 has been taken as a good outcome because it

denotes complete functional independence. GOS-E score was further dichotomized at 1 and 2-8 for death and survival respectively. Table I shows how we divided the GOS-E score.

Statistical Analysis

All data were analyzed using JMP 7.0.2, SAS Institute, Cary, NC. Chi square test was performed for rate vs. rate and logistic regression was used for rate vs. continuous variable or between 2 continuous variables. p values and 95% confidence were calculated and reported. Multivariate analysis was done to compare the effect of serum glucose, cerebral glucose and SAH grade with outcome. Inverse prediction from logistic regression was done to find out the maximum serum and csf glucose threshold level. Relationship between serum and csf glucose is established via Spearman's rank correlation coefficient.

Results

Among the 2000 patients in the study, 789 were males and 1211 were females. However the mean age of the females were 4 years less than that of the males. 899 (75.42%) patients had serum glucose > 140 mg/dl on admission; among them 20.48% had a good outcome compared to 64.85% of the patients who were not hyperglycemic (p < 0.0001).

Odds ratio for a poor outcome with per 1 mg/dl increase of the glucose level on the day of the admission was 1.015 (95% confidence interval, 1.013-1.017). Patients hyperglycemic at admission also had a higher risk of mortality (20.58%). Odds ratio for death with per 1 mg/dl increase of the glucose level on admission is 1.0175 (95% confidence interval, 1.015-1.02). Individuals having a serum glucose reading of > 200 mg/dl even once in the 2 weeks following the surgery had a 29.46% chance of a good outcome and 20.49% chances of death compared to a 65.4% chance of good outcome in those who did not have such a hyperglycemic episode (both *p* < 0.0001). The mean level of serum glucose in the period of 14 days post-surgery was 5.46 mg/dl higher in patients having a worse prognosis (GOS-E score \leq 6) than those having a good one (GOS-E score \geq 7).

Hypoglycemia was considered in patients having serum glucose < 80 mg/dl; it was prevalent in 13.25% of the patients. 5.7% of patients with hypoglycemia had a good outcome compared to 75.85% of those who had not (p < 0.0001). 48.10% hypoglycemic died compared to only 10.54% of those who did not have hypoglycemia (p < 0.0001). 95.57% of the hypoglycemic patients, have had a previous episode of hyperglycemia (serum glucose > 200 mg/dl), whereas only 72.73% of the non-hypoglycemic patients had even a single reading of serum glucose > 200 mg/dl. Hypoglycemic patients who did not have an occurrence of high serum glucose had better chances of prognosis, both in terms of chances of good outcome and mortality rates, than those who had a hyperglycemic patients with and without hyperglycemia. Figure II shows the distribution of hyper and hypoglycemia for the different H-H grades.

The csf glucose had an odds ratio of 1.087 (95% confidence interval, 1.078-1.096) for a poor outcome with per 1 mg/dl increase and an odds ratio of 1.048 (95% confidence interval, 1.041-1.055) for death per 1 mg/dl rise. However, csf glucose < 38 mg/dl also led to increased

mortality. Figure III and IV shows the relationship of the level of csf glucose with mortality and good outcome respectively.

Correlation between csf and serum glucose at admission was 0.52. Figure V shows the relation between serum and csf glucose. Figure VI shows the mean admission serum and csf glucose levels for each of the grades. The mean admission serum and csf glucose levels both increased with a rising H-H grade. While studying the relationship between serum and csf glucose for the individual H-H grades, it is found to be growing from Grade 1-4 (Spearman's ρ increases form 0.41 - 0.87). Csf glucose however unlike serum glucose was found independent of SAH grade in determining both good outcome and mortality.

As hyperglycemia and hypoglycemia were both found to be unfavorable to patient prognosis, inverse prediction was used to find out 50% chance of good outcome at the maximum serum glucose level and it was found to be 151.58 mg/dl (95% confidence interval, 141.36—160.63). Likewise, the 50% chance of good outcome at the maximum csf glucose level was found to be 77.83 mg/dl (95% confidence interval, 75.05—80.61).

Discussion

Hyperglycemia is a frequent finding in various types of brain injury (e.g. strokes) and may be associated with premorbid diabetic glucose metabolism [12] or a stress response [13, 14]. Many experimental studies have indicated that hyperglycemia may increase brain edema [5], inflammatory reaction [15], free radical injury [16] or apoptotic cell death after stroke [17], although nothing has been confirmed on human models. A recent study on glucose and ischemic stroke has shown that the viability of less perfused cerebral tissue is diminished by hyperglycemia [18], while another showed that permanent CSF diversion after aneurysmal SAH may be independently predicted by hyperglycemia at admission [19].

There have been several studies on the association between hyperglycemia and clinical outcome in SAH patients [4, 7, 8, 11, 20-28]. There is also considerable argument over the effect of hyperglycemia in the mortality of aSAH patients- with certain studies certifying its association with increased short-term mortality rates [25] and some others dismissing its link with hospital mortality [28]. However there has been little published literature regarding the role of csf glucose and its relation with serum glucose.

Also the debate on the ideal serum glucose level to be maintained in post-surgical aSAH patients, gets further fuelled up with the evidences of even moderate hypoglycemia being associated with associated with cerebral infarction, vasospasm, and worse functional outcomes [29]. There is also controversy regarding whether or not the adverse outcome with acute-phase hyperglycemia is mediated by cerebral glucose metabolism. One recent study showed that cerebral glucose increased at blood glucose levels > 140 mg/dl and is associated with bad prognosis [27], while a previous study had revealed that low cerebral glucose accounted for severe metabolic distress [26] as evidenced by increased levels of glutamate, glycerol and lactate: pyruvate ratio in micro-dialysate. We have recently published literature suggesting csf parameters, including csf glucose, giving the best prognostic results in their median values [30].

In our study we found out that hyperglycemia at admission or anytime during the first fortnight following the aSAH accounts for unfavorable patient outcome; for functional outcome as well as

mortality. Figure VII and Figure VIII shows mean glucose levels from day of admission through day 14 for poor and good outcome and for death and survival respectively. Poor functional outcome is shown to be accompanying higher serum glucose levels than good outcome. Death is found to be concomitant with fluctuating level of serum glucose, while those maintaining a more stable range tend to survive. Inverse prediction was used to find out 50% chance of good outcome at the maximum serum glucose level and it was found to be 151.58 mg/dl (95% confidence interval, 141.36—160.63).

Incidences of hypoglycemia in aSAH patients are associated with a previous incidence of hyperglycemia in 95.57% of the cases and hypoglycemic patients with prior hyperglycemia also had poorer outcome than hypoglycemic patients having no past episode of hyperglycemia or hyperglycemic patients having no occurrence of hypoglycemia. These made us conclude that hypoglycemia in SAH patients mainly arise due to the intensive insulin therapy given to combat a previous hyperglycemic episode. This questions the utility of intensive insulin therapy in aSAH patients. Hypoglycemia also illustrated a higher incidence in patients with poorer SAH grades, confirming its dependence with the degree of SAH in predicting patient outcome.

Csf glucose and serum glucose were found to be having a linear relationship with correlation coefficient being 0.52; the relationship becomes stronger from H-H grades 1 to 4 and then negative but more tightly bound at HH5. Increasing csf glucose indicated worse outcome and was found to be independent of the severity of the SAH. 50% chance of good outcome at the maximum csf glucose level was found to be 77.83 mg/dl (95% confidence interval, 75.05—80.61).

Our study has the limitations of being a retrospective analysis and not a prospective one, but it has been collected from a prospectively collected database. We have calculated the outcome score at 14 days post the surgery only and have not considered the outcome after 3 months of follow up in order to assess the long term mortality. Another limitation is related to not documenting the fact that whether the patients were baseline diabetic or not and there can be further research taking this aspect in account.

However unlike the previous studies, we included SAH cases admitted within 72 hours of onset only. Most of the previous studies either did not stated the time between onset of SAH and admission or were limited by an enrollment period that was too long. Long interval between the SAH and admission might explain the reason behind an independent association between glucose levels and poor outcome because clinical status can improve dramatically within 72 hours of SAH, whereas high glucose level on day 3 can still be a reflection of the severity of the SAH on day 1. Also we have the taken a large sample size to validate the study.

Conclusion

We conclude that, csf glucose although is related with serum glucose is not dependent on disease severity for predicting poor prognosis. Hyperglycemia on admission is associated with both the severity of the SAH and with poor outcome and overcorrection of a previous hyperglycemic episode is the commonest cause of hypoglycemia in SAH patients. Hence aSAH patients in neuro-critical care units should undergo a vigilant anti-hyperglycemic therapy where their serum glucose should be maintained between 80- 140 mg/dl and their csf glucose be sustained between 38-75 mg/dl.

Conflict of Interest: None.

References

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GOS-E Score	Categories	Division of Good and Bad Prognosis	Division of Death and Survival
1	Dead		DEATH
2	Vegetative State		
3	Lower Severe Disability	BAD	
4	Upper Severe Disability		
5	Lower Moderate Disability		
6	Upper Moderate Disability	PROGNOSIS	
7	Lower Good Recovery	GOOD	
8	Upper Good Recovery	PROGNOSIS	
			SURVIVAL

Table 1: The Extended Gla	asgow Outcome Scale (GOS-E) and the wa	v we dichotomized it.



Figure I: The rate of good outcome in hypoglycemic and non hypoglycemic patients with and without hyperglycemia.



Figure 2: The distribution of hyper and hypoglycemic readings for the different H-H grades



Figure 3: The relationship of csf glucose level with mortality.



Figure 4: The relationship of csf glucose level with good outcome.



Figure 5: The relation between serum and cerebral glucose.



Figure 6: Mean admission serum and csf glucose levels for each of the grades.



Figure 7: Mean glucose levels from day of admission through day 14 for poor and for good outcome, with 95% confidence interval.



Figure 8: Mean glucose levels from day of admission through day 14 for death and survival, with 95% confidence interval.