Effect of different levels of glucose in the dialysate on the risk of hypoglycemia during hemodialysis in diabetic patients

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ABSTRACT

Introduction: Hypoglycemia can occur during hemodialysis in diabetic chronic renal failure patients when using a dialysate without glucose. With dialysis solutions with glucose 90 mg/dL or more, this is preventable, but diabetic patients could present higher intradialytic glycemias. **Objective:** We tested a dialytic fluid with a lower level of glucose trying to prevent both hypo and hyperglycemia in these patients. **Methods:** Twenty diabetic individuals from our hemodialysis unit were submitted to 3 sessions with dialysis solutions with two different glucose concentrations - 55 mg/dL (Phase 55), and 90 mg/dL (Phase 90) - and a glucose-free one (Phase ZERO). Plasma glucose levels were measured at five moments during each session - before and at 30, 60, 90 and 240 min. Results under 70 mg/dL were considered as hypoglycemia. **Results:** Three patients presented 6 episodes of hypoglycemia in Phase 55, but no patient presented any episode in Phase 90. In Phase ZERO, five patients presented 7 episodes. **Conclusion:** This dialysate with a low level of glucose (55 mg/dL) did not prevent hypoglycemia episodes during hemodialysis in diabetic patients, these occurrences being similar to that when using a dialysate without glucose. The use of a 90 mg/dL glucose dialysis solution did not induce higher intradialytic glycemia levels than the other dialysis solutions.

Keywords: diabetes mellitus, hemodialysis solutions, hypoglycemia, kidney failure, chronic.

INTRODUCTION

Previous studies have reported that diabetic patients with chronic renal failure may have episodes of hypoglycemia (HG), usually asymptomatic, during hemodialysis sessions when dialysate without glucose is used.[1-8] These events tend to recur often,[1-6] and this recurrence has been identified as a cause for the absence of symptoms.[9] Furthermore, these recurrences may expose such patients to the risk of progressive cognitive impairment.[3,9-13]

The use of glucose-containing dialysis solutions significantly reduces the risk of HG episodes,[3,6,14] and currently, they are widely used. However, it was observed that a dialysate containing around 100 mg/dl of glucose causes average intradialytic blood glucose level higher than a glucose-free dialysate;[6,14] a similar finding was noted when comparing a dialysis solution containing glucose 200 mg/dl and another containing 100 mg/dl of glucose.[3,15]

In chronic renal failure diabetic patients on hemodialysis, hyperglycemia can be proinflammatory[16] and could obviously worsen glycemic control in the long term. There is some controversy on whether poor glycemic control in diabetic patients on dialysis may be related to higher mortality rates.[17-25] However, a recent study in a cohort of 54,757 diabetic patients on hemodialysis showed that poor glycemic control, can be related to a higher mortality, due either to cardiovascular or to any other causes.[26] Moreover, it is logical to assume that frequent episodes of hyper- and/or hypoglycemia during dialysis may be associated with a high long-term morbidity in these individuals.

Since previous studies on glucose-containing dialysates were performed with solutions containing glucose concentrations between 90 and 200 mg/dl,

this study was conducted to test whether a dialysis solution with a lower concentration of glucose can prevent HG during hemodialysis sessions in diabetic patients, but without producing blood glucose levels as high as those observed with other solutions richer in glucose.

Material and Methods

This was a randomized clinical trial conducted on 20 (58.8%) of the 34 diabetic patients being managed at the ULBRA Hemodialysis Unit. The following were the inclusion/exclusion criteria: age, minimum 18 years; receiving regular dialysis treatment for at least 2 months; not hospitalized (by any cause) in the past 30 days; and absence of any systemic infectious process at the time of the study. All patients agreed to participate.

The Ethics on Research Committee of the Lutheran University of Brazil (ULBRA), which adheres to the Declaration of Helsinki, approved the research project. An informed consent form was obtained from all patients.

All patients used some oral hypoglycemic medication or insulin. In our hospital, tests for glycosylated hemoglobin levels were not performed in diabetic patients on a regular basis, but monthly blood glucose levels obtained before a dialysis session had a reasonably average result, at 199.8 ± 77.7 mg/dl (mean ± standard deviation), for the 20 individuals in the month preceding the study. The patients had no change in their dietary habits or drug treatment, before or during the days of the study, since they were not previously informed of the dates of the study. During the sessions, none of them ingested any kind of food.

The study was conducted during 3 dialysis sessions a week apart from one another. In the first session, 4-hour hemodialysis was performed using a standard dialysis solution containing bicarbonate but not glucose (Glu ZERO). In the second week, the same procedure was performed, now with a dialysis solution containing glucose, added to obtain a final concentration of 55 mg/dl (Glu 55). Finally, in the third week, the patients underwent another dialysis session, with a standardized solution containing 90 mg/dl glucose. The dialysis sessions were conducted on Bellco Formula (Italy) or Gambro AK-95 (Sweden) equipment using polysulphone Fresenius (Germany) dialyzers, reprocessed and reused up to 12 times according to the stipulations of the Ministry of Health, Brazil. Two commercially available bicarbonate-containing dialysis solutions obtained from Salbego-Manifórmula (Porto Alegre, Brazil) were used - one glucose-free and another, containing 90 mg/dl glucose. For the present study, the manufacturer produced a special solution containing 55 mg/dl glucose. The serum glucose levels were measured for each patient immediately before starting hemodialysis and at 30, 60, 150, and 240 minutes (end of session) after the start of the session. Blood samples were collected from the dialysis line from the patient's circulation immediately before entering the dialysis circuit, one minute after reducing the blood pump flow to 100 mL/min in order to prevent recirculation through the vascular access. Another blood sample was also collected simultaneously from a peripheral vein from the non-fistulated arm, in order to measure the glucose level and compare its results with that obtained for the blood samples collected from the initial dialysis circuit (described above); this was to exclude the possibility of differences, which would be indicative of the recirculation of blood in the vascular access. This verification was performed on 37 occasions throughout the study (one for approximately every 7 sequential sampling of blood in the dialysis line).

Blood glucose level was measured using a spectrophotometer by the enzymatic method. HG was defined as a blood glucose value below 70 mg/dL, regardless of symptoms, as described previously.[1,6]

The researchers followed the patients closely to identify any signs or symptoms of HG during the dialysis sessions. Capillary blood glucose was measured using a glucometer in any situation suspicious for HG and, if blood glucose was < 70 mg/dL, the patient would be medicated according to our clinical protocols.

Bivariate statistical analysis was performed using the GraphPad InStat 3.05 software for Windows (GraphPad Software, San Diego, California USA). Fisher's test was used to compare categorical variables, and ANOVA or *Student's t* test was used for continuous variables. Statistical significance was set at $p < 0.05$.

Results

The age (mean and standard deviation) of the patients was 56.3 (11.9) years. They were on dialysis treatment for 56.3 months (mean), and 12 of them (60%) were male.

Table 1 shows the number of HG episodes (and mean blood glucose levels) at different stages of the study and at different time points in the dialysis session. In Phase ZERO, 5 patients had 7 episodes of HG; in Phase 55, 3 patients had 6 episodes; and finally, in Phase 90, no patient had any episode. Given that a total of 80 blood samples were obtained for glucose measurements (20 at each time point during the dialysis sessions, i.e., 30, 60, 150, and 240 minutes after commencement), the differences in the HG prevalence between Phase ZERO and Phase 90 (p = 0.0136, Fisher's exact test), as well as that between Phase ZERO and Phase 55 (p = 0.0284, Fisher's exact test) are noteworthy (Table 1).

Table 2 shows that there were no significant differences between the means of blood glucose levels in the different phases of the study, at any of the time points.

Table 3 shows that the glucose levels measured in blood samples from the arterial line of the extracorporeal circuit of hemodialysis did not differ from those measured in blood samples obtained simultaneously from a peripheral vein of the arm opposite to the vascular access in use; this result rules out the possibility for vascular access recirculation.

Discussion

The presence of glucose in hemodialysis solutions appears to greatly reduce the risk of intradialytic episodes of HG,[3,6,14] and it is being widely used since some years. Glucose-containing solutions offer other general beneficial effects, such as protection of erythrocytes,[27] low and stable blood pressure levels,[3,14] and improved stability of blood glucose levels during dialysis.[14] The optimum concentration of glucose in the dialysate has not been defined, but it can be assumed that it should be the minimum that could prevent HG.

In a previous study, we compared a dialysis solution containing 90 mg/dL of glucose to a glucose-free solution and observed frequent episodes of HG with the latter, and none with the former, but at the expense of significantly higher blood glucose levels in diabetic patients (average of 171 ± 106 *vs*. 136 ± 189 mg/dL; $p < 0.01$).[6] Sangill *et al.*[14] also found significant differences (but without such high values) when comparing dialysis solutions with and without glucose (125 ± 25 *vs*. 110 ± 26 mg/dL, respectively; $p < 0.001$). Simic-Ogrizovic *et al.*, in 2001,[3] as well as Ferrario *et al.*, in 2011,[15] compared 2 solutions containing glucose at 2 concentrations, namely, 100 and 200 mg/dL; both found higher blood glucose levels in the case of the latter solution. In the light of these findings, we sought to investigate whether a dialysate containing low glucose concentration would prevent both hypo and hyperglycemia.

Our experimental dialysis solution containing 55 mg/dL glucose, however, did not show results similar to the one containing 90 mg/dL glucose in preventing HG; 3 patients (15% of 20) developed 6 episodes of HG (7.5% for all dosages) during use. These data are comparable to those obtained with the use of the glucose-free dialysate (5 patients and 7 HG episodes) (Table 1). Furthermore, we did not find higher levels of blood glucose in patients treated with the dialysate containing 90 mg/dL glucose than in those treated with the other 2 solutions, one with 55 mg/dL of glucose and the other, glucose free (Table 2). This finding is contrary to that observed in our previous study,[6] which had motivated the current one. Since there was no difference in mean blood glucose levels of all patients at each time point in the dialysis session (including pre-dialysis) in any of the 3 phases of the study (Table 2), we can assume that the difference observed in our previous study may have been due to a bias, perhaps due to the presence of high levels of blood glucose before dialysis (not measured at that point) among the patients on the day of the study. Moreover, in our current study, we confirmed again that no episode of HG was observed in the 20 patients

Table 1 Measurement of hypoglycemia (HG) and average blood glucose levels at each time point of the dialysis session for the 20 patients in the 3 phases of the study

	Time point of measurement during the dialysis session	30 min	60 min	150 min	240 min	All
Phase ZERO	HG (n)	1	2	2	2	7[a]
	HG (average ± SD)	66.0	69.0 ± 0.0	42.0 ± 14.1	69.0 ± 0.0	63.7 ± 9.2
Phase 55	HG (n)	2	3	1	0	6[b]
	HG (average ± SD)	52.0 ± 9.0	57.7 ± 17.9	35.0		5.0 ± 15.4
Phase 90	HG (n)	0	0	0	0	0[a,b]

[a] p = 0.0136 (95% CI: 1.77-2.47); [b] p = 0.0284 (95% CI:1.76-2.43). Fisher test.

Table 2 Glucose levels in mg/dL (average ± SD; and median) at different dialysis time points, in the 3 phases of the study (for the 20 patients)

	Pre-dialysis	30 min	60 min	150 min	240 min	All
Phase ZERO	243.4 ± 101.8 (228.0)	170.8 ± 81.7 (148.5)	147.7 ± 68.0 (129.0)	146.1 ± 67.2 (144.5)	143.3 ± 64.7 (138.0)	170.2 ± 76.7 (157.6)
Phase 55	215.7 ± 108.3 (201.0)	170.0 ± 87.4 (157.0)	156.9 ± 72.8 (143.5)	165.4 ± 71.8 (156.0)	168.6 ± 58.7 (168.0)	175.3 ± 79.8 (165.1)
Phase 90	207.8 ± 113.7 (174.5)	166.5 ± 90.5 (132.0)	158.6 ± 79.3 (119.5)	158.6 ± 71.7 (130.0)	146.9 ± 61.9 (123.5)	167.7 ± 83.4 (135.9)
*p**	0.5529	0.9862	0.8807	0.6801	0.3814	0.7912

* ANOVA.

Table 3 Simultaneous measurements of glucose levels (mg/dL) in blood samples from the arterial line of the dialysis machine and from a peripheral vein of the arm opposite the vascular access

Blood samples	All (n = 37)	Phase ZERO (n = 16)	Phase 55 (n = 13)	Phase 90 (n = 8)
Peripheral vein (n = 37)	170.1 ± 75.1	162.1 ±75.2	176.5 ± 56.9	175.8 ± 105.4
Dialysis line (n = 37)	167.9 ± 70.2	158.2 ± 72.9	176.6 ± 56.1	173.1 ± 90.3
*p**	0.8968	0.8826	0.9857	0.9569

* *Student's t* test.

when using dialysate with 90 mg/dL glucose, as described in previous studies using similar concentrations of glucose,[1,6] thereby reinforcing the importance of the use of such solutions.

On the other hand, the occurrence of 7 HG episodes (8.8% of all 80 cases of HG) in 5 patients (25% of all 20) when glucose-free dialysate was used is a result similar to that observed in our previous study, where we recorded HG episodes in 11.9% of all cases of HG and 23.8% of the patients[6] treated using glucose-free solutions, whereas Jackson *et al.* found HG in 33% of their patients,[1] all asymptomatic and occurring at all times of the dialysis session.

Finally, the blood samples collected from the extracorporeal circuit of the dialysis system can lead to errors in the case of recirculation in the vascular access, as reported previously.[28] However, when the collection is done with proper care, as described above, this simple method can be useful and reliable, as shown by our results (Table 3).

The small number of patients, the absence of information on glucose metabolism, variations in the prescriptions for the treatment of diabetes, and different ranges of time of dialysis in relation to mealtimes and schedule of insulin administration (when in use) are all factors that may have influenced our results; they are, therefore, the limitations of our study. However, the fact that this study was conducted under the day-to-day clinical conditions implies that it can be interpreted as reflecting the daily reality of the dialysis treatment of these patients.

In conclusion, our results suggest that a reduced concentration of glucose (55 mg/dL) in the HD solution seems to be ineffective in preventing HG in chronic renal dialysis patients with diabetes; our findings also confirm and reinforce the importance of the presence of glucose at a concentration of 90 mg/dL in the dialysate as suitable for preventing intradialytic HG.

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