

Comparison of Effects of the Hypoglycemia Management Protocol with 40% Dextrose Concentrated Solution to the Post-correction Blood Sugar Response through Intravenous Infusion and Intravenous Bolus

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Abstract

Hypoglycemic patients who receive 40% dextrose (D40%) concentrated solution in the correction process need to avoid excessive blood glucose spikes. Administration of D40% was found in two different ways, through intravenous infusion (iv infusion) and intravenous bolus (iv bolus) and the effects of both types of administration were unknown. The purpose of this study was to compare the effect of a hypoglycemia treatment protocol using D40% concentrated solution to the post-correction blood sugar response through iv infusion and iv bolus at two different hospitals with two distinct protocols. This comparative analytical cross-sectional study was conducted retrospectively at St. Carolus Hospital (D40% iv infusion group) and Bella Hospital (D40% iv bolus group). Blood glucose responses, in form of coefficient of variation and degree of overcorrection, were compared between groups. The overall median blood glucose response was 69.5 (3–195) mg/dL for iv infusion group (n=60) and 77 (15–249) mg/dL for iv bolus group (n=62) (p=0.259). The coefficient of variation with iv infusion and iv bolus group were 47.18% and 52.75%, respectively. The median of degree of overcorrection in iv infusion group was lower compared with iv bolus group, 10% (0–138%) versus 23% (0–195%), respectively. Both D40% protocols did not have a significant correlation with the degree of overcorrection (Mann-Whitney test; p=0.099). D40% iv infusion and bolus administration had no effect to the post-correction blood sugar response.

Keywords: Blood glucose, dextrose 40%, hypoglycemia, intravenous bolus, intravenous infusion

Perbandingan Efek Protokol Manajemen Hipoglikemia dengan Larutan Pekat Dekstrosa 40% secara Intravena Infus dan Intravena Bolus terhadap Respon Gula Darah Pascakoreksi

Abstrak

Pasien hipoglikemia yang menerima larutan pekat dekstrosa 40% (D40%) dalam proses koreksinya perlu menghindari lonjakan gula darah yang berlebih. Cara pemberian D40% diberikan dengan dua cara yang berbeda yaitu melalui intravena infus (iv infus) dan intravena bolus (iv bolus), dan efek dari kedua jenis pemberian tersebut belum diketahui. Tujuan dari penelitian ini adalah membandingkan efek protokol manajemen hipoglikemia dengan larutan pekat D40% secara iv infus dan iv bolus terhadap respon gula darah pascakoreksi di dua rumah sakit dengan protokol yang berbeda. Penelitian analitik komparatif secara potong lintang ini dilakukan secara retrospektif di RS St. Carolus (kelompok iv infus D40%) dan RS Bella (kelompok iv bolus D40%). Respon gula darah, dalam bentuk koefisien variasi dan derajat overkoreksi, dibandingkan antara kedua kelompok. Median kenaikan gula darah pada kelompok iv infus D40% 69,5 (3–195) mg/dL (n=60 pasien) dan kelompok iv bolus D40% 77 (15–249) mg/dL (n=62 pasien) (p=0,259). Koefisien variasi dengan iv infus adalah 47,18% dan iv bolus 52,75%. Median derajat overkoreksi iv infus D40% lebih rendah dibandingkan iv bolus D40%, dengan masing-masing 10% (0–138%) dan 23% (0–195%). Kedua cara pemberian D40% tidak memiliki hubungan yang bermakna dengan derajat overkoreksi (uji *Mann-Whitney*; p=0,099). Pemberian iv infus dan bolus D40% tidak memiliki pengaruh terhadap respon gula darah pascakoreksi.

Kata kunci: Dekstrosa 40%, gula darah, hipoglikemia, intravena bolus, intravena infus

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Introduction

Both glucose spikes^{1,2} and blood glucose fluctuation³⁻⁵ have been proven through a series of studies to be capable of increasing oxidative stress and more dangerous than the conditions of persistent hyperglycaemia. It is therefore necessary for finding hypoglycaemia treatment protocol that is not only to ensure hypoglycaemia resolution, but also to avoid excessive post-correction blood sugar response. Hypoglycaemia treatment protocol endorsed by The Indonesian Society for Endocrinology (Perkumpulan Endokrinologi Indonesia or PERKENI) was to give 20% dextrose (D) as much as 50 mL (if forced, D40% can be given as much as 25 mL), followed by D5% or D10% infusion.⁶ In fact, there are two different ways found in giving D40%, as the only dextrose concentrated solution available in Indonesia, to hypoglycaemic patients, through intravenous (iv) infusion and bolus. The recommendation differs from the latest guideline by Joint British Diabetes Societies, that is to give 75–100 mL of D20% for 15 minutes.⁷

The search of previous literature showed various potential strategies in optimizing the management of hypoglycemia. Experimental research by Moore *et al.* compared the use of 10% and 50% dextrose solution for treatment of hypoglycemia in pre-hospital setting. There was no difference in time to reach full awareness with the two types of solution.⁸ A subsequent research conducted by Kiefer *et al.* (2014) proved that the use of D10% in the management of hypoglycemia had little or no short-term decay in subsequent blood glucose values.⁹ As it has been known that the speed of giving dextrose solution also needs to pay attention to the body's ability to carry out the oxidation process,¹⁰ we could then hypothesize that by giving D40% at a slower rate, that is through iv infusion, there would be less glucose spike while still achieving the resolution of hypoglycaemia. This study

aims to compare the effect of a hypoglycemia treatment protocol using D40% concentrated solution to the post-correction blood sugar response through iv infusion and bolus at two different hospitals with two distinct protocols in Indonesia.

Methods

This was a comparative cross-sectional study conducted at St. Carolus Hospital (D40% iv infusion group) and Bella Hospital (D40% iv bolus group). This study had been ethically approved by Research Ethic Committee from Faculty of Medicine Universitas Indonesia (10343/UN2.F1/ ETIK/2018).

Adult patients were included if they were admitted to the emergency department (ED) or inpatient wards with hypoglycemia receiving D40%. For iv infusion group, D40% must be diluted with NaCl 0.9% to ensure the same amount of dextrose given between groups. Dilution with NaCl 0.9% resulted in less concentrated dextrose solution. Hence, it was acknowledged that the solution was no longer 40% in concentration, but the total amount of dextrose given, 20 grams, was still the same between the compared groups. Patients were excluded if admitted for diabetic ketoacidosis, hyperosmolar hyperglycemic state, currently in pregnancy, and suffered from refractory hypoglycemia. A review of the electronic medical record was done between January 2016 and December 2018 for iv infusion group and between January 2014 and December 2018 for iv bolus group. Patient information collected included age, sex, use of D10% after initiation of D40%, time to recheck blood glucose, use of insulin, insulin secretagogue, other oral antidiabetic drugs (OAD), chronic kidney disease (CKD), liver disease, and status of recurrent hypoglycaemia, and were assessed as confounders. CKD was defined as creatinine >2 mg/dL within 24 hours up to the time of the event or requiring ongoing

dialysis or diagnosis of with CKD stage III, IV, or V on the medical record. Liver disease was defined as diagnosis of cirrhosis or acute fulminant hepatitis on the medical record.

The primary outcome was blood glucose response, in form of coefficient of variation and degree of overcorrection. The coefficient of variability defined as standard deviation/mean blood glucose and the degree of overcorrection defined as (first blood glucose value after treatment-100 mg/dL)/100. Using a conservative estimate of the confidence interval, we chose to target 120 patients (60 patients per group) to provide us with a 95% confidence level and confidence interval of $\pm 5\%$. For statistical analysis, data that did not have parametric distribution were analyzed using a Chi-Square test, Fisher's exact test, or Mann-Whitney U test as indicated. Confounding variables were analyzed via multivariate logistic regression. All statistical analysis was conducted via IBM SPSS.

Results

A total of 70 patients who received iv infusion D40% and 74 patients who received iv bolus D40% were eligible for the study inclusion (Figure 1). Further matching of variable of time to recheck blood glucose (1st; 1.5th; 2nd hour) was done on both groups. The management of hypoglycaemia using D40% concentrated solution varied between subject in this study. The use of D40% varied from 10, 20, 30, and 40 grams of dextrose. This study used 20 grams of D40% data as the majority data to be processed statistically. It was notable that for the iv infusion group, the concentration of dextrose given was no longer 40% due to dilution with 0.9% normal saline. The term D40% iv infusion was still used to depict the same amount of dextrose given between compared groups, that was 20 grams of dextrose.

As a result, 122 patients were included for final analysis. Baseline patient characteristics

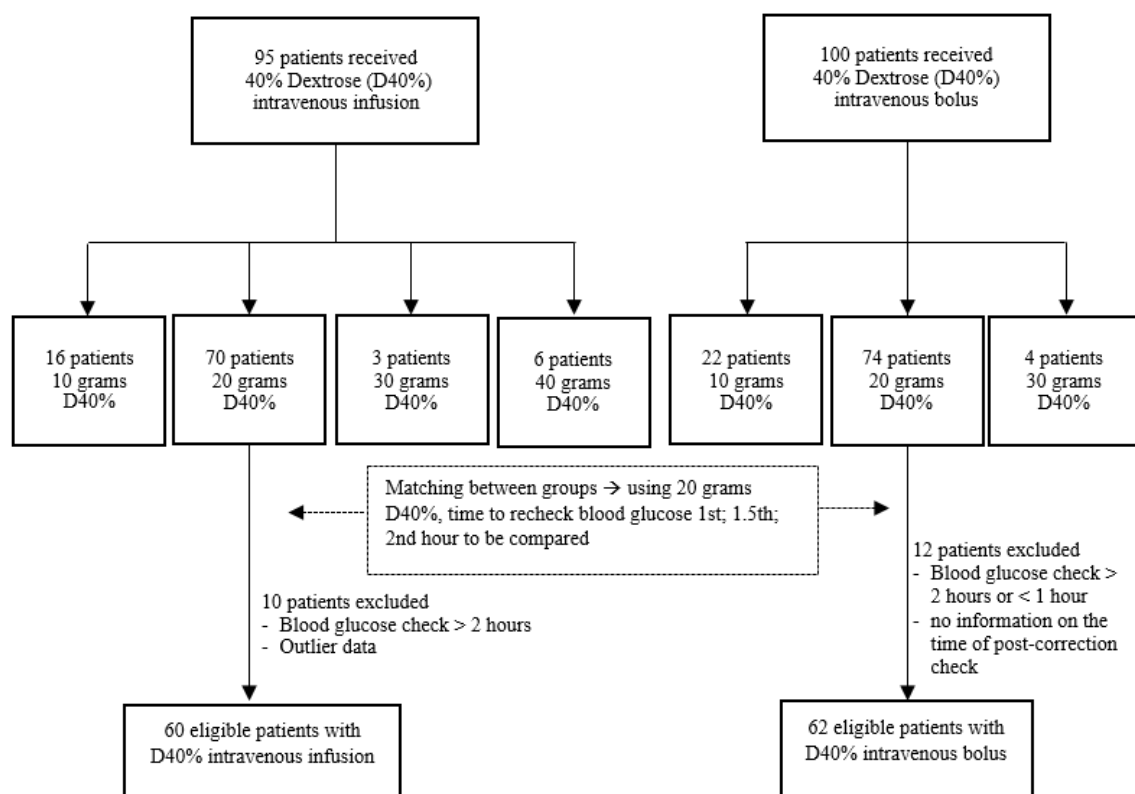


Figure 1 Patient Selection

Table 1 Patient Characteristics

Characteristics	Category	D40% Intravenous Infusion (n=60)	D40% Intravenous Bolus (n=62)	p-value
Age	Adult (18–<60 years)	13	25	0.026
	Geriatric (>60 years)	47	37	
Sex	Male	30	26	0.468
	Female	30	36	
D10% Infusion	Not using D10% infusion	45	17	<0.001
	Using D10% infusion	15	45	
Time to Recheck	2 hours	21	16	0.453
	1.5 hours	8	12	
	1 hour	31	34	
Insulin	Not using insulin	40	51	0.048
	Using insulin	20	11	
Insulin Secretagogue	Not using insulin secretagogue	31	24	0.203
	Using insulin secretagogue	29	38	
Oral Antidiabetics (OAD)	Not using OAD	41	29	0.018
	Using OAD	19	33	
Diabetes Mellitus (DM) Status	No DM	6	4	0.475
	DM	54	58	
Chronic Kidney Disease (CKD)	No CKD	23	34	0.073
	CKD	37	28	
Liver Disease	No liver disease	56	60	0.38
	Liver disease	4	2	
Recurrent Hypoglycemia	No recurrent hypoglycemia	49	47	0.429
	Recurrent hypoglycemia	11	15	

Note: n=number of patients; Diabetes mellitus (DM) status=type 2 DM; Chronic kidney disease (CKD)=creatinine >2 mg/dL within 24 hours up to the time of the event or requiring ongoing dialysis or diagnosis of with CKD stage III, IV, or V; Liver disease=cirrhosis or acute fulminant hepatitis; Recurrent hypoglycemia=history of hypoglycaemia prior to the event

were presented on Table 1. The majority of patient in both groups were diabetics (54 patients iv infusion vs 58 patients iv bolus, 90% vs 93.5%). All those diabetics were type 2 DM since no type 1 DM was found in this study. Length of iv infusion in this study was 15 minutes, as it was the protocol of using D40% in St. Carolus Hospital.

The majority of patient in this study were given D10% infusion following D40%. Patients with D10% were given before D40% were excluded. Iv D40% infusion at St. Hospital Carolus was not given at the same time with D10%. It was written in the medical

record that D10% infusion was installed after the D40% infusion was used up. The infusion drip of D10% in each patient in both hospitals varied, consisting of D10% per 8 hours and per 12 hours, with the decision to terminate infusion depending on blood sugar testing in the following hours. The glucometer used by each hospital is different, with Terumo® at St. Carolus Hospital and Accucheck® at Bella Hospital.

The endpoint comparisons were presented in Table 2. The difference or increase in blood sugar before and after correction was expressed as change in blood glucose (change in BG).

Table 2 Endpoint Comparison

	D40% Intravenous Infusion (n=60)	D40% Intravenous Bolus (n=62)	p-value
Change in Blood Glucose [median (min-max)]	69.5 (3–195)	77 (15–249)	0.259 ^a
Coefficient of Variation	47.18%	52.75%	
Degree of Overcorrection [median (min-max)]	10% (0–138%)	23% (0–195%)	0.099 ^a

Note: n=number of patients; a=Mann-Whitney test; Change in blood glucose=difference in blood sugar before and after correction with D40% (mg/dL); Coefficient of variation=standard deviation/mean blood glucose (%); Degree of overcorrection=(first blood glucose value after treatment – 100 mg/dL)/100 (%); for hypoglycaemic value that was less than 100 mg/dL posttreatment, the degree of overcorrection was expressed as a value of 0

The overall median of change in BG was 69.5 (3–195) mg/dL for iv infusion group (n=60) and 77 (15–249) mg/dL for iv bolus group (n=62) (p=0.259). The change in BG also became the basis for calculating the coefficient of variation. The coefficient of variation with iv infusion and iv bolus group were 47.18% and 52.75%, respectively. The degree of overcorrection was calculated if post-correction blood glucose exceeded 100 mg/dL. If the patient's post-correction blood sugar did not exceed 100 mg/dL, then the degree of overcorrection was expressed as a value of 0. The median of degree of overcorrection in iv infusion group was lower compared with iv bolus group, 10% (0–138%) versus 23% (0–195%), respectively. The degree overcorrection in these patients was also defined categorically and then analysed the proportion and relationship between the way of administering D40% and overcorrection of blood sugar by Chi-Square test. This analysis was as shown in the Table 3. The proportion of the prevalence of blood sugar overcorrection in the iv bolus group was 45/62 (72.6%) vs iv infusion group was 38/60 (63.3%). The risk of patients in the iv bolus group to

experience blood sugar overcorrection was higher compared to the iv infusion group, with prevalence ratio (PR) of 1.15 and 95% CI 0.896–1.465. Statistically by Chi-square test, the incidence of blood sugar overcorrection between groups did not differ significantly, with a p-value=0.274.

Discussion

To the best of our knowledge, this is the first study which compares the effect on D40% administration, intravenous infusion and bolus, to blood sugar response in hypoglycaemic patients. The time to recheck blood sugar in this study was not the same as the recommendation of PERKENI, which was 15 minutes after correction.⁶ Time to recheck blood glucose in this study was carried out varied at the 1st hour, 1.5th hour and 2nd hour. The retrospective study by Bilhimeret *et al.* at University of Rochester Teaching Hospital provided an overview of the management of hypoglycemia in the ED.¹¹ The median time for blood sugar examination after intravenous bolus administration of 50% dextrose solution was 22 (IQR 8–44) minutes. The time of rechecking might also depend on

Table 3 Proportion of Overcorrection Events

Variable	D40% Intravenous Bolus (n)	D40% Intravenous Infusion (n)	PR (CI 95%)	p-value
Overcorrection	45	38	1.15	0.274 ^a
Without overcorrection	17	22	(0.896–1.465)	

Note: n=number of patients; a=Chi-Square test; PR=prevalence ratio; CI=confidence interval

the bustle of the staff. Therefore, it could be understood that difference in rechecking time would occur anywhere else.

Previous study examining serum glucose changes after administration of D50% in diabetic patients admitted to ED varied from 37 to 379 mg/dL.¹² The median change in BG in this study was 69.5 mg/dL and 77 mg/dL the iv infusion group and iv bolus group, respectively. Dextrose infusion rate needs to consider the rate of glucose oxidation. Dextrose's oxidation can be reduced in patients with hypermetabolic conditions, patients with diabetes, elderly patients, and interaction with concurrent medications.¹³ Most of the studied patient population was diabetics, yet we did not find any difference regarding their blood sugar response compared to non-diabetics. No difference was also found between elderly in comparison with adult patient population. Result of this comparative study was unable to explain the correlation between D40% rate of administration to blood sugar response. We could only state that the variability of glucose rise was less in iv infusion group, while change in BG was not statistically different between groups.

This study tried to find better protocols to reduce blood sugar spike. The term degree of overcorrection, with a threshold of 100 mg/dL, was used to describe an increase in post-correction blood glucose regardless of the initial blood sugar value at the time of hypoglycaemia. The limit of 100 mg/dL was based on previous study by Murthy *et al.*¹⁴ The study provided an overview of the blood glucose response by administering D50% in critically ill patients receiving insulin infusion. A total of 49% of patients experiencing an increase in blood glucose above 100 mg/dL post-correction indicated a high glycemic variability. The smaller the degree of overcorrection in the iv infusion or bolus D40%, the smaller the blood sugar spike that occurred. Patient factors such as age, sex, use of D10% after initiation of

D40%, time to recheck blood glucose, use of insulin, insulin secretagogue, other OAD, CKD, liver disease, and status of recurrent hypoglycaemia were found to have minimal impact to blood sugar response. This finding was in an agreement with previous study by Arnold *et al.*¹⁵

Non-significant differences in post-correction blood sugar response from administration of D40% iv bolus and infusion in this study can be caused by the small number of samples. The preference for using D40% concentrated solution for the management of hypoglycaemia at this time is by iv infusion for 15 minutes until proven through further research. The use of iv infusion by diluting D40% in NaCl 0.9% also decreases the osmolality of the infusion, providing safer method for peripheral vein administration. The latter was the reason for the studied hospital to use different protocol as it was recommended by PERKENI.

Our study has noted limitations. We did not quantify the amount of D10% received after D40% administration. This might lead to unforeseen variability in subsequent serum glucose levels. The glucometer used between groups were also different, that might affect the blood glucose readings. However, both hospitals provided the evidence of routine calibration of the glucometers to ensure the validity of the blood glucose readings. Due to retrospective nature of this study, we were unable to relate the pharmacokinetics profile from insulin, insulin secretagogue, and OAD to blood sugar response, as the data of last time the patient took the medicine were unavailable. Other concurrent medications used by subjects of this study were not also considered.

Conclusions

D40% iv infusion and bolus administration had no effect to the post-correction blood sugar response. Further prospective study may

address any bias issues in this study.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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