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Low dose versus standard dose Insulin infusion therapy in Pediatric Diabetic Ketoacidosis - A Randomized Clinical Trial

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Abstract

Introduction: Diabetic ketoacidosis (DKA) in pediatric patients is a serious complication and the search for the perfect dose of insulin which will correct the metabolic derangements optimally without side effects like cerebral edema, hypoglycemia and hypokalemia is still ongoing.
Material and Methods: The present study was done in pediatrics department of Govt Medical College Amritsar, Punjab over one year. Study design was randomized control trial. Patients with DKA were enrolled after they had received rehydration fluid in first hour and randomized to two groups with one receiving insulin at standard dose (SD) of 0.1 U/kg/hr and other group receiving low dose (LD) at 0.05 U/kg/hr. Rate of fall of blood glucose (BG) and the incidence of therapy related complications were recorded.
Results: The mean (S.D.) rate of BG decrease, until a level of 250 mg/dL or less was achieved, was 47.21 (15.35) mg/dL/hr in the LD group & 47.51 (10.72) mg/dL/hr in the SD group. The mean (S.D.) time taken for the BG to fall to ≤ 250 mg/dL was 6.04 (2.44) hours in the LD group & 5.88 (1.76) hours in the SD group. Difference in incidence of hypoglycemia, hypokalemia, cerebral edema and other side effects were statistically insignificant between two groups
Conclusions: LD insulin and SD insulin were comparable in terms of management outcomes in DKA. Though the difference didn't reach statistical significance, the incidence of therapy related hypoglycemia and hypokalemia is higher in the SD group.

Keywords: DKA, LD insulin and SD insulin, hypoglycemia and hypokalemia.

Introduction

Type 1 Diabetes Mellitus (T1DM) accounts for 10% of all diabetes and affects approximately 15 million people in the world. Diabetic ketoacidosis (DKA) is a severe complication of pediatric diabetes. Overcoming hyperglycemia & dehydration is the major goal in the management of DKA. Fluid correction and insulin therapy are therefore the cornerstones of management.[1] The current standard of care in management of DKA is to start insulin infusion, without a bolus, at the rate of 0.1 U/kg/hr.[2] Previously, insulin bolus & very high dose of insulin(1 U/kg/hr) were being used for the treatment of DKA. Insulin bolus was identified as a risk factor for cerebral edema.[3] Various studies were conducted in 1970s & 80s, which proved that lowering the dose of i/v insulin infusion to 0.1 U/kg/hr reduces the incidence of therapy related hypokalemia & hypoglycemia. Kitabchi et al, in 1976, demonstrated in their study that low dose intramuscular insulin therapy is as effective as high dose insulin therapy by i/v or subcutaneous routes, but is without the risk of hypoglycemia and has a reduced incidence of hypokalemia.[4] Similar results were concluded by Burghen GA et al in 1980, who compared i/v 1 U/kg/hr with 0.1 U/kg/hr, the latter dose was proven to have reduced potential for hypoglycemia and hypokalemia.[5] Fort P et al, in 1980, concluded that initial i/v bolus was not desirable in DKA treated by continuous i/v insulin infusion of 0.1 U/kg/hr.[6] After these studies, high dose insulin became obsolete & the continuous i/v insulin infusion at 0.1 U/kg/hr became the standard of care in management of DKA.

In the recent years, various studies have compared still lower dose of insulin at 0.05 U/kg/hr against the current standard dose. The results of these studies have been encouraging, since the efficacy of LD therapy has been similar to that of the SD. The gentler electrolyte shift with the lower dose might carry a lower risk of therapy related hypoglycemia, hypokalemia & cerebral edema. In 2010, Puttha et al concluded that LD (0.05 U/kg/hr) is equally effective as SD (0.1 U/kg/hr) i/v insulin infusion for the initial treatment (<6 hours) of DKA in children with T1DM, both in terms of fall in BG as well as rise in pH.[7] Noyes et al observed that insulin doses of 0.03 to 0.05 U/kg/hr could adequately normalise the ketosis in DKA.[8]In 2012, Kapellen T et al compared the treatment of DKA with two different regimens (0.025 vs 0.1 U/kg/hr).[9] In their study they found that low dose insulin substitution was as safe as the recommended standard dose with respect to the occurrence of acute complications, namely hypoglycemia, hypokalemia & cerebral edema. In India, Nallasamy et al in 2014 found similar efficacy of LD with SD insulin infusion therapy.[10] Additionally, in the developing economies like ours, the children with DKA are expected to be more benefitted with a lower dose of insulin than their western counterparts because associated comorbidities such as malnourishment, carry a high risk of therapy related hypokalemia & hypoglycemia in these children.[11,12] Hence, we planned this trial to compare the efficacy as well as safety profile of LD with the SD insulin infusion in treatment of patients with DKA.

Materials and Methods

This randomized control trial was conducted in the department of Pediatrics, Bebe Nanki Mother & Child Care Centre, Amritsar. Aim of this study was to compare the rate of decrease in BG until a level of 250 mg/dL or less is reached and time taken to achieve this target, and to compare the episodes of treatment failures, and incidences of hypokalemia and hypoglycemia between the low dose and standard dose Insulin therapy.

The study was conducted after taking permission from Ethics and Thesis Committee, Government Medical College, Amritsar. The study was conducted on 50 children from 1st March 2016, through July 31st 2017. All children who were of 12 years of age or younger, who presented with DKA, were screened. DKA was defined as hyperglycemia, with BG >200 mg/dL & acidosis with venous pH <7.3 and bicarbonate <15 mEq/L.[13] The eligible children were enrolled at 1 hour of admission, after they had received the rehydrating fluid during the first hour. Written informed consent was taken from the parents or guardians of the eligible children prior to enrolment. Inclusion criteria were Age 12 years or less, BG > 200 mg/Dl, Venous pH < 7.3, Venous HCO_3^- < 15mEq/L. Children with symptomatic cerebral edema, septic shock, anuria for longer than 6 hours ,children who had already taken insulin therapy just prior to admission and of age more than 12 years were excluded.

Randomization of the participants into the LD and SD groups was done using sequentially numbered opaque sealed envelopes (SNOSE).[14] We combined the 25 sealed 'Low dose' envelopes with the 25 sealed 'Standard dose' envelopes and shuffled them very thoroughly. Next, we piled up all the envelopes together. A random number sequence, of numbers 1 to 50, was obtained from internet, using website www.random.org. This random number sequence was used to label the front of each envelope, from top to bottom. These envelopes were then arranged numerically in ascending order from 1 to 50 and placed into a plastic container. The assignment of the 50 enrolled patients to either group was done by opening the sealed envelope. The first enrolled patient in our study was given the envelope numbered '1', the second was given '2', and so on. Sixty one patients were screened during the period of our study, out of which 11 were excluded. Amongst the excluded children, 7 had symptomatic cerebral edema at the time of admission, 3 children had anuria for more than 6 hours & 1 had already taken insulin therapy prior to admission in our hospital. The remaining 50 patients were enrolled to the study.

Intervention:

Insulin therapy was started at 2nd hour of admission, as a continuous i/v infusion, using an infusion pump. The LD group was given regular insulin at 0.05 U/kg per hour, whereas the SD group was given insulin at 0.1 U/kg/hour. The rates of reduction of BG (until 250 mg/dl or less), from the start of insulin therapy, and time taken to achieve this target BG; as well as the incidences of hypokalemia, hypoglycemia & treatment failure, were compared in the two groups. It is important to note that reduction in BG taking place prior to start of insulin infusion was not included in our outcome. Patients were managed as per the Department's protocol for DKA. Glucose was added to the rehydrating fluids, as 5% solution, if BG was < 300 mg/dL & as 10% solution, if BG reduced to <200 mg/dL. Tapering of insulin infusion was considered if the BG continued to fall despite addition of glucose in the rehydrating fluids. Addition of KCl (40 mEq/L) was done to the rehydrating fluids, in order to maintain the serum potassium levels between 3.5 and 5.5 mEq/L. Insulin infusion was continued until DKA resolved (defined with total CO_2>15 mEq/L; pH >7.30; sodium stable between 135 and 145 mEq/L; no emesis[2]) and thereafter the child was shifted to subcutaneous regular insulin with an overlap of 30 minutes. Capillary BG was checked hourly and hypoglycemia was defined as BG level below 60 mg/dL.[10] Serum electrolytes, urea and creatinine were repeated every 4 hourly. Fluid intake, urine output & vital parameters were monitored continuously. Children were assessed neurologically every two hourly, for development of signs of cerebral edema. Hypokalemia was defined as a serum potassium level less than 3.5 mEq/L and/or suggestive electrocardiographic changes. Treatment Failure was defined as failure to achieve a BG reduction of 18 mg/dL/hr for two consecutive hours.[10] Data was analyzed using appropriate statistical tools and methods, including intention to treat analysis.

Results

The study was conducted in the Department of Pediatrics, Government Medical College & Hospital, Amritsar. The eligible children were enrolled at one hour of admission, after they had received the rehydration fluid during that hour. Insulin therapy was started at the second hour of admission, the LD group was given regular insulin infusion at 0.05 U/kg/hour, and the SD group was given insulin at 0.1 U/kg/hour. The following observations were recorded pertaining to the study. Table 1 shows the baseline characteristics of the two study groups.

Table 1: Baseline characteristics of study population

Parameter (at admission) {Mean,S.D.}	Low Dose Group	Standard Dose group	Chi squared; dF OR Difference bw means (95% CI)	p Value
Male: Female	5 (20%): 20 (80%)	13 (52%): 12 (48%)	$x^2 = 5.555$; df = 1	0.018
New onset T1DM	11(44%)	10 (40%)	$x^2 = 0.082$; df = 1	0.774
GCS <8	1(4%)	0 (0%)	-	-
Dehydration	11 (44%)	5 (20%)	$x^2 = 3.308$; df = 1	0.068
Malnutrition	10 (40%)	9 (36%)	$x^2 = 0.0849$;df = 1	0.770
Mean venous pH	7.07 (0.13)	7.15 (0.11)	-0.08 (-0.14 to -0.011)	0.023
Mean Venous CO2	14.1 (4.51)	12.7 (3.1)	1.35 (-0.85 to 3.55)	0.22
Severe DKA	12 (48%)	9 (36%)	$x^2 = 1.120$; df 2	0.570
Mean BG (mg/dl)	576.72 (103.21)	573.88 (79.24)	2.84 (-49.48 to 55.16)	0.91
Mean venous HCO_3^-	9.08 (4.77)	10.26 (4.19)	-1.18 (-3.73 to 1.37)	0.35
Mean Na^+ (mEq/L)	133.44 (5.51)	132.71 (5.95)	0.73 (-2.53 to 3.99)	0.65
Mean Eff. osmolality (mOsm/kg)	298.93 (11.82)	297.27 (13.29)	1.66 (-5.49 to 8.81)	0.64
Mean K^+ (mEq/L)	4.23 (0.91)	4.51 (0.70)	-0.28 (-0.74 to 0.18)	0.22
Mean fall in BG in 1^{st}hr with rehydrating fluid (mg/dL)	70.52 (41.93)	71.20 (31.99)	-0.68 (-21.88 to 20.52)	0.94

Table 2: Primary Outcome in two study groups

Measure	Low Dose group Mean (S.D.) n=25	Standard Dose group Mean (S.D.) n=25	Difference bw the means (95% CI)	p Value
Fall in BG (mg/dL/hr)	47.21 (15.35)	47.51 (10.72)	-0.30 (-7.82 to 7.22)	0.93
Time taken till BG ≤ 250 mg/dL (Hours)	6.04(2.44)	5.88(1.76)	0.16 (-1.049-1.369)	0.79

Table 2 compares the primary outcomes in the two study groups.

Table 3: Secondary outcomes in two study groups

Measure	Low Dose group n=25	Standard Dose group n=25	Chi squared (x^2)	p Value
Children with Hypokalemia	6 (24%)	10 (40%)	1.441	0.229
Children with Hypoglycemia	2 (8%)	4(16%)	0.742	0.388
Treatment Failure	3 (12%)	2 (8%)	0.218	0.640
BG<200 mg/dl in first 6 hours of therapy	3 (12%)	6 (24%)	1.195	0.274
Cerebral edema	0	0	-	-

Table 3 compares the therapy related complications between both the study groups.

Though statistically insignificant, the incidence of hypoglycemia and hypokalemia was higher in the SD group than in the LD group by 8% in the current study. Out of 25 patients in the LD group, 15 (60 %) were malnourished. Of these 15, five developed hypokalemia & one developed hypoglycemia. In the SD group, 16 (64%) patients were malnourished. Of these 16, six children developed hypokalemia & three developed hypoglycemia. Treatment failure was defined as failure to achieve a decrease in BG more than 18mg/dL/hr for two consecutive hours & hence it required escalation of the rate of insulin infusion. Three patients (12%) in the LD group & 2 (8%) in the SD group developed treatment failure (p = 0.640). Three patients (12%) in the LD group & 6 (24%) in the SD group had BG less than 200 mg/dL in first 6 hours (p = 0.274). The difference between the two groups was statistically insignificant. None of the patients in either group developed cerebral edema during the course of treatment.

Discussion

We analyzed the data and observations to compare the efficacy as well as the safety profile of LD (0.05 U/kg/hr) and SD (0.1 U/kg/hr) insulin infusion therapy in treatment of DKA. The efficacy was compared with regard to the rate of decrease in BG until a level of 250 mg/dL or less was reached and the time taken to achieve this target BG. The safety profile was compared by comparing the episodes of treatment failures, and incidences of hypokalemia and hypoglycemia in both the groups. Statistically, p value < 0.05 was considered significant. The following analysis was made:

Primary Outcomes

The mean rate of fall in BG till the desired BG level was achieved was 47.21 ± 15.35 mg/dL/hr in the LD group. Whereas in the SD group, it was 47.51 ± 10.72 mg/dL/hr, the difference is statistically insignificant. Similar study by Putha et al and Nallasamy et al concluded that LD (0.05 U/kg/hr) is equally effective as SD (0.1 U/kg/hr) i/v insulin infusion in terms of fall in BG as well as rise in pH, for the initial treatment (<6 hours) of DKA in children with T1DM.[7,10]The mean time taken for the BG to fall to ≤ 250 mg/dl was 6.04 ± 2.44 hours in the LD group (Table 2). In the SD group, this was 5.88 ± 1.76 hours, which was similar in both the groups. Similarly in a study by Nallasamy et al in 2014, the LD insulin infusion was found to be equally effective as the SD, in terms of the mean time taken for BG to decrease to level of ≤ 250 mg/dl.[10]In the current study, the LD insulin therapy has similar efficacy to the SD insulin, in terms of severity of acidosis at admission, with regards to both the rate of BG decrease as well as the time taken to achieve BG ≤ 250 mg/dL. These results are similar to study by Putha et al.[7] Both the treatment groups have similar efficacy for the rate of BG fall & time taken to reduce BG ≤ 250 mg/dl in patients with new onset T1DM presenting with DKA. Putha et al also found similar results.

Therapy Related Complications:

Six children (24%) in the LD group & 10 (40%) in the SD group developed at least one episode of hypokalemia (p = 0.229). Although the difference didn't reach statistical significance, the incidence is 16% higher in the SD group. In the LD group, out of 6 children, 5 were malnourished. In the SD group, out of 10 patients, 6 were malnourished. Thus in either of the groups, malnourished children tend to be more prone to develop hypokalemia. In the study by Nallasamy et al, the 20% patients in the LD group & 48% in the SD group developed hypokalemia. Although statistically insignificant (p=0.07), higher proportion of children developed hypokalemia in the SD group. Moulik et al in their study found the incidence as well as the severity of therapy related hypokalemia to be significantly higher in the malnourished as compared to the normally nourished children with DKA.[11]

In our study, 2 children in the LD group (8%) & 4 in the SD group (16%) developed hypoglycemia during the course of therapy (x^2=0.742, p = 0.388). Although statistically the difference is insignificant, the incidence of hypoglycemia is higher in the SD group by 8% .Similar results were found in the study by Nallasamy.[10] However, the study by Moulik et al reported the incidence as well as the severity of therapy related hypoglycemia to be significantly higher in the malnourished as compared to the normally nourished children with DKA.[11] Three patients in the LD group (12%) & 2 in the SD group (8%) developed treatment failure & insulin infusion rate was increased in these children (p= 0.64). The difference was statistically insignificant amongst the two groups of treatment (Table 3). Three patients (12%) in the LD group & 6 patients (24%) in the SD group had BG < 200 mg/dL, requiring addition of 10% Dextrose, during the first 6 hours of insulin infusion. Although statistically insignificant, greater number of patients developed BG < 200 mg/dl in the SD group than in the LD group. None of the patients in either group developed cerebral edema during the course of treatment.

Therefore, the LD insulin therapy, at 0.05 U/kg/hr, is comparable to the SD insulin therapy, at 0.1 U/kg/hr, in terms of rate of BG decrease & time taken to achieve the desired BG level. The difference in the incidence of important therapy related complications, namely hypokalemia & hypoglycaemia, is statistically insignificant between both the groups. Although the difference couldn't attain statistical significance, the incidence was lesser in the LD group for both the complications. As mentioned previously, other studies in Indian population have also shown a reduced incidence of these complications in the LD group. This is particularly relevant in developing economies like ours. Here, the burden of malnourishment is greater than our western counterparts & at the same time, the severity of the illness is also greater owing to reasons like ignorance on the part of patient or caretaker, missing of diagnosis by healthcare provider, delay in start of treatment or referral etc. Such factors predispose our children to develop these dangerous complications, especially when the insulin infusion is given. Therefore in our setup, the lower dose of insulin might prove to be a safer option than the SD insulin, with respect to the therapy related complications, at the same time being equally efficacious to the latter, in terms of BG decrease. More studies are required to compare the therapy related complications with the lower & conventional dose insulin, especially in the malnourished children, to throw more light upon this subject.

Conclusion

The low dose insulin infusion at 0.05 U/kg/hr has similar efficacy to the currently recommended standard dose insulin infusion (0.1 U/kg/hr) in terms of the mean rate of BG decrease till the level of ≤ 250 mg/dL is achieved and mean time taken to achieve the target BG. Children who receive higher insulin dose and are malnourished are more likely to develop hypoglycemia and hypokalemia during treatment of DKA.

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