Original Article

Efficacy and Safety of Low Dose Insulin Infusion against Standard Dose Insulin Infusion in Children with Diabetic Ketoacidosis- An Open Labelled Randomized Controlled Trial

Diganta Saikia, Medha Mittal, Chapala Kanakaraju, Dhulika Dhingra, Manish Kumar
Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, Delhi, India

Abstract

Objective: To compare the efficacy and safety of low dose insulin infusion (0.05 U/kg/h) against the standard dose insulin infusion (0.1 U/kg/h) in children with diabetic ketoacidosis. **Method:** Children (age <12 years, n = 30) presenting with diabetic ketoacidosis were enrolled and randomised to receive insulin infusion either as 0.05 U/kg/h (low dose) or 0.1 U/kg/h (standard dose) as an open labelled randomised controlled trial. The rest of the management was identical in both groups. The time taken for resolution of acidosis (pH ≥7.3 and HCO_3 ≥15) was the primary outcome variable. The secondary outcome variables included the time taken until a decline in blood glucose to 250 mg/dl, the proportion of children developing hypoglycemia and hypokalemia, and any treatment failure. **Results:** The two groups were similar with respect to mean age, weight and gender distribution. New-onset diabetes was diagnosed on 24/30. The mean ± SD time for resolution of acidosis was similar between the groups; 27.0 ± 6.1 hours in the low dose group vs 23.4 ± 7.3 hours in standard dose group, $P = 0.16$. The mean time for the decline in blood glucose to 250 mg/dl was 13.0 ± 5.9 hours in low dose vs 11.6 ± 6.0 hours in standard dose group, $P = 0.52$. A lesser proportion of participants developed hypoglycemia and hypokalemia in the low dose group, though not statistically significant. There was no incidence of treatment failure in either group. **Conclusion:** Low dose insulin infusion is equally effective and safe as standard dose insulin infusion in children with diabetic ketoacidosis.

Keywords: Acidosis, children, regular insulin

Introduction

Diabetic ketoacidosis is the leading cause of mortality and morbidity in children with type 1 diabetes (T1DM).[1] It is the initial presentation of 15% to 70% of children with diabetes and has a mortality of 0.3 to 0.5% in developed countries and 10-13% in developing countries.[2-6] The pillars of treatment are appropriate fluid therapy and insulin infusion. Both have seen radical changes over the years. With evidence supporting similar efficacy of lower insulin doses along with the reduced rate of complications, insulin infusion has been scaled down from 1 unit/kg/hour (U/kg/h) to 0.1 U/kg/h and the initial insulin bolus has also been discontinued.[7-10] With a lower insulin infusion rate there was a gradual reduction of blood glucose that allowed a corresponding increase in the serum sodium concentration resulting in a gradual reduction in the effective plasma osmolality (plasma glucose concentration in mmol/L plus twice the plasma sodium concentration in mmol/L).[11,12] The rate of change of plasma osmolality is an important, though not the only factor, influencing the risk of cerebral edema.[13-17] While a rate of 0.1 U/kg/h became accepted as the standard of care, there was no evidence to suggest that lower rates were not effective.[9,10] Since then, there have been reports of the use of lower infusion rates with good success. In the retrospective studies by Puttha *et al*.,

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Address for correspondence: Dr. Medha Mittal, Associate Professor, Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, Delhi - 110 031, India.
E-mail: goelmedha@gmail.com

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and by Al Hanshi and Shann, similar resolution of acidosis and hyperglycemia was reported with insulin infusion rates of 0.05 U/kg/h and 0.1 U/kg/h.[12,18] Noyes *et al*.,[19] have reported adequate resolution of ketosis with rates as low as 0.03 U/kg/h. Though most of the studies were observational studies they demonstrated that diabetic ketoacidosis (DKA) could be optimally treated with lower doses. Recently a few clinical trials have also been conducted comparing the two doses but still, the use of 0.1 U/kg/hour remains the standard practice.[20,21]

The present study was planned to compare an insulin infusion rate of 0.05 U/kg per hour against the standard infusion rate of 0.1 U/kg per hour in children with DKA for its efficacy and safety.

Materials and Methods

This, open labelled, randomized interventional study was carried out at a tertiary care hospital receiving patients from Delhi and surrounding states, after obtaining approval from an institutional ethical committee. The study was planned to evaluate and compare the response to low dose (0.05 U/kg/h) insulin infusion versus standard dose (0.1 U/kg/h) insulin infusion in children younger than 12 years with DKA. Diabetic ketoacidosis was defined as presence of hyperglycemia (blood glucose >200 mg/dl), acidosis (pH <7.3 or bicarbonate <15 mEq/L) and ketonuria (Urine dipstick test result ≥2+).[22] The primary hypothesis was that the low dose insulin infusion would be equally effective as standard dose insulin infusion in achieving resolution of acidosis with a lower incidence of hypokalemia and hypoglycemia. The primary objective was to compare the time taken for resolution of acidosis (pH ≥7.3 and HCO_3 ≥15) using low dose insulin infusion (0.05 U/kg/h) versus standard dose insulin infusion (0.1 U/kg/h) in children (age <12 years) who present with DKA. The secondary objectives were to compare the time taken for the decline of blood glucose to 250 mg/dl, to compare the proportion of participants who develop hypoglycemia (blood glucose <70 mg/dl)[23] and hypokalemia (serum potassium <3.5 mEq/L) and the incidences of treatment failure in the two study arms. Treatment failure was defined as failure to achieve a reduction in blood glucose of 18 mg/dl per hour for 2 consecutive hours and/or a decrease or failure of rise in serum bicarbonate with persistent high anion gap acidosis. A careful review of insulin therapy was done for errors in dose, preparation, or infusion rate before labelling the non-response as treatment failure. The existing infusion rate was planned to be increased by 0.02 U/kg/h in such cases.

Participant selection- Consecutive children, younger than 12 years, presenting to paediatric emergency were screened for eligibility for inclusion in the study. The inclusion criteria were the presence of features of DKA, that is, hyperglycemia (blood glucose >200 mg/dL), acidosis (pH <7.3 or bicarbonate <15 mEq/L) and ketonuria (urine dipstick test result ≥2+).[22] The blood glucose was done as a bedside finger prick test, blood gas analysed in an analyser and urine ketones tested using urine ketone strips. The exclusion criteria were the presence of symptomatic cerebral edema upon admission, septic shock and participant having received insulin infusion at some other facility before arriving at our centre. The participants thus fulfilling the enrolment criteria were included after providing detailed information about the study and taking the written consent of one of the parents.

Randomisation and intervention- The randomisation sequence was generated using block randomisation with variable sizes and 1:1 group allocation using web based software (www. randomization.com). A person not directly involved in the study generated the sequence and transcribed it to serially numbered opaque sealed envelopes. The intervention was an infusion of regular insulin at 0.05 U/kg/h (in the low dose insulin group) against the standard dose of 0.1 U/kg/h (standard dose insulin group). The regular insulin used in the study was Huminsulin R (40 IU/ml).

Procedures and data collection- Venous samples were drawn at admission for blood gas, complete blood count, kidney and liver function test, and electrolytes. Finger prick blood glucose was checked hourly; urine ketones and electrolytes were repeated 4-6 hourly. Each participant was initially stabilised in the emergency and thereafter shifted to the paediatric intensive care unit. DKA was considered severe at pH <7.1 and serum bicarbonate <5 mEq/L. The fluids were calculated and administered as per recommendations, beginning with an initial fluid bolus, followed by uniform infusion at the calculated rate.[22] Regular insulin was infused beginning after the first hour at a rate of 0.05 U/kg/h in the low dose group and at 0.1 U/kg/h in the standard dose group. The dose of insulin was kept the same until resolution of acidosis (pH ≥7.3 and HCO3 ≥15). Dextrose (5%) was added to the fluid if blood glucose was reduced to 250-300 mg/dl and acidosis was continuing (and 10% dextrose if blood glucose fell further).[22] After the resolution of acidosis, the insulin was gradually tapered and subcutaneous insulin was initiated with overlap periods as per the type of insulin. An independent observer checked and verified all the calculations and administration of fluids and insulin. A predesigned proforma was used to collect all relevant details after a thorough history and physical examination. All the vital signs were recorded upon admission and serially monitored every hour. Neurological status was noted at admission and hourly thereafter. Urine output was measured.

Outcome variables- The primary outcome variable was the time taken for the resolution of acidosis. The secondary outcome variables included the time taken for the decline of blood glucose to 250 mg/dl, the proportion of participants developing hypoglycemia, the proportion of participants developing hypokalemia and the incidence of treatment failure in the two study arms.

Statistical analysis- The sample size was calculated based on a previous study wherein the mean time for resolution of acidosis was 21.2 hours ± 2.3 hours,[6] at a 5% level of

significance and 90% power and assuming that 3 hours more might be required with the lower dose, the calculated sample size was 15 per study arm. We enrolled 30 participants, 15 in each arm. The data were entered in a Microsoft excel sheet and transferred to SPSS software. The continuous variables were expressed as means and compared using an unpaired *t*-test whereas Mann-Whitney U test was used for variables not normally distributed. Categorical variables were expressed as absolute numbers and percentages compared using Chi-square test or Fisher's exact test. Where the parameter to be compared involved multiple serial readings, repeated-measures ANOVA was used. Survival statistics were applied for outcomes of resolution of acidosis and decline of blood glucose and hazard ratios estimated using the Cox proportional model. For all analyses, *P* values less than 0.05 were considered significant. Statistical analysis was performed using IBM SPSS Statistics for Windows version 24, Armonk, New York.

Results

Thirty-five children were screened for inclusion in the study. Two had cerebral edema upon admission and consent was declined in three. None had a septic shock or received insulin infusion prior to arriving at our emergency. Thirty children satisfying the inclusion criteria were thus enrolled and randomised to low dose and standard dose groups as per the web-generated sequence [Figure 1]. All the enrolled subjects completed the study. Baseline demographic and biochemical characteristics are presented in Table 1 and were closely similar in the two groups. The children ranged from 3 to 12 years, with most being between 5 to 8 years (n = 14). Females outnumbered the males. The common presenting features were fast breathing, vomiting, pain abdomen, polyuria and polydipsia. Twenty-four children presented with new onset diabetes with DKA. The rest were already diagnosed cases and using insulin though not consistently as prescribed and had poor control. Four of these had not seen their physician for over 6 months. Severe dehydration was present in 16.

Table 1: Baseline demographic, clinical and biochemical characteristics of the two groups

Characteristic	Group A (*n*=15)	Group B (*n*=15)	*P*
Age in years [mean±SD]	6.83±2.678	8.30±2.576	0.136
Age range (years)	3-12	3-12	
Weight in kg [mean±SD]	17.42±5.906	20.19±9.070	0.33
Males	7	4	0.26
Initial pH [mean±SD]	7.04±0.141	6.96±0.338	0.43
Initial HCO_3[mean±SD]	6.36±3.475	7.28±3.580	0.48
Initial BG mg/dl [mean±SD]	491.7±49.7	478.5±49.5	0.47
Initial serum creatinine	0.67±0.22	0.63±0.23	0.63
Severe dehydration	8	8	1.00
Known diabetic	3	3	1.00
Severe DKA	10	11	0.69
Initial GCS (mean)	14.2	12.8	0.06

Resolution of acidosis-The two different insulin infusion rates achieved resolution of acidosis in a similar mean duration of time; 27 ± 6.1 hours in the low dose and 23.4 ± 7.3 hours in the standard dose group [Table 2]. The bicarbonate values in the two groups at various time points were similar and repeated measures ANOVA yielded F = 0.66, *P* = 0.46. Kaplan-Meier survival curve, depicted in Figure 2, comparing the resolution of metabolic acidosis in the two treatment groups showed that median time was similar in the two treatment groups (28 hours, log rank test *P* value 0.12). Cox proportional hazard regression analysis showed that participants receiving low dose insulin had a 25% lesser chance of resolution of acidosis at 36 hours of therapy in comparison to those who received standard dose insulin, though it was not statistically significant (aHR 0.75, 95% CI 0.3-1.8). Each meq increase in serum bicarbonate level at admission increased the chances of resolution of acidosis by 18% irrespective of insulin infusion rate and age of the child (aHR 1.18, 95% CI 1 to 1.3).

The decline in blood glucose-The rate of decline in blood glucose values and the mean time to achieve blood glucose reduction to 250 mg/dl was similar in the two groups (13.0 ± 5.9 hours in the low dose group vs 11.6 ± 6.0 hours in the standard dose group). There was no instance of a rapid fall in blood glucose (>90 mg/dl in an hour) in either group. On analysis of multiple values by repeated measures ANOVA, blood glucose values were similar in the two groups (F ratio = 0.91, *P* = 0.39). Kaplan-Meier survival curve, Figure 3, depicting normalization of blood glucose in two treatment groups showed that the median time to achieve a blood glucose level of 250 mg/dl was shorter in children who received standard dose insulin in comparison to those who received low dose insulin, though the difference was not statistically significant (8 hours versus 12 hours, log rank test *P* value 0.55). Cox- proportional hazard regression analysis showed that children in the low dose treatment group had a 10% increased chance of normalization of blood glucose at 24 hours in comparison to the standard dose insulin group, though it was not statistically significant (aHR 1.1, 95% CI 0.46 to 2.7). Each meq increase in serum bicarbonate level at admission increased the chances of the decline of blood glucose to 250 mg/dl in the first 24 hours of therapy by 20% irrespective of the age of the child and dose of insulin (aHR 1.20 95% CI 1 to 1.3).

Hypokalemia-In the standard dose group 7/15 participants had hypokalemia and in the low dose group, there were 3/15. Though the low dose group had fewer instances of hypokalemia, the difference was not statistically significant.

Hypoglycemia-In the low dose group, 4/15 participants had one or more instances of hypoglycemia while in standard dose group, 8/15 had such episodes. The difference was, however, not statistically significant.

Treatment Failure-There was no treatment failure in either group. All patients completed the study duration. There were no instances of cerebral edema and no deaths.

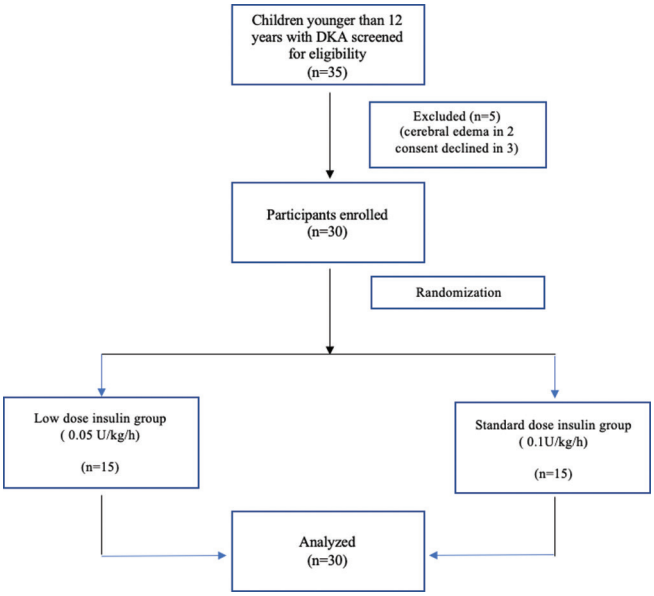

Figure 1: Study CONSORT flow diagram

Table 2: Outcome measures in the two study groups

Characteristic	Group A (*n*=15)	Group B (*n*=15)	*P*	95%CI
Time for resolution of acidosis in hours [mean±SD]	27.0±6.1	23.4±7.3	0.16	-8.6 to 1.4
pH 4 hours [mean±SD]	7.12±0.12	7.12±0.14	0.91	-0.09 to 0.10
pH 12 hours [mean±SD]	7.23±0.13	7.21±0.14	0.87	-0.11 to 0.09
pH 24 hours [mean±SD]	7.33±0.02	7.28±0.09	0.14	-0.09 to0.01
HCO3 4 hours [mean±SD]	7.34±3.96	8.45±4.32	0.46	-1.99 to 4.22
HCO3 12 hours [mean±SD]	10.45±3.16	10.34±4.68	0.94	-3.09 to 2.88
HCO3 24 hours [mean±SD]	12.8±2.33	11.13±3.06	0.09	-3.78 to 0.29
Time to achieve blood glucose 250 mg/dl in hours [mean±SD]	13.0±5.9	11.6±6.0	0.52	-5.8 to 3.0
BG 4 hours (mg/dl) [mean±SD]	349.07±99.35	342.93±105.61	0.87	-82.83 to 70.56
BG12 hours (mg/dl) [mean±SD]	234.31±76.40	244.50±92.49	0.77	-59.76 to 80.15
BG 24 hours (mg/dl) [mean±SD]	210.83±83.61	221.90±70.77	0.78	-72.67 to 94.81
Hypoglycemia, *n* (%)	4 (26%)	8 (53.3%)	0.26	
Hypokalemia, *n* (%)	3 (20%)	7 (46.6%)	0.25	
Treatment failure	0	0		

BG blood glucose; HCO_3 serum bicarbonate

Discussion

DKA is often the initial presentation of children with diabetes and carries a high mortality.[6] The risk of DKA in established type 1 diabetes is 1-10% per patient per year.[24,25] The management of DKA has evolved over the years with the primary consideration of reducing the occurence of complications, the greatest risk being that of cerebral edema. The pathogenesis of cerebral edema is not clearly understood and includes osmotic, vasogenic, metabolic and inflammatory factors.[26-28] It seems prudent to avoid abrupt changes in serum osmolality that may occur during treatment. A rapid fall in blood glucose may not allow enough time for osmolar and electrolyte shifts that prevent rapid changes in serum osmolality. A marked decrease in serum effective osmolality and an attenuated rise in serum sodium concentration has been identified as potential risk factors for the development of cerebral edema.[10,16,29,30] The management of DKA has evolved to the current guidelines with an aim of avoiding rapid falls in effective plasma osmolality. A gradual reduction in blood glucose is the key and a low dose insulin infusion achieves exactly this.

Our study was thus planned to compare the efficacy and safety of low dose insulin infusion (0.05 U/kg/h) vs standard dose insulin infusion (0.1 U/kg/h) in Indian children with DKA. The study was performed as a randomised controlled trial and the two groups were similar in the baseline parameters. The participants in either group received similar management except for the dose of insulin infusion. The study results demonstrate that participants who received low dose insulin infusion achieved resolution of acidosis and hyperglycemia in a similar duration of time as those who received standard dose insulin infusion. In addition, they had less incidence of

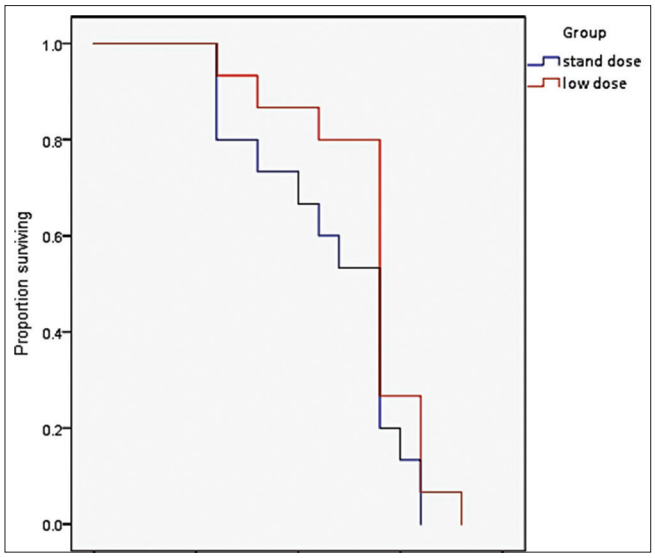

Figure 2: Kaplan Meier survival curve depicting time taken for achieving resolution of acidosis in the two groups

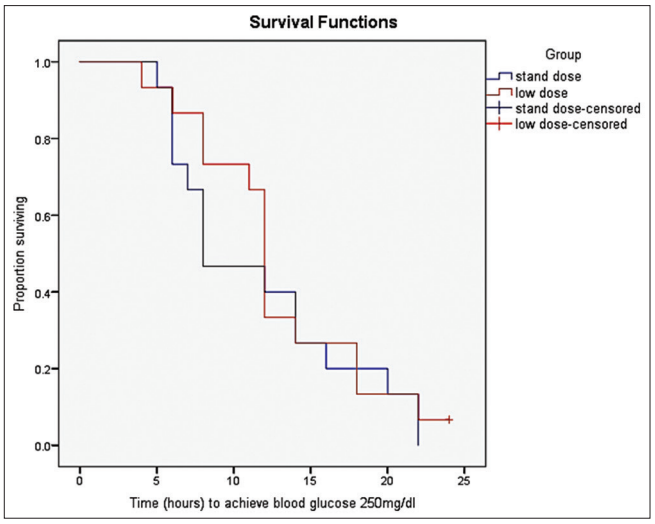

Figure 3: Kaplan Meier Survival curve depicting time taken to achieve blood glucose 250mg/dl in the two groups

hypokalemia and hypoglycemia. The duration of time taken for resolution of acidosis and decline of blood glucose to 250 mg/dl is similar to other published Indian data.[6]

Our results are in agreement with the observational study by Puttha *et al*.[18] The study reports a similar fall in blood glucose and a rise in pH in the low and standard dose groups at 6 hours following admission. Despite the retrospective data collection method and other limitations of differing management practices at the five study centres including the absence of a standardised protocol, this was an important initial study reporting the effectiveness of low dose insulin infusion in correcting the biochemical abnormalities in the initial phase of DKA when the risk of cerebral edema is particularly high.

Lower dose of insulin allows for a gradual reduction in effective plasma osmolality which reduces the risk of cerebral edema. A retrospective data analysis of 67 children with DKA who received a low dose (0.05 U/kg/h) and standard dose insulin (0.1 U/kg/h) infusion revealed a smaller reduction in effective plasma osmolality in the former group.[12] In the group that received low dose insulin infusion, there was a smaller reduction in plasma glucose and a higher increase in serum sodium tthat allowed a gradual reduction in effective plasma osmolality. Acidosis and ketosis also resolved resolved adequately in both groups, and the groups had similar duration stay in the intensive care unit.[12] However, the biochemical observations were made only for the first 12 hours of treatment. Also, since the allocation to the two treatment groups was not randomised, the smaller reduction in effective osmolality may not necessarily have been due to the lower infusion rate of insulin. A clinical translation to lower risk of cerebral edema could not be demonstrated.

A randomized controlled trial in this regard was much needed and Nallasamy *et al*.,[20] conducted an open labelled randomised controlled trial. They randomised 50 children with DKA to receive low dose and standard dose insulin infusion with the primary objective of comparing the rate of decrease in blood glucose from initial till it reached 250 mg/dl. Their observations revealed a similar rate of decline in blood glucose in the two groups. The mean fall of blood glucose in the first hour of insulin infusion was, however, more in the standard dose group as compared to the low dose group (69 vs 31 mg/dl). The rate of resolution of acidosis (secondary outcome) was also similar in the two groups. More children had therapy-related complications (hypokalemia and hypoglycemia) in the standard dose group, though statistically similar. Our results are in agreement with the above observations.

Another randomised controlled trial comparing 0.05 U/kg/h versus 0.1 U/kg/h in 60 children with DKA has been recently reported by Rameshkumar *et al*.[21] They too observed that the mean time taken for resolution of ketoacidosis was similar in both groups. The rate of decline of blood glucose and the time taken to reach a level of 250 mg/dl were similar in both groups. The hazard ratio of achieving blood glucose of 250 mg/dl or less by the end of six hours of insulin infusion was 1.35 times higher in the low dose insulin group. A difference in effective serum osmolality could not be shown in the two study arms. Hypokalemia and hypoglycemia, though less frequent in the low dose group were statistically comparable with the standard dose group.

A low dose insulin infusion seems a safe approach for the management of diabetic ketoacidosis as it minimises the rapid osmolar and electrolyte shifts that might incur the risk of cerebral edema. As mentioned previously, therapy-related complications also seem less. Comparable resolution of acidosis and hyperglycemia and no treatment failure in our study assures one of its efficacy in achieving the primary outcome irrespective of the severity of initial presentation. This also indirectly indicates that plasma insulin levels reached with the lower dose were adequate enough to achieve the said objectives. There have been only a limited number of

controlled studies till now and our results further advocate for the use of low dose insulin as a possible 'standard' therapy for diabetic ketoacidosis. In both the study arms a relatively higher initial serum bicarbonate level predicted a faster resolution of hyperglycemia and acidosis. Our hospital is a tertiary care referral centre in the public domain and predominantly serves the lower sections of society. A high proportion of severe DKA might be due to delayed presentation to the hospital.

The advantages of a randomised controlled study design provide strength to our results. Even though it was an open labelled study, the objective nature of the study observations preclude any bias on that account. Observations were prospectively recorded till 48 hours after enrolment. However, there are several limitations as well. Our research work was conducted as a postgraduate thesis work over 18 months and hence, a larger population could not be enrolled. We also could not conclude if instances of cerebral edema would be less with the lower dose. We also did not measure insulin levels to conclusively say that therapeutic levels were reached with either dose. More such trials in different populations would further add much-needed evidence on this significant issue that could have far-reaching effects on the lives of children with diabetes.

Conclusion

Our research demonstrates that low dose insulin is equally effective and safe as standard dose insulin infusion in the management of children with DKA.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their clinical information to be reported in this journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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