ORIGINAL RESEARCH

To Study efficacy and safety of low dose insulin against standard dose insulin infusion inchildren with diabetic ketoacidosis: An open label randomized controlled trail.

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ABSTRACT

Background: The primary objective was to compare time taken until resolution of acidosis in standard dose insulin infusion group and low dose insulin infusion group. The secondary objectives were to compare the time taken until decline in blood glucose till 250 mg/dl in both the groups, to compare the proportion of children developing Hypoglycemia in both the groups, to compare the proportion of children developing Hypokalemia in both the groups, to compare the episodes of treatment failures in both the groups.

Materials and Methods: This study was conducted from March 2017 to August 2018, atMamatha Medical College,Khammam with aim to compare efficacy and safety of low dose insulin infusion against standard dose insulin infusion in children with diabetic ketoacidosis. All consecutive children 12 years of age or younger, admitted with diagnosis of Diabetic Ketoacidosis were enrolled for the study. Children who present with symptomatic cerebral edema were excluded from the study. Cases were enrolled after valid consent obtained from the parents. Among 34 eligible cases, 30 were randomized equally into two groups and 4 cases were excluded due to symptomatic cerebral edema. Total 30 cases 15 in each group completed the study and were available for data analysis.

Results: In our study mean age in standard dose insulin infusion group was 8.30+/- 2.57 years and in low dose insulin infusion group was 6.83+/- 2.67 years. After fast breathing (93.3%), vomiting (90%), and pain abdomen (76.6%), polyurea (76.6%), polydypsia (73.7%), fever (56.7%), altered sensorium (53.3%), were the predominant presenting complaints of DKA. Signs of dehydration (100%) were the most common presenting signs of DKA followed by acidotic breathing (93%) and tachycardia (86%). In our study, most common precipitating causes of DKA, infection (46.7%), followed by unknown cause (26.7%), and dose omitted (23.3%), and insufficient dose (3.3%). Family history was present in 16.7% patients. Malnutrition was present in 40% cases of DKA.

Conclusion: To conclude, the time taken to resolution of acidosis is similar in standard dose insulin infusion group and low dose insulin infusion group and time taken to decline blood glucose till 250 mg/dl or less is similar in both the groups. Incidence of hypoglycemia and hypokalemia comparatively less in low dose insulin infusion group. Treatment failure was not found in both the groups.

Keywords: Diabetic Ketoacidosis, Hypokalemia, Hypoglycemia, sensorium, polydypsia.

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INTRODUCTION

Diabetic ketoacidosis (DKA), is a life-threatening complication of diabetes mellitus (DM), occurs more commonly in children with type 1 DM than type 2 DM.Biochemical criteria for

diagnosis of DKA are hyperglycemia (Blood glucose> 200 mg/dL), metabolicacidosis (Blood pH<7.3 and bicarbonate<15 mEq/L) andketonemia and ketonuria.Lowering the insulin dose may be advantageous in the initial hours of therapy when a gradual decrease in glucose, electrolytes, and resultant osmolality is desired. The smaller dose of insulin may make it easier to lower the effective plasma osmolality gradually and might, therefore, reduce the risk of cerebral edema and reduce the incidences of hypoglycemia and hypokalemia.[1-6]

A few articles have highlighted the utility of insulin doses lower than the standard recommended one. Noyes et al observed that insulin doses of 0.03and 0.05 U/kg per hour could adequately normalize ketosis in DKA. Puttha et al and Al Hanshi and Shann, in their respective pediatric studies, have reported that a dose of 0.05U/kg per hour was as effective as the standard dose in correcting acidosis.[7,8]

Physiologic dose-effect studies have also found that even lower doses could adequately normalize ketonemia and acidosis. Lowering the insulin dose may be advantageous in the initial hours of therapy when a gradual decrease in glucose, electrolytes, and resultant osmolality is desired. The smaller dose of insulin may make it easier to lower the effective plasma osmolality gradually and might, therefore, reduce the risk of cerebral edema and reduce the incidences of hypoglycemia and hypokalemia.[8]

Due to the lack of prospective studies, we aimed to determine the efficacy of low dose (0.05U/kg/hr) compared with standard dose (0.1U/kg/hr) insulin with respect of time to resolution of acidosis, time to decline in blood glucose, episodes of treatment failures and incidences of hypokalemia and hypoglycemia in children with diabetic ketoacidosis.

Aims & Objective

Aim

To compare the efficacy and safety of low-dose insulin infusion against the standard dose insulin infusion in children with Diabetic Ketoacidosis.

Primary Objective

To compare the time taken until resolution of acidosis in low-dose insulin infusion group and standard dose insulin infusion group.

Secondary Objectives

- To compare the time taken until decline in blood glucose till 250 mg/dl in both the groups
- To compare the proportion of children developing hypoglycemia in both the groups
- To compare the proportion of children developing hypokalemia in both the groups
- To compare the episodes of treatment failures in both the groups.

MATERIALS & METHODS

Study Design: Open label randomized controlled trial

Place of Study: Pediatric emergency and pediatric intensive care unit of Mamatha Medical College, Khammam, Telangana.

Study Period: One and half year.

Study Population: All consecutive children 12 years of age or younger, admitted with diagnosis of Diabetic ketoacidosis.

Sample Size: As per previous admission data of diabetic ketoacidosis in theMamatha Medical College, sample size is taken as 30(15 in each group).

Inclusion criteria:

- All consecutive children 12 years of age or younger, who presented with DKA defined as Hyperglycemia (BG >200mg/dL),Acidosis (pH <7.3 or bicarbonate<15 mEq/L), Ketonuria (urine dipstick test result ≥2+) will be enrolled.

Exclusion criteria:

Children who present with following criteria will be excluded:

- Symptomatic cerebral edema.

Methodology

All consecutive children 12 years of age or younger, who presents to the pediatric emergency with symptoms and signs of diabetic ketoacidosis will be clinically evaluated to confirm the diagnosis and determine the cause of diabetic ketoacidosis. The severity of dehydration and level of consciousness will be assesed. Samples for venous blood gas analysis and other tests will be drawn along with bedside finger- prick blood glucose will be done by glucometer and urinary ketones by dipstick method. Weight of the child will be recorded. Children meeting the inclusion criteria will be enrolled at 1 hour of admission after taking written consent from parent or guardian.

Samples will be drawn for following investigations:

- Blood glucose
- Serum Electrolytes
- Kidney function tests
- Venous blood gas
- Complete blood count
- Urinalysis for ketones
- Appropriate specimens for culture (blood, urine)will be taken, only if there is evidence of infection.

Oxygen or ventilator assistance will be given whenever required.

Statistical Tests and Analysis

All the data will be entered in a pre-designed proforma, following which they will be transferred to an excel sheet and then exported to SPSS version 23 software. Continuous variables will be summated as mean with standard deviation, categorical variables will be summated as frequency and percentage. Proportions will be compared by chi-square test. Means will be compared by" one sided t-test".

RESULTS

This is a hospital based prospective open labelled randomized controlled trial conducted on all consecutive children aged 12 years or younger, who presents to the pediatric emergency, Chacha Nehru Bal chikitsalaya hospital with symptoms and signs of diabetic ketoacidosis were clinically evaluated to confirm the diagnosis.

A total of 30 children with symptoms and signs of diabetic ketoacidosis, who fulfilled the inclusion and exclusion criterion and who reported to the pediatric emergency, Mamatha Medical College & General Hospital were included in the study. Written informed consent was obtained from the parents enrolled in the study.

Table 1: Distribution of Diabetic Ketoacidosis children among two treatment groups

Treatment Groups	Frequency	Percent

Treatment Group with Insulin 0.1 U/kg/hour	15	50.0
Treatment Group with Insulin 0.05 U/kg/hour	15	50.0
Total	30	100.0

Table 2: Mean age wise Comparison of Diabetic Ketoacidosis children among two treatment groups

	Treatment Groups	N	Mean	Std.Deviation	Std. Error Mean	P value
Age	Treatment Group with Insulin 0.1 U/kg/hour	15	8.30	2.576	0.665	0.136
	Treatment Group with Insulin 0.05 U/kg/hour	15	6.83	2.678	0.691	

The mean age in the treatment Group with Insulin 0.1 U/kg/hour was 8.30 ± 2.57 years where as mean age in the treatment Group with Insulin 0.05 U/kg/hour was 6.83 ± 2.67 years.

Table 3: Age group wise Comparison of Diabetic Ketoacidosis children among two treatment groups

Treatment Groups	Statistics	Age Group			Total
		< 5 Years	5 to 8 years	> than 8 years	
Treatment Group with Insulin 0.1 U/kg/hour	Count	1	8	6	15
	% within Age Group	16.7%	57.1%	60.0%	50.0 %
Treatment Group with Insulin 0.05 U/kg/hour	Count	5	6	4	15
	% within Age Group	83.3%	42.9%	40.0%	50.0 %
Total	Count	6	14	10	30
	% within Age Group	100.0%	100.0%	100.0%	100.0 %

Majority of the patients in the treatment Group with Insulin 0.1 U/kg/hour was i.e. 8(57.1%) were found in the age group 5 to 8 years of age group, where as majority of the patients in the treatment Group with Insulin 0.05 U/kg/hour was i.e. 6(42.9%) were found in the age group 5 to 8 years of age group.

Table 4: Mean Weight wise Comparison of Diabetic Ketoacidosis children among two treatment groups

Statistics	Treatment Groups	N	Mean	Std. Deviation	Std. Error Mean	P value
Weight at admission	Treatment Group with Insulin 0.1 U/kg/hour	15	20.19	9.070	2.342	0.330
	Treatment Group with Insulin 0.05 U/kg/hour	15	17.42	5.906	1.525	
Weight after DKA Correction	Treatment Group with Insulin 0.1 U/kg/hour	15	21.207	9.0383	2.3337	0.592

	Treatment Group with Insulin 0.05 U/kg/hour	15	25.077	6.0946	6.7376	

The mean weight at the admission in the treatment Group with Insulin 0.1 U/kg/hour was 20.19 ± 9.07 kg where as mean weight in the treatment Group with Insulin 0.05 U/kg/hour was 17.42 ± 5.90 years. This difference between two means was statistically non significant (p value=0.330).

The mean weight after Diabetic Ketoacidosis correction in the treatment Group with Insulin 0.1 U/kg/hour was 21.20 ± 9.03 kg where as The mean weight in the treatment group with Insulin 0.05 U/kg/hour was 25.07 ± 6.09 years. This difference between two means was statistically non significant (p value=0.592).

Table 5: Case wise Comparison of Diabetic Ketoacidosis children among two treatment groups

Case	**Statistics**	**Treatment Groups**		**Total**
		Treatment Group with Insulin 0.1 U/kg/hour(n=15)	**Treatment Group with Insulin 0.05 U/kg/hour(n=15)**	
Newely diagnosed case of DKA	Count	10	6	16
	% within group	66.7%	40.0%	53.3%
Previously diagnosed case of DKA	Count	5	9	14
	% within group	33.3%	60.0%	46.7%
Total	Count	15	15	30
	% within group	100.0%	100.0%	100.0%

Majority of the patients in the treatment Group with Insulin 0.1 U/kg/hour i.e. 10(66.7%) were new cases where as majority of the patients i.e. 9(60 %) in the treatment Group with Insulin 0.05 U/kg/hour were old cases.

Table 6: Distribution of Signs and symptoms of the patients among two treatment groups of Diabetic ketoacidosis

Signs and Symptoms	**Treatment Groups**		**Total(n=30**	**P Value**
	Treatment Group with Insulin 0.1 U/kg/hour(n=15)	**Treatment Group with Insulin 0.05 U/kg/hour(n=15)**		
Fever	7(46.7%)	10(66.7%)	17(56.7%)	0. 269
Cough	1(6.7%)	3(20.0%)	4(13.3%)	0.283
Fast breathing	15(100%)	13(86.7%)	28(93.3%)	0.143
Vomiting	13(86.7%)	14(93.3%)	27(90.0%)	0.543
Pain abdomen	15(100%)	8(53.3%)	23(76.7%)	0.003
Seizure	0(0%)	0(0%)	0(0%)	N/ap
Altered sensorium	9(60%)	7(46.7%)	16(53.3%)	0.464
Polyuria	13(86.7%)	10(66.7%)	23(76.7%)	0.195
Polydipsia	12(80.0%)	10(66.7%)	22 (73.7%)	0.409
Diarrhoea	1(6.7%)	0(0%)	1(3.3%)	0.309

Almost all i.e. 15(100%) of the patients in the treatment Group with Insulin 0.1 U/kg/hour were presented with Fast breathing and pain abdomen
Almost all i.e. 14(93.3%) and 13(86.7%)of the patients in the treatment Group with Insulin 0.05 U/kg/hour were presented with Fast breathing and pain abdomen.

Table 7: Distribution of the patients among two treatment groups of Diabetic ketoacidosis as per Previous DKA and Drug use.

History	Treatment Groups		Total(n=30	P Value
	Treatment Group with Insulin 0.1(n=15)	Treatment Group with Insulin 0.05(n=15)		
Previous DKA	6(40.0%)	7(46.7%)	13(43.3%)	0.713
Drug Use(Insulin)	6(40.0%)	7(46.7%)	13(43.3%)	0.269

Around 6(40%) patients were found with previous DKA and drug use in the treatment Group with Insulin 0.1 U/kg/hour, whereas Around 7(46.7%) patients were found with previous DKA and drug use in treatment Group with Insulin 0.05 U/kg/hour.

Table 8: Distribution of Diabetic Ketoacidosis children among two treatment groups according to Degree of Dehydration

Degree of Dehydration	Statistics	Treatment Groups		Total
		Treatment Group with Insulin 0.1 U/kg/hour(n=15)	Treatment Group with Insulin 0.05 U/kg/hour(n=15)	
Mild	Count	3	2	5
	% within group	20.0%	13.3%	16.7%
Moderate	Count	2	3	5
	% within group	13.3%	20.0%	16.7%
Severe	Count	10	10	20
	% within group	66.7%	66.7%	63.3%
Total	Count	15	15	30
	% within group	100.0%	100.0%	100.0%

In the both the treatment Groups i.e. with Insulin 0.1 U/kg/hour and with Insulin 0.05 U/kg/hour, 10% (66.7%) patients were found with severe dehydration each.

Table 9: Distribution of Glassgow Comma Scale Score among different groups at different time points

	Treatment Groups	N	Mean	Std. Deviation	Std. Error Mean	
GCS 1Hr	Treatment Group with Insulin 0.1	15	12.80	2.541	.656	.060
	Treatment Group with Insulin 0.05	15	14.27	1.387	.358	.063
GCS 4Hr	Treatment Group with Insulin 0.1	15	13.67	1.988	.513	.120
	Treatment Group with Insulin 0.05	15	14.60	1.056	.273	.123

GCS 8Hr	Treatment Group with Insulin 0.1	15	14.2667	1.66762	.43058	.405
	Treatment Group with Insulin 0.05	15	14.6923	.75107	.20831	.384
GCS 12Hr	Treatment Group with Insulin 0.1	15	14.57	1.342	.359	.778
	Treatment Group with Insulin 0.05	15	14.69	.751	.208	.774

Table 10: Comparison of treatment failure in both the groups

Treatment failure	**Treatment Groups**		**Total(n=30)**
	Treatment Group with Insulin 0.1(n=15)	**Treatment Group with Insulin 0.05(n=15)**	
Yes	0(0%)	0(0%)	0(0%)
No	15(100%)	15(100%)	30(100%)

Treatment failure was not found in both the groups and no deaths occurred during the study period.

DISCUSSION

Diabetes mellitus is one of the chronic diseases of the children worldwide. Very little is known about the magnitude or determinants of childhood onset diabetes in India.

In our study, 30 patients completed the trail, 15 in each group. Mean age (SD) of standard dose insulin infusion group was 8.30 ±2.57 years and Mean age (SD) of low dose insulin infusion group was 6.83±2.67 years, similar to study by Nallaswamy et al,[9] and kapallen et a In our study male percentage was 26.7% in standard dose insulin infusion group and 46.7% in low dose insulin infusion group which was similar to Nallaswamy et al.[9]

The mean weight at the admission in the treatment Group with Insulin 0.1 U/kg/hour was 20.19 ± 9.07 kg whereas mean weight in the treatment Group with Insulin 0.05 U/kg/hour was 17.42 ± 5.90 kg. This difference between two means was statistically non-significant (p value=0.330).

The mean weight after Diabetic Ketoacidosis in the treatment Group with Insulin 0.1 U/kg/hour was 21.20 ± 9.03 kg whereas the mean weight in the treatment group with Insulin 0.05 U/kg/hour was 25.07± 6.09 kg. This difference between two means was statistically non-significant (p value=0.592). This was similar to other studies.[9]

In our study we found that most common symptoms were fast breathing 93.3 %,vomiting 90 %,pain abdomen 76.6%, polyuria 76.6%,polydypsia 73.7%, fever 76.7%, altered sensorium 53.3%.Most commonly found signs were dehydration 100%, acidotic breathing 93%, tachycardia 86 %. Another study reported that polyuria, polydypsia, abdominal pain and vomiting as the predominant clinical features.[10]

In our study, the commonest precipitating factor was infection 46.7%, followed by unknown cause 26.7% and dose omission 23.3 %. Other studies have also shown that the most common cause in the development of diabetic ketoacidosis is infection and others were dose omission.[10]

In both the treatment Groups i.e. with Insulin 0.1 U/kg/hour and with Insulin 0.05 U/kg/hour, only 6(40%) patients were found with Malnutrition. In other study they found that 70% had malnutrition in diabetes.[8]

Glassgow Coma Scores of 13 or less at 4h following admission were more frequent in the standard group similar to study by Puthta R et al.[8]

The mean time taken until resolution of acidosis in the treatment Group with Insulin 0.1 U/kg/hour was 27.17 ± 12.50 hours whereas the mean time taken until resolution of acidosis in the treatment Group with Insulin 0.05 U/kg/hour was 29.60 ± 11.15 hours. This difference between two means was statistically non-significant (p value=0.209),which also shows rate of resolution of acidosis was similar in both the groups. In another study mean time of recovery of acidosis in treatment group with insulin 0.1U/kg/hour was 16.5±7.2 hours whereas the mean time of recovery of acidosis in the treatment group with insulin 0.05 U/ kg/hour was 17.2 ± 7.7 hours (p=0.73). In our study rise in PH in the standard dose versus low dose group, at 4 hour following admission were 1.51+/- 2.67 Vs 1.18+/-0.91, (P=0.654), were similar to study by Puttha R et al.[8]

In our study The mean rate of blood glucose decrease until a level of 250 mg/ dl or less is reached in standard dose insulin infusion group was 36.4±5.2 mg/dl/hr and in low dose insulin infusion group was 32.8±4.6 mg/dl/hr and the mean time taken until decline in blood glucose level of 250 mg/ dl or less in standard dose insulin infusion group was 8.8 ± 6.13 hrs and in low dose insulin infusion group was 9.93 ± 5.82 hrs which were similar in the standard dose and low dose insulin infusion groups(p=0.613). Similar to study by Nallaswamyet al.[9]

Hypokalemia was seen in 7(46.6%) children receiving standard dose insulin infusion group versus 3 (20%) children those received low dose insulin infusion (p=0.245). In other study also hypokalemia wasfound in12(48%) children receiving standard dose versus 5 (20%) of children those received low dose.[9] Incidence of acute complications of insulin infusion like hypokalemia was less in low dose insulin infusion group which is similar to other studies.[11]

In our study 8 children (53.3%) and 3children (20%) receiving standard and low dose insulin infusion (p=0.128) respectively, developed hypoglycemia. In a similar study. 5 children (20%) and 1 child (4%) receiving standard and low dose insulin infusion (p=0.17), respectively developed hypoglycemia. Treatment failure was not found in both the groups and no deaths occurred during the study period, similar to Nallasamy et al study.[9]

CONCLUSION

We concluded, low dose insulin infusion is as effective as standard dose insulin infusion with respect to time taken to resolution of acidosis and time taken to decline blood glucose till 250mg/dl or less.

Proportion of children developing hypoglycemia and proportion of children developing hypokalemia less in low dose insulin infusion group. Treatment failure was not found in both the groups so low dose insulin infusion is as safe as standard dose insulin infusion in the treatment of diabetic ketoacidosis.

Acknowledgment

The author is thankful to Department of Paediatrics for providing all the facilities to carry out this work.

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