The long-term insulin management with premixed insulin in neonates and infants with diabetes

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BACKRAUND

- To describe a new therapy protocol for the long-term insulin management in neonates and infants with diabetes.acts on neonatal body weight gain.

MARERIALS AND METHODS

- Male and female infants younger than 36 months, who had ND or T1D, were enrolled the study.
- All the infants were fed with three hours intervals.
- Before six months old, the infants were allowed to take breast milk or formula as much as they wanted at each feeding time.
- Three main meals and three snacks were organised.
- The patients were started insulin therapy with 0.6 U/kg/day divided equally into four doses.
- All the insulin doses were given as premixed insulin (Humalog Mix25 cartridge, Eli Lilly&Co; 25% insulin lispro and 75% neutral protamine Hagedorn (NPH) insulin) when the number of breast feed was more than 3 during the night, while if the patient had less than 3 breast feeds, only the last insulin (night) dose was administered as NPH insulin (Humulin N cartridge, Eli Lilly&Co).
- At the insulin dose time, fasting and post prandial (120 minute) plasma glucose levels were measured. At 03:00 AM, one more plasma glucose level was obtained.
- The blood sugar normal ranges for fasting and postprandial measurements were determined as 70-180 and 70-200 mg/dl, respectively. Insulin doses and the amount of carbohydrate in the diet were adjusted according to the patients' food demands and the blood glucose levels.
- If the patient was less than one year old, and the antibodies (glutamic acid decarboxylase-65 antibody, anti-islet antibody, and islet cell autoantibody) for T1D were negative, genetic analysis for neonatal diabetes was done.
- Parents received training by a certified diabetes educator.
- The study staff monitored the subjects' glucose records, insulin doses, hypoglysemic events, and medication adherence and compliance.
- Office visits occurred at weeks 1, 2, and then every 3 months.
- Parents recorded blood glucose meter values and associated symptoms of hypoglycemia.
- Mild hypoglycemia was defined as any symptom of hypoglycemia with a confirmed blood glucose meter reading <70 mg/dL (3.9 mmol/L), or any asymptomatic blood glucose meter reading <70 mg/dL (3.9 mmol/L), and which was handled by the parents.
- Severe hypoglycemia was defined as symptoms (semiconscious or unconscious, coma, convulsions) that might require parenteral therapy (glucagon or i.v. glucose) and associated with a blood glucose meter reading <70 mg/dL (3.9 mmol/L) and requiring third-party assistance..
- A glucose level higher than 180 for fasting and 200 mg/dl for post prandial measurement was considered hyperglycemia.
- Antropometric measurements including body weight and height were performed at the diagnosis and every visit.
- The primary endpoints included 9-point plasma glucose profiles (fasting and post prandial at insulin dose time and at 3 AM) and sufficient weight gain. Secondary efficacy endpoint was change in HbA1c at the last visit.

RESULTS

- Of the 11 patients who entered the study, five patients were diagnosed as ND. The other six patients had T1D.
- Case 4 was consulted by another medical centre while he was 2 months old because his blood sugar levels showed rapid fluctuations under insulin pump therapy.
- The mean diagnosis ages of the patients with ND and T1D were 59.4±101.1 day and 19.1±4 month, respectively.
- None of the patients with ND had ketoacidosis, while four patients with T1D presented with it.
- At the diagnosis, the mean blood glucose level of the patients was 460.3±195.4 mg/dl.
- The mean HbA1c level of the patients with T1D at diagnosis was 10.4±0.9%. The patients with ND had not antibodies for T1D.
- Four patients had mutant genes for ND, while one patient (Case 5) had no genetic mutation.
- Four patients with T1D only had glutamic acid decarboxylase-65 antibody.
- The diabetes antibodies could not be done in two patients (Case 10 and 11).
- One infant (Case 1) successfully transitioned from insulin to sulphonylurea (glibenclamide) at the age of 6 months (Table 1).
- The mean 9-point blood glucose profiles showed none of the patients had rapid fluctuations for glucose measurements (Table 2).
- Hypoglycemia, normoglycemia and hyperglycemia were reported by 8%, 81%, and 11% of all the blood glucose measurements, respectively.
- % 96 of the hypoglycemic measurements was between 62 and 70 mg/dl. Of the mild hypoglycemic episodes, 92% of the patients were asymptomatic.
- Severe hypoglycemia was not experienced by any patients.

Table 1. Clinical and laboratory characteristics of neonates and infants with diabetes

Case	Sex	Diagnosis	Chronological age at diagnosis	Gestational age (wk)	Birth weight (g)	KA at diagnosis	Blood glucose at diagnosis (mg/dl)	HbA1c at diagnosis (%)	Antibodies for diabetes	Mutant genes	Insulin dose at discharge (U/kg/d)	Chronological age at the last visit	Insulin dose at the last visit (U/kg/d)	HbA1c at the last visit* (%)
1	Female	ND	22 days	40	2200	No	752	--	Negative	KCNJ11	1	430 days	0.35-SU	6.2±0.2
2	Male	ND	8 months	40	NF	No	167	9.4	Negative	KCNJ11	0.5	23 months	0.57	6.6±0.3
3	Male	ND	15 days	38	2300	No	562	--	Negative	KCNJ11	0.6	24 months	0.35	6.4±0.2
4	Male	ND	4 days	36	1630	No	800	--	Negative	PTF1A	0.7	6 months	0.4	8.0±0.3
5	Male	ND	16 days	35	1700	No	565	--	Negative	NF	0.8	6 months	0.35	6.8±0.1
6	Male	T1D	14 months			Yes	396	9.4	Positive GAD65	--	0.6	28 months	0.5	7.4±0.1
7	Female	T1D	18 months			Yes	422	11.9	Positive GAD65	--	1	24 months	0.6	8.0±0.1
8	Male	T1D	25 months			Yes	258	10.6	Positive GAD65	--	1	32 months	0.53	7.8±0.2
9	Female	T1D	16 months			No	322	9.6	Positive GAD65	--	0.8	36 months	0.55	6.9±0.3
10	Male	T1D	20 months			No	358	10.1	NF	--	0.8	34 months	0.54	7.0±0.2
11	Male	T1D	22 months			Yes	462	11.1	NF	--	0.9	30 months	0.6	7.6±0.3

Table 2. 9-point blood glucose (mg/dl) measurements from the diagnosis to the last follow-up

Case	MB	M120	NB	N120	EB	E120	NGB	NG120	3 AM
1	92 ±25	84±12	139±32	122±39	107±25	109±28	130±42	112±40	116±25
2	118±22	159±12	91±30	192±30	98±27	127±32	123±42	95±26	169±25
3	84±24	165±21	155±32	159±35	176±22	82±32	99±18	120±43	129±44
4	108±45	124±55	81±25	158±35	160±27	135±33	152±45	110±51	164±22
5	101±25	164±28	134±35	145±55	86±35	126±44	148±49	132±25	129±72
6	125±48	162±39	131±23	145±52	122±42	135±40	155±41	142±33	162±31
7	110±36	132±44	97±36	162±26	174±29	99±34	157±28	138±35	165±23
8	98±45	124±48	99±38	158±31	162±26	105±39	169±28	115±55	110±29
9	95±39	144±22	141±29	110±48	137±37	118±39	102±51	125±48	135±33
10	112±27	82±35	129±44	138±40	123±43	125±29	158±32	102±33	125±33
11	114±22	145±38	156±44	137±55	112±62	131±38	79±28	133±28	138±35

CONLUSION

- We described a specific therapy protocol for long-term insulin management of neonates and infants with diabetes.
- The findings of this study suggest that the method is effective, convenient, and successful.
- However, prospective studies including a large number of the subjects are required.

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