Original Article

Clinical Profile and Efficacy of Long-Acting Octreotide in Hyperinsulinemic Hypoglycaemia

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Abstract

Introduction: Hyperinsulinemic hypoglycaemia (HH) is characterised by unregulated insulin secretion, leading to persistent non-ketotic hypoglycaemia with a lack of alternate fuel that induces a severe risk for brain damage and neurodevelopmental abnormalities. Octreotide, a somatostatin analogue, has been effectively administered as subcutaneous injections or depot preparations in diazoxide-unresponsive HH. **Methods:** Children and infants with HH receiving short-acting octreotide injections were included. Anthropometric values, hypoglycaemic episodes, HbA1C, and side effects were noted from the records and were followed up for 12 months. Informed written consent was obtained from the parents before administration of a single dose of LAR (long-acting octreotide). Based on home-based glucose monitoring (HBGM), the dosage of LAR was modified, and short-acting octreotide was eventually withdrawn. The patients shared the injection's cost for cost-effectiveness. HH affects the quality of life (QoL) if not diagnosed and controlled adequately. A QoL questionnaire was given before starting LAR and after 6 months of receiving LAR, and the changes were noted accordingly. **Results:** Twenty-two patients were diagnosed with HH, of which 11 infants and children were included in the study. Mutations were identified in 7 (63.63%) children. Daily octreotide could be tapered and stopped with the addition of sirolimus in one patient with an increasing dose of LAR to maintain euglycaemia. The hypoglycaemic episodes decreased with increasing dose of LAR with a decrease in the severity. Eight (72.7%) patients showed an improved lifestyle on LAR quantified through a QoL questionnaire. **Conclusion:** LAR was found effective in reducing hypoglycaemic episodes with no adverse effects. The patient's parent's satisfaction was higher. Given its high cost, this trial achieved cost-effectiveness by sharing a single sitting of LAR injection.

Keywords: Cost-effectiveness, hyperinsulinemic hypoglycaemia, long-acting octreotide, mutations, quality of life

Introduction

Hyperinsulinemic hypoglycaemia (HH) is characterised by dysregulated insulin secretion from pancreatic beta cells leading to hypoglycaemia. It is a common cause of non-ketotic hypoglycaemia and induces a severe risk for brain damage and neurodevelopmental abnormalities.[1,2] In cases of diazoxide-unresponsive congenital HH, octreotide, a somatostatin analogue, has been successfully used as depot preparations or subcutaneous injections.[3,4] HH was first clearly described by Stanley.[5] He explained most of the clinical features and named it Idiopathic hypoglycemia of Infancy as it was the most common cause of persistent hypoglycaemia at that age. The estimated incidence of HH was 1:28,000–50,000 in the general population and increased to 1:2500 in the case of consanguinity.[6]

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CHH (congenital hyperinsulinemic hypoglycaemia) can be diagnosed when the intravenous glucose infusion rate of >8 mg/kg/min (normal 4–6 mg/kg/min) with inappropriately elevated serum insulin and c-peptide along with features like low/absent serum ketone bodies and fatty acids during the hypoglycaemic episode, which are the diagnostic parameters. The diagnostic criteria for HH are summarised in Table 1.[7] HH can be congenital (congenital hyperinsulinism, CHI) or transient due to risk factors such as perinatal asphyxia, intra-uterine growth restriction (IUGR), and maternal diabetes

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Table 1: Diagnostic criteria for patients with HH

-Glucose infusion rate >8 mg/kg/min
-Laboratory blood glucose <3 mmol/l (<54 mg/dl) with
Detectable serum insulin/C-peptide
Suppressed/low serum ketone bodies
Suppressed/low serum fatty acids
-Serum ammonia level may be raised (HI/HA syndrome)
-Raised plasma hydroxybutyrylcarnitine and urinary
3-hydroxyglutarate (HADH deficiency)
-Supportive evidence (when diagnosis is in doubt or difficult):
Positive glycaemic (>1.5 mmol/L) (>27 mg/dl) response to intramuscular/intravenous glucagon
Positive glycaemic response to a subcutaneous/intravenous dose of octreotide
Low serum levels of IGFBP1 [insulin negatively regulates the expression of IGFBP1]
Suppressed branch chain (leucine, isoleucine and valine) amino acids
Provocation tests (leucine loading or exercise testing) if indicated.

Table 2: Home-based glucose monitoring schedule

Date	7 am	1 pm	4 pm	8 pm

mellitus.[8,9] CHH is caused due to defects in genes regulating pancreatic β-cell function. Common mutations include 14 essential genes controlling insulin secretion, GLUD1, GCK, HADH1, UCP2, HNF4A, HNF1A, PGM1, PMM2, HK1, SLC16A1, FOXA2, CACNA1D, and the most important being ABCC8 and KCNJ11. ABCC8 and KCNJ11 genes encode the KATP channel subunits SUR1 and Kir6.2, respectively, and mutations in these genes represent the most common cause of CHH.[10] CHH can be categorised into diffuse or focal forms histopathologically. The focal forms are amenable to cure by resection of the lesion or partial pancreatectomy. In diffuse CHI, medical treatment with diazoxide forms the first line of management, octreotide and long-acting octreotide (LAR), nifedipine being the second line treatment option. Newer treatments include sirolimus, GLP-1 receptor antagonist, and ketogenic diet.[11] Because diazoxide is expensive, octreotide is more commonly used in responsive and unresponsive children.[4] Surgical management is preferred only in focal disease where partial pancreatectomy is possible. Children with diffuse disease or the non-responders were noted to have a high rate of side effects like recurrent hypoglycaemia, pancreatic exocrine insufficiency, and diabetes. They are rarely cured after surgery in long-term follow-up.[12]

Octreotide, a somatostatin (SST) analogue, is secreted by δ-cells in the pancreatic islets and by extra-islet neuroendocrine cells. SST is used in the medical management of CHH because it inhibits glucagon and insulin secretion. This is achieved by activating potassium channels at the β-cell membrane, inhibiting the intra-cellular mobilisation of calcium and decreasing the activity of the insulin gene promoter.[13] The LAR preparations are the preferred treatment with improved patient compliance in the recent past due to the reduced number of injections.[14] The initial phase of treatment should involve short-acting octreotide along with LAR or depot preparations with continuous glucose monitoring for optimal glucose management to prevent problems associated with hypoglycaemia. When CHH is diagnosed and normoglycaemia is achieved quickly, most children develop a standard range of cognitive, emotional, and social abilities. Consequences related to the disease and its treatment significantly impact the quality of life (QoL) of those affected.[15] This includes the effects of illness, treatment, and treatment cost on the perception of health. In India, there are limited data on the medical management of CHH and the QoL in infants and children with CHH. Hence, this study was conducted to determine the efficacy, clinical profile, and QoL of children on LAR with HH. We also describe the use of LAR with cost-effective benefits by sharing the drug and the cost among the families in low-income families of a developing country with the QoL and healthcare satisfaction.

Materials and Methods

The study consisted of 22 HH patients who received treatment with short-acting octreotide. A written informed consent was obtained from the parents after explaining the purpose of the study in their local language. Children with transient CHH or unwillingness to participate in the study were excluded. Eleven patients enrolled in the study, and their data were collected as per Annexure 1 from records who were on regular follow-up in the endocrinology out-patient department (OPD) in the hospital. Genetic analysis was sent to the Madras Diabetes Research Foundation (MDRF), Chennai. The relevant information regarding the number of hypoglycaemic episodes, glycated haemoglobin (HbA1C), liver function test (LFT), complete blood count (CBC), and ultrasound abdomen to look for cholelithiasis 3 months before the starting of LAR was collected. The costs of short-acting octreotide and LAR per month were noted and compared. A QoL questionnaire, PedsQL (Paediatric Quality of Life Inventory Scale version 4), parent report for infants and young children, was given to the parents in the study at the start of the study before the first dose of LAR.

LAR was given a deep SC route under strict aseptic precautions. The dose was calculated based on the cumulative dose of multiple daily injections. LAR, which is available in 20 mg and 30 mg vials, was mixed with 10 ml of normal saline/distilled water, and the dose was adjusted based on weight and hypoglycaemic episodes. The required dose was withdrawn into a sterile syringe and, under aseptic precautions, was injected into the children using a 22-gauge needle. A single dose was given every 28 days (e.g., for a 5 kg baby, if the child is receiving daily multiple injections of octreotide at a dose of 10 mcg/kg/day, then the cumulative dose for 28 days will be $10 \times 5 \times 28 = 1400$ mcg, i.e., 1.4 mg). The daily subcutaneous dose of octreotide given 6th hourly was continued, slowly

tapered, and stopped over the next 2 months based on the maintenance of glucose values. Glucose monitoring was done using on a home-based glucose monitor. Monitoring was done every day four times as in Table 2 (to maintain uniform glucose monitoring) and as and when required, and the dose was adjusted every month during follow-up visits. The child's weight and height were recorded during every visit. In the follow-up period, information like the number and severity of hypoglycaemic episodes was documented, as mentioned in Table 3.[16] HbA1C, thyroid function test, liver function tests, and ultrasound abdomen were monitored third monthly for side effects related to the drug. The hypoglycaemic episodes and their severity and complications were compared before and after starting LAR. LAR strengths of 30 mg and 20 mg were available, so the cost of this injection was divided among the patients. The costs of short-acting octreotide and LAR per month were noted and compared. The QoL questionnaire was assessed based on physical functioning, physical symptoms, emotional symptoms, and social and cognitive functioning, as given in Annexure 2. The questionnaire was again given after receiving 6 months of LAR, and the transform scores were noted, which explains the general well-being along with the emotional well-being of the child. Analysis of the questionnaire was defined as the higher the score, the better the quality of life with fewer problems or symptoms.

Statistical analysis

Descriptive statistics of the explanatory and outcome variables were calculated by the mean and standard deviation for quantitative variables and frequency and proportions for qualitative variables. The items of the QoL questionnaire were analysed separately as ordinal categorical variables. A higher transform score signifies better quality with fewer symptoms. The two groups were compared using the Chi-square test for the number and severity of hypoglycaemic episodes; a *P*- value <0.05 is considered statistically significant.

Ethical aspects

Written informed consent was obtained from patients parents for the participation in the study and use of patients data for research and educational purposes. The procedures in the study follow the guidelines laid down in Declaration of Helsinki.

The study underwent approval of the Institutional Review board and institutional Ethics Committe vide letter no P72/3rd/nov/2022 on 3rd Novemeber 2022.

Results

A total of 22 patients were diagnosed with HH, of which 11 infants and children (5 males) were included in the study after eliminating 11 patients who were unwilling to participate or lost to follow-up. Seven patients presented with HH in the neonatal period and four in infancy. The median age of onset was day 2 of life. Consanguinity was present in eight families. The mean birth weight was 3.52 kg, with three children being macrocosmic, one underweight, and the rest of the infants being average weight. Three families had a history of previous neonatal deaths. The hypoglycaemic seizure was the most common presentation and was the same presentation in all 11 children, irrespective of the age of presentation. The other blood investigations done when investigating the cause of hypoglycaemia are as follows in Table 4.

TMS was negative in all 11 patients. Genetic analysis was done in all 11 patients, and mutations were identified in 7 (63.6%) children. ABCC8 gene mutations with an autosomal recessive mode of inheritance were identified in all these patients. Four of the seven patients with positive autosomal recessive mutations had inherited heterogeneously from both parents. The genetic report and hypoglycaemic episodes, as monitored in the 11 patients, are shown in Table 4. It was observed that there was a steady increase in the weight Z score from -1.9 to -1.6 at 3 months and to -1.3 at 6 months and to -0.9 at 1 year follow-up after starting LAR. Similarly, the height Z score showed a steady elevation from -2.6 to -2.2 at 3 months and to -1.88 at 6 months and -1.87 at 1 year follow-up after starting LAR [Figure 1]. The number of patients having hypoglycaemic episodes in the preceding 3 months is as shown in Figure 2, which explains that few of the children had <5 episodes of hypoglycaemia after starting LAR, but the hypoglycaemic episodes were of mild or moderate intensity. The mean dose of daily short octreotide was 15.45 mcg/kg/day, and the median age of initiation of LAR was

Table 3: Severity of hypoglycemic episodes

Severity	Description
Mild	Glucose value <70 mg/dl (3.9 mmol/L)
Moderate	Glucose value <54 mg/dl (3 mmol/L)
Severe	Severe hypoglycemia <54 mg/dl with severe cognitive impairment requiring assistance for recovery

Table 4: Blood investigations at the time of diagnosis

Investigation parameters	Mean	SD
Blood glucose (mg/dl) (*n*=11)	34.91	9.40
Insulin levels (µIU/ml) (*n*=11)	37.96	52.16
Cortisol (µg/dl) (*n*=11)	13.88	10.12
Growth hormone (µg/L) (*n*=11)	14.01	13.71

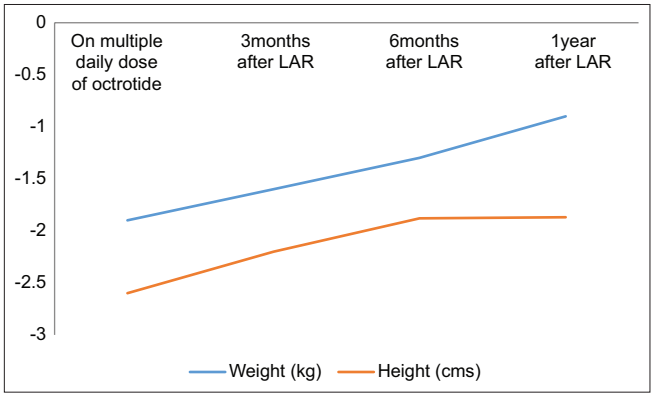

Figure 1: Anthropometric Z scores

Table 5: Hypoglycemic details and genetic reports of the subjects

	Genetic analysis	Age at onset of LAR Octreotide	Hypoglycemic episodes on short-acting octreotide			Hypoglycemic episodes on long-acting monthly dose octreotide			Additional drugs	Side effects
			Mild	Moderate	Severe	Mild	Moderate	Severe		
Patient 1	No mutation	21 months	4			2			Nil	Nil
Patient 2	ABCC8	31 months		NIL			NIL		Nil	Nil
Patient 3	ABCC8	10 months	4			2			Nil	Nil
Patient 4	ABCC8	49 months	3	1			NIL		Nil	Nil
Patient 5	No mutation	23 months	7				NIL		Nil	Gall bladder calculus
Patient 6	ABCC8	36 months		2	1		NIL		Nil	Nil
Patient 7	ABCC8	7 months	4			4			Tab sirolimus	Gall bladder calculus
Patient 8	No mutation	42 months	4				NIL		Nil	Nil
Patient 9	No mutation	7 years	4				NIL		Nil	Nil
Patient 10	ABCC8	32 months	5				NIL		Nil	Nil
Patient 11	ABCC8	3 months	3				NIL		Nil	Nil

1.9 years. The mean dose of LAR started initially was 5.45 g/month, which was gradually increased to a mean of 7.6 g/month based on the number and severity of hypoglycaemic episodes. There was an increase in the dose of LAR for the maintenance of euglycaemia. The number and severity of hypoglycaemic episodes were reduced on LAR with better patient compliance and a reduced number of injections.

Infants and children were monitored for side effects before starting LAR, and two patients were found to have 3–4 mm asymptomatic gallstones. These patients were followed up every 3 months for any increase in the side of gallstones. Liver function tests, thyroid function tests, ultrasound of the abdomen, and complete blood counts were monitored every 3rd month and were normal. One patient in the study was started on Tab Sirolimus (dose 1 mg/m2) in view of continued hypoglycaemic episodes and was stopped in 4 months. The QoL questionnaire given to the parents included 36 items under the domain of physical functioning, physical symptoms, emotional symptoms, social functioning, and cognitive functioning in infants and 15 items in children under the domain of physical health and activity, emotional health, social activities, and school activities. The QoL scores were calculated using the transform scores, which were defined as a better QoL with fewer problems and symptoms with higher scores. Eight (72.7%) patients had a higher score defining a better QoL on LAR, and 3 (27.2%) patients had the same score defining no significant changes in the QoL on LAR. The genetic analysis and hypoglycemic episodes (the number of hypoglycemic episodes and severity of hypoglycemic episodes) for all the patients are recorded as depicted in table 5, with the pictorial representation of hypoglycemic episodes in Figure 2.The number and severity of hypoglycemic episodes are significantly reduced on LAR octrotide, as depicted in Table 6.

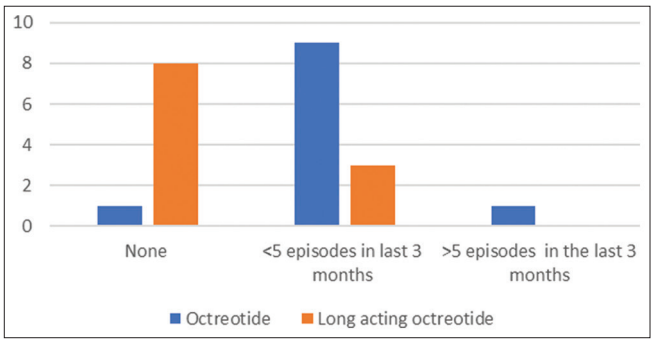

Figure 2: Pictorial representation of hypoglycemic episodes

Discussion

CHH is the most common cause of persistent non-ketotic hypoglycaemia in neonates and infants. They carry a significant risk of irreversible brain damage, so it is crucial to diagnose the condition as soon as possible and start treating it right away to avoid complications like epilepsy, cerebral palsy, and neurodevelopmental deficits.[10] The insulin production is unregulated in children with CHI due to the inactivating mutations caused by KATP channel mutations most commonly. Insulin's effects on glucose and fuel metabolism increase the danger of brain damage. By promoting peripheral glucose consumption, insulin decreases blood glucose levels, thus promoting glycogen synthesis and inhibiting glycogenolysis and gluconeogenesis. Insulin has an anabolic effect. It stimulates lipogenesis, inhibits free fatty acid release and beta-oxidation, and therefore inhibits ketone body formation, leading to hypo ketosis, thereby decreasing the alternative fuels for the brain.[17,18] Hence, children with CHI brain are deprived of both glucose and ketones as insulin inhibits lipolysis and ketogenesis. As the brain of neonates and infants has a higher glucose consumption rate than adults, it is more vulnerable to serious hypoglycaemic brain injury. HH typically presents in the newborn period with severe hypoglycaemia but can also present in infancy, childhood, and even as late as adulthood with variable severity and aetiology.[19,20]

Octreotide is an octapeptide that mimics natural somatostatin pharmacologically and is a potent inhibitor of insulin,

Table 6: Cost comparison between short-acting octreotide and LAR shared between all patients

Dose of octreotide before changing to LAR	Cost of octreotide/ month (INR)	Dose of LAR/ month	Cost of LAR/month (INR)
20 mcg/kg/day	7098	7.8 mg	5668
15 mcg/kg/day	12328	8 mg	5813
10 mcg/kg/day	4670	2.5 mg	1816
10 mcg/kg/day	6071	8.1 mg	5886
18 mcg/kg/day	7565	10.5 mg	7630
16 mcg/kg/day	7023	6.8 mg	4941
25 mcg/kg/day	7355	12.5 mg	9083
20 mcg/kg/day	10778	7 mg	5086
9 mcg/kg/day	6556	7 mg	5086
18 mcg/kg/day	14290	10.5 mg	7630
10 mcg/kg/day	3362	3 mg	2180

glucagon, and growth hormones compared to the naturally available hormones. Octreotide is available as a short-acting subcutaneous injection and long-acting or depot preparations. The active peptides in LAR are encapsulated in biodegradable polymer microspheres. Following a single intra-muscular injection, the concentrations of plasma octreotide stay incredibly low for the first 2 weeks before rapidly rising to a plateau that remains stable between day 14 and day 45.[14] This pharmacokinetic profile ensures a continuously stable plasma concentration of octreotide over at least 4 weeks. Hence, the first 2 months of LAR and the multiple doses of subcutaneous octreotide are given together to enter the plateau phase, and after 3–4 months, the multiple doses of subcutaneous octreotide are stopped, as shown in our study. In a study done by Sharma *et al*.,[21] in 5 out of 9 patients who were started on LAR, short-acting octreotide could be tapered and stopped and euglycaemia could be maintained thereafter, whereas in our study, all the 11 patients were tapered and stopped with short-acting octreotide within 4 months after starting LAR. The dose of LAR required to maintain euglycaemia was higher than the multiple subcutaneous doses, as observed in the study. Patients in this study were treated with short octreotide 6th hourly at a dose (ranging from 10 to 35 mcg/kg per day). However, when CHH children were shifted to LAR, the mean octreotide dose required was 5.45 g/month, which was gradually increased to 7.6 g/month, which is the average octreotide dose needed for treatment. There were no severe side effects noted. We therefore recommend close monitoring of the side effects during treatment with LAR. A study done by Kim-Hanh Le Quan Sang *et al*.[14] showed that there was no increase in the LAR dose required, unlike in our study, where the dose of LAR was increased when the patients were shifted to LAR, and no significant side effects were noted. A study done by Bingyan Cao *et al*.[22] explains transient elevation of liver enzymes and asymptomatic gallbladder pathology as the most prevalent side effects of octreotide therapy occurring after a mean treatment duration of 1 month. These side effects required no special treatment and resolved spontaneously, similar to that seen in two patients in our study requiring no special treatment and being followed up for symptoms and liver function test.

There are very few studies based on the QoL in children with CHH in India. QoL is a subjective, self-assessed, and multi-dimensional construct that describes a person's perception of their physical, psychological, and social health status.[23,24] This includes the impact of illness and treatment on the perception of health. Hence, this study used the PedsQL (Pediatric Quality of Life Inventory Scale version 4, long form for infants and short form for young children). We used the parent report form for the study. It was noted that the parents reported an improvement in their children's QoL.

All parents declared improvements in their daily lives, like avoiding multiple daily injections at school and reducing pain. All families are continuing with LAR after the end of this study and are currently on LAR. The benefit of this study was the cost-effectiveness when the drug was shared among the patients by forming a group of 2–3 families and getting the drug by pooling the amount as the drug, which is available as 30 mg and 20 mg vials in low-income families of a developing country like India. A few drawbacks of the study include the glucose monitoring of these children with home-based glucose monitoring instead of continuous glucose monitoring, which is the standard of care, and also, the number of children included is a small group of 11. Hence, more extensive data would be required to prove the results.

Conclusion

LAR contributes to an undeniable simplification of the medical care of children with HH as a monthly intra-muscular injection can replace 3–4 daily subcutaneous injections of octreotide in medically treated Indian children with cost-effectiveness by sharing the drug in low-income families with CHH. The main challenges were related to frequent monitoring, compliance with medication, and the high cost of therapy. These challenges were encountered by home-based glucose monitoring and sharing of the cost of the drug between the families. 72.7% of the parents described an improved QoL and are willing to continue the monthly injections, which are cost-effective with better QoL noticed through the QoL questionnaire.

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Authors' contribution

Dr.P.S.K contributed substantially to the study conception, data collection ,analysis, interpretation and patient management. Dr.V.H.N provided critical intellectual content and helped in final editing of the manuscript. Dr.T.S and Dr. R.P helped in management of the patient and revised the manuscript critically.

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Nil.

Conflicts of interest
There are no conflicts of interest.

Data Availability statement
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References
1. Senniappan S, Shanti B, James C, Hussain K. Hyperinsulinaemic hypoglycaemia: Genetic mechanisms, diagnosis and management. J Inherit Metab Dis 2012;35:589–601.
2. Lord K, Radcliffe J, Gallagher PR, Adzick NS, Stanley CA, De Leon DD. High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. J Clin Endocrinol Metab 2015;100:4133–9.
3. Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: Long-term octreotide treatment without pancreatectomy. J Pediatr 1993;123:644–50.
4. Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. J Pediatr 1993;123:637–43.
5. Stanley CA, Baker L. Hyperinsulinism in infants and children: Diagnosis and therapy. Adv Pediatr Infect Dis 1976;23:315–55.
6. Vora S, Chandran S, Rajadurai VS, Hussain K. Hyperinsulinemic hypoglycemia in infancy: Current concepts in diagnosis and management. Indian Pediatr 2015;52:1051–9.
7. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. Lancet Diabetes Endocrinol 2017;5:729-42.
8. Senniappan S, Arya VB, Hussain K. The molecular mechanisms, diagnosis and management of congenital hyperinsulinism. Indian J Endocrinol Metab 2013;17:19-30.
9. Arya VB, Flanagan SE, Kumaran A, Shield JP, Ellard S, Hussain K, *et al*. Clinical and molecular characterisation of hyperinsulinaemic hypoglycaemia in infants born small-for-gestational age. Arch Dis Child Fetal Neonatal Ed 2013;98:F356–8.
10. Mohamed Z, Arya VB, Hussain K. Hyperinsulinaemic hypoglycaemia: Genetic mechanisms, diagnosis and management. J Clin Res Pediatr Endocrinol 2012;4:169-81.
11. Demirbilek H, Hussain K. Congenital hyperinsulinism: Diagnosis and treatment update. J Clin Res Pediatr Endocrinol 2017;9(Suppl 2):69-87.
12. Sikimic J, Hoffmeister T, Gresch A, Kaiser J, Barthlen W, Wolke C, *et al*. Possible new strategies for the treatment of congenital hyperinsulinism. Front Endocrinol 2020;11:545638.
13. Haris B, Saraswathi S, Hussain K. Somatostatin analogues for the treatment of hyperinsulinaemic hypoglycaemia. Ther Adv Endocrinol Metab 2020;11:2042018820965068.
14. Le Quan Sang KH, Arnoux JB, Mamoune A, Saint-Martin C, Bellanné-Chantelot C, Valayannopoulos V, *et al*. Successful treatment of congenital hyperinsulinism with long-acting release octreotide. Eur J Endocrinol 2012;166:333-9.
15. Rosenfeld E, Ganguly A, De Leon DD. Congenital hyperinsulinism disorders: Genetic and clinical characteristics. Am J Med Genet C Semin Med Genet 2019;181:682–92.
16. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: A joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155-7.
17. Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fékété C, De Lonlay-Debeney P, *et al*. Practical management of hyperinsulinism in infancy. Arch Dis Child Fetal Neonatal Ed 2000;82:F98-107.
18. Hussain K, Aynsley-Green A. Hyperinsulinism in infancy: Understanding the pathophysiology. Int J Biochem Cell Biol 2003;35:1312-7.
19. Ajala ON, Huffman DM, Ghobrial II. Glucokinase mutation-a rare cause of recurrent hypoglycemia in adults: A case report and literature review. J Community Hosp Intern Med Perspect 2016;6:32983.
20. Gutgold A, Gross DJ, Glaser B, Szalat A. Diagnosis of ABCC8 congenital hyperinsulinism of infancy in a 20-year-old man evaluated for factitious hypoglycemia. J Clin Endocrinol Metab 2017;102:345-9.
21. Sharma R, Roy K, Satapathy AK, Kumar A, Nanda PM, Damle N, *et al*. Molecular characterization and management of congenital hyperinsulinism: A tertiary centre experience. Indian Pediatr 2022;59:105-9.
22. Cao B, Wu D, Su C, Chen J, Liang X, Liu M, *et al*. Efficacy and safety of octreotide treatment for diazoxide-unresponsive congenital hyperinsulinism in China. Pediatr Investig 2020;4:29-36.
23. Männistö JME, Jääskeläinen J, Huopio H. Health-related quality of life in children with congenital hyperinsulinism. Front Endocrinol (Lausanne) 2019;10:670.
24. Chassany O, Sagnier P, Marquis P, Fullerton S, Aaronson N. Patient-reported outcomes: The example of health-related quality of life—A European Guidance Document for the improved integration of health-related quality of life assessment in the drug regulatory process. Drug Inf J 2002;36:209–38.

Annexure 1

ANNEXURE – I (PROFORMA)

Serial no:
PAE:
Gender:
DOB:
Address and phone number:
Age at onset:
Birth Weight:
Blood glucose (mg/dl) at the time of diagnosis:
Insulin levels(μIU/ml):
C Peptide:
Cortisol:
Growth Hormone:
TMS:
Ketone Body:
Ammonia:
Lactate:
Free fatty acids:
Developmental delay:
Seizures:
Consanguinity:
HbA1C:

- Prior to Long-Acting Octreotide
- Post Long – acting octreotide

Treatment:
Family details:
Other illness:
Genetics:
Mutations:
Inheritance :
Type:
PET scan
Dose of Octreotide received Starting: Q6H
Dosage of Long-acting Octreotide initially:
Dosage of Long-acting Octreotide after 6 months:
Age at initiation:
Weight at 1st follow up
Weight at 3rd follow up
Z Score -
Height at 1st follow up
Height at 3rdt follow up
Z Score
Quality of life Index initially – QoL 1
Quality of life Index after 6 months – QoL 2
Side effects
Associated Medication

INFORMATION SHEET

TITLE: CLINICAL PROFILE AND EFFICACY OF LONG-ACTING OCTREOTIDE IN HYPERINSULINEMIC HYPOGLYCEMIA.

1. What is Congenital Hyper insulinemic hypoglycaemia?
   Congenital hyperinsulinism (CHI) is characterized by a dysregulated secretion of insulin from pancreatic β-cells. It is the most common cause of persistent hypoketotic hypoglycaemia in neonates and infants.

2. What are the signs and symptoms of Congenital Hyper insulinemic hypoglycaemia and its treatment?
   The signs and symptoms include low sugars, convulsions, lethargy with elevated serum insulin. The treatment includes glucagon infusion, diazoxide, nifedipine and octreotide. Diazoxide unresponsive children are initiated on Octreotide.
3. What is the study about?
   This study is about the efficacy of Long acting octreotide instead of subcutaneous octreotide which is given four times a day.
4. How can you enter the study?
   You can enter the study by signing the assent form. Your parents or legally accepted representative (LAR) can sign the consent form.
5. What will be the benefit to me if I participate in the study?
   You can be part of the study and change the daily 4 injection to a single dose of injection of the drug – octreotide.
6. Will it cause any harm to me?
   No.
7. Will I have to pay anything?
   Yes , the amount for the injection octreotide.
8. Can I withdraw from the study?
   Yes. By not signing the assent form. If your parents or LAR do not sign the consent form.
9. Will the results of the study be told to us?
   Yes. After the study is over.
10. Any compensation will be given for injury?
    No injury is expected and hence no compensation will be given.
11. Will our personal records be maintained confidentially?
    Yes.
12. Will you inform us about any new information about the study ?
    Yes.
13. Whom to contact in case of any questions?
    The investigators.

INFORMED CONSENT

STUDY TITLE-

Subject's Name:

Date of Birth /Age:

1. I confirm that I have read and understood the details of information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]
2. I understand that my participation in the study is voluntary, without my medical care or legal rights being affected. [ ]
3. I have been explained about the adverse effects like gall stones, diarrhoea, nausea or vomiting and I hold no doctor responsible for the untoward consequences of the treatment. [ ]
3. I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records. I agree to this access
   However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]
4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]
5. I agree to take part in the above study. [ ]
   Signature (or Thumb impression) of the subject
   Name
   Name/Signature of Witness:_____
   Signature of the investigation

Annexure 2

PedsQL Paediatric Quality of life Inventory scale

Please tell how much of problem each one has been for your child.

0-If it is never a problem

1-If it is almost never a problem

2-If it is sometimes a problem

3-It is often a problem

4-If it almost always a problem.

PHYSICAL FUNCTIONING	Never	Almost never	sometimes	Often	Almost always
1 Low energy level					
2. Difficulty participating in active play					
3. Having hurts or aches					
4. Feeling tired					
5. Being lethargic					
6. Resting a lot					

PHYSICAL SYMPTOMS	Never	Almost never	sometimes	Often	Almost always
1. Having gas					
2. Spitting up after eating					
3. Difficulty breathing					
4. Being sick to his/her stomach					
5. Difficulty swallowing					
6. Being Constipated					
7. Having a rash					
8. Having diarrhoea					
9. Wheezing					
10. Vomiting					

EMOTIONAL SYMPTOMS	Never	Almost never	sometimes	Often	Almost always
1. Feeling afraid or scared					
2. Feeling angry					
3. Cryimg or fussing when left alone					
4. Difficulty soothing					
5. difficulty falling asleep					
6. crying or fussing when cuddled					
7. Feeling Sad					
8. Difficulty being soothed when picked up or held					
9. difficulty sleeping mostly through the night					

10. Crying a lot
11. Feeling cranky
12. Difficulty taking naps during the day

SOCIAL FUNCTIONING	Never	Almost never	sometimes	Often	Almost always
1. Not smiling at others					
2. Not laughing when tickled					
3. Not making eye contact with the caregiver					
4. Not laughing when cuddled.					

COGNITIVE FUNCTIONING	Never	Almost never	sometimes	Often	Almost always
1. Not imitating care givers action					
2. Not imitating caregivers' facial expression					
3. Not imitating care givers sounds					
4. Not able to fix his/ her attention on objects					