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Alternative management of persistent Hyperinsulinemic hypoglycemia in a neonate: A case report on octreotide and nifedipine therapy

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Abstract: This case report highlights the successful management of Persistent Hyperinsulinemic Hypoglycemia in Infancy (PHHI) using alternative therapies, demonstrating their efficacy and practical implications in resource-limited settings. A 48-hour-old neonate presented with severe hypoglycemia unresponsive to high-dose glucose infusion. Laboratory investigations confirmed PHHI with elevated insulin and C-peptide levels. Due to the unavailability of diazoxide, treatment involved subcutaneous octreotide and oral nifedipine. The clinical course was managed and monitored according to international guidelines for hyperinsulinemic hypoglycemia. The combination therapy successfully stabilized blood glucose levels, enabling cessation of intravenous glucose infusion by day 10. The patient also recovered fully from hospital-acquired pneumonia with antibiotic treatment. These outcomes underscore the potential efficacy of nifedipine as a viable second-line therapy for PHHI in contexts where standard treatments are inaccessible. This case underscores the importance of flexible, evidence-based therapeutic approaches tailored to individual patient needs, especially in resource-constrained environments. The findings highlight nifedipine's clinical utility in PHHI management and emphasize the need for further research, including large-scale studies, to establish standardized treatment protocols and expand access to effective therapies globally.

Keywords: *Hyperinsulinism, Hypoglycemia, Neonate, Nifedipine, Octreotide.*

1. Introduction

Persistent Hyperinsulinemic Hypoglycemia in Infancy (PHHI) is a rare but critical metabolic disorder characterized by unregulated insulin secretion despite hypoglycemia. As the leading cause of severe and persistent neonatal hypoglycemia, it poses significant risks for neurological damage, including seizures and developmental delays, if not promptly treated. While its incidence is low globally, PHHI is more prevalent in consanguineous populations, reflecting its genetic basis [1]. Globally, its incidence is estimated at 1 in 50,000 live births, but this increases significantly in consanguineous populations due to the genetic basis of the condition.

The 2023 International Guidelines for the Diagnosis and Management of Hyperinsulinemic Hypoglycemia emphasize diazoxide as the first-line therapy for PHHI due to its effectiveness in suppressing insulin secretion through KATP channel modulation. However, in many low- and middle-income countries (LMICs), access to diazoxide is often limited due to high costs, supply chain issues, and regulatory barriers [2].

Octreotide, a somatostatin analog, and nifedipine, a calcium channel blocker, have emerged as viable second-line therapies in such contexts. Several case studies from LMICs, including reports from South Asia and Sub-Saharan Africa, have demonstrated successful outcomes with these alternatives when diazoxide is unavailable. For instance, a study in India reported stabilization of blood glucose levels in infants treated with nifedipine, while similar results were observed in Nigeria with a combination of octreotide and nifedipine [3].

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Despite their promise, challenges remain. The efficacy of nifedipine is inconsistent, with some studies reporting suboptimal outcomes, particularly in cases with severe genetic mutations in KATP channels. Octreotide, although effective, is associated with dose-dependent side effects and requires careful monitoring. The variability in responses to these therapies highlights the need for individualized treatment plans tailored to the specific needs and contexts of each patient [1].

This case report illustrates the successful management of PHHI in a neonate using octreotide and nifedipine as alternative therapies due to the unavailability of diazoxide. It contributes to the growing body of evidence supporting the use of these agents and emphasizes the importance of adaptable, evidence-based approaches in addressing the unique challenges of PHHI in resource-limited settings [2,4].

2. Case Presentation

A 48-hour-old baby girl presented to the emergency department with weakness and refusal to breastfeed. She was born at 39 weeks of gestation to a 32-year-old primigravida mother via spontaneous vaginal delivery, with no complications during pregnancy or delivery. Her birth weight was 2,800 grams, and her APGAR scores were 8 and 9 at 1 and 5 minutes, respectively. The neonate was discharged in stable condition 24 hours postpartum, but the mother noted increasing lethargy and feeding difficulties after discharge.

Upon admission, the baby was lethargic but responsive, with normal vital signs except for hypoglycemia, with a blood glucose (BG) level of 30 mg/dL. Initial physical examination showed no dysmorphic features, no signs of organomegaly, and normal growth parameters. There was no family history of diabetes, metabolic disorders, or consanguinity.

Laboratory investigations revealed a normal complete blood count and serum electrolytes but confirmed profound hypoglycemia. Initial management included intravenous (IV) glucose infusion at 8 mg/kg/min, which temporarily raised BG levels to 55 mg/dL. However, hypoglycemia recurred within hours, necessitating an increased glucose infusion rate to 12 mg/kg/min, then 20 mg/kg/min. Figure 1 illustrates the blood glucose levels during the initial days of hospitalization, showing severe hypoglycemia despite high glucose infusion rates before initiating octreotide therapy.

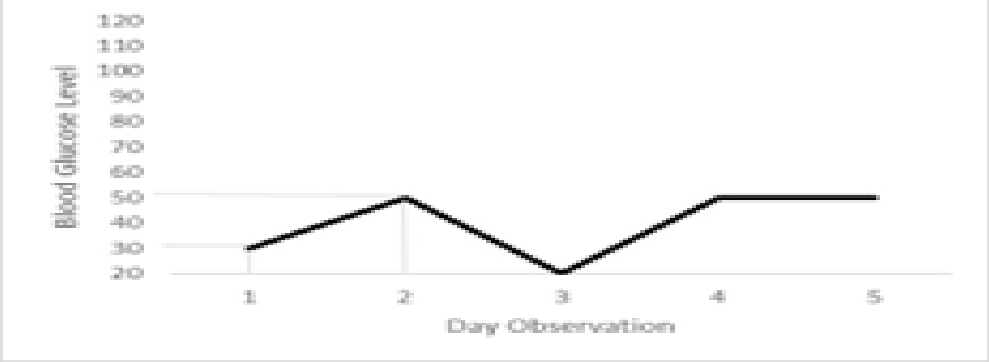

Figure 1.
Blood glucose levels during the initial days of hospitalization before initiation of octreotide therapy.

Further endocrinological evaluation included measurements of serum insulin, C-peptide, growth hormone (GH), cortisol, and ACTH during hypoglycemia episodes. The results showed elevated insulin (5.9 µU/mL), detectable C-peptide (4.4 ng/mL), and normal GH and cortisol levels, consistent with persistent hyperinsulinemic hypoglycemia. Imaging studies, including abdominal ultrasound, showed no evidence of pancreatic lesions, ruling out focal hyperinsulinism. Genetic testing to identify mutations commonly associated with PHHI could not be performed due to resource limitations.

Based on the diagnostic criteria from the 2023 International Guidelines for the Diagnosis and Management of Hyperinsulinism, the patient was diagnosed with Persistent Hyperinsulinemic Hypoglycemia in Infancy (PHHI), likely of diffuse etiology. Diazoxide, the first-line therapy, was

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unavailable, prompting the initiation of subcutaneous octreotide injections at 5 μg/kg/day. Despite initial improvements, BG levels fluctuated, necessitating dose adjustments up to 10 μg/kg/day. However, hypoglycemia episodes persisted. Figure 2 demonstrates the blood glucose levels after the initiation of octreotide therapy, indicating partial stabilization but with persistent fluctuations.

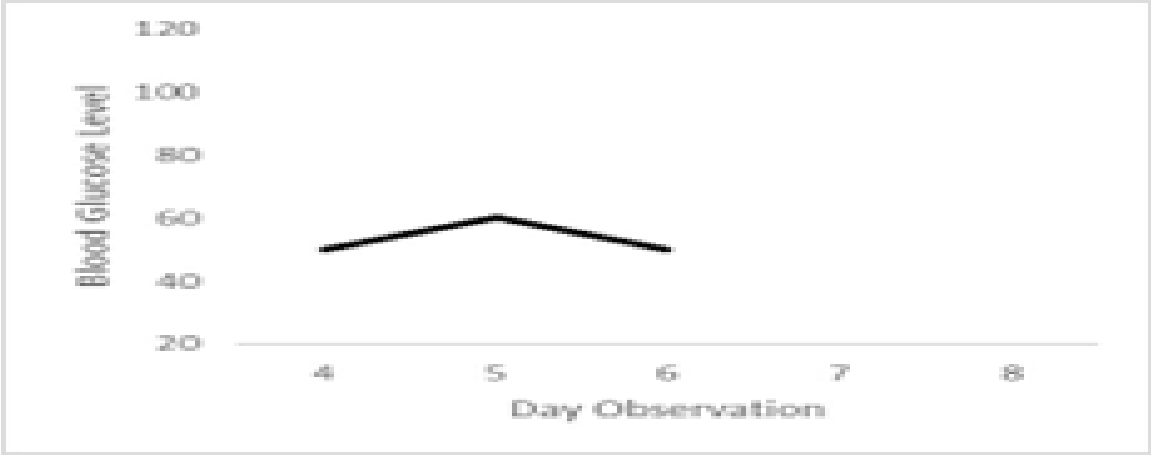

Figure 2.
Blood glucose levels after the initiation of octreotide therapy, showing partial stabilization with persistent fluctuations.

Given the suboptimal response to octreotide alone, oral nifedipine was introduced at 1 mg/kg/day in divided doses. Within 48 hours, BG levels stabilized between 66–90 mg/dL. The combination therapy allowed for gradual tapering of glucose infusion, eventually discontinuing IV glucose by day 10. The patient tolerated nifedipine well, with no adverse effects noted on cardiovascular monitoring. Figure 3 shows the blood glucose levels after combined treatment with octreotide and nifedipine, reflecting stable glycemic control achieved with the dual therapy.

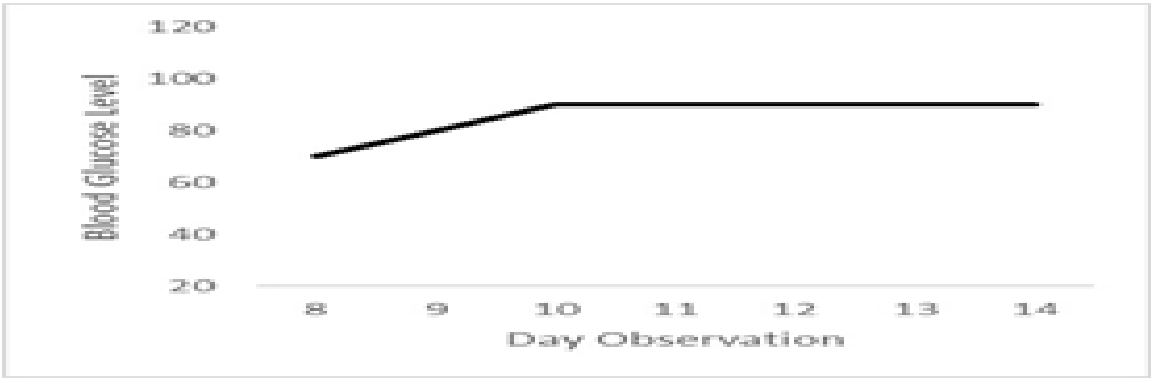

Figure 3.
Blood glucose levels after combined treatment with octreotide and nifedipine, showing stable glycemic control.

During the hospitalization, the baby developed hospital-acquired pneumonia (HAP) on day 6, presenting with fever, respiratory distress, and leukocytosis. Chest radiography confirmed bilateral infiltrates shown in Figure 4. She was treated with levofloxacin for 5 days, with complete resolution of symptoms. Subsequent cultures were negative, and inflammatory markers normalized.

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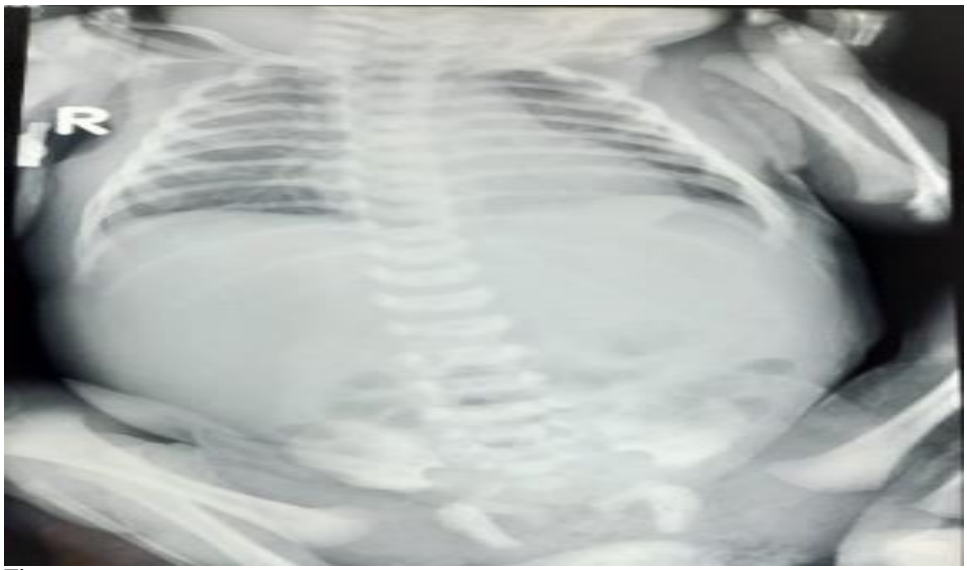

Figure 4.
Chest X-ray of the neonate demonstrating bilateral infiltrates consistent with pneumonia.

By day 14, the patient showed no signs of hypoglycemia, respiratory distress, or other complications. She was discharged on oral nifedipine with a scheduled follow-up in the pediatric endocrinology clinic. Parents were educated on recognizing hypoglycemia symptoms and instructed on home BG monitoring.

Discussion

Persistent Hyperinsulinemic Hypoglycemia in Infancy (PHHI) represents a significant challenge in neonatal metabolic management due to its rarity and potential for severe neurological complications [5]. This case highlights the complexity of diagnosing and managing PHHI, emphasizing the need for prompt, flexible, and evidence-based approaches to avoid long-term sequelae [2].

The clinical presentation of this neonate, including lethargy, poor feeding, and seizures within 48 hours of birth, aligns with established descriptions of PHHI. Early neonatal hypoglycemia often presents with nonspecific symptoms, potentially delaying diagnosis without vigilant monitoring. According to recent guidelines, PHHI should be suspected when hypoglycemia persists despite glucose infusion rates exceeding 8 mg/kg/min, as seen in this case [6].

Elevated insulin and C-peptide levels confirmed the diagnosis, consistent with the diagnostic criteria outlined in recent studies. This highlights the critical role of biochemical markers in diagnosing PHHI [7].

In this case, the unavailability of diazoxide necessitated alternative therapies, illustrating disparities in healthcare resource access. The successful management of the patient using a combination of octreotide and nifedipine underscores the importance of second-line therapies when standard treatments are not feasible [8]. Recent studies also document variable responses to nifedipine in PHHI, with promising but limited evidence supporting its efficacy, particularly in diazoxide-unresponsive cases [3].

The pathophysiology of Persistent Hyperinsulinemic Hypoglycemia in Infancy (PHHI) involves mutations in the ATP-sensitive potassium (KATP) channels within pancreatic β-cells, leading to dysregulated insulin secretion. These mutations, particularly in the KCNJ11 or ABCC8 genes, impair the functionality of the KATP channels, causing unregulated insulin release even under hypoglycemic conditions [9].

While focal PHHI cases often respond well to surgical resection, diffuse cases, as suspected in this neonate, require medical management due to the absence of localized pancreatic lesions. Imaging that fails to reveal focal lesions and a favorable clinical response to pharmacological therapy further supports

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a diffuse etiology [7]. Early diagnosis is crucial to mitigate the risk of permanent brain injury caused by prolonged hypoglycemia and neurotoxicity [10].

Nifedipine, a calcium channel blocker typically used for hypertension, may also influence insulin release in PHHI. By reducing calcium influx, it potentially modulates insulin secretion, offering a novel therapeutic pathway. However, its variable efficacy across cases highlights the need for further investigation to develop standardized treatment protocols [10].

Octreotide, a somatostatin analog, exerts its effect by binding to somatostatin receptors, predominantly SSTR2 and SSTR5, on pancreatic β-cells. This binding inhibits cyclic adenosine monophosphate (cAMP) production, subsequently reducing calcium influx and insulin secretion. Despite its efficacy in suppressing insulin secretion, studies have reported tachyphylaxis with prolonged use, necessitating dose adjustments or combination therapy [1]. Research has shown octreotide to be effective in managing hyperinsulinism, particularly in diazoxide-unresponsive cases [7]. However, side effects such as gastrointestinal disturbances and growth suppression remain concerns, particularly with long-term use [5].

Conversely, nifedipine blocks L-type calcium channels, directly inhibiting the calcium influx necessary for insulin granule exocytosis. This mechanism aligns with studies that report effective glycemic control in infants with PHHI treated with nifedipine [4]. A recent study highlighted that nifedipine achieved glycemic stability in 70% of cases when combined with octreotide. However, other studies question its standalone efficacy, with some reporting inadequate glycemic control or lack of response, particularly in cases associated with severe genetic mutations in KATP channels [7]. The variability in response necessitates a cautious, case-by-case approach [2].

The unavailability of diazoxide presented a significant challenge in this case. Octreotide, a somatostatin analog, was successfully used to suppress insulin secretion, although its efficacy fluctuated. This aligns with its recommended use in cases where diazoxide is ineffective or contraindicated, as supported by recent studies [8].

The combination of octreotide with nifedipine was pivotal in achieving stable blood glucose levels, facilitating the gradual reduction and eventual cessation of intravenous glucose infusion. This therapeutic combination highlights the potential role of calcium channel blockers in PHHI management when conventional treatments are insufficient [3].

This approach reflects the growing trend towards individualized patient care, particularly in resource-constrained settings. The success of such strategies underscores the need for further research to evaluate the long-term safety and efficacy of nifedipine in PHHI management. Additionally, this case emphasizes the importance of following updated international guidelines that advocate for a multidisciplinary approach to optimize clinical outcomes [7].

The occurrence of hospital-acquired pneumonia (HAP) during hospitalization illustrates the heightened vulnerability of neonates with PHHI to secondary infections. Prompt identification and treatment with levofloxacin were crucial in averting further complications [11]. This underscores the necessity for vigilant monitoring of nosocomial infections, particularly in neonates undergoing prolonged hospital stays and invasive procedures [12].

Despite these challenges, the neonate in this case showed marked improvement, attaining stable glycemic control without requiring surgical intervention. This favorable outcome, including normal growth and development at discharge, contrasts sharply with reports highlighting the high morbidity and mortality rates in untreated or poorly managed PHHI cases [13]. Research indicates that severe PHHI, if not adequately managed, can lead to neurological impairments in up to 50% of cases [14].

This case contributes significantly to the emerging evidence supporting the use of nifedipine in the management of PHHI. Its successful application here not only underscores an alternative therapeutic avenue but also prompts the reevaluation of treatment protocols in resource-limited settings. This adaptability aligns with international guidelines, suggesting a model for other clinicians facing similar resource constraints [6].

Moreover, the synergistic use of octreotide and nifedipine may represent an innovative therapeutic approach, meriting further exploration. Such combinations could expand the treatment arsenal for PHHI, particularly in cases where surgery is not an option or monotherapy proves insufficient [2].

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The primary limitation of this case is the short follow-up period, which restricts the ability to assess long-term outcomes, such as neurodevelopmental delays or the potential risk of diabetes mellitus. Longitudinal studies are essential to evaluate the sustainability of glycemic control and broader patient outcomes, as highlighted in similar research focusing on chronic conditions in neonates [15].

While this case underscores the utility of nifedipine in managing PHHI, the absence of large-scale, randomized controlled trials limits the generalizability of these findings. Future research should prioritize these trials to establish nifedipine's efficacy, optimal dosing, and safety profile in PHHI management. Such studies would strengthen the evidence base and provide clear guidance for clinical practice [16].

The significance of this case lies not only in its management strategy but also in its potential to broaden the understanding of therapeutic flexibility in PHHI. It underscores the importance of tailoring treatment to individual patient needs, particularly in resource-constrained settings where standard therapies may be inaccessible [1]. Additionally, it provides valuable clinical insights into the efficacy of nifedipine in managing a condition historically treated with more conventional pharmacological agents.

This case serves as an important contribution to the growing body of knowledge on PHHI, illustrating the critical need for early diagnosis and intervention to prevent severe outcomes. It also opens a dialogue on the potential role of alternative therapies, paving the way for further research and consideration of novel management strategies in the context of persistent neonatal hypoglycemia.

3. Conclusion

This case highlights the successful management of PHHI using octreotide and nifedipine, demonstrating their potential as effective alternatives when first-line therapy is unavailable. It underscores the importance of early diagnosis and individualized treatment in preventing severe complications. The findings suggest a broader exploration of nifedipine's role in PHHI, especially in resource-limited settings, and emphasize the need for updated clinical protocols to optimize neonatal outcomes. This case serves as a critical reference for advancing future research and clinical practice.

4. Recommendation

Based on this case, we recommend expanding the use of nifedipine as a second-line therapy for Persistent Hyperinsulinemic Hypoglycemia in Infancy (PHHI), especially in settings where diazoxide is unavailable. Standardizing dosing and evaluating long-term efficacy through multicenter clinical trials is essential. Early diagnosis and adherence to international guidelines are critical to preventing severe complications.

To address challenges in resource-limited settings, we advocate for the development of regional guidelines that integrate alternative therapies like nifedipine and octreotide. Structured training programs for healthcare professionals in low- and middle-income countries are crucial to enhance diagnostic and therapeutic capacity.

Multidisciplinary collaboration among neonatologists, endocrinologists, and pediatricians is essential for holistic management. Establishing registries to systematically collect data on alternative therapies will strengthen evidence-based practice and inform clinical protocols. These efforts aim to improve PHHI outcomes globally, particularly in resource-constrained environments, while paving the way for innovative and accessible treatment approaches.

Conflict of Interest:

The authors declare that there is no conflict of interest regarding the publication of this manuscript. No financial support, sponsorship, or external funding was received for this case report. The authors affirm that there are no personal or institutional relationships that could be perceived as influencing the work presented in this manuscript.

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