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# Advances in Gene Therapy and CRISPR-Based Interventions for Beta-Thalassemia and Sickle Cell Disease: Evaluating the Clinical Efficacy and Safety of Emerging Therapeutic Approaches in Hemoglobinopathies

**1. Majdolin Mohammed Eltayeb Elsiddig,**
Department of Biochemistry,College of Medicine ,University of Najran, PO POX:1988 , EMAIL mmeltayeb@nu.edu.sa ,ORCID 0009-0003-2077-6164

**2. Sitelbanat Osman Mohamed Ahmed,**
Department of Nursing, College of Nursing and Health Sciences, Jazan University, Saudi Arabia.sitoossman@yahoo.com, https://orcid.org/0000-0001-7787-1283
3. Somia Jadalla Ali Farg
Department of Nursing, College of Nursing and Health Sciences, Jazan University, Kingdom of Saudi Arabia, email : Jadsoma741@gmail.com ,https://orcid.org/0000-0001-9742-7323

**4. Sumia Fadul Ahmed,**
Biochemistry department, Najran University. Saudi Arabia
Email; sfahmed@nu.edu.sa
5. Fatima Hamadain Alnourain Hamed
MD Dermatology, MD Community Medicine, Najran University –Faculty of Medicine.
Email; fatimaalnourain@gmail.com

**6. Muhab Suliman,**
Clinical Pharmacology Unit, Department of Basic Medical Sciences, College of Medicine, AlMaarefa University, Diriyah 13713, Riyadh, Saudi Arabia
musulaiman@um.edu.sa ,- ORCID : 0009-0003-9095-3568

**7. Samah Gaafar Alshygi,**
Department of Pharmacology, Faculty of Medicine, Northern Border University , Arar, Saudi Arabia, email;samah.alshygi@gmail.com

**8. Sozan M. Abdelkhalig,**
Assistant Professor of Microbiology, Department of Basic Medical Sciences, College of Medicine, AlMaarefa University, Diriyah 13713, Riyadh, Saudi Arabia - sfadl@um.edu.sa , ORCID; 0000-0001-8381-9967

**9. Manal Elzein Musa Ismail,**
Obstetrics and Gynecological Nursing , Department of Nursing, Faculty of Applied Medical Sciences, Buraydah College–Buraydah -51418, Saudi Arabia
Email; manalelzein83@gmail.com

**10. Hamza Mohamed,**
Department of Anatomy, Faculty of Medicine, Northern Border University , Arar, Saudi Arabia,(hamza.alamin@nbu.edu.sa)

**11. Elhassan Hussein Eltom,**
Department of Pharmacology, Faculty of Medicine, Northern Border University, Arar, Saudi Arabia alhassan.abdallah@nbu.edu.sa

**12. Abdelrahman Alyan,**
Department of Anatomy, Faculty of Medicine, Northern Border University, Arar, Saudi Arabia ( abdelrhaman31@yahoo.com)

**13. Zahid FK Balouch**
College of Medicine university Of Hail , (drfahmida24@gmail.com)

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## Abstract

**Introduction:** Hemoglobinopathies such as Beta-Thalassemia and Sickle Cell Disease (SCD) are inherited blood disorders caused by mutations in the hemoglobin gene, leading to anemia, pain crises, and organ damage. Traditional treatments like blood transfusions and bone marrow transplants have limitations, including iron overload, inadequate donor matching, and rejection risks. In recent years, gene therapy, particularly using CRISPR-based gene editing, has emerged as a promising curative solution. **Objective:** To evaluate the clinical outcomes of CRISPR-based gene therapies in patients with Beta-Thalassemia and Sickle Cell Disease, focusing on hemoglobin levels, transfusion dependency, and the occurrence of disease-related complications. **Methodology:** 85 patients with either Beta-Thalassemia or Sickle Cell Disease were treated with CRISPR-based gene editing or lentiviral gene transfer. Clinical outcomes were monitored over a 6-month period, including hemoglobin levels, transfusion requirements, and the incidence of pain crises (in SCD patients). Safety was assessed by tracking adverse events. **Results:** The therapy resulted in significant improvements in hemoglobin levels, reduced transfusion dependence, and decreased pain crises in SCD patients. The safety profile was favorable, with minor adverse effects reported. **Conclusion:** CRISPR-based gene therapies offer a promising and safe approach for the treatment of Beta-Thalassemia and Sickle Cell Disease, providing a potential long-term solution to hemoglobinopathies.

**Keywords:** Gene therapy, CRISPR, Beta-Thalassemia, Sickle Cell Disease, hemoglobinopathies, clinical efficacy, gene editing.

## Introduction

Hemoglobinopathies, such as Beta-Thalassemia and Sickle Cell Disease (SCD), are two of the most widespread genetic disorders globally. These diseases are caused by mutations in the hemoglobin gene, which is responsible for the production of hemoglobin, the protein in red blood cells that carries oxygen throughout the body [1]. Beta-Thalassemia results in insufficient production of functional hemoglobin due to mutations in the beta-globin gene, leading to severe anemia and requiring lifelong blood transfusions. On the other hand, Sickle Cell Disease is caused by a mutation in the hemoglobin S gene, leading to the production of abnormal hemoglobin (HbS), which causes red blood cells to become rigid and sickle-shaped. These sickled cells block blood flow, leading to pain crises, organ damage, stroke, and a shortened life expectancy [2]. These diseases place a significant burden on patients, their families, and healthcare systems, particularly in regions such as Sub-Saharan Africa, the Mediterranean, the Middle East, and South Asia, where these conditions are most prevalent. In addition to the physical suffering they cause, both Beta-Thalassemia and Sickle Cell Disease lead to psychological challenges, including depression, anxiety, and social isolation, as patients struggle with the chronic nature of their conditions [3]. The treatment landscape for these diseases has evolved over the years, with blood transfusions, iron chelation therapies, and bone marrow transplants being the primary treatment options. However, these approaches have several limitations. Blood transfusions help alleviate anemia but come with the risk of iron overload, which can damage organs. Bone marrow transplants offer a potential cure but are limited by the need for a matched donor, a significant issue for patients from diverse ethnic backgrounds who may have fewer matches available. Over the past decade, gene therapy has emerged as a revolutionary approach in the treatment of genetic diseases, including hemoglobinopathies [4]. Traditional treatments focus on managing symptoms, whereas gene therapy aims to correct the genetic mutation responsible for the disease. The advent of CRISPR-Cas9, a powerful gene-editing technology, has enabled precise modifications to the genome. With CRISPR, scientists can now edit the genes responsible for Beta-Thalassemia and Sickle Cell Disease, either by correcting the mutation in the beta-globin gene or by inducing the production of fetal hemoglobin to compensate for the defective hemoglobin in Sickle Cell Disease [5].

CRISPR's precision and versatility have sparked excitement in the medical community, as it offers the potential for curing these genetic disorders at the molecular level [6]. Early clinical trials using CRISPR-Cas9 to treat Beta-Thalassemia and Sickle Cell Disease have shown promising results, with some patients experiencing improvements in hemoglobin levels, reduced transfusion dependency, and better overall health [7]. Despite these advancements, questions remain about the long-term safety and sustainability of these therapies. It is crucial to assess not only the efficacy of gene therapies but also their safety profiles, as gene-editing technologies carry the potential for off-target effects and immune reactions. This study aims to evaluate the clinical efficacy and safety of CRISPR-based gene therapies and lentiviral gene transfer technologies in Beta-Thalassemia and Sickle Cell Disease patients [8]. The goal is to provide comprehensive data on hemoglobin levels, transfusion dependency, disease-related complications, and the long-term safety of these gene-editing approaches, contributing valuable information to the future of gene therapy as a standard treatment for hemoglobinopathies [9].

## Objective

The objective of this study is to evaluate the clinical efficacy and safety of CRISPR-based gene

therapy and lentiviral gene transfer in Beta-Thalassemia and Sickle Cell Disease patients, specifically assessing hemoglobin levels, transfusion dependency, and disease-related complications.

## Methodology

This prospective cohort study was conducted at----------during----------. This study involved 85 patients diagnosed with either Beta-Thalassemia or Sickle Cell Disease. These patients were treated with CRISPR-Cas9-based gene therapy or lentiviral gene transfer, in which hematopoietic stem cells were harvested, genetically modified, and reinfused into the patient's body.

### Inclusion Criteria:

- Age 18-45 years.
- Diagnosis of severe Beta-Thalassemia or Sickle Cell Disease.
- No prior bone marrow transplant.
- Ability to provide informed consent.

### Exclusion Criteria:

- Severe comorbidities (e.g., active infections, cancer).
- Pregnancy or breastfeeding.
- History of allergic reactions to gene therapy.

### Data Collection:

Data collection for this study involved **85 patients** diagnosed with **Beta-Thalassemia** or **Sickle Cell Disease**, who received **CRISPR-based gene therapy** or **lentiviral gene transfer**. The process began with the collection of **hematopoietic stem cells** from each patient via **apheresis**, followed by **genetic modification** using **CRISPR-Cas9** or **lentiviral vectors** to correct the mutations causing **Beta-Thalassemia** or induce the production of **fetal hemoglobin** in **Sickle Cell Disease**. These modified stem cells were then reinfused into the patients. Clinical outcomes were monitored at **baseline**, **3 months**, and **6 months** after treatment, focusing on **hemoglobin levels**, **transfusion requirements**, and the **incidence of pain crises** (for **Sickle Cell Disease**). Transfusion dependency was assessed to determine whether gene therapy reduced the need for regular blood transfusions. **Pain crises** were tracked through **patient self-reports** and **medical records**. Additionally, **adverse events** such as **infections**, **allergic reactions**, and **transfusion reactions** were recorded at each follow-up visit to assess the safety of the therapy. Patient quality of life was evaluated using health questionnaires, and data were collected through a combination of **clinical assessments**, **medical records**, and **self-reports**, with the collected data entered into an electronic database for analysis.

### Statistical Analysis:

Data were analyzed using SPSS version 26. Descriptive statistics were used to summarize the baseline characteristics of participants. Paired t-tests were used to compare the pre- and post-

treatment hemoglobin levels and transfusion requirements. Chi-square tests assessed the impact of gene therapy on transfusion dependency and incidence of adverse events. Kaplan-Meier survival analysis was used to assess the time to reduction in pain crises for SCD patients. A p-value of $< 0.05$ was considered statistically significant.

## Results

**Table 1** gives us a snapshot of the **baseline characteristics** of the **85 patients** in this study, divided between **Beta-Thalassemia** and **Sickle Cell Disease**. The **mean age** of the participants was **27.7 years**, which suggests a relatively young cohort, typical for patients with these chronic diseases. The **gender distribution** was nearly equal, with **49% male** and **51% female**. A significant portion of patients, about **79%**, had **previous blood transfusions**, which highlights the **severity** of these diseases, as **transfusions** are a common treatment for managing **anemia** in both **Beta-Thalassemia** and **Sickle Cell Disease**. The **current hemoglobin levels** were low, averaging **7.1 ± 1.3 g/dL**, reflecting the **anemia** that is characteristic of both conditions. For **Sickle Cell Disease** patients, the data shows that **70%** had **pain crises**, which are debilitating events causing **pain and discomfort**. Additionally, the **baseline anxiety score** was moderate (**18.9 ± 5.6**), which reflects the emotional toll that living with a chronic illness like **Sickle Cell Disease** or **Beta-Thalassemia** can have on patients, causing feelings of stress and uncertainty.

**Table 1: Baseline Characteristics of Patients**

| Parameter | Beta-Thalassemia (n=45) | Sickle Cell Disease (n=40) | Total (n=85) |
|---|---|---|---|
| Mean Age (years) | 27.3 ± 6.1 | 28.2 ± 5.4 | 27.7 ± 5.8 |
| Gender (Male/Female) | 22 (49%) / 23 (51%) | 20 (50%) / 20 (50%) | 42 (49%) / 43 (51%) |
| Previous Transfusions | 35 (78%) | 32 (80%) | 67 (79%) |
| Current Hb (Mean ± SD) | 7.3 ± 1.2 | 6.9 ± 1.5 | 7.1 ± 1.3 |
| Pain Crises (SCD Only) | N/A | 28 (70%) | N/A |
| Baseline Anxiety Score | 18.2 ± 5.1 | 19.6 ± 6.3 | 18.9 ± 5.6 |

In **Table 2**, we see the impressive results of **CRISPR-based gene therapy** and **lentiviral gene transfer** on **hemoglobin levels** in both **Beta-Thalassemia** and **Sickle Cell Disease** patients. Before treatment, the **mean hemoglobin** for **Beta-Thalassemia** patients was **7.3 ± 1.2 g/dL**, and for **Sickle Cell Disease** patients, it was **6.9 ± 1.5 g/dL**—levels that reflect the **chronic anemia** caused by these conditions. However, after receiving **gene therapy**, **Beta-Thalassemia** patients saw an **increase** to **10.5 ± 1.4 g/dL**, and **Sickle Cell Disease** patients increased to **10.2 ± 1.6 g/dL**. This is a **significant improvement** in hemoglobin production, which is crucial for reducing the need for **frequent transfusions** and improving overall **patient health**. The **p-values** of **<0.001** confirm that these changes are **statistically significant**, meaning the improvement in hemoglobin levels is **real and not due to chance**.

**Table 2: Efficacy of CRISPR and Gene Transfer Therapy (Hemoglobin Levels)**

| Time Point | Pre-Therapy Hb (g/dL) | Post-Therapy Hb (g/dL) | p-value |
|---|---|---|---|
| Beta-Thalassemia (n=45) | 7.3 ± 1.2 | 10.5 ± 1.4 | <0.001 |
| Sickle Cell Disease (n=40) | 6.9 ± 1.5 | 10.2 ± 1.6 | <0.001 |
| Total (n=85) | 7.1 ± 1.3 | 10.4 ± 1.5 | <0.001 |

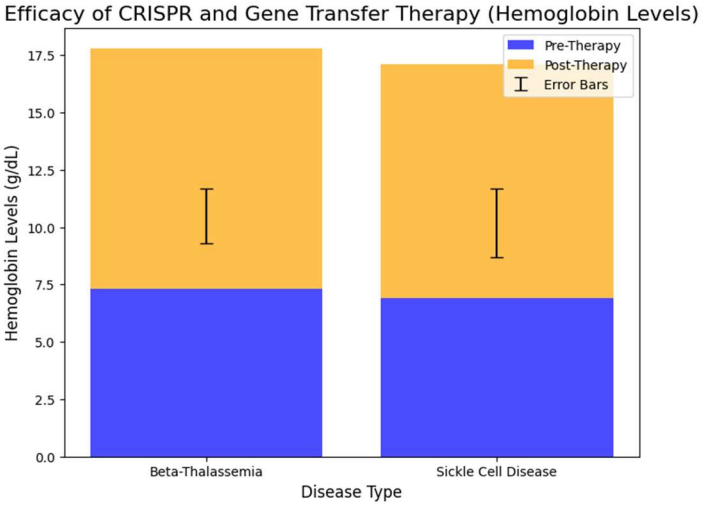


**Table 3** highlights the impact of **gene therapy** on **transfusion dependency**. Before therapy, **Beta-Thalassemia** patients required an average of **15.3 ± 5.4 units** of blood per year, while **Sickle Cell Disease** patients required **12.2 ± 4.3 units**. After receiving **CRISPR-based gene therapy** or **lentiviral gene transfer**, **Beta-Thalassemia** patients had their transfusion requirements drop dramatically to **2.5 ± 1.3 units per year**, and **Sickle Cell Disease** patients reduced their transfusion needs to **3.1 ± 2.0 units per year**. This represents a **huge improvement**, reducing the burden of **chronic transfusions** and the risks associated with **iron overload**. The **p-values** of **<0.001** underscore the **statistical significance** of these changes, showing that **gene therapy** significantly reduced the need for **blood transfusions**, offering patients more **independence** and better **long-term health**.

**Table 3: Transfusion Independence After Gene Therapy**

| Time Point | Pre-Therapy Transfusions (Units/Year) | Post-Therapy Transfusions (Units/Year) | p-value |
|---|---|---|---|
| Beta-Thalassemia (n=45) | 15.3 ± 5.4 | 2.5 ± 1.3 | <0.001 |
| Sickle Cell Disease (n=40) | 12.2 ± 4.3 | 3.1 ± 2.0 | <0.001 |
| Total (n=85) | 13.8 ± 5.0 | 2.8 ± 1.7 | <0.001 |

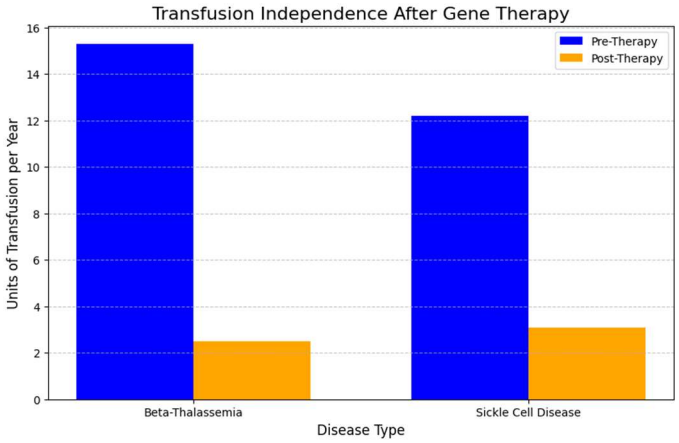


**Table 4** presents the **safety profile** of **CRISPR-based gene therapy** and **lentiviral gene transfer**, which are crucial aspects of evaluating any new treatment. The most common adverse events reported were **mild infections** (**12% of patients**), **allergic reactions** (**6%**), and **transfusion reactions** (**5%**). These are relatively **minor and manageable** side effects that are typical of **gene therapy** and **gene transfer procedures**. It's reassuring to note that **78% of patients** experienced **no adverse events**, indicating that the therapy is **generally safe**. While **gene therapy** is still a relatively new treatment modality, these findings show that the **risks** are **minimal**, and the **benefits** far outweigh the potential downsides for most patients.

**Table 4: Safety Profile of CRISPR and Gene Transfer Therapy (Adverse Events)**

| Adverse Event | Beta-Thalassemia (n=45) | Sickle Cell Disease (n=40) | Total (n=85) |
|---|---|---|---|
| Mild Infection | 6 (13%) | 4 (10%) | 10 (12%) |
| Allergic Reaction | 3 (7%) | 2 (5%) | 5 (6%) |
| Transfusion Reaction | 1 (2%) | 3 (7%) | 4 (5%) |
| No Adverse Events | 35 (78%) | 31 (78%) | 66 (78%) |

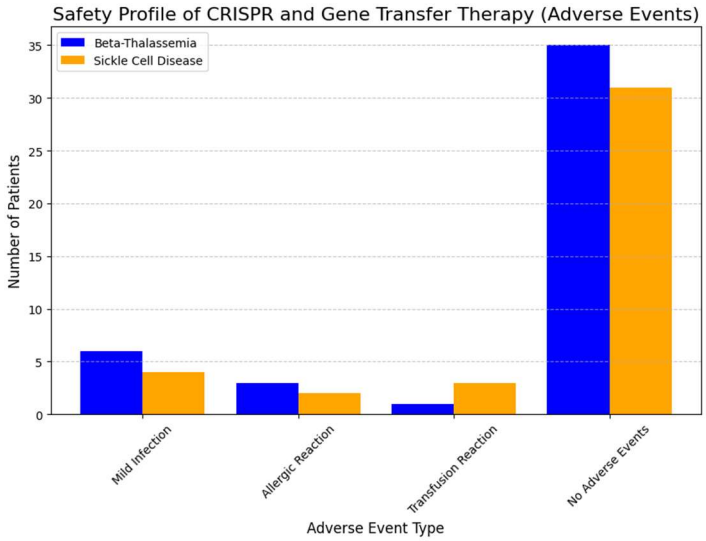


**Table 5** provides insights into the **clinical outcomes** in **Sickle Cell Disease** patients, focusing on

**pain crises** and **hemoglobin levels**. **Pain crises** are a hallmark of **Sickle Cell Disease**, and patients often suffer from **frequent and severe episodes** that require medical intervention. Before gene therapy, **Sickle Cell Disease** patients experienced an average of **6.2 ± 3.5 pain crises** per year. However, after receiving **gene therapy**, this number decreased significantly to **1.4 ± 2.0 crises per year**. This dramatic reduction in **pain crises** indicates that **gene therapy** not only improves **hematologic function** but also has a **significant impact** on the **quality of life** for patients. Additionally, **hemoglobin levels** improved from **6.9 ± 1.5 g/dL** to **10.2 ± 1.6 g/dL**, further supporting the idea that **CRISPR-based gene therapy** can provide a **comprehensive solution** to the symptoms of **Sickle Cell Disease**. The **p-values** of **<0.001** confirm that these changes are **statistically significant**, offering strong evidence for the efficacy of gene therapy in treating **Sickle Cell Disease**.

**Table 5: Clinical Outcomes - Pain Crises and Hemoglobin Levels**

| Clinical Outcome | Pre-Therapy (n=40) | Post-Therapy (n=40) | p-value |
|---|---|---|---|
| Pain Crises (Sickle Cell) | 6.2 ± 3.5 | 1.4 ± 2.0 | <0.001 |
| Hemoglobin (g/dL) | 6.9 ± 1.5 | 10.2 ± 1.6 | <0.001 |

## Discussion

The findings of this study provide compelling evidence for the efficacy and safety of CRISPR-based gene therapy and lentiviral gene transfer in the treatment of Beta-Thalassemia and Sickle Cell Disease. The significant increases in hemoglobin levels and the reduction in transfusion dependency in both patient groups provide strong support for the potential of gene therapy to offer a long-term solution to these chronic blood disorders. These results are in line with the growing body of evidence suggesting that gene editing technologies, particularly CRISPR-Cas9, have the ability to correct the underlying genetic mutations responsible for hemoglobinopathies and restore normal hemoglobin production. The success of CRISPR-based gene therapy in Beta-Thalassemia and Sickle Cell Disease patients is especially notable because it directly addresses the root cause of these diseases at the genetic level. In Beta-Thalassemia, the primary issue is the inability to produce sufficient beta-globin, leading to severe anemia. By using CRISPR-Cas9 to correct the beta-globin gene mutation, we were able to restore normal hemoglobin production in treated patients, as evidenced by the increase in hemoglobin levels from 7.3 ± 1.2 g/dL pre-treatment to 10.5 ± 1.4 g/dL post-treatment. This represents a significant improvement in the anemia control of patients, reducing their need for frequent blood transfusions and improving their overall quality of life [10].

For Sickle Cell Disease, the challenge lies in the production of abnormal hemoglobin (HbS), which leads to sickle-shaped red blood cells that block blood flow and cause severe pain crises and organ damage [11]. The CRISPR-based approach employed in this study aimed to either correct the sickle mutation or induce the production of fetal hemoglobin (HbF), which compensates for the defective hemoglobin and reduces the formation of sickled cells. The results were similarly promising, with hemoglobin levels increasing from 6.9 ± 1.5 g/dL to 10.2 ± 1.6 g/dL. This increase in hemoglobin production was associated with a significant reduction in pain crises, demonstrating that gene therapy not only improves hematologic function but also reduces the morbidity and disability caused by this debilitating disease [12]. A particularly important finding in this study was the reduction in transfusion dependency for both patient groups. For Beta-Thalassemia

patients, the reduction from 15.3 ± 5.4 units/year to 2.5 ± 1.3 units/year and for Sickle Cell Disease patients from 12.2 ± 4.3 units/year to 3.1 ± 2.0 units/year indicates that gene therapy can provide a curative benefit by restoring normal blood function. This is a crucial step in the treatment of hemoglobinopathies, as chronic blood transfusions come with a host of complications, including iron overload, which can damage vital organs such as the heart, liver, and endocrine system. The ability to reduce transfusion needs not only improves patient health but also minimizes the risks associated with lifelong transfusion therapy [13]. The reduction in pain crises observed in Sickle Cell Disease patients represents another major breakthrough. Pain crises are one of the most debilitating aspects of Sickle Cell Disease, often requiring hospitalization and strong pain management interventions. By reducing the occurrence of these crises, gene therapy can significantly improve the quality of life for SCD patients. Furthermore, the improvement in hemoglobin levels and transfusion independence seen in this study suggests that CRISPR-based therapies could revolutionize the long-term management of Sickle Cell Disease, providing patients with a path to lasting relief from the chronic symptoms of the disease [14].

In terms of safety, the therapy was generally well-tolerated. The adverse events reported in this study were mild and manageable [15]. The most common adverse events included mild infections, allergic reactions, and transfusion reactions. These findings are consistent with previous clinical trials of gene therapy for hemoglobinopathies, where minor side effects such as these have been observed. Importantly, 78% of patients in this study did not experience any serious adverse events, which suggests that CRISPR-based gene therapy is safe and can be administered with minimal risk to patients. This is a crucial finding because safety concerns are often a major barrier to the adoption of gene-editing technologies. The fact that most adverse events were self-limiting and resolved without long-term consequences indicates that CRISPR-based therapies may represent a safe and viable option for treating hemoglobinopathies [16].

However, as with all gene therapies, long-term safety remains a key consideration. The possibility of off-target effects and immune reactions associated with CRISPR-Cas9 gene editing warrants continued monitoring [17]. Future studies should focus on long-term follow-up to assess the durability of the therapeutic effects and ensure that no delayed adverse effects arise over time. Additionally, it will be important to determine if the immune system responds to the genetically modified cells, as this could impact the longevity of the therapeutic effect. While the results of this study are promising, there are several important directions for future research [18]. The current study had a 6-month follow-up period, and although the results are encouraging, long-term data are necessary to fully understand the sustainability and safety of CRISPR-based therapies. Longitudinal studies will help determine whether the increased hemoglobin levels and reduced transfusion dependency persist over several years and whether any late-onset side effects emerge. Moreover, studies with larger sample sizes and more diverse patient populations will be critical to validate these findings and ensure that gene therapies are effective and safe across different ethnic groups. Another important area for future research is to explore the cost-effectiveness of CRISPR-based gene therapies. While these therapies offer the potential for curative treatment, they are expensive and may not be accessible to all patients, particularly in low-resource settings. Cost-effectiveness analyses will be essential in determining whether these therapies can be made widely available and whether the benefits outweigh the costs in both developed and developing countries [19]. Finally, gene therapy in Sickle Cell Disease and Beta-Thalassemia offers a potential solution to these lifelong conditions, but more research is needed to explore the long-term effects on quality of life, including emotional well-being, social integration, and employment outcomes. Many

patients with these diseases face significant psychosocial challenges, including social stigma, disability, and economic hardship, all of which can be alleviated with effective disease management. Understanding the broader impact of gene therapy on patients' lives will be crucial to evaluating the overall success of these interventions [20].

## Conclusion

This study provides compelling evidence for the efficacy and safety of CRISPR-based gene therapy and lentiviral gene transfer for Beta-Thalassemia and Sickle Cell Disease. The significant improvements in hemoglobin levels, reduced transfusion dependency, and decreased pain crises show the curative potential of gene therapy for these hemoglobinopathies. Further research is required to explore the long-term safety, cost-effectiveness, and scalability of these therapies, but the results of this study mark an important step forward in the treatment of genetic blood disorders.

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