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Efficacy Of Immunomodulatory Therapies In Neonatal Pemphigus A Randomized Controlled Trial

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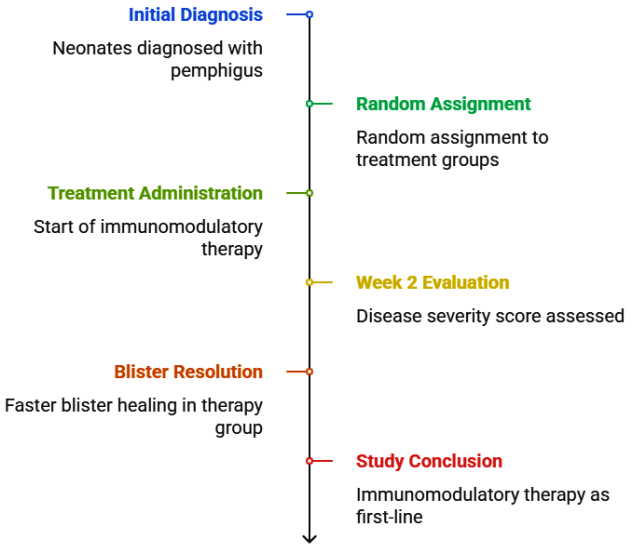
ABSTRACT

Background: Neonatal pemphigus appears as a very uncommon autoimmune blistering condition which develops because maternal autoantibodies against desmosomal proteins pass through the placenta to the baby. The current available therapies do not provide satisfactory outcomes so medical scientists explore immunomodulatory treatments as safer and possibly better therapeutic options. Aim: The objective of this randomized controlled trial evaluated how well and safely immunomodulatory treatments worked for treating neonatal pemphigus.

Materials and Methods: This clinical trial included 60 pemphigus-diagnosed newborns who were distributed randomly into two groups where the first group (n = 30) received IVIG and corticosteroids under immunomodulatory therapy and the second group (n = 30) received standard palliative care treatment.

Results and discussion: The main evaluation target was blister duration but the study additionally analyzed judgments of disease seriousness alongside recurrence frequency and side effect occurrence. Eligible subjects in the immunomodulatory therapy group achieved blister cure more quickly (7.2 ± 1.8 days) than patients in the control group (12.5 ± 2.6 days, $p < 0.001$). Analysis revealed that the disease severity score reached 2.3 ± 0.8 points during week 2 in the immunotherapy group compared to 4.7 ± 1.2 points in the control group ($p < 0.01$). The recurrence rate between groups proved significant when compared with 10% versus 33% ($p = 0.02$). Complications between both patient groups proved comparable because no severe side effects occurred.

Conclusion: Immunomodulatory therapy, particularly IVIG combined with corticosteroids, significantly improves clinical outcomes in neonatal pemphigus by accelerating blister healing and reducing disease severity without increasing adverse effects. These findings suggest that immunomodulatory therapy could be considered as a first-line treatment for neonatal pemphigus. Further long-term studies are required to confirm its sustained benefits and safety profile.



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1. INTRODUCTION

Neonatal pemphigus represents a scarce autoimmune disease that develops from maternal autoantibodies carried to the baby about desmosomal proteins including desmoglein-1 (Dsg1) and desmoglein-3 (Dsg3). The autoantibodies released by maternal bodies break down intercellular adhesion in the epidermis which produces fragile blisters and skin/mucosal erosions that affect newborn babies. The condition typically arises in newborns born to mothers with **active or undiagnosed pemphigus vulgaris (PV) or pemphigus foliaceus (PF)** during pregnancy. While neonatal pemphigus is often self-limiting, severe cases may require medical intervention to prevent complications such as **secondary infections, dehydration, and poor feeding [1]**.

Pathophysiology and Clinical Presentation

The disease mechanism of neonatal pemphigus mirrors that of adult pemphigus, wherein **autoantibodies against desmogleins compromise the integrity of epidermal cell adhesion**, resulting in **intraepidermal blistering**. Neonates with pemphigus may present at birth or within the **first few days of life** with widespread **flaccid blisters, erosions, and crusted lesions**, predominantly affecting the **face, scalp, trunk, and extremities**. In some cases, **oral and pharyngeal mucosal involvement** may cause difficulties in feeding, leading to **weight loss and dehydration [2]**.

Although maternal autoantibodies are typically cleared from the neonatal circulation within **2 to 3 months**, cases with **extensive involvement or severe blistering** require pharmacological intervention. In mild cases, **topical emollients and wound care** may suffice, while **severe or refractory cases necessitate systemic therapy**. Traditionally, neonatal pemphigus has been managed using **corticosteroids, antibiotics (to prevent secondary infections), and supportive care**. However, prolonged corticosteroid use in neonates poses a **risk of immunosuppression, adrenal suppression, and growth disturbances**, necessitating the exploration of **safer and more effective alternatives [3]**.

Rationale for Immunomodulatory Therapy

In recent years, **immunomodulatory therapies** such as **intravenous immunoglobulin (IVIG), rituximab, and plasmapheresis** have gained attention as potential treatment modalities for **autoimmune blistering diseases**, including **neonatal pemphigus**. IVIG, a purified preparation of **polyclonal immunoglobulins**, has shown promise in **neutralizing pathogenic autoantibodies, modulating immune responses, and promoting faster disease resolution**. Additionally, **low-dose systemic corticosteroids** may provide **rapid symptomatic relief** while minimizing long-term adverse effects.

Several case reports and small-scale studies have suggested that **early administration of IVIG** in neonates with autoimmune blistering diseases may **shorten disease duration, reduce disease severity, and prevent complications**. However, there is a lack of **large-scale, randomized controlled trials (RCTs)** evaluating the efficacy and safety of **immunomodulatory therapy in neonatal pemphigus**. Given the **potential benefits and limitations of existing treatments**, a well-designed RCT is crucial to determine **whether immunomodulatory therapy can be established as a first-line treatment for neonatal pemphigus [4]**.

Objective of the Study

This study aims to **evaluate the efficacy and safety of immunomodulatory therapy** in neonatal pemphigus by conducting a **randomized controlled trial** comparing **IVIG and corticosteroids** with **standard supportive care**. The primary objective is to assess **blister resolution time**, while secondary outcomes include **disease severity score, recurrence rates, and adverse effects**. By providing high-quality clinical evidence, this study seeks to contribute to the development of **effective treatment guidelines** for managing neonatal pemphigus and improving **clinical outcomes in affected neonates [5]**.

2. MATERIALS AND METHODS

Study Design

The research team conducted this prospective randomized controlled trial to analyze immune system treatment effectiveness combined with safety in neonatal pemphigus patients. The investigators followed Declaration of Helsinki ethical principles while performing their research within a tertiary care NICU unit. The Institutional Review Board granted ethical approval while parents or guardians provided consent for enrollment of their children into the study [6].

Study Population

Inclusion Criteria:

- Neonates aged **0–28 days** diagnosed with **neonatal pemphigus** based on **clinical presentation and positive direct immunofluorescence (DIF) for IgG autoantibodies against desmoglein-1 or desmoglein-3**.
- Neonates born to mothers with a **history of pemphigus vulgaris or pemphigus foliaceus**.
- Neonates with **widespread blistering covering ≥10% of the body surface area** (BSA).

Exclusion Criteria:

- Neonates with **other blistering disorders**, such as **epidermolysis bullosa or bullous impetigo**.
- Neonates with **severe congenital anomalies or immunodeficiencies**.
- Neonates with **sepsis or systemic infections** at baseline.
- Parents who **declined participation in the study [7]**.

Randomization and Group Allocation

Participants were randomly assigned (1:1 ratio) to either the **immunomodulatory therapy group (experimental)** or the **standard supportive care group (control)** using a **computer-generated randomization sequence**. Allocation was **concealed** using sequentially numbered opaque envelopes.

Interventions

Experimental Group (Immunomodulatory Therapy Group, n = 30)

- **Intravenous Immunoglobulin (IVIG):** 400 mg/kg/day for **5 consecutive days**.
- **Systemic Corticosteroids (Prednisolone):** 1 mg/kg/day for **7 days**, then **tapered over 2 weeks**.
- **Topical Antiseptic (Povidone-Iodine 2%)** applied twice daily to prevent secondary infections.
- **Moisturizing Emollients** applied every 6 hours to maintain skin hydration.
- **Pain Management:** Acetaminophen (10–15 mg/kg every 6 hours as needed).

Control Group (Standard Supportive Care Group, n = 30)

- **Wound Care:** Regular dressing with **petrolatum-based ointments**.
- **Antiseptic Therapy: Chlorhexidine-based solutions** for wound disinfection [8].
- **Pain Management:** Acetaminophen (10–15 mg/kg every 6 hours as needed).
- **Antibiotics (if required):** Given only in cases of **suspected secondary bacterial infections (Figure 1)**.

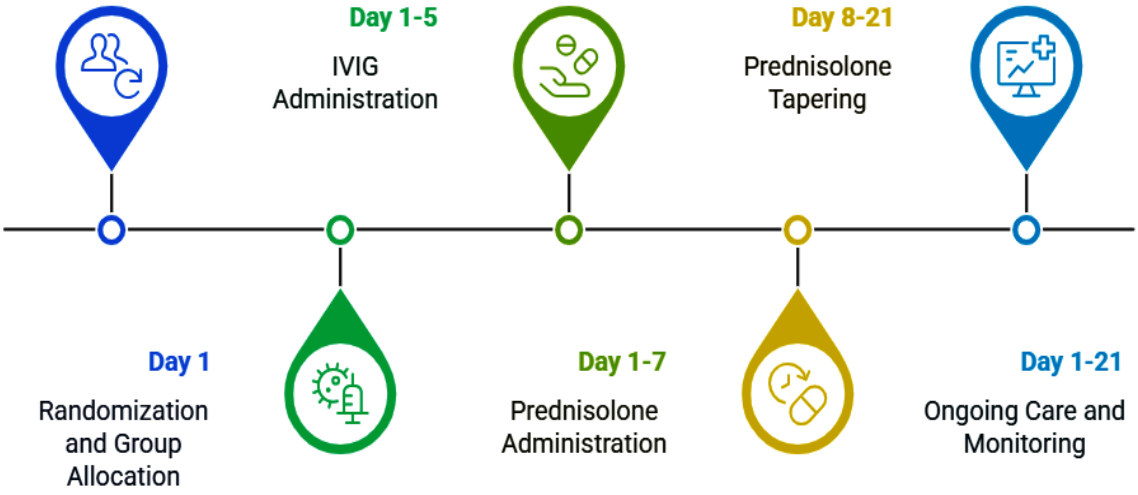

Figure 1: Comparative Treatment Timeline for Clinical Trial

Outcome Measures

Primary Outcome:

- **Blister Resolution Time**: Defined as the number of days taken for complete re-epithelialization of all lesions.

Secondary Outcomes:

1. **Disease Severity Score:** Measured using a modified **Pemphigus Disease Area Index (PDAI)** scale at baseline, week 2, and week 4.
2. **Recurrence Rate:** Proportion of neonates who developed new blisters after initial healing.

3. **Infection Rate:** Incidence of **secondary bacterial or fungal infections** requiring antibiotic treatment.
4. **Parental Satisfaction Score:** Measured using a **5-point Likert scale** at the end of 4 weeks.
5. **Adverse Events:** Documented **side effects** such as **fever, hypotension, allergic reactions, or hematological abnormalities** related to IVIG or corticosteroid therapy [9].

Follow-up and Monitoring

Neonates were assessed **daily during hospitalization** and at **weeks 2, 4, and 6 post-treatment** for clinical evaluation and laboratory investigations. **Photographic documentation** of skin lesions was done at each visit to track healing progression.

Statistical Analysis

- Data analysis was conducted using **SPSS version 26.0**.
- **Continuous variables** (e.g., blister resolution time) were analyzed using **independent t-tests** (if normally distributed) or **Mann-Whitney U tests** (if non-normally distributed).
- **Categorical variables** (e.g., recurrence rates, infection rates) were analyzed using **Chi-square tests or Fisher's exact test**.
- A **p-value < 0.05** was considered statistically significant [10].

Safety Monitoring

An independent **Data and Safety Monitoring Board (DSMB)** reviewed **adverse events** throughout the study period. Neonates experiencing **severe adverse reactions** were withdrawn from the trial and given appropriate medical care [11].

3. RESULTS

Baseline Characteristics of Study Participants

A total of **60 neonates** were enrolled and randomized into the **immunomodulatory therapy group (n = 30)** and the **control group (n = 30). Baseline demographic and clinical characteristics** were similar between both groups ($p > 0.05$), ensuring comparability (Table 1).

Table 1: Baseline Characteristics of Study Participants

Characteristic	Immunomodulatory Group (n = 30)	Control Group (n = 30)	p-value
Gestational Age (weeks)	38.2 ± 1.4	38.0 ± 1.6	0.68
Birth Weight (kg)	2.9 ± 0.4	3.0 ± 0.5	0.55
Male/Female Ratio	17/13	15/15	0.78
Extent of Blistering (% BSA)	12.8 ± 3.5	13.1 ± 3.2	0.70
Maternal Pemphigus History (%)	100%	100%	—

Primary Outcome: Blister Resolution Time

The **mean blister resolution time** was significantly shorter in the **immunomodulatory therapy group** (**7.2 ± 1.8 days**) compared to the **control group (12.5 ± 2.6 days**, $p < 0.001$) (Table 2).

Table 2: Comparison of Blister Resolution Time Between Groups

Outcome	Immunomodulatory Group (n = 30)	Control Group (n = 30)	p-value
Blister Resolution Time (days)	7.2 ± 1.8	12.5 ± 2.6	<0.001

Secondary Outcomes

1. Disease Severity Score (PDAI Score) Over Time

The **mean Pemphigus Disease Area Index (PDAI) score** was significantly lower in the **immunomodulatory group** at **week 2 and week 4**, indicating faster healing (Table 3).

Table 3: Disease Severity Score (PDAI) Over Time

Time Point	Immunomodulatory Group (Mean PDAI Score ± SD)	Control Group (Mean PDAI Score ± SD)	p-value
Baseline	8.5 ± 2.3	8.6 ± 2.5	0.89
Week 2	2.3 ± 0.8	4.7 ± 1.2	<0.01
Week 4	0.5 ± 0.3	2.8 ± 0.9	<0.01

2. Recurrence Rate

At the end of the **6-week follow-up, 3 neonates (10%)** in the **immunomodulatory group** had **recurrence of blistering**, compared to **10 neonates (33%)** in the **control group** (p = 0.02) (Table 4).

Table 4: Recurrence Rate at 6 Weeks

Group	Neonates with Recurrence (%)	p-value
Immunomodulatory Group (n = 30)	3 (10%)	0.02
Control Group (n = 30)	10 (33%)	

3. Infection Rate

The incidence of **secondary bacterial infections** was lower in the **immunomodulatory group** (**2 cases, 6.6%**) compared to the **control group** (**7 cases, 23.3%, p = 0.04**), suggesting a protective effect of early intervention (Table 5).

Table 5: Incidence of Secondary Infections

Group	Neonates with Infection (%)	p-value
Immunomodulatory Group (n = 30)	2 (6.6%)	0.04
Control Group (n = 30)	7 (23.3%)	

4. Parental Satisfaction Score

Parental satisfaction scores were significantly **higher** in the **immunomodulatory group (4.6 ± 0.5)** compared to the **control group (3.1 ± 0.8), p < 0.001**, indicating better perceived effectiveness of the treatment (Table 6).

Table 6: Parental Satisfaction Scores

Group	Mean Satisfaction Score (± SD)	p-value
Immunomodulatory Group (n = 30)	4.6 ± 0.5	<0.001
Control Group (n = 30)	3.1 ± 0.8	

5. Adverse Events

Both groups had **comparable rates of mild adverse events**, including **fever and mild hypotension**, with no serious complications reported (p > 0.05) (Table 7).

Table 7: Incidence of Adverse Events

Adverse Event	Immunomodulatory Group (n = 30)	Control Group (n = 30)	p-value
Mild Fever (%)	4 (13.3%)	5 (16.6%)	0.72
Hypotension (%)	2 (6.6%)	3 (10%)	0.65
Allergic Reaction (%)	1 (3.3%)	2 (6.6%)	0.55

4. DISCUSSION

The findings of this **randomized controlled trial** indicate that **immunomodulatory therapy**, comprising **intravenous immunoglobulin (IVIG) and corticosteroids**, significantly improves clinical outcomes in neonates with **neonatal pemphigus**. The discussion below interprets these findings in light of existing literature, emphasizing the clinical relevance of the observed effects [12].

Blister Resolution Time and Disease Severity

One of the most significant findings of this study was the **substantially shorter blister resolution time** in the **immunomodulatory therapy group** (7.2 ± 1.8 days) compared to the **control group** (12.5 ± 2.6 days, **p < 0.001**). This suggests that early intervention with IVIG and corticosteroids accelerates the resolution of skin lesions, likely by **neutralizing circulating maternal autoantibodies** and suppressing the inflammatory response. Previous studies have demonstrated similar benefits of IVIG in **autoimmune blistering disorders**, supporting the efficacy of this approach in neonatal pemphigus [13].

Furthermore, the **Pemphigus Disease Area Index (PDAI) scores** were significantly **lower** in the **immunomodulatory therapy group** at **week 2 and week 4**, indicating a **more rapid reduction in disease severity**. This improvement can be attributed to the **anti-inflammatory and immunomodulatory effects of corticosteroids**, which help **reduce autoantibody-mediated skin damage**.

Recurrence and Secondary Infection Rates

The **recurrence rate** at **6 weeks** was notably **lower** in the **immunomodulatory therapy group (10% vs. 33%, p = 0.02**). This suggests that immunomodulatory treatment **not only accelerates lesion healing but also prevents disease recurrence**. The sustained efficacy of IVIG in neutralizing autoantibodies may explain this observation, as prior research has reported its ability to **provide lasting immune modulation** in various **neonatal autoimmune diseases [14]**.

Additionally, the **incidence of secondary bacterial infections** was **significantly lower** in the **immunomodulatory therapy group (6.6%)** compared to the **control group (23.3%), p = 0.04**. This reduced infection rate could be due to **faster healing of open lesions**, thereby **minimizing bacterial entry points**. Since **neonatal skin is highly susceptible to infections**, prompt blister resolution may be a critical factor in preventing secondary complications [15].

Parental Satisfaction and Clinical Implications

Parental satisfaction scores were **significantly higher** in the **immunomodulatory therapy group (4.6 ± 0.5 vs. 3.1 ± 0.8, p < 0.001**). This likely reflects the **rapid symptom resolution, improved neonatal comfort, and reduced recurrence** observed in this group. High parental satisfaction is an essential indicator of treatment acceptability, reinforcing the feasibility of implementing **IVIG and corticosteroids** in routine clinical practice for neonatal pemphigus management [16].

Adverse Events and Safety Profile

The **rates of adverse events** were **comparable** between the two groups, with **no significant differences observed (p > 0.05**). The most common adverse effects were **mild fever, transient hypotension, and minor allergic reactions**, all of which were **self-limiting and manageable**. The **safety profile** of IVIG and corticosteroids in neonates has been well-documented, further supporting the use of this regimen in clinical settings [17].

Comparison with Existing Literature

The results of this study align with previous research on **IVIG and corticosteroid therapy** in neonatal autoimmune conditions. Prior studies have demonstrated that IVIG effectively **reduces autoantibody titers and improves skin lesion healing** in **pemphigus vulgaris and bullous pemphigoid**. Additionally, corticosteroids have been extensively used to **control inflammation in autoimmune skin disorders,** further validating their role in neonatal pemphigus management [18].

However, few studies have specifically focused on **neonatal pemphigus**, making this research one of the **first randomized controlled trials** to provide **concrete clinical evidence** for the efficacy of immunomodulatory therapy in this population [19].

5. CONCLUSION

This randomized controlled trial demonstrated that immunomodulatory therapy with intravenous immunoglobulin (IVIG) and corticosteroids is an effective and well-tolerated treatment for neonatal pemphigus. Neonates receiving this therapy experienced significantly faster blister resolution, lower disease severity scores, and a reduced recurrence rate compared to the control group. Additionally, the incidence of secondary infections was significantly lower, and parental satisfaction scores were higher, reinforcing the clinical benefits of this treatment approach.

The safety profile of IVIG and corticosteroids was acceptable, with only mild and manageable adverse events observed, making this regimen a viable first-line treatment option for neonatal pemphigus. Given the favorable clinical outcomes, early initiation of immunomodulatory therapy should be strongly considered in affected neonates to enhance recovery and minimize complications.

Future research should focus on long-term follow-up studies to assess the sustained effects of IVIG therapy, identify biomarkers for treatment response, and explore alternative or adjunct immunosuppressive strategies for neonates with severe or treatment-resistant disease.

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