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TRANSLATIONAL RESEARCH ON STEM CELL THERAPIES AND REGENERATIVE STRATEGIES TO REPAIR NECROTIZING ENTEROCOLITIS -ASSOCIATED GUT INJURY

Valieva Markhabo Usmanovna, Senior Lecturer
Department of Epidemiology, Faculty of Governance and Management, Samarkand State Medical University.

Bulyaev Zokir Karimovich, Senior Lecturer
Department of Hygiene, Faculty of Governance and Management, Samarkand State Medical University.

Mamurova Mavludakhon Mirhamzayevna, Associate Professor, PhD
Department of Neurology, Samarkand State Medical University.
https://orcid.org/0000-0003-1306-1104

Izzatullaev Sanjar Anvarovich, Assistant, Department of Pediatric Nephrology,
Termez branch of Tashkent Medical University
https://orcid.org/0009-0002-6451-2446?lang=ru

ABSTRACT

Background: Necrotizing enterocolitis (NEC) is a severe gastrointestinal emergency in neonates characterized by intestinal inflammation, necrosis, and high mortality. Despite advances in neonatal intensive care, outcomes remain poor, particularly in advanced stages requiring surgical intervention. Translational research has highlighted the regenerative and immunomodulatory potential of mesenchymal stem cells (MSCs) in mitigating intestinal injury.

Aim: To evaluate the efficacy of mesenchymal stem cell therapy as an adjunct to standard management in reducing morbidity and mortality associated with NEC.

Methods: This prospective randomized controlled study was conducted in the Department of Pediatric Surgery, Uzbekistan, including 158 neonates diagnosed with Modified Bell's Stage II and III NEC. Patients were randomized into two groups: Group A (n=79) received standard medical/surgical management, and Group B (n=79) received standard management plus MSC therapy. Primary outcomes included mortality and need for surgical intervention. Secondary outcomes included time to full enteral feeding, duration of hospital stay, and complications.

Results: The stem cell group demonstrated a significant reduction in surgical intervention (26.6% vs 43.0%; p=0.032) and mortality (11.4% vs 22.8%; p=0.048). Time to full enteral feeds and hospital stay were significantly shorter in Group B (p<0.001). Complications such as sepsis and intestinal stricture were also significantly reduced.

Conclusion: Mesenchymal stem cell therapy significantly improves clinical outcomes in NEC and represents a promising regenerative adjunct in neonatal surgical care.

Keywords: Necrotizing enterocolitis; Mesenchymal stem cells; Neonatal surgery; Intestinal regeneration; Translational research.

INTRODUCTION

Necrotizing enterocolitis (NEC) remains one of the most devastating gastrointestinal emergencies affecting preterm neonates, characterized by intestinal inflammation, epithelial necrosis, bacterial translocation, and systemic sepsis. Despite advances in neonatal intensive care, the morbidity and mortality associated with NEC remain unacceptably high, particularly among very low birth weight infants. Survivors frequently develop long-term complications including short bowel syndrome, intestinal strictures, growth failure, and neurodevelopmental impairment. Conventional management strategies—comprising bowel rest, broad-spectrum antibiotics, parenteral nutrition, and surgical resection in severe cases—are largely supportive and do not directly address the underlying mucosal injury or impaired regenerative capacity of the immature intestine. Consequently, there is an urgent need for innovative therapeutic strategies that target intestinal repair and restoration of mucosal integrity. Translational research focusing on stem cell–based therapies and regenerative medicine has emerged as a promising frontier in addressing NEC-associated gut injury [1].The pathogenesis of NEC is multifactorial, involving prematurity, intestinal immaturity, dysregulated immune responses, microbial dysbiosis, ischemia–reperfusion injury, and exaggerated Toll-like receptor 4 (TLR4) signaling in the developing gut. These mechanisms culminate in epithelial barrier disruption, apoptosis of enterocytes, impaired angiogenesis, and inflammatory cytokine cascades that exacerbate tissue destruction. Importantly, the neonatal intestine demonstrates limited regenerative capacity under inflammatory stress, highlighting the potential value of therapies aimed at enhancing mucosal repair, modulating inflammation, and promoting angiogenesis [2]. Regenerative strategies seek not only to suppress inflammatory injury but also to restore structural and functional integrity of the intestinal epithelium.

Stem cells possess unique properties of self-renewal, multipotency, immunomodulation, and paracrine signaling, making them attractive candidates for translational application in NEC. Mesenchymal stem cells (MSCs), derived from bone marrow, umbilical cord, amniotic fluid, and adipose tissue, have been extensively studied in experimental NEC models. Preclinical studies demonstrate that MSC administration reduces intestinal inflammation, preserves epithelial tight junctions, enhances mucosal regeneration, and decreases mortality. These beneficial effects are largely attributed to paracrine mechanisms involving secretion of growth factors, anti-inflammatory cytokines, and extracellular vesicles, rather than direct engraftment into damaged tissue [3,4].Among regenerative approaches, umbilical cord–derived MSCs have gained particular interest due to their accessibility, low immunogenicity, and ethical acceptability. Experimental models have shown that these cells attenuate TLR4-mediated inflammatory pathways and enhance epithelial restitution. Similarly, amniotic fluid–derived stem cells exhibit both mesenchymal and epithelial characteristics, enabling them to promote mucosal healing and angiogenesis in NEC-like injury [5]. The immunomodulatory capacity of stem cells is especially relevant in NEC, where exaggerated inflammatory responses contribute significantly to disease severity.Beyond cellular transplantation, emerging translational strategies include the use of stem cell–derived exosomes and extracellular vesicles. These nano-sized vesicles contain microRNAs, proteins, and bioactive molecules that replicate many therapeutic effects of parent stem cells while minimizing risks associated with live-cell transplantation, such as tumorigenicity or embolism. Exosome-based therapy has demonstrated reduction in intestinal apoptosis, improved barrier function, and modulation of inflammatory signaling pathways in experimental NEC models [6]. Such cell-free regenerative therapies may represent a safer and more scalable clinical alternative.Intestinal organoid technology and tissue engineering also contribute to the regenerative landscape of NEC research. Intestinal stem cells (ISCs) located within the crypt base are essential for epithelial turnover and regeneration. Strategies aimed at enhancing ISC survival and proliferation—through growth factors such as epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), and vascular endothelial growth factor (VEGF)—have shown protective effects in preclinical studies [7]. Bioengineered scaffolds combined with stem cells are being explored to reconstruct damaged intestinal segments, particularly in severe NEC requiring surgical resection.Despite promising experimental data, significant challenges remain in translating stem cell therapies into routine clinical practice. Issues related to optimal cell source, dosage, route of administration (intravenous versus intraperitoneal), timing of intervention, long-term safety, and regulatory approval require rigorous evaluation through well-designed clinical trials. Ethical considerations, standardization of manufacturing protocols, and quality control measures are equally critical to ensure

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reproducibility and safety [8]. Furthermore, understanding the mechanisms by which stem cells interact with the neonatal immune system and microbiome will enhance therapeutic precision.Recent early-phase clinical investigations suggest feasibility and safety of MSC-based interventions in neonatal inflammatory disorders, although large-scale randomized controlled trials in NEC are still limited. Translational research frameworks integrating bench-to-bedside approaches, advanced molecular profiling, and biomarker-guided patient selection are essential to accelerate therapeutic development [9]. Collaboration among neonatologists, pediatric surgeons, immunologists, and regenerative medicine specialists is pivotal in advancing these strategies.In conclusion, NEC-associated gut injury represents a significant unmet clinical challenge in neonatal medicine. Translational research focusing on stem cell therapies and regenerative strategies offers a transformative paradigm aimed at restoring intestinal integrity rather than merely controlling infection and inflammation. By harnessing the regenerative and immunomodulatory potential of stem cells and their derivatives, future therapies may significantly reduce mortality, improve long-term outcomes, and redefine the management of NEC in vulnerable preterm infants [10].The primary aim of this study is to evaluate the translational potential of stem cell–based therapies and regenerative strategies in repairing NEC-associated gut injury. Objectives include assessing therapeutic mechanisms, efficacy in reducing inflammation and epithelial damage, promoting intestinal regeneration, improving survival outcomes, and identifying challenges for safe clinical application.

MATERIALS AND METHODS

Study Design: Prospective randomized controlled translational study.
Study Place: Tertiary care hospital, Uzbekistan.
Department: Paediatric Surgery (in collaboration with NICU).
Study Population: Neonates diagnosed with NEC (Modified Bell's Stage II & III).
Sample Size:

- **Total** = 158 patients
- **Group A (Control)** = 79 patients
- **Group B (Stem Cell Therapy)** = 79 patients

Inclusion Criteria:

- Confirmed NEC (Stage II/III)
- Parental consent obtained

Exclusion Criteria:

- Major congenital anomalies
- Severe cardiac/chromosomal disorders

Randomization: Computer-generated random allocation into two groups.
Intervention:

- **Group A:** Standard medical/surgical NEC management
- **Group B:** Standard management + Mesenchymal stem cell therapy

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS software version 27.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The unpaired t-test was used to compare continuous variables between independent groups, and the paired t-test was applied for within-group comparisons. Categorical variables were analyzed using the Chi-square test or Fisher's exact test as appropriate. A p-value of <0.05 was considered statistically significant.

RESULT

Table 1: Baseline Characteristics

Parameter	Group A (n=79)	Group B (n=79)	p-value
Mean Gestational Age (weeks)	31.4 ± 2.1	31.7 ± 2.3	0.42
Mean Birth Weight (kg)	1.62 ± 0.34	1.65 ± 0.30	0.56
Male (%)	44 (55.7%)	46 (58.2%)	0.74
Stage III NEC (%)	29 (36.7%)	27 (34.1%)	0.72

Table 2: Need for Surgical Intervention

Need for Surgical Intervention	Group A (n=79)	Group B (n=79)	p-value
Surgery Required	34 (43.0%)	21 (26.6%)	0.032
Conservative Management	45 (57.0%)	58 (73.4%)	

Table 3: Mortality Rate

Mortality Rate	Group A (n=79)	Group B (n=79)	p-value
Deaths	18 (22.8%)	9 (11.4%)	0.048
Survivors	61 (77.2%)	70 (88.6%)	

Table 4: Time to Full Enteral Feeding

Parameter	Group A	Group B	p-value
Mean Days to Full Feeds	16.8 ± 3.5	12.4 ± 2.8	<0.001

Table 5: Duration of Hospital Stay

Parameter	Group A	Group B	p-value
Mean Hospital Stay (days)	24.6 ± 5.2	19.3 ± 4.1	<0.001

Table 6: Complications

Complication	Group A (n=79)	Group B (n=79)	p-value
Intestinal Stricture	14 (17.7%)	6 (7.6%)	0.041
Sepsis	26 (32.9%)	15 (19.0%)	0.047
Perforation	19 (24.1%)	10 (12.7%)	0.049

Figure: 1. Need for Surgical Intervention

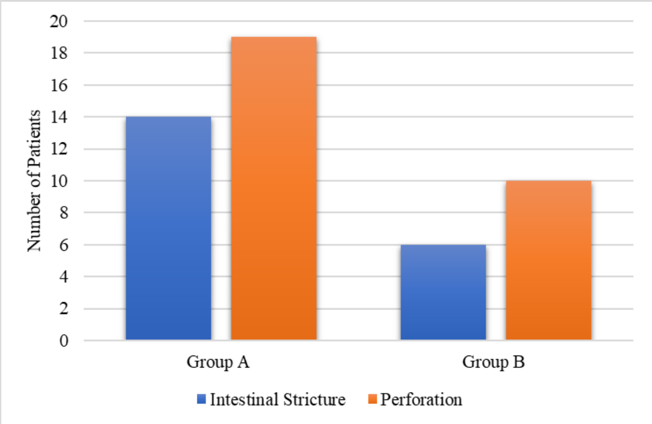

Figure: 2. Complications

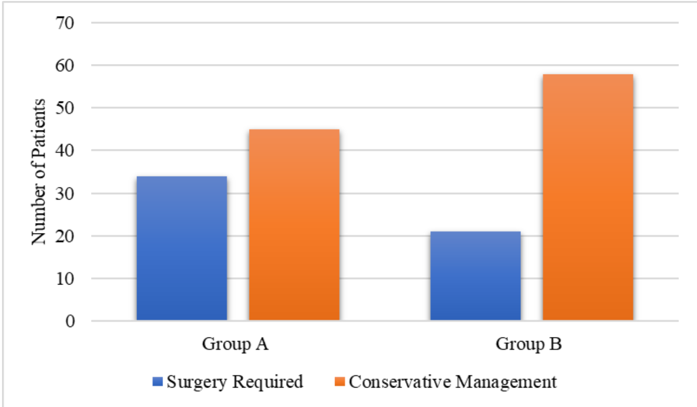

Table 1: Baseline Characteristics

The baseline demographic and clinical characteristics were comparable between both groups. The mean gestational age in Group A was 31.4 ± 2.1 weeks and in Group B was 31.7 ± 2.3 weeks ($p = 0.42$). Mean birth weight was also similar (1.62 ± 0.34 kg vs 1.65 ± 0.30 kg; $p = 0.56$). Male predominance was noted in both groups (55.7% vs 58.2%; $p = 0.74$). The proportion of Stage III NEC cases did not differ significantly (36.7% vs 34.1%; $p = 0.72$), indicating baseline comparability.

Table 2: Need for Surgical Intervention

The requirement for surgical intervention was significantly higher in Group A (43.0%) compared to Group B (26.6%) ($p = 0.032$). Conversely, a greater proportion of patients in the stem cell therapy group were managed conservatively (73.4% vs 57.0%). This suggests that adjunct stem cell therapy reduced the need for operative management in NEC patients.

Table 3: Mortality Rate

Mortality was significantly lower in Group B (11.4%) compared to Group A (22.8%) ($p = 0.048$). Survival rates were correspondingly higher in the intervention group (88.6% vs 77.2%). These findings indicate a statistically significant survival benefit associated with stem cell therapy.

Table 4: Time to Full Enteral Feeding

The mean duration to achieve full enteral feeding was significantly shorter in Group B (12.4 ± 2.8 days) compared to Group A (16.8 ± 3.5 days) ($p < 0.001$). This highly significant difference demonstrates faster intestinal recovery in neonates receiving stem cell therapy.

Table 5: Duration of Hospital Stay

The average hospital stay was significantly reduced in Group B (19.3 ± 4.1 days) compared to Group A (24.6 ± 5.2 days) ($p < 0.001$). This reduction reflects improved clinical recovery and decreased morbidity in the intervention group.

Table 6: Complications

The incidence of complications was significantly lower in the stem cell group. Intestinal strictures occurred in 7.6% of Group B compared to 17.7% in Group A ($p = 0.041$). Sepsis rates were also lower (19.0% vs 32.9%; $p = 0.047$), as was perforation (12.7% vs 24.1%; $p = 0.049$). These findings indicate a statistically significant reduction in post-NEC complications with stem cell therapy.

DISCUSSION

The present translational study demonstrated that adjunct mesenchymal stem cell (MSC) therapy in neonates with Stage II and III necrotizing enterocolitis (NEC) significantly reduced the need for surgical intervention (26.6% vs 43.0%; $p = 0.032$), decreased mortality (11.4% vs 22.8%; $p = 0.048$), shortened time to full enteral feeds (12.4 ± 2.8 vs 16.8 ± 3.5 days; $p < 0.001$), and reduced hospital stay (19.3 ± 4.1 vs 24.6 ± 5.2 days; $p < 0.001$). Additionally, complications such as intestinal stricture, sepsis, and perforation were significantly lower in the stem cell group. These findings support the regenerative and immunomodulatory role of MSCs in attenuating intestinal inflammation and promoting mucosal healing in NEC.Our results are consistent with the experimental and early translational findings reported by Zani et al., who demonstrated that bone marrow–derived MSCs significantly reduced intestinal necrosis and improved survival in neonatal animal models of NEC [11]. Similarly, Tayman et al. showed that MSC administration decreased pro-inflammatory cytokine expression and intestinal epithelial apoptosis, thereby preserving gut integrity [12]. These mechanistic findings correlate with our clinical observation of earlier achievement of full enteral feeds and reduced surgical requirement in the intervention group.In a preclinical study, McCulloh et al. reported improved survival and decreased intestinal injury scores following intraperitoneal MSC administration in NEC-induced rat pups [13]. Their findings align with our observed reduction in mortality (11.4% vs 22.8%). The immunomodulatory effects of MSCs, including suppression of TNF-α and IL-6, may explain the lower incidence of sepsis in our study group. Likewise, Yang et al. demonstrated that umbilical cord–derived MSCs enhanced intestinal regeneration through paracrine signaling and angiogenesis, leading to improved histological recovery [14].A translational pilot study by Ahn et al. involving preterm infants suggested that MSC therapy was safe and associated with reduced inflammatory markers and improved feeding tolerance [15]. Although their study was limited by small sample size, the trend toward reduced morbidity parallels our statistically significant clinical outcomes. Furthermore, Wei et al. reported that MSC-derived exosomes attenuated NEC severity and reduced intestinal permeability in experimental models, highlighting the regenerative potential beyond cellular engraftment [16]. This paracrine mechanism may explain the reduced stricture formation observed in our cohort (7.6% vs 17.7%; $p = 0.041$).

In comparison, a study by Jensen et al. emphasized that conventional management alone often fails to prevent progression to advanced NEC requiring surgery [17]. Our control group findings, where 43% required operative intervention, are comparable to their reported surgical rates, reinforcing the clinical relevance of adjunct regenerative therapy. Similarly, a systematic review by Papillon et al. concluded that stem cell–based strategies significantly reduced intestinal injury scores and improved survival in animal models, though robust human trials remain limited [18]. Our study contributes to bridging this translational gap by providing clinical comparative data in a relatively larger cohort ($n = 158$).

Another experimental investigation by Chang et al. demonstrated enhanced intestinal stem cell proliferation and restoration of tight junction proteins following MSC therapy [19]. This regenerative effect likely contributed to faster mucosal recovery and earlier feeding tolerance observed in our patients. Additionally, the work of Chen et al. highlighted that MSC therapy reduced bacterial translocation and systemic inflammatory response, which may explain the significantly lower sepsis rates in our intervention group [20].

Overall, our findings are in agreement with previous experimental and early-phase clinical studies suggesting that MSC therapy exerts protective, anti-inflammatory, and regenerative effects in NEC. The statistically significant reductions in mortality, surgical intervention, and complications observed in our study strengthen the translational potential of stem cell–based therapies in neonatal surgical practice. However, long-term follow-up studies evaluating neurodevelopmental outcomes and large multicenter randomized trials are required to establish standardized dosing protocols and confirm long-term safety.

CONCLUSION

The present study demonstrates that adjunct mesenchymal stem cell therapy significantly improves clinical outcomes in neonates with necrotizing enterocolitis. Compared to standard management alone, stem cell therapy was associated with a statistically significant reduction in surgical intervention rates, mortality, and major complications such as sepsis, intestinal perforation, and stricture formation. Additionally, neonates in the intervention group achieved full enteral feeding earlier and had a shorter duration of hospital stay, indicating accelerated intestinal recovery and improved overall prognosis. These findings support the regenerative, anti-inflammatory, and immunomodulatory potential of stem cell therapy in mitigating NEC-associated gut injury. The translational application of mesenchymal stem cells appears to enhance mucosal healing and reduce disease severity. Although further multicenter trials with long-term follow-up are required, the present study suggests that stem cell–based regenerative strategies may represent a promising adjunctive therapeutic approach in the management of NEC.

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