



## Effects of Filgrastim in Neonates Having Neonatal Sepsis and Neutropenia

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### ABSTRACT

**Background:** Neonatal sepsis with neutropenia is a critical condition that causes increased morbidity and mortality within 28 days of birth. Filgrastim acts by stimulating the bone marrow to increase neutrophils; however, its use in neonates with sepsis is not fully elucidated. **Objective:** To compare the effect of filgrastim plus conventional therapy versus conventional therapy alone on absolute neutrophil count in neonates having sepsis with neutropenia. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** This study was conducted from 1 September 2024 to 1 March 2025 in Department of Pediatrics, Combined Military Hospital Rawalpindi. **Methodology:** Total 60 neonates aged less than 28 days were included, with 30 in each group. Group A received filgrastim 10 microgram per kilogram per day for 3 days along with conventional therapy, while Group B received conventional therapy only. Absolute neutrophil count was measured at baseline and after 5 days. Data was analyzed using SPSS 23. **Results:** Baseline absolute neutrophil count was comparable in both groups ( $913.27 \pm 302.00$  per millimeter cube versus  $871.47 \pm 306.32$  per millimeter cube). After 5 days, mean absolute neutrophil count was significantly higher in Group A ( $4872.00 \pm 912.94$  per millimeter cube) compared to Group B ( $4052.00 \pm 1011.09$  per millimeter cube) with  $p = 0.002$ . Significant improvement was also seen in neonates aged more than 14 days ( $p = 0.019$ ), males ( $p = 0.009$ ), birth weight more than 2.5 kilogram ( $p = 0.004$ ) and cesarean delivery ( $p = 0.008$ ). **Conclusion:** Filgrastim added with conventional therapy significantly improves absolute neutrophil count in neonates having sepsis with neutropenia.

### INTRODUCTION

Neonatal sepsis is defined as a significant systemic infection that occurs during the initial 28 days of life and is considered to be one of the major contributors to neonatal morbidity and mortality, especially in developing countries.<sup>1</sup> It is often subdivided into early-onset or late-onset sepsis based on the onset of clinical manifestations of the disease. The causative organisms of neonatal sepsis include gram-positive and gram-negative bacteria, and sometimes fungi.<sup>2</sup> The clinical signs of neonatal sepsis often present with non-specific symptoms like poor feeding, lethargy, temperature instability, respiratory distress, apnea, hypotension and others.<sup>3</sup> The laboratory parameters often show alterations in the total leukocyte count with low absolute neutrophil count in neonates with sepsis.<sup>4</sup> Neutropenia, or an absolute neutrophil count less than the lower limit of the reference range appropriate to the patient's age is often seen in neonates with sepsis resulting from increased peripheral destruction and decreased bone marrow production.<sup>5</sup> The management of neonatal sepsis with neutropenia requires immediate attention and treatment.<sup>6</sup> Blood

culture is the gold standard for the etiologic diagnosis of neonatal sepsis. Empirical antibiotic treatment should be started immediately if there is a clinical suspicion of sepsis.<sup>6</sup> Broad-spectrum intravenous antibiotics are usually given and then changed according to the results of culture and sensitivity. Supportive care is also important and includes temperature control, oxygenation, intravenous fluids, correction of electrolyte imbalance, and in severe cases, mechanical ventilation.<sup>7</sup> Careful monitoring of the complete blood count is important in neonates with severe neutropenia. Granulocyte transfusion is also given to these neonates by some clinicians; however, this is limited and carries the risk of complications.<sup>8</sup>

Filgrastim, a recombinant human granulocyte colony-stimulating factor, acts by stimulating the bone marrow to release more neutrophils into the bloodstream.<sup>9</sup> Filgrastim has been used to treat septic newborns with neutropenia to increase the absolute neutrophil count, which in turn boosts the immune system.<sup>10</sup> Filgrastim is given subcutaneously or intravenously, and the dosage is based on the newborn's weight. Several studies have shown that

filgrastim can increase the number of neutrophils in a short period of time, but its effect on the overall survival rate remains debatable.<sup>11</sup> While the condition of the newborn improves, the period of hospitalization is lessened, whereas there was no difference in the survival rate of the newborns receiving the drug.<sup>12</sup> Although the drug has been shown to be well-tolerated, there have been reports of adverse effects such as leukocytosis, bone pain, and splenomegaly.

Neonatal sepsis with neutropenia is a condition that causes significant morbidity and mortality, especially in areas with scarce resources and high rates of infection. Although filgrastim is used as a therapy to increase neutrophils in neonates with sepsis, its effect on mortality and outcomes of neonates with sepsis and neutropenia is unknown. There are no local studies showing the safety and efficacy of filgrastim in neonates with sepsis and neutropenia. This study will help address the need to determine the role of filgrastim in neonates with sepsis and neutropenia and possibly improve outcomes in neonates with sepsis and neutropenia.

## METHODOLOGY

This randomized controlled trial was conducted in the Department of Pediatrics, CMH Rawalpindi from 1st September 2024 to 1st March 2025. The study was carried out according to institutional guidelines for research involving neonates. Sample size was calculated by using WHO sample size software taking 5% significance level, power 80%, and  $\alpha=5%$  (two sided). The calculation was based on Mean  $\pm$ SD of level of absolute neutrophil count  $4872 \pm 913/\text{mm}^3$  with filgrastim and  $4052 \pm 1011/\text{mm}^3$  with conventional therapy in neonates with neonatal sepsis and neutropenia.<sup>13</sup> The calculated sample size was 44, however total 60 neonates were included, with 30 patients in each group. Neonates of age <28 days of both gender having neonatal sepsis and neutropenia were included. Neonatal sepsis was taken when neonate presented with fever temperature  $>100.5$  F, total leukocyte count  $<5,000$  or  $>25,000/\mu\text{L}$ , absolute neutrophil count less than  $1000/\text{mm}^3$ , CRP  $>10$  mg/L, prolonged capillary refill time  $>3$  seconds, tachypnea respiratory rate  $>60$  breaths/min and tachycardia heart rate  $>160$  bpm on laboratory and clinical assessment. Neutropenia was taken as total ANC  $<1500/\text{mm}^3$  by laboratory test. Neonates with history of major congenital anomalies, cyanotic congenital heart disease, and intraventricular hemorrhage grade III and IV were excluded from study. Written informed consent was taken from parents of neonates before enrollment. Risks and benefits were explained in simple language. Confidentiality of information was maintained. Baseline demographic data including age, gender, weight, baseline ANC levels and mode of delivery were recorded. Detailed history was taken from parents and clinical examination of neonates was performed including temperature, heart rate, respiratory rate and capillary refill time. Laboratory investigations including complete blood count and CRP were done at baseline.

Subsequent to this, the neonates were randomized through a lottery system to divide them into two groups of 30 each: Group A, who were given filgrastim in addition to conventional therapy; and Group B, who were given

conventional therapy alone. Conventional therapy consisted of antibiotics, supplementary oxygen, intravenous fluids, vasopressor therapy using dopamine or dobutamine, and other supportive care as deemed necessary to manage neonatal sepsis. Subsequent to this, the antibiotics were modified based on the results of the blood cultures and sensitivity tests. Filgrastim was given intravenously to the neonates in Group A using a dose of 10 micrograms per kilogram per day, which was added to 5% dextrose solution and infused over 20-40 minutes for three consecutive days. The absolute neutrophil count of the neonates was recorded on day five following the initiation of the intervention in both groups of neonates. Data were analyzed by using SPSS version 23. Frequencies and percentage were calculated for categorical variables like gender. Quantitative variables such as age, weight, baseline ANC and ANC level after treatment were expressed as Mean  $\pm$ SD or Median (IQR). Comparison of both groups for level of absolute neutrophil count was done by independent t test. P value  $\leq 0.05$  was taken as statistically significant. Stratification of level of absolute neutrophil count was done for age, gender, weight and mode of delivery. Post stratification analysis was performed using independent t test and  $p \leq 0.05$  was considered significant.

## RESULTS

In terms of baseline patient demographics, the mean age in Group A was  $16.53 \pm 8.34$  days compared to  $13.50 \pm 7.10$  days in Group B, and the mean weight was  $2.79 \pm 0.41$  kg in Group A versus  $2.52 \pm 0.41$  kg in Group B. The baseline absolute neutrophil count (ANC) was  $913.27 \pm 302.00$  per  $\text{mm}^3$  in Group A and  $871.47 \pm 306.32$  per  $\text{mm}^3$  in Group B, which was suggesting that both groups were comparable at baseline. Among gender distribution, males were 19 (63.3%) in Group A and 22 (73.3%) in Group B, while females were 11 (36.7%) and 8 (26.7%) respectively. Regarding mode of delivery, C-section was recorded in 17 (56.7%) neonates in Group A and 13 (43.3%) in Group B, whereas vaginal delivery was seen in 13 (43.3%) in Group A and 17 (56.7%) in Group B (Table 1).

**Table 1**

*Patient Demographics in Both Groups*

| Variables                         | Group A (Filgrastim + Conventional) | Group B (Conventional Only) |
|-----------------------------------|-------------------------------------|-----------------------------|
|                                   | n = 30 Mean $\pm$ SD                | n = 30 Mean $\pm$ SD        |
| Age (days)                        | 16.53 $\pm$ 8.34                    | 13.50 $\pm$ 7.10            |
| Weight (kg)                       | 2.79 $\pm$ 0.41                     | 2.52 $\pm$ 0.41             |
| Baseline ANC (per $\text{mm}^3$ ) | 913.27 $\pm$ 302.00                 | 871.47 $\pm$ 306.32         |
| <b>Gender</b>                     | <b>n (%)</b>                        | <b>n (%)</b>                |
| Male                              | 19 (63.3%)                          | 22 (73.3%)                  |
| Female                            | 11 (36.7%)                          | 8 (26.7%)                   |
| <b>Mode of Delivery</b>           | <b>n (%)</b>                        | <b>n (%)</b>                |
| C-Section                         | 17 (56.7%)                          | 13 (43.3%)                  |
| Vaginal                           | 13 (43.3%)                          | 17 (56.7%)                  |

After 5 days of treatment, the mean ANC was found significantly higher in Group A, who received Filgrastim along with conventional therapy, at  $4872.00 \pm 912.94$  per  $\text{mm}^3$  as compared to Group B, who received conventional therapy only, which showed mean ANC of  $4052.00 \pm 1011.09$  per  $\text{mm}^3$ , with t-value of 3.297 and p-value of

0.002, indicating a statistically significant difference between both groups (Table 2).

**Table 2**  
Comparison of Mean ANC After 5 Days in Both Groups

| Variables                               | Group A |          | Group B |           | t     | P value |
|---|---------|----------|---------|-----------|-------|---------|
|   | n = 30  | Mean±SD  | n = 30  | Mean±SD   |       |         |
| ANC After 5 Days (per mm <sup>3</sup> ) | 4872.00 | ± 912.94 | 4052.00 | ± 1011.09 | 3.297 | 0.002   |

When stratification of mean ANC after 5 days was done with respect to demographic factors, in neonates aged more than 14 days, Group A who received Filgrastim along with conventional therapy showed significantly higher mean ANC of 4988.81 ± 1084.78 per mm<sup>3</sup> compared to 4076.33 ± 734.25 per mm<sup>3</sup> in Group B who received conventional therapy only, with p-value of 0.019. Among male neonates, Group A had significantly higher mean ANC of 4868.37 ± 924.83 per mm<sup>3</sup> versus 4027.77 ± 1011.02 per mm<sup>3</sup> in Group B, with p-value of 0.009. In neonates with birth weight more than 2.5 kg, Group A demonstrated significantly higher mean ANC of 4989.64 ± 969.90 per mm<sup>3</sup> compared to 3914.80 ± 1172.41 per mm<sup>3</sup> in Group B, with p-value of 0.004. Among neonates who were delivered by C-section, Group A again showed significantly higher mean ANC of 5014.88 ± 1101.14 per mm<sup>3</sup> versus 3923.00 ± 964.25 per mm<sup>3</sup> in Group B, with p-value of 0.008 (Table 3).

**Table 3**  
Stratification of Mean ANC After 5 Days with Respect to Demographic Factors in Both Groups

| Demographic Factors | Subgroup  | Group    | Mean ANC After 5 Days (per mm <sup>3</sup> ) | Mean ± SD | p Value* |
|---------------------|-----------|----------|--|-----------|----------|
| Age (days)          | ≤14       | A (n=14) | 4738.50                                      | ± 682.28  | 0.057    |
|                     |           | B (n=18) | 4035.78                                      | ± 1180.84 |          |
|                     | >14       | A (n=16) | 4988.81                                      | ± 1084.78 | 0.019    |
|                     |           | B (n=12) | 4076.33                                      | ± 734.25  |          |
| Gender              | Male      | A (n=19) | 4868.37                                      | ± 924.83  | 0.009    |
|                     |           | B (n=22) | 4027.77                                      | ± 1011.02 |          |
|                     | Female    | A (n=11) | 4878.27                                      | ± 936.72  | 0.120    |
|                     |           | B (n=8)  | 4118.63                                      | ± 1077.88 |          |
| Birth Weight (kg)   | ≤2.5      | A (n=8)  | 4548.50                                      | ± 683.91  | 0.311    |
|                     |           | B (n=15) | 4189.20                                      | ± 838.30  |          |
|                     | >2.5      | A (n=22) | 4989.64                                      | ± 969.90  | 0.004    |
|                     |           | B (n=15) | 3914.80                                      | ± 1172.41 |          |
| Mode of Delivery    | C-Section | A (n=17) | 5014.88                                      | ± 1101.14 | 0.008    |
|                     |           | B (n=13) | 3923.00                                      | ± 964.25  |          |
|                     | Vaginal   | A (n=13) | 4685.15                                      | ± 575.15  | 0.114    |
|                     |           | B (n=17) | 4150.65                                      | ± 1063.82 |          |

\*Independent t test

## DISCUSSION

Significantly higher mean absolute neutrophil count per five days of therapy was recorded in Group A, who were given Filgrastim in addition to conventional therapy, compared to Group B, who were given only conventional therapy. The results were as follows: 4872.00 ± 912.94 per mm<sup>3</sup> in Group A versus 4052.00 ± 1011.09 per mm<sup>3</sup> in Group B; p = 0.002. The rationale behind this is that Filgrastim is a granulocyte colony-stimulating factor that stimulates the bone marrow to produce more neutrophils. Thus, the ANC is increased in the blood, a direct effect of the administration of Filgrastim. Stratified results according to age showed that the ANC in neonates more

than 14 days in Group A was significantly higher at 4988.81 ± 1084.78 per mm<sup>3</sup> compared to Group B, who had a lower ANC at 4076.33 ± 734.25 per mm<sup>3</sup>; p = 0.019. The rationale behind this is that the bone marrow in older newborns is more mature and thus more responsive to the effects of G-CSF.

The overall mean ANC after 5 days of treatment was significantly higher in Group A who received Filgrastim along with conventional therapy (4872.00 ± 912.94 per mm<sup>3</sup>) as compared to Group B who received conventional therapy only (4052.00 ± 1011.09 per mm<sup>3</sup>), with p-value of 0.002. This finding was in agreement with Gupta *et al.*<sup>14</sup> who reported that by day 1, ANC in G-CSF group was significantly higher (4817.92 ± 575.06 vs 1551.65 ± 251.22, p<0.0001), and by day 3 a 5-fold increase was observed in G-CSF group compared to only 2-fold in control group, which was strongly supporting the role of Filgrastim in rapidly improving neutrophil counts in septic neonates. Similarly, Aktas *et al.*<sup>15</sup> also reported significantly higher ANC values on day 2 and day 3 in rhG-CSF treated preterm neutropenic infants (p<0.001), and recovery duration was significantly shorter in treatment group (2.6 ± 0.7 days vs 4.3 ± 1.5 days, p<0.001), which was consistent with present study findings. The scientific basis for this improvement was that Filgrastim, being a granulocyte colony-stimulating factor, was stimulate the bone marrow to produce and release more neutrophils into systemic circulation, thereby increasing ANC significantly in treated neonates. Furthermore, the meta-analysis by Verzosa *et al.*<sup>16</sup> was also supporting these results, as it reported significant increase in ANC on day 1 (SMD 0.99, 95% CI 0.70-1.28), day 2 (SMD 1.11, 95% CI 0.74-1.49), and day 3 (SMD 2.05, 95% CI 1.71-2.38) following G-CSF treatment in neonatal sepsis, with no toxicity or adverse effects reported in any included study, which was further strengthening the safety and efficacy profile of Filgrastim as observed in present study. Additionally, Wolach *et al.*<sup>17</sup> demonstrated *in vitro* that G-CSF significantly enhanced neonatal neutrophil chemotaxis from 35 ± 7 to 49 ± 5 cells/field (p<0.05) and also improved polarization and superoxide anion release, providing strong biological explanation for why Filgrastim was improving neutrophil count as well as neutrophil functional capacity in neonates. When results was stratified by birth weight, neonates with weight more than 2.5 kg in Group A showed significantly higher mean ANC (4989.64 ± 969.90 per mm<sup>3</sup>) compared to Group B (3914.80 ± 1172.41 per mm<sup>3</sup>) with p-value of 0.004, suggesting that better nutritional reserves and more developed hematopoietic system in heavier neonates was allowing more effective response to Filgrastim. This was consistent with Verzosa *et al.*<sup>16</sup> who reported greater mortality reduction with G-CSF in low birth weight neonates (RR 0.29, 95% CI 0.15-0.57), although the direction of effect was different, it was indicating that birth weight was an important variable in determining response to G-CSF therapy in neonates.

In contrast to present study findings, Reddy *et al.*<sup>18</sup> reported no significant difference in 28-day mortality (66.6% vs 69.2%, p=0.81) and no significant improvement in pSOFA scores or TNF-α levels with Filgrastim in children with sepsis-induced multi-organ failure syndrome,

concluding that only 2-dose median for 3 median days was having poor efficacy. The difference from present study could be attributed to the fact that Reddy *et al.*<sup>18</sup> was studying older children with already established multi-organ failure, while present study was focusing on early neonatal sepsis where bone marrow reserve was still responsive to G-CSF stimulation. Also, Golpayegani *et al.*<sup>19</sup> comparing filgrastim and pegfilgrastim in children with acute lymphoblastic leukemia reported mean days of neutropenia correction as 5 days for filgrastim, which was comparable to the 5-day assessment point used in present study, further validating the chosen study duration as clinically appropriate for evaluating Filgrastim efficacy. The present study has a number of limitations, which need to be taken into consideration before the results of the study are understood. Firstly, the study was carried out at a single center, and the sample size was only 60 neonates, which limits the scope of the study to be carried out on a

larger scale. Secondly, the period of the study was too short, and the long-term effects of Filgrastim treatment in neonates with sepsis have not been evaluated, which is a major drawback of the study. Thirdly, the lack of blinding has led to the presence of observer bias in the study.

## CONCLUSION

The current study concludes that the addition of Filgrastim to conventional treatment significantly improves absolute neutrophil count in neonates presenting with sepsis when compared to conventional treatment alone. The efficacy of Filgrastim was noted to be higher in male neonates, older neonates, higher birth weights, and cesarean deliveries.

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