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Effect of granulocyte colony-stimulating factor (G-CSF) in functional outcome of acute spinal cord injury patients: A single-blinded randomized controlled trial

Prabu Mounissamy [a], Premraj A.C. [a], Sushma Chanadrashekar [a], Naveen Jeyaraman [b], Swaminathan Ramasubramanian [c], Madhan Jeyaraman [b,*]

[a] Department of Orthopaedics, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, 605006, India
[b] Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, 600077, Chennai, Tamil Nadu, India
[c] Department of Orthopaedics, Government Medical College, Omandurar Government Estate, 600002, Chennai, Tamil Nadu, India

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ABSTRACT

Background: Spinal Cord Injury (SCI) is a major public health issue causing significant disability and economic burden. Current treatments primarily focus on mitigating secondary injury, with limited effective therapies available. This study explores the efficacy of the Granulocyte Colony-Stimulating Factor (G-CSF) in improving functional outcomes in acute SCI patients.

Materials and methods: This single-blinded randomized control trial was conducted at JIPMER's orthopedic department. Patients with acute spinal cord injury (SCI) were enrolled based on specific inclusion and exclusion criteria. Participants were divided into two groups: Group A (n = 16) received a G-CSF injection whereas Group B (n = 18) received a placebo (normal saline) injection. The primary evaluation was based on the changes in the ASIA impairment scale at 1-, 3-, and 6-months post-injury.

Results: The study involved 34 participants, predominantly male. Initial assessments showed significant differences in ASIA scores between the groups. Group A demonstrated marked improvement in neurological status at 1, 3, and 6 months post-treatment compared to Group B. The frequency of adverse events was comparable between the two groups.

Conclusion: G-CSF showed significant improvement in ASIA scores at various time points post-administration compared to placebo. These findings suggest G-CSF as a potential therapeutic agent in acute SCI treatment. However, due to the small sample size, further research is necessary to confirm these results.

1. Introduction

In 2023, the National Spinal Cord Injury Data Center reported the incidence of traumatic spinal cord injuries (tSCI) ranges from 3.3 to 195.4 cases per million (CPM) based on subnational studies and from 5.1 to 150.48 CPM based on national studies.[1] tSCIs are profound life-altering events, leading to limb paralysis and a range of complications including sensory disturbances, neuropathic pain, and dysfunctions in bowel, bladder, and sexual health. These physical impairments are accompanied by significant emotional, social, and occupational challenges for the individual. Moreover, tSCI places a substantial economic burden on the affected individuals and their support networks, highlighting its severity as a public health concern.[2–5]

SCI pathophysiology is characterized by primary and secondary damage. Primary damage is the immediate mechanical injury to the spinal cord caused by trauma, underscoring the necessity of preventive strategies. Secondary damage includes a cascade of biological responses triggered by the primary injury, involving hemorrhage, electrolyte imbalances, excitotoxicity, ischemia, inflammation, cytokine upregulation, and the destruction of axons and myelin sheaths. The focus of current therapeutic interventions is to mitigate this secondary damage, with ongoing research required to fully understand its long-term impacts. Protection against secondary injury is crucial for enhancing functional recovery prospects.[6–9] In Japan, methylprednisolone sodium succinate (MPSS) is the only pharmacologically approved SCI treatment, aimed at reducing inflammation and stabilizing cell membranes. However, its use

* Corresponding author.
E-mail address: madhanjeyaraman@gmail.com (M. Jeyaraman).

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is controversial due to its minimal impact on SCI recovery and associated risks, such as infections and gastric ulcers.[10–15] This controversy underscores an urgent need for effective SCI treatments with fewer side effects. Granulocyte colony-stimulating factor (G-CSF), typically used in neutropenia treatment, has emerged as a potential therapeutic agent for SCI.[16,17] G-CSF, known for its role in promoting granulocyte lineage development and survival, also exhibits beneficial non-hematopoietic effects in brain injury management.[18] In preclinical and clinical studies of SCI, G-CSF has been observed to aid functional recovery through various mechanisms, including mobilizing bone marrow cells to the injured spinal cord, reducing neuron and oligodendrocyte death, inhibiting inflammatory cytokines, and stimulating angiogenesis.[19–23]

Two theories propose G-CSF's potential role in acute tSCI treatment: either G-CSF-mobilized hematopoietic cells contribute to CNS repair via secreted substances or direct integration into the CNS,[24] or G-CSF directly targets CNS cells expressing the G-CSF receptor, facilitating spinal cord repair.[25] In light of these findings, this study aims to evaluate the efficacy of G-CSF in improving functional outcomes in acute SCI patients. By exploring the role of G-CSF in SCI treatment, this research seeks to contribute valuable insights into novel therapeutic strategies, addressing the critical need for effective and safe SCI treatments.

2. Materials and methods

After obtaining institutional ethics committee clearance (JIP/IEC/2021/010, dated July 06, 2021), a total of 34 patients suspected of acute SCI and neurological deficit attending the orthopedic casualty at JIPMER, Puducherry, had undergone an initial clinical and radiological screening to establish their eligibility for enrolment in the single-blinded randomized controlled trial.

2.1. Inclusion criteria

Patients aged >18 years with tSCI within 48 h of injury, patients with ASIA grade A, B, C, and D neurological status assessed within 48 h post-injury, and patients with AO type A, B, and C fracture patterns of thoracic and lumbar vertebra (T1 up to L5 vertebrae)

2.2. Exclusion criteria

Patients who are allergic to G-CSF, patients with hematological malignancy, splenomegaly, GCS less than 13, and within 6 months after invasive coronary intervention, pregnant women, patients with neurological disorders that can affect neurological evaluation in the present trial, patients with fracture of extremities that can affect the neurological evaluation, patients who undertaken a massive dose administration of methylprednisolone [bolus of 30 mg per kilogram of body weight for 15 min, followed by infusion at 5.4 mg per kilogram per hour for 23 h], and patients with pathological vertebral body fractures.

2.3. Randomization

After obtaining informed written consent, the demographic details of all the patients were collected. To ensure single blinding, the patients assigned to either group were not informed regarding the treatment (G-CSF or NS) given to them. The patients were randomized and divided into two groups namely group A (n = 16) received 400 μg of IV G-CSF injection for 5 successive days and group B (n = 30) received IV saline infusion for 5 successive days.

Patients in Group A received a test dose of G-CSF via skin prick test and were monitored for adverse reactions for 30 min. In case of an instant adverse reaction, the patients were not allowed to participate in the trial and were excluded from the study. The first dose of G-CSF was administered IV in 100 ml of normal saline over 30 min, followed by 2nd, 3rd, 4th, and 5th doses of 400 μg, where each injection was given 24 h apart on succeeding days. Patients in Group B received their first dose of normal saline (NS) by IV infusion on the following five consecutive days. Patients in both groups received daily monitoring with full blood count evaluations, clinico-abdominal examinations for splenomegaly, and UGS abdomen in the event of any dubious splenomegaly.

2.4. Follow-up

Depending on the degree of the injury, the patient was triaged either for surgery or conservative management, and those patients underwent pre-operative evaluation for surgical fitness. Within a week of surgery, patients were mobilized on either a walker or wheeler chair depending on the neurological status of the tSCI individual. Post-operative rehabilitation for the limb and bladder was given to required patients. After a standard 2-view post-op radiograph of the affected spine and a wound check on days 4 and 8, the patient was discharged with adequate analgesic and antibiotics coverage. For neurological evaluation, all the patients were followed up at 1-, 3-, and 6- months following post-tSCI as measured by the ASIA impairment scale.

2.5. Statistical analysis

The statistical analysis was performed by Statistical Package for Social Sciences (SPSS) Version 26.0, IBM Corp, Chicago, Illinois, USA. The demographic variables were compared using the Chi-square test for categorical variables and the Mann -Whitney *U* test for continuous variables. The comparison of ASIA scores within groups A & B, at different time points was performed using the McNemar-Bowker Test. The change observed in the ASIA score over some time between the groups was compared using generalized estimating equations. The frequency of adverse events (AEs) was compared using Fisher's exact test. A p-value of <0.05 was considered statistically significant.

3. Results

A total of 34 participants were included in the study. The majority of the participants were males, constituting 91.2 % (n = 31) of the total sample, while only 8.8 % (n = 3) were females. The age distribution of the participants was compared between two groups, Group A and Group B. The median age in Group A was 26 years (IQR: 18, 41), while in Group B, it was 39 years (IQR: 24, 50). The difference in age between the two groups was not statistically significant (p = 0.102), as assessed by the Mann-Whitney *U* test. Within the individual groups, Group A consisted of 81.3 % (n = 13) male participants and 18.8 % (n = 3) female participants. In contrast, Group B had 100 % (n = 18) male participants and no female participants. The difference in gender distribution between the two groups was not statistically significant (p = 0.094). Overall, there was no significant difference in either the age or gender distribution between the two groups.

3.1. Assessment of neurological recovery

Neurological recovery was assessed using the ASIA impairment scale at various time intervals: baseline, 1-, 3-, and 6-months as shown in Table 1.

3.2. Rate of neurological improvement over time

The rate of neurological improvement in Group A and Group B over different time intervals was analyzed and represented in Table 2.

These results demonstrate a statistically significant improvement in neurological recovery in Group A compared to Group B across all time intervals, particularly at 3 and 6 months.

4. Discussion

One of the most common causes of orthopaedic emergencies in India

Table 1
ASIA score assessment between Group A and Group B at various time points.

Time points	Groups	ASIA score				P-value
		Class A	Class B	Class C	Class D	
Baseline	A (n = 16)	1 (6.3 %)	9 (25 %)	6 (62.5 %)	0 (0 %)	0.019
	B (n = 18)	9 (50 %)	6 (33.3 %)	3 (16.7 %)	0 (0 %)	
1-month	A (n = 16)	1 (6.3 %)	4 (25 %)	10 (62.5 %)	1 (6.3 %)	0.005
	B (n = 18)	9 (50 %)	6 (33.3 %)	3 (16.7 %)	0 (0 %)	
3-months	A (n = 16)	0 (0 %)	1 (6.3 %)	9 (56.3 %)	6 (37.5 %)	<0.001
	B (n = 18)	8 (44.4 %)	5 (27.8 %)	5 (27.8 %)	0 (0 %)	
6-months	A (n = 16)	0 (0 %)	1 (6.3 %)	7 (43.8 %)	8 (50 %)	0.005
	B (n = 18)	4 (22.2 %)	7 (38.9 %)	5 (27.8 %)	2 (11.1 %)	

is traumatic spinal cord injury (tSCI). The morbidity and mortality associated with delayed or incomplete treatment of tSCI is high and therefore, it is prudent to diagnose and treat tSCI with the best possible treatment available. Treatment with G-CSF is one of the treatment modalities employed in the treatment of tSCI.[17,20,23] Though the literature contains studies that compared and studied the effectiveness and safety of G-CSF for the treatment of tSCI, there are no studies conducted in India on the Indian population to the best of our knowledge. Being a high-volume center, that receives patients from various regions across south India, our study aimed at identifying the effectiveness of G-CSF for the treatment of tSCI in our population. By conducting this randomized controlled trial, we aimed to provide the highest form of evidence on the usage of G-CSF as a treatment option for patients with tSCI.

In our study, age did not show any significant difference between the two groups though the median age in group B (placebo) was more compared to group A (G-CSF). In the study by Koda et al.[20] which included a total of 88 patients (G-CSF = 43; placebo = 45), age did not show a significant difference between the two groups. Derakhshanrad et al.[22] study which compared the effectiveness of G-CSF for patients with SCI (GSF = 56; placebo = 58) also showed no significant difference in age between the two groups.

In Devivo's review of the epidemiology of tSCI,[26] the author concluded that the average age of both newly injured persons and all persons who are currently alive with SCI will increase slowly. It was also concluded that the percentage of new injuries among the elderly population (age more than 60 years) will rise. The author also suggested that the elderly population due to cognitive difficulties will face challenges in following up long term and thus will not be able to be compliant with protocol. It was also concluded that the outcomes will be less favorable in the future owing to trends in age and injury severity.[26] Given these challenges in the treatment of tSCI, it is prudent to identify a modality of treatment that will impact the elderly population with tSCI significantly. Henceforth, the advantage of G-CSF in improving the morbidity and mortality rates in the older population should be studied further.

Usually, the female gender is at a higher risk of fracture due to the propensity of osteoporosis cases occurring commonly in the female gender. This is due to the estrogen effect on bone metabolism. Therefore, one can conclude that tSCI will have a significant impact on the female gender and therefore G-CSF can help in the treatment. In our study, gender did not show any significant difference between the two groups. However, the majority of the study population were males. In the studies by Koda et al.[20] and Derakhshanrad et al.[22] Yoon et al., gender did not show any significant difference between the groups. Future studies should involve determining whether G-CSF has a significant impact on the prognosis in female patients with tSCI.

In our study, the assessment of the neurological status was done using the ASIA score. Other scoring systems include the Japanese Orthopaedic Association scoring for thoracic myelopathy. The assessment was done at one, three, and six months after the initial injury. The ASIA scores at different time points were compared with each other. At the time of admission, the initial ASIA score showed a significant difference between the two groups in our study. ASIA scoring was used at one, three, and six months of follow-up after administration of G-CSF. ASIA scores at 1-, 3-, and 6 months showed statistically significant differences between the two groups. This shows that the administration of G-CSF helped in the improvement of the neurological status of patients with tSCI from Class A to B, C, or D. Takahashi et al. conducted a phase I/IIa clinical trial to study the neuroprotective effects of G-CSF for the treatment of SCI. A total of 16 patients with SCI (within 48 h of onset) were included in the trial. G-CSF (Dose = 5 μg/kg/day) was given to five patients for the first five days. The rest 11 patients received G-CSF with a dose of 10 μg/kg/day and were evaluated for neurological response using the ASIA score. A significant improvement in ASIA score was observed especially in patients who received a G-CSF dose of 10 μg/kg/day. In our study also, we used G-CSF with a dose of 10 μg/kg/day with a maximum dose being 400 μg/day. G-CSF with a dose of 10 μg/kg/day has shown to be the standard dose with proven efficacy and safety.

In the phase I/IIa clinical trial, Sakuma et al. observed a significant improvement in the neurological status of the patients with thoracic myelopathy who received G-CSF μg/kg per day IV for 5 consecutive days.[27] In a phase III double-blinded, placebo-controlled RCT, Koda et al.[20] randomized patients into two groups where the G-CSF group (n = 44) received 400 μg/m^2/day for 5 consecutive days in normal saline via IV infusion and the placebo group (n = 44) received normal saline via IV infusion for 5 consecutive days. There was no significant difference in the ASIA score at baseline and 3-month follow-up between both groups. However, the ASIA score at 6- and 12-months was significantly higher in the group that received G-CSF than placebo. This study failed to demonstrate a clinical improvement at 3 months of G-CSF injection.[20] SCI recovery takes 3–12 months where 3 months is the expected minimal recovery period for SCI recovery which was accepted by Koda et al.[20] Yet in our study, the ASIA score was significantly higher at 1-, 3-, and 6-month follow-up after administration of G-CSF for SCI.

Various studies in the literature investigated the role of G-CSF in the treatment of patients with SCI. A few studies involving animal models with cerebral infarction have proved the neuroprotective properties of G-CSF.[28–32] G-CSF was shown to inhibit the neuronal apoptosis and expression of cytokines involved in neural inflammation.[18,33–37] Takahashi et al.'s clinical trial was the first one to conduct the trial of G-CSF usage for patients with acute SCI.[38] In almost all the studies, the dose

Table 2
Neurological improvement between Group A and Group B at various time points.

Time points	Group A (n = 16)	Group B (n = 18)
1 month	6 out of 16 patients showed improvement, with 5 moving from Class B to Class C, and 1 patient from Class C to Class D	Group B exhibited no improvement in the first month
3 months	5 patients in Group A improved from Class C to Class D	3 out of 18 patients in Group B showed improvement, with 2 moving from Class B to Class C, and 1 from Class A to Class B
6 months	2 more patients in Group A advanced from Class C to Class D	Group B showed improvement in 10 out of 18 patients, with 5 moving from Class A to Class B, 3 from Class B to Class C, and 2 from Class C to Class D

and duration of G-CSF administration was 5–10 μg/kg/day for 4–6 days.[38,39] Shyu et al. administered G-CSF at 15 μg/kg/day for 5 days in patients with cerebral infarction.[40] In our study, we administered G-CSF at 10 μg/kg/day for 5 days with the maximum dose being 400 μg/day for 5 days. The safety profile of G-CSF is also good, as it involves only minimal side effects that last only for a short duration.[16,27,41] The higher dose of G-CSF administration is involved with a higher risk of adverse events.[42,43]

To the best of our knowledge, our study is the first trial which is conducted on the Indian population. The cost of G-CSF (Filgrastim) in India is around 80–100 rupees and the overall cost for five days will be around 400–500 rupees. Being a cost-effective alternative and with a significant impact on the prognosis, the usage of G-CSF for the treatment of SCI should be researched further in the elderly population and female population.

The strengths of this study are the study design being a single-blinded randomized controlled trial and the first clinical trial of G-CSF tested for neurological recovery of acute SCI patients in the Indian setting. The only limitation of the study is the inability to achieve a desirable sample size due to the COVID-19 pandemic.

5. Conclusion

G-CSF had a significant role in the improvement of ASIA score at 1-, 3-, and 6- months following administration from the baseline. Being a cost-effective modality, the administration of G-CSF should be considered in patients with tSCI. However, due to the small sample size, we cannot conclude the results of this study with absolute certainty.

CRediT authorship contribution statement

Prabu Mounissamy: Conceptualization, Manuscript, Data curation, Data collection. **Premraj A.C.:** Manuscript writing, Data collection. **Sushma Chanadrashekar:** Manuscript writing, Data collection. **Naveen Jeyaraman:** Literature review. **Swaminathan Ramasubramanian:** Literature review, Manuscript, Data curation. **Madhan Jeyaraman:** Conceptualization, Literature review, All authors agreed to publish the manuscript.

Patient consent

All patients consented for participating in the study.

IEC clearance

JIPMER, Puducherry – JIP/IEC/2021/010, dated July 06, 2021.

Institutional ethics committee

IEC - JIP/IEC/2021/010, dated July 06, 2021.

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Conflict of interest

All authors declare no conflict of interest in publishing the manuscript.

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