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Systematic Review

Effect of Granulocyte Colony-Stimulating Factor (G-CSF) on Improving Impairment Scale After Acute Spinal Cord Injury: An Individual Participant Data Meta-Analysis

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ABSTRACT

Background and Aim: The present study was conducted to investigate the effects of granulocyte colony-stimulating factor (G-CSF) after acute spinal cord injury on increasing a grade of improvement entitled American spinal cord injury association impairment scale (AIS) as an individual participant data (IPD) meta-regression analysis of clinical trials.

Methods and Materials/Patients: According to our search strategy, four studies were selected. Multilevel ordered logistic regression modeling was used to predict AIS grade with G-CSF administration and time variable (first day and a 3-month follow-up). The IDs of the studies as well as the time series variable were imported to the random part of the model. Odds ratio (OR) and 95% confidence interval (CI) were reported.

Results: A total of 277 samples were studied. A fixed effect model was performed at first. Accordingly, using G-CSF was associated with increased AIS grade (lower impairment) (OR=1.503, 95% CI=1.110-2.035) adjusted with time series (OR=1.868, 95% CI=1.378-2.532). In the mixed effect model, G-CSF was again associated with increased AIS grade (OR=1.780, 95% CI=1.301-2.436) adjusted with time series (OR=2.152, 95% CI=1.406-3.294).

Conclusion: The present meta-analysis showed the protective effect of GCS-F observed as an improvement in AIS grade. This protecting effect was further after adjusting the random effects of time series and individual studies. Although multilevel modeling could reduce our limitations, it should be regarded that the number of trials was not enough to establish strong conclusions.

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Highlights

- High-dose methylprednisolone may be used after acute spinal cord injury.
- There are some controversies about the effects of methylprednisolone in this regard.
- Granulocyte colony-stimulating factor (G-CSF) was proposed in such conditions due to its non-hematopoietic effects.
- A meta-analysis was performed to investigate this issue using multilevel mixed effect models.
- G-CSF showed a protecting effect with and without adjusting random effects.
- Despite finding a protective effect for G-CSF, the number of trials is not enough to establish strong conclusions.

Plain Language Summary

Today's world is trauma-prone. Spinal cord trauma leads to a spinal cord injury causing neurological impairment. Therefore, some drugs may be used on the first day of injury to prevent such impairments. Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic (blood-making) drug that also has other effects such as tissue protection. It was proposed that G-CSF could be used after acute spinal cord injury. As a meta-analysis (a type of study summarizing numerically the results of previous studies), we tested this hypothesis that G-CSF might be effective in improving an impairment scale called AIS after acute spinal cord injury. Finally, G-CSF showed a protective effect; but the number of previous trials was not enough to judge.

1. Introduction

Acute spinal cord injury (SCI) involves two pathological phases termed primary and secondary injuries. Focal tissue destruction as a primary injury is made by direct mechanical trauma. The secondary injury phase as a pathophysiological reaction of spinal cord is initiated by this physical trauma [1]. Many factors could worsen the secondary injury phase consisting of vascular changes, increased levels of free radicals and free fatty acids, ionic mechanisms that occurred during axonal injury, glutamate excitotoxicity mechanism [2], and immune and inflammatory reactions [3, 4].

The neurons and the glial cells not being damaged by initial trauma undergo apoptosis during the secondary phase. Furthermore, apoptosis of the oligodendrocytes far from a recent site of injury occurs [5]. Maximum cell death takes place one week after injury and directly causes demyelination [6]. Several in vivo studies have illustrated a correlation between the amount of white matter sparing and residual locomotor function. Thus, oligodendrocytes protected from apoptotic cell death might decrease demyelination and enhance functional recovery [7]. Neural tissue lacks extremely active oxidative protection mechanisms. Unlike many other cells, neurons are unable to have mitosis, and so, they are vulnerable by any means, especially destructive damage of free radicals that may cause permanent lesions [8]. Tissue oxidative stress and function loss of spinal cord are caused by a traumatic injury, and physical deformation of the spinal cord as a primary injury directly damages some axons. Although, it is probably being lost a large number of axons caused by enormous pathophysiological processes as a secondary injury initiated by the original injury [9].

Granulocyte colony-stimulating factor (G-CSF) as a protein (cytokine) is broadly well-known to induce differentiation, proliferation, and survival of cells in granulocytic lineage. In the event of SCI, G-CSF therapy which several research groups previously reported, promoted functional recovery in mouse and rat SCI models [10]. Although the favorable effects of G-CSF on neurons are partially recognized, little evidence is known about G-CSF-mediated apoptosis decrease of oligodendrocytes after SCI [11]. Therfore, it is presupposed that G-CSF can diminish oligodendrocytes apoptosis and subsequently enhance white matter conservation and functional recovery. These results can be represented by another mechanism which G-CSF supplies neuroprotection following SCI [12].

Methylprednisolone sodium succinate (MPSS) is one of the effective neuroprotective drugs in extensive use for the remedy of SCI [13]. Presently, high-dose MPSS is an accepted therapeutic agent in acute SCI which has been used considerably to diminish secondary effects of SCI via its anti-inflammatory characteristics which have been attributed to the relief of spinal cord edema [14]. Although, it recently has become controversial because of the risk of serious side effects and its modest neurological advantages [15]. Hence, improvement of new drug treatments which can be a replacement for high-dose MPSS is an area of study [16].

Objectives

The present study was designed to investigate the effects of G-CSF after acute SCI on increasing a grade of improvement entitled American SCI Association Impairment Scale (AIS) as an individual participant data (IPD) meta-regression analysis on the related clinical trials. We intended to investigate whether G-CSF shifts the complications to higher AIS grades (reduction in complications) or not.

2. Methods and Materials/Patients

Study design

The present study was performed as an IPD meta-analysis with a multilevel approach to adjust the effects of the study centers. The method of using multilevel modeling in a meta-analysis has been published previously [17]. The outcome variable was AIS grade (in ordinal scale) at two different times including at the time of injury and at the time of a 3-month follow-up (a before-after design). The independent variable was G-CSF intervention.

Literature search

The meta-search engines Google Scholar, PubMed and Scopus were used. PubMed (n=9) and Scopus (n=32) were used as the primary sources where we searched for the relevant words in titles and abstracts. Google Scholar (n=1) was used as the secondary source to find missing documents from other indexing databases. After removal of duplicates, the texts of the remained documents (n=39) were evaluated. Among them, 28 documents were review articles, 6 documents were animal studies and 1 document was on chronic SCI. Finally, 4 documents that were original articles on the administration of GCS-F in SCI were used for IPD meta-analysis.

Eligibility criteria

The studies which were performed on humans as clinical trials or cohorts, assessing both G-CSF and MPSS (one study used a placebo instead of MPSS) were included in the study.

Data collection and Preparation

Protocol similarities of the papers were the same doses of G-CSF (10 µg/kg/day) and MPSS (high-dose) administration, same time of administration after injury, same complication scaling system (AIS), and same time frame for follow-up the complications (three months). One of these studies used a placebo instead of MPSS. Data were collected as the number of cases in each administration group divided by AIS grades (A to E) and the two evaluated times. Higher grades indicated lower injury. Definitions of AIS grades are shown in Figure 1 (caption).

Statistical analysis

Multilevel ordered logistic regression modeling was used to predict AIS grade with G-CSF and time variable. The IDs of the studies were imported to the random part of the models to adjust the random effects (random intercepts) of the centers. In addition, the random effect of the time variable nested in ID was adjusted. Odds Ratio (OR) and 95% Confidence Interval (CI) were reported. Stata14 (Stata Corp. LLC, Texas, US) was used to analyze the data.

3. Results

A total of 277 cases were collected from the 4 studies including the studies of Takahashi et al. (2012, Japan) [18], Kamiya et al. (2015, Japan) [19], Yousefzadeh-Chabok et al. (2016, Iran) [20] and Derakhshanrad et al. (2019, Iran) [21]. The study of Derakhshanrad et al. had some differences in its protocol such as using a placebo, subacute injury cases and a GCS-F dose 300 µg/day for all the patients for 7 consecutive days.

Distribution of AIS grade among the samples divided by drug group and time of evaluation is shown (Table 1, Figure 1). For modeling, a fixed effect model was performed at first. Accordingly, using G-CSF was associated with increased AIS grade (lower impairment) (OR=1.503, 95% CI=1.110-2.035) adjusted with time series (OR=1.868, 95% CI=1.378-2.532) (Table 2, Figure 2). For the mixed effect model, random intercepts of ID and time series were added. Accordingly, G-CSF was again associated with increased AIS grade (lower

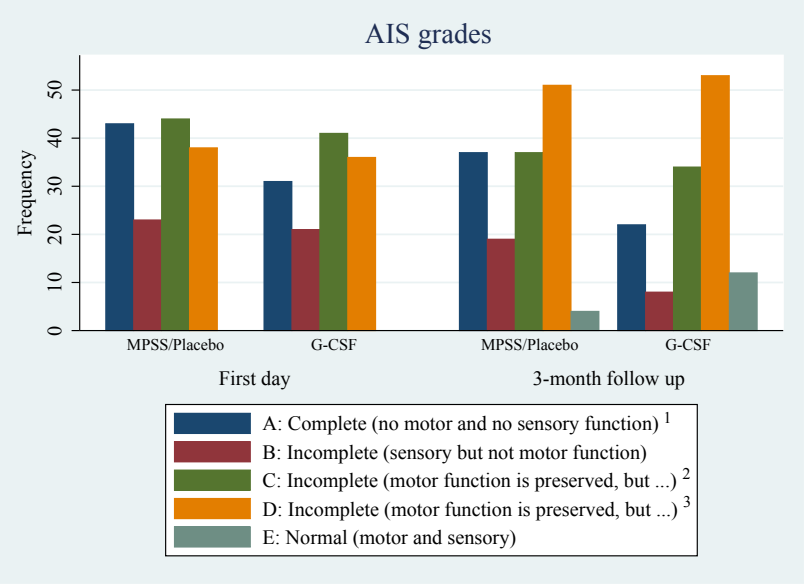

Figure 1. Frequency of AIS grades based on time and type of drug

1: All the definitions belong to below the level of injury; 2: More than 50% of key muscles below the neurological level have a muscle grade < 3; 3: At least 50% of key muscles below the neurological level have a muscle grade ≥ 3.

impairment) (OR=1.780, 95% CI=1.301-2.436) adjusted with time series (OR=2.152, 95% CI=1.406-3.294) (Table 3). Since the random effects of IDs (study centers) could influence the effects of the covariates, the IDs were also added to the mixed effect model as a factor covariate. The study of Derakhshanrad et al. was considered as a reference category (because of its differences) and then we found that the Iranian study done by Yousefzadeh-Chabok et al. was per se associated with decreased AIS grade (higher impairment) in comparison to the reference (OR=0.463, 95% CI=0.313-0.485). The effects of the other studies are also presnted (Table 4).

4. Discussion

Summary of evidence

The current study was conducted to show the effect of G-CSF administration on the improvement of AIS grades. A rather novel meta-analytic approach was utilized for a before-after design. Multilevel modeling seemed to be the best choice to adjust the random effects of times as

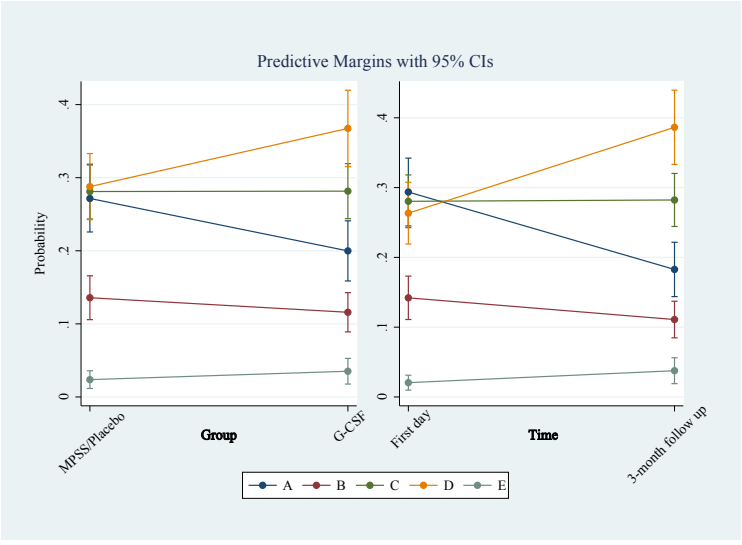

Figure 2. Prediction of the probability of each AIS grade based on time and type of drug according to Table 2

Table 1. Individual participant data of the studies (number of patients in each subcategory)

Study	AIS	Follow-up (3 months)	G-CSF (n)	MPSS/Placebo (n)
Derakhshanrad et al., 2019 [21]	A	Before	0	0
		After	0	0
	B	Before	11	11
		After	6	11
	C	Before	11	9
		After	11	9
	D	Before	6	6
		After	10	6
	E	Before	0	0
		After	1	0
Yousefzadeh-Chabok et al., 2016 [20]	A	Before	28	27
		After	20	23
	B	Before	6	6
		After	2	4
	C	Before	19	16
		After	20	19
	D	Before	9	11
		After	20	14
	E	Before	0	0
		After	0	0
Kamiya et al., 2015 [19]	A	Before	2	9
		After	1	8
	B	Before	4	3
		After	0	1
	C	Before	8	11
		After	3	6
	D	Before	14	11
		After	15	16
	E	Before	0	0
		After	9	3
Takahashi et al., 2012 [18]	A	Before	1	7
		After	1	6
	B	Before	0	3
		After	0	3
	C	Before	3	8
		After	0	3
	D	Before	7	10
		After	8	15
	E	Before	0	0
		After	2	1

The study of Derakhshanrad et al. used a placebo while the other studies used MPSS.

Table 2. Multilevel ordered logistic regression for prediction of AIS grade based on using GCS-F and time series (fixed effect)

Covariates						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
G-CSF (use)	1.503	0.232	2.64	0.008	1.110	2.035
Time (after follow-up)	1.868	0.290	4.03	<0.001	1.378	2.532
Cuts						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
1	-0.696	0.139	-5.02	<0.001	-0.968	-0.424
2	-0.071	0.134	-0.54	<0.001	-0.333	0.190
3	1.124	0.142	7.91	<0.001	0.846	1.402
4	4.075	0.283	14.38	<0.001	3.520	4.631

AIS grades: A=1, B=2, C=3, D=4 and E=5

Table 3. Multilevel ordered logistic regression for prediction of AIS grade based on using GCS-F and time series (mixed effect)

Covariates						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
G-CSF (use)	1.780	0.285	3.60	<0.001	1.301	2.436
Time (after follow-up)	2.152	0.467	3.53	<0.001	1.406	3.294
Cuts						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
1	-0.907	0.367	-2.47	0.013	-1.627	-0.188
2	-0.239	0.364	-0.66	0.512	-0.953	0.475
3	1.066	0.367	2.90	0.004	0.346	1.785
4	4.251	0.451	9.43	<0.001	3.367	5.135
Random effects						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
ID						
Variance (constant)	0.415	<0.001			0.089	1.934
ID → Time						
Variance (constant)	0.036	<0.001			0.001	1.498

Times series was considered as level 1 that is nested within ID as level 2.

AIS grades: A=1, B=2, C=3, D=4 and E=5

Table 4. Multilevel ordered logistic regression for prediction of AIS grade based on using GCS-F, time series and study ID (mixed effect)

Covariates						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
G-CSF (use)	1.797	0.288	3.66	<0.001	1.313	2.460
Time (after follow-up)	2.090	0.333	4.63	<0.001	1.530	2.856
ID						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
Derakhshanrad	Reference					
Yousefzadeh-Chabok	0.463	0.093	-3.85	<0.001	0.313	0.485
Kamiya	2.412	0.580	3.86	<0.001	1.506	3.865
Takahashi	2.170	0.597	2.82	0.005	1.268	3.723
Cuts						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
1	-0.708	0.202	-3.50	<0.001	-1.104	-0.312
2	-0.036	0.196	-0.18	0.853	-0.421	0.349
3	1.273	0.208	6.13	<0.001	0.866	1.680
4	4.438	0.336	13.20	<0.001	3.779	5.097
Random Effects						
Model Characteristics	**Odds Ratio**	**Standard Error**	**Z-Value**	**P**	**95% CI Limits**	
ID						
Variance (constant)	<0.001	<0.001				
ID → Time						
Variance (constant)	<0.001	<0.001				

Times series was considered as level 1 that is nested within ID as level 2.

AIS grades: A=1, B=2, C=3, D=4 and E=5. Maximum possible number of iterations was 122 and they were performed in this model. Actually, no random effect was found.

well as the random effects of individual studies caused by differences in study characteristics. Hereby, we found a protective effect for G-CSF (increasing 1.503 folds of a chance to improve one grade) which was elevated after adjustment of the random effects (increasing 1.868 folds of a chance to improve one grade). Although a significant protecting association was found for G-CSF, this effect was not greater than time series effect. It meant that three months of waiting had more contribution to patient improvement than G-CSF administration.

According to the literature, four studies were eligible for this meta-analysis. Two studies had been conducted in Japan [18, 19] and the two other ones had been performed in Iran [20, 21]. Based on our investigations, the Japanese studies showed better effects for G-CSF than

the Iranian studies. The whys and wherefores of this difference were not clear.

MPSS is one of the most studied factors for its neuroprotective capability. This drug is usually administrated for acute SCI all over the world based on National Acute Spinal Cord Injury Study (NASCIS) trials despite some controversies [22, 23]. High-dose MPSS may be the standard treatment for SCI [18, 19, 24]. Studies have indicated that the usage of this drug eight hours after an injury has enhanced sensory and motor results [25]. Along with this accepted role of MPSS, there was a need to investigate further drugs because of MPSS limitations and complications. Hereby, the non-hematopoietic effects of G-CSF were proposed for brain tissue protection. Many experimental models approved the association of G-CSF administration with neurological improvements. Teixeira et al. studied the effects of G-CSF and MPSS combination on an experimental rat model of acute SCI. They found a better functional and neurological improvement in the combined group compared to the effects of each G-CSF and MPSS alone [26].

5. Conclusion

Neuroprotection after acute SCI is emergent and should be performed by acceptable management like administration of high dose MPSS. Therefore, the administration of some other drugs like G-CSF needs strong evidence. The present meta-analysis showed the protective effect of GCS-F seen as an improvement in AIS grade. This protecting effect was further after adjusting the random effects of vising times (first day and a 3-month follow-up) and individual studies. Although multilevel modeling could reduce our limitations, it should be regarded that the number of trials was not enough to establish strong conclusions.

Limitations

The most important limitation of this meta-analysis was the low number of randomized controlled trials for the foreground question. Differences in the results of Iranian and Japanese studies indicated that this trial should be repeated in many other populations. However, we could adjust the random effects of the individual studies using the multilevel mixed-effect model.

Ethical Considerations

Compliance with ethical guidelines

No human or animal sample was directly used in this study. In addition, no information related to privacy and secrecy was used. All the information used in this meta-analysis was based on published data.

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Authors' contributions

Conception and design: Seyyed Amir Yasin Ahmadi, Jafar Rezaian, Babak Alijani, Shahrokh Yousefzadeh-Chabok. Data collection: Mohammad Javad Nourmohammadi, Ahmed Sayahi. Data analysis and interpretation: Seyyed Amir Yasin Ahmadi. Drafting the article: Mohammad Javad Nourmohammadi, Ahmed Sayahi, Seyyed Amir Yasin Ahmadi. Critically revising the article: Babak Alijani, Shahrokh Yousefzadeh-Chabok, Jafar Rezaian. Reviewing submitted version of manuscript: All the authors. Approving the final version of the manuscript: All the authors.

Conflict of interest

The authors declare no conflicts of interest other than Shahrokh Yousefzadeh-Chabok is a journal staff.

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