

# The Effects of Filgrastim on Complications of Patients with Cerebral Hemorrhage Due To Head Trauma

Morteza Qaribi<sup>1</sup>, Arash Yazdanbakhsh<sup>1</sup>, Koorosh Ahmadi<sup>2</sup>, Mohammad Reza Maghsoudi<sup>2</sup>, Vagefe Farshin<sup>1</sup>, Ali Ahmadi<sup>3</sup>, Abolfazl Jokar<sup>1\*</sup>

<sup>1</sup>Department of Emergency Medicine, Arak University of Medical Sciences, Arak, Iran; <sup>2</sup>Department of Emergency Medicine, Alborz University of Medical Sciences, Karaj, Iran; <sup>3</sup>Iran University of Medical Sciences, Iran

## Abstract

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**\*Correspondence:** Abolfazl Jokar, Department of Emergency Medicine, Arak University of Medical Sciences, Arak, Iran. E-mail: Dr.a.jokar@gmail.com

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**BACKGROUND:** Filgrastim, a neopogen brand, is a blood-forming agent and a natural protein in the body that plays a role in stimulating the growth of white blood cells and protecting them against infectious agents. To the best of knowledge, human and animal specimens have shown the effect of Filgrastim on treating brain injuries regarding bone marrow transfusion into the blood, neuroprotection, stimulation of neurons for forming new neural networks and reducing the risk of bacterial infections.

**AIM:** This study aimed to investigate the effect of Filgrastim on the prognosis of a cerebral haemorrhage in patients with traumatic brain injury.

**METHODS:** This study was conducted as a clinical trial, in which the initial diagnosis of patients with cerebral haemorrhage due to head trauma was performed with a clinical examination and CT scan. After the patient arrives at the emergency room, the patient's initial examination is performed, and blood tests are taken from the patient. Moreover, CBC values (Hb, Platelet, Hematocrit) were checked and recorded in the checklist. The intervention group received 150 mcg/day Filgrastim injected subcutaneously for 4 days. Furthermore, patients in the control group received the same amount of sterile water. At the end of the treatment period, blood tests were performed again in all patients, and their results were then recorded. All data were analysed by SPSS v.21 software package.

**RESULTS:** Our findings revealed that the mean volume of bleeding in the intervention group based on CT scan was significantly reduced after four days as compared to the control group. Moreover, the mean score of consciousness and muscular strength of patients in the intervention group was significantly higher than the control group. Also, WBCs in the intervention group exhibited a significant increase after four days of intervention, while platelet and hematocrit levels in the intervention group decreased significantly compared to the control group.

**CONCLUSION:** Regarding the results, the therapeutic application of filtration is considered to be effective. Given the lack of serious complications of the proposed dosages, the use of this drug can be suggested.

## Introduction

Brain trauma and its complications, such as cerebral haemorrhage results from a blow or jolt to the head and have led to the loss of high-yielding years in the community, which is a leading cause of mortality. Traumatic brain injury is one of the key factors in public health, where is considered to be one of the most important causes of death among *young people* in rich countries.

Given the growing growth of motor vehicles,

the rate of brain injury in the world is increasing. It is estimated that more than 10 million brain injury occurs annually worldwide in need of hospital care. It is worth noting that 9% of all deaths in the world are due to traumatic brain injury. Surviving patients are likely to be affected by permanent or temporary disabilities. The financial burden of traumatic brain injury has been estimated to be more than \$ 60 billion annually (only in the United States). Many traumatic brain damage develops during hospitalisation and increases the need for surgery or the degree of complications and mortality of patients [1]. Trauma is the most

common cause of death for *people* ages 1 to 44 years. Head trauma is the most common cause of hospitalisation and death of traumatic patients (40 to 50%), [2]. The traumatic brain haemorrhages are divided into *delayed* and early traumatic intracerebral haemorrhages. Early haemorrhages are related to patients who have been diagnosed with haemorrhage in a CT scan for up to six hours after the trauma. However, haemorrhage is likely to appear after 6 hours with CT scans for various reasons, where such haemorrhage is called delayed intracerebral haemorrhage. Delayed traumatic intracerebral hematoma (DTICH) is one of the most important treatable complications of secondary brain damage in patients with brain trauma [3].

Since CT scan has become commonplace as a good diagnostic tool, the DTICH incidence in all patients with brain damage is reported to be between 0.6% and 7.4%. DTICH can include all kinds of cerebral haemorrhages, including intraparenchymal haemorrhage (IPH), *subdural haemorrhage* (SDH), and extradural haemorrhage (EDH) or *epidural haemorrhage* (EDH). Although DTICH may be present in a patient who has already had a history of brain damage, it can occur in patients with primary normal CT scan results. The death rate for DTICH is more than 35% to 40% [2]. Nevertheless, various studies have shown that mortality rates are significantly reduced in the event of timely diagnosis and rapid treatment [3]. In the absence of timely diagnosis and treatment, the mortality rate may even be higher than 50% [4]. Studies show that DTICH can occur in each age group with varying degrees of trauma and with different levels of patient alertness, even in patients with GCS of 15, as well as patients with a completely normal CT scan or without a skull fracture [5].

Granulocyte colony stimulator (G-CSF) is a glycoprotein that generates a hematopoietic cell colony in the culture of bone marrow cells. G-CSF is an important factor in neutrophil-based immune defence system due to a regulatory role in growth, differentiation, survival and activation of neutrophils and precursors [6].

Filgrastim is a blood-forming agent and a natural protein called Neupogen, which stimulates the growth of white blood cells in the body and protects these cells against infection. Filgrastim is used for several therapeutic purposes, including neutropenia, the loss of some white blood cells from cancer, bone marrow transplantation, chemotherapy, or other conditions. Filgrastim is considered to be the synthetic form of G-CSF (Granulocyte Stimulator), a natural protein that promotes the production of white blood cell production. It should be taken into consideration that G-CSF deficiency increases the risk of bacterial infections.

This drug induces bone marrow to produce white blood cells and thereby reduce the risk of infection. Therefore, bone marrow cells enter the

bloodstream to make bone marrow transplantation easy [7]. Recent studies on human and animal specimens have revealed the effect of filgrastim on the treatment of brain injuries for several functions, such as the entrance of bone marrow cells into the blood, neuroprotection, stimulation of neural cells for forming new neural networks and reducing the risk of bacterial infections [2] [8].

Despite extensive research in recent years, there is still no drug that can protect against the effects of brain damage and subsequent bleeding from brain cells. Therefore, this study aimed to investigate the effect of Filgrastim on the prognosis of a cerebral haemorrhage *in patients with traumatic brain injury*.

## Material and Methods

This randomised, double-blind clinical study was conducted among patients referred to the emergency department of Vali-e-Asr Hospital in Arak for head trauma. Patients were selected based on the initial diagnosis with a clinical examination and CT scan. All patients with inclusion criteria were entered into intervention and control groups at the time of arrival using a random number table. After the patient's arrival, the patient's primary examination was performed and the patient's background information, including age, sex, and the cause of the trauma, were recorded. Blood tests were performed from patients, and the complete blood count (CBC) (Hct and PLt, Hb) were checked and recorded on the checklist. Patients in the case group (34 patients) received a subcutaneous injection of 150 mg Filgrastim weekly for 4 days. Before and during treatment with this drug, vital signs, haemoglobin and electrolytes were carefully checked.

On the other hand, patients in the control group (34 patients) received the same amount of distilled water. It should be noted that the patient was not aware of the type of treatment received. Patients were monitored for the type of brain injury, CBC, vital signs, and coagulation tests, as well as some electrolytes. At the end of the course of treatment, blood tests were repeated in all patients. If the laboratory factors were normal, response to the treatment was recorded for patients.

Finally, the data were analysed by SPSS v.21 software using SPSS software. To evaluate the results, indicators such as mean, standard deviation, standard error, frequency percentage were employed. For analytical analysis, the covariance test, Chi-div test and Independent T-test or its nonparametric equivalents were used to compare the mean. Meanwhile, values of  $p < 0.05$  were considered as significant levels.

Entry criteria included: 1) aged 18 years and above; 2) patients with head trauma, 3) consciousness (GCS) between 9 and 13; 4) Filling out the informed consent.

Exclusion criteria included: 1) Inclination to participate in the study; 2) Alcohol, and drug use, or any factor other than brain trauma that reduces the level of consciousness in the patient; 3) Acute hypersensitivity to the drug; 4) history of hypertension, diabetes, embolism and DVT; 5) Alertness below 9 and above 13; 6) Patient's death 72 hours after entering the emergency room.

In all stages of the project, ethical considerations such as informed consent for participating in the study and withdrawal were voluntarily, and the confidentiality of the information was observed. This research project was approved by the ethical committee of Arak University of Medical Sciences (No. 1173 and the code of ethics: IR.ARAKMU.REC.1395.100).

## Results

Most of the patients in the experimental group (76.7%) were male, and the remaining was female. Furthermore, most of the patients in the control group (83%) belonged to men and 17% of the remaining was women. To examine the homogeneity of the two groups, the Chi-square test was applied. The findings revealed that there was no significant difference in sex between the two groups ( $P = 0.22$ ). In the test group, the majority of patients (46.6%) were in the age group of 21-30 years and the lowest (10%) in the age group of 20 to 20 years old. Furthermore, most of the patients in the control group (50%) were in the age group 40, and the lowest (6%) belonged to the age group of 40-31 years old (Figure 1).

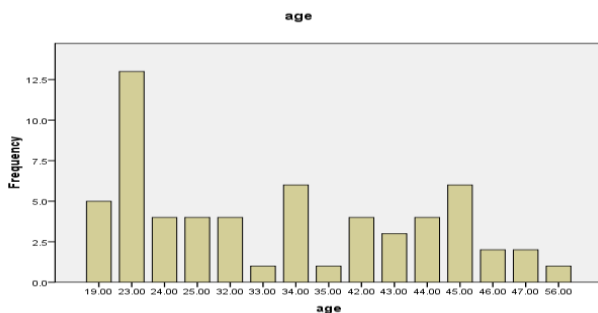


Figure 1: Age distribution in the intervention and control group

It should be taken in to account that the Fisher test was employed to check the homogeneity of the two groups. Based on the results, there was no significant difference between the two groups

regarding age ( $P = 0.42$ ). Chi-square test exhibited no significant difference regarding height and weight between the two groups (Table 1).

Table 1: Frequency distribution of patients in two groups of intervention and control regarding height and weight

Sex	Height	Weight
Intervention	32.166 ± 89.10	96.72 ± 43.11
Control	2.168 ± 55.10	3.72 ± 58.10
P-value	0.580	0.420

Based on the results of t-test presented here, the level of consciousness of both groups did not show any significant difference ( $P = 0.65$ ) and also after the intervention, no significant difference was found in consciousness level of both groups ( $P = 0.05$ ) based on the use of t-test (Table 2).

Table 2: Frequency distribution of patients in two groups of intervention and control regarding the level of consciousness

GCS	Intervention	controls	P-value
GCS0	80.10 ± 12.1	76.10 ± 16.1	0.650
GCS4	56.11 ± 22.1	36.10 ± 24.1	0.05

The t-test demonstrated that the mean scores of vital signs before and after intervention in both groups were not statistically significant ( $P > 0.05$ ; Table 3).

Table 3: Frequency distribution of patients in two groups of intervention and control regarding vital signs

Variables	Intervention	Control	P-value T-test
SBP before intervention	3.130 ± 3.73	12.137 ± 41.14	0.150
SBP after intervention	23.132 ± 19.8	6.132 ± 70.9	0.430
DBP before intervention	93.77 ± 93.6	76.81 ± 41.7	0.770
DBP after intervention	10.75 ± 44.5	86.75 ± 78.6	0.390
PR before intervention	43.100 ± 55.5	03.94 ± 8.5	0.300
PR after intervention	76.936 ± 90.5	40.96 ± 26.6	0.710
RR before intervention	4.18 ± ½	1.19 ± 17.2	0.880
RR after intervention	3.17 ± .91	9.16 ± 1.1	0.780
T before intervention	1.37 ± .36	08.37 ± .3	0.380
T after intervention	1.37 ± .3	1.37 ± .37	0.550

As shown in Table 4, the mean scores of hospitalisation days in both groups were statistically significant ( $P = 0.000$ ).

Table 4: Distribution of hospitalisation days in two groups of intervention and control

Variable	Intervention	Control	Test
hospitalisation days	7±0 .90	53.9±32.1	0.000

Based on the data presented in Table 5, independent t-test indicated no significant difference regarding the mean blood volume in both groups ( $P = 0.3$ ), while it was statistically significant after four days ( $P = 0.000$ ).

Table 5: Computed tomography from the first to fourth days

Variable	Intervention (cm3)	Control (cm3)	T-test P-value
Scan the first day	83.14±52.2	50.15±93.2	0.003
Scan the second day	82.10±88.1	60.14±86.1	0.000
Scan the third day	36.9±37.1	06.13±70.1	0.000
Scan the fourth day	66.7±.86	06.11±59.1	0.000

Moreover, we found that the mean of muscle strength of the first day was not statistically different in

both groups ( $P = 0.3$ ), while its values were statistically significant after four days in two groups ( $P = 0.000$ ) (Table 6).

**Table 6: Muscle strength on days 1 to 4 in both groups**

Variable	Intervention	Control	T-test P-value
Muscle strength the first day	2.1±71.0	20.2±56.0	0.300
Muscle strength the second day	36.2±61.0	30.2±53.0	0.06
Muscle strength the third day	26.3±73.0	70.2±65.0	0.30
Muscle strength the fourth day	3.3±86.0	96.2±55.0	0.005

The mean of HCT, WBC and PLT in both groups did not show a significant difference by t-test before the intervention ( $P > 0.05$ ), while the mean values of these variables in both groups were not significantly different after four days of intervention ( $P > 0.05$ ) (Table 7).

**Table 7: Frequency distribution of CBC in the control and intervention groups**

Variable	Intervention	Control	T-test P-value
Hematocrit before intervention	76.43±78.3	52.42±52.3	0.30
Hematocrit after intervention	83.41±21.4	26.45±71.3	0.10
WBC before intervention	95.10±41.2	83.10±66.1	0.90
WBC after intervention	36.20±42.4	50.15±39.3	0.000
Platelet before intervention	27.302±23.83	53.295±05.71	0.080
Platelet after intervention	53.241±52.83	23.306±89.85	0.020

Based on t-test, mean PT and PTT before and after intervention were not significantly different in both groups ( $P > 0.05$ ; Table 8). However, after four days of intervention, mean PT in both intervention and control groups exhibited a significant difference ( $P < 0.05$ ). Where the PTT coagulation test did not show a significant difference after four days, as a comparison of the two groups ( $P = 0.4$ ).

**Table 8: Frequency distribution of patients in two groups of intervention and control according to coagulation tests**

Variable	Intervention	Control	T-test P-value
PT before intervention	7.13±2.97	9.14±52.2	0.09
PT after intervention	03.15±96.2	03.16±96	0.05
PTT before intervention	13.20±25.2	13.20±65.1	0.01
PTT after intervention	30.20±83	13.20±03.1	0.04

## Discussion

This study aimed to investigate the effects of filgrastim on the complications of patients with a head traumatic brain haemorrhage. The present study showed that the majority of patients in the intervention group (46.6%) were in the age group of 21-30 years old and the lowest number of patients (10%) was in the age group of 10 to 20 years old.

In the control group, the majority of patients (50%) were in the 40-year-old age group, while fewer patients (6%) were in the age group of 31-40 years...

According to the results presented in this study, most of the patients (76.7%) belonged to men. These statistics vary in different societies, but the

most common age group with traumatic brain injury has been reported to be between 20-29 years old in most countries, including Taiwan. In concurring with the present study, various international and regional studies have reported that the prevalence of head injuries in men was higher than in women [9].

The results of the current study demonstrated that the level of consciousness in both groups was not significantly different on the first day; however, after 4 days of administration, the level of consciousness in the intervention group based on Glasgow criteria was significantly higher than that of the control group.

To the best of our knowledge, a similar study was not found on the effects of filgrastim and consciousness levels, but Zareian et al., have revealed that using Epigallocatechin-3-gallate over 7 days has been able to increase the level of consciousness in the intervention group compared to the control group, which is consistent with our study [10]. Furthermore, our findings emphasised that the number of hospital admissions days in the intervention group was significantly lower than those in the control group. One of the important issues that have always been addressed by the managers of hospitals and health centres is the length of stay that is both economically and organizationally important.

The length of hospitalisation can be employed as a factor in assessing the efficiency and effectiveness of hospital services. These criteria can be applied for various purposes such as healthcare management, quality control of hospital services [11].

It should be noted that the use of filtration in controlling the complications of head trauma patients has been able to reduce the length of hospitalisation. The location, volume of bleeding and the amount of pressure on the brain tissue are important factors for hematoma. CT scan is a tool that, in addition to being able to perform in emergency situations, has the ability to detect the exact location of the hematoma, the volume of the hematoma, and the amount of pressure on one part of the brain (shifts), so it is very helpful in determining the therapeutic strategies. To diagnosis the volume of hematoma, Epperson and Peterson criteria can be employed, which is found by multiplying the length, width and height of the hematoma in 0.5 [12]. Based on the results presented here, using filgrastim drug significantly reduced the volume of bleeding in CT scan on days 3 and 4, as compared to the patients in the control group. In other words, filgrastim has been able to reduce the volume of bleeding in patients with a brain hemorrhage, when comparing with the control group. Shabiri et al. measured the *hemorrhage volumes* on CT in the *bleeding trauma patients*, concluding that reducing the volume of cerebral hemorrhage is associated with an increase in the level of consciousness [13], which is consistent with our study outcomes. In addition, the results of this study revealed that the patients in both groups did not differ in muscle strength before the

study, but the mean scores of muscle strength increased significantly in the intervention group after four days of using filgrastim. Studies have emphasised that lower levels of brain injury and bleeding complications could be linked to an increase in muscle strength, which is directly related to the patient's level of consciousness [14].

Moreover, our findings suggested that after four days of taking filgrastim, the hematocrit levels, platelet counts in the intervention group were lower than the control group, were showed a statistically significant difference. Nevertheless, WBCs in the intervention group showed a significant increase after four days of intervention. We can point out that the extracted results of this study are consistent with the properties of Filgrastim (Neupogen).

The effects of filgrastim on the complications of patients with cerebral haemorrhage due to positive trauma were evaluated, where it was positively effective. Because there is no serious complication on the days recommended, the use of this medication can be suggested.

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