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The Role of Plasma G-CSF and Bone Marrow Dysfunction after Severe Trauma

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Abstract

Background—Bone marrow (BM) dysfunction is common in severely injured trauma patients with release of hematopoietic progenitor cells (HPC) into the peripheral blood. Granulocyte colony stimulating factor (G-CSF) is a potent stimulator of HPC mobilization. We hypothesized that plasma G-CSF levels are elevated following trauma and correlate with post-injury anemia and infection

Study Design—Blood from 83 severely injured patients was collected at several time points for determination of G-CSF levels and HPC mobilization and compared to healthy volunteers. Data were categorized by age, gender, Injury Severity Score (ISS), and whether patient was in shock. Hemoglobin and transfusion requirements as well as hospital acquired infection data was recorded. Data are expressed as mean $\pm$ SEM.

Results—After trauma, there is a 50-fold increase in plasma levels of G-CSF in trauma patients compared to controls (1640.4 $\pm$ 304.3 vs. 33.0 $\pm$ 6.8, $p<0.001$). Patients who presented in shock had 5 time higher G-CSF levels than non-shock trauma patients and 75-fold increase compared to control (2528.7 $\pm$ 536.4 vs. 728.0 $\pm$ 191.0 vs. 33.0 $\pm$ 6.8, $p<0.001$). Age, gender and ISS had no effect on G-CSF levels. HPC mobilization was sustained for up to 10 days following injury and involved multiple cells types. Higher G-CSF levels were also associated with lower hemoglobin levels and greater transfusion requirements 3 weeks after injury and a higher incidence of hospital acquired pneumonia and bacteremia.

Conclusions—Plasma G-CSF is markedly elevated after injury and is greater in patients who present in shock. The rise in G-CSF was also associated with prolonged mobilization of HPC. Elevation of G-CSF in humans following severe trauma may play a significant role in the development of post traumatic BM dysfunction, anemia and infection.

Introduction

Bone marrow (BM) dysfunction is a common feature following severe injury. Changes in bone marrow physiology include increased release of erythroid and myeloid progenitors into

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the circulation, a decrease in progenitor cell growth within the bone marrow and an impaired growth of bone marrow stroma.¹ Clinically BM dysfunction is observed as a persistent anemic state which persists for several weeks following injury. The anemia leads to repeated transfusion requirement despite no ongoing blood loss. Transfusion in trauma patients is an independent risk factor for death, infection, organ failure and ICU admission² and understanding the mechanism behind post traumatic BM dysfunction is important in order to design successful therapeutic strategies.

Severe injury leads to a hypercatecholamine state that persists for several weeks.^{3,4} Exogenous administration of norepinephrine to normal animals results in a dose-dependent reduction of BM hematopoietic progenitor cell (HPC) growth along with increased HPC mobilization from the BM to the peripheral blood.⁵ Granulocyte colony stimulating factor (G-CSF) is one potent stimulator of hematopoietic mobilization, and has been well studied in neutropenic patients, but little is known about its release and effects in injured patients.⁶⁻⁸ We hypothesize that severe trauma, a high stress state, will result in an early and sustained mobilization of hematopoietic progenitor cells into the periphery and that this mobilization will correlate with an elevated plasma granulocyte colony stimulating factor level.

Patients and Methods

Patient Selection

Peripheral blood (PB) samples were collected prospectively from adult trauma patients admitted to the Surgical Intensive Care Unit at the New Jersey Trauma Center at University Hospital from October 2010 to June 2011. Patients were excluded if they had a history of hematological diseases, pre-existing anemia, or were immunocompromised (HIV, chemotherapy, steroids) because of their possible independent direct effect on the BM. Patients who died within 24 hours of admission were also excluded from the study. Peripheral blood samples were obtained from healthy volunteers as controls. This study was reviewed and approved by the Institutional Review Board of the New Jersey Medical School.

Sample Collection and Processing

PB was collected in EDTA coated tubes via indwelling catheters or direct venipuncture. Samples were processed within 24 hours of collection. Briefly, whole blood samples were centrifuged at 10,000 RPM x 10 minutes at 4°C. Plasma was frozen at -80°C until further processing. Multiple samples were collected during patient from day 1 (within 24 hours of admission) through hospital day 14.

Hematopoietic Progenitor Cell Clonogenic Assay

CFU-E and BFU-E—Mononuclear cells in the peripheral blood were separated by Ficoll-Hypaque density gradient (Pharmacia LKB Biotechnology, Piscataway, NJ) and then resuspended in RPMI 1640 (Sigma) containing 10% fetal calf serum (FCS, Hyclone Laboratories, Logan UT). The number of BM mononuclear cells (BMMNCs) was then enumerated using an inverted microscope and plated (1×10^6 cells/ml) in duplicate in Iscoves media containing 30%FCS, 2% BSA, 1% methylcellulose, 2×10^{-4} mol/L 2-ME and glutamine (Cellgro; Mediatech, Herndon VA) supplemented with 2 U/ml recombinant human erythropoietin (rhEpo) and 6 U/ml recombinant human interleukin-3 (rhIL-3) (Genetics Institute, Cambridge MA) for burst forming units-erythroid (BFU-E) or 3 U/ml recombinant human granulocyte macrophage stimulating factor (rhGM-CSF) for colony forming unit granulocyte-macrophage (CFU-GM). Cultures were incubated at 37°C in 5% CO₂. Colonies (clusters of greater than 10 cells) were enumerated at the end of incubation

(10 days and 14 days for CFU-GM and BFU-E colonies respectively) by a single observer, blinded to the origin of the sample, using an inverted microscope.

CFU-GEMM—BMNC cells (1×10^5) were cultured in methylcellulose as described above. GEMM-CFU cultures contained 3 u/mL rhIL-3, 3U/mL GM-CSF and 2U/mL rEpo. Cultures were incubated at 37°C in 5% CO₂. At day 18, CFU-GEMM colonies with a mixture of hemoglobinized and myeloid type cells were enumerated microscopically.

Mesenchymal Stem Cell Measurement

Mononuclear cells isolated from the peripheral blood were processed using flow cytometry with specific cell-surface markers for mesenchymal stem cells (CD29+/CD44+/CD105+). 30,000 cells were counted per sample for mesenchymal stem cells. Data is reported as percent positive cells.

Plasma G-CSF measurement

Plasma levels of G-CSF were analyzed using commercially available ELISA kit (R&D Systems, Minneapolis MN) according to manufacturer instructions. The minimum detectable level of G-CSF is 20 pg/mL. All cytokine assays were performed in duplicate and the results reported at pg/mL.

Clinical Data Analysis

Patients' charts and the trauma registry were reviewed for demographic data on age, gender, injury severity score (ISS), mechanism of injury, and presence of shock on admission (defined as a systolic blood pressure <90mmHg), and initial blood transfusion requirement. In addition, initial laboratory values including hemoglobin (Hgb), serum lactate and arterial base deficit were collected. Patients were followed during their hospital stay and outcome data including hemoglobin trend, ICU length of stay (LOS), days on the ventilator (DOV), number of packed red blood cells (pRBCs) required following their initial resuscitation and incidence of infection were collected. The diagnosis of hospital acquired pneumonia was determined based on a bronchoalveolar lavage that yielded 1×10^5 organisms or documentation from the treating physician. Blood stream infections were defined by positive blood cultures for pathogenic organisms.

Statistical Analysis

All data are expressed as mean $\pm$ SEM. Statistical analyses were performed using a Student's t test or analysis of variance and Tukey-Kramer multiple comparisons test where appropriate. Spearman rank correlation was used to determine correlations between variables. P values <0.05 were considered statistically significant

Results

Patient Population

Peripheral blood was collected from 83 patients between 18 years and 90 years of age, with a mean age of 38 years. 78% of patients were male and presented with a mean Injury Severity Score of 23. Approximately half of the patients presented with blunt injury and half presented to the trauma bay in shock (systolic blood pressure <90 mmHg). Patient characteristics are listed in Table 1.

Hematopoietic Progenitor Cell Mobilization to the Peripheral Blood

a. BFU-E and CFU-GM Colony Growth in the Peripheral Blood—Peripheral blood samples collected from 23 severely injured patients (ISS >25) were cultured for

hematopoietic colony growth at four different time periods. These samples were arbitrarily grouped into 4 time periods: Period 1 (0-2days), Period 2 (3-4days), Period 3 (5-8 days) and Period 4 (9-21 days). These data were compared to 14 volunteer blood samples. The number of bone marrow progenitor cells in the PB (BFU-E and CFU-GM) increased significantly starting at 3 days following injury (Period 2) compared to matched controls. The peak levels of circulating HPCS are noted during at 5 to 8 days following injury (Period 3) and remain above baseline levels until at least 21 days post injury. (FIGURE 1)

b. CFU-GEMM colony growth in peripheral blood—Results of GEMM colony growth analysis of PB samples from 5 patients showed an early and persistent rise in the number of circulating early progenitors at days 1 (6 ± 2 colonies/plate), 2 (16 ± 9) and 7 (19 ± 12) post injury, though this did not reach statistical significance compared to control (3 ± 2). (FIGURE 2)

c. Mesenchymal stem cell—Flow cytometric analysis was performed in 5 trauma patients between days 1 and 3. The mean percentage of CD29+/CD44+/CD105+ cells in the trauma patients was significantly greater 3.2% (range 0.9 to 4.8%) compared to control values (0.07%; $p<0.01$).

G-CSF is elevated after trauma

Following severe injury, there was a 50-fold increase in plasma levels of G-CSF compared to control (1640 ± 304 vs. 33 ± 7 , $p<0.001$). Analyzing the data with respect to shock (FIGURE 3), demonstrate that patients presenting in shock had 5-fold greater G-CSF levels than non-shock counterparts and 75-fold increase compared to controls (2529 ± 536 vs. 728 ± 191 vs. 33.0 ± 7 , $p<0.001$). Following an initial rise, there is a rapid decline in plasma in all patients within the first 48 hours, though these levels remain significantly elevated in shock patients compared to controls until post-injury week two.

Patient Data

Factors present on admission and plasma G-CSF levels

Patients presenting in shock as defined by blood pressure have a significantly higher G-CSF than their non-shock counterparts. Elevation in G-CSF is also observed in patients with a greater arterial base deficit (BD) >4 vs. ≤ 4 (2574 ± 504 vs. 516 ± 129 , $p<0.05$), and higher plasma lactate >4 vs. ≤ 4 (2475 ± 576 vs. 871 ± 180 , $p<0.05$). Patients who required transfusion had a significantly higher G-CSF than those who did not require any blood (2215 ± 445 vs. 781 ± 238 , $p<0.05$). Those patients that required 10 or more units of blood initially had a higher G-CSF than those who required less blood (1-9 units pRBC) (3422 vs. 1410 , $p<0.01$) (FIGURE 3)

In contrast to these physiologic variables, there was no difference in G-CSF levels in patients with Injury severity scores (ISS) <20 vs. ≥ 20 (1515 ± 377 vs. 2293 ± 772 , $p>0.05$). Age, gender and mechanism of injury had no effect on plasma G-CSF levels.

Outcome data vs. G-CSF levels

Analyzing the data with respect to the various outcome variables, there appeared to be a break-point which differentiated groups at approximately 500pg/ml. Thus for the following analysis we defined low G-CSF as <500 pg/ml and high G-CSF as ≥ 500 pg/ml. High G-CSF was associated with a greater ICU length of stay (16 ± 17 days vs. 7 ± 7 days) and a greater number of days on the ventilator (11 ± 11 days vs. 3.5 ± 4 days). Of note, high G-CSF was also associated with a lower hemoglobin at 3 weeks post admission and in this group the anemia resulted in a greater blood transfusion requirement following initial resuscitation;

approximately 2 units more per patient. Higher G-CSF was also associated with a 3-fold greater incidence of hospital acquired pneumonia and blood stream infection (Table 2, Figure 4).

Discussion

Trauma and hemorrhagic shock results in profound changes in hematopoiesis in both experimental animals and humans. Livingston et al demonstrated that following severe trauma, there is a decrease in bone marrow erythroid progenitor growth that lasts at least two weeks which parallels a persistent anemic state.¹ The data presented in this study begins to provide a potential etiology accounting for this bone marrow dysfunction. To our knowledge, this is the first time that a persistent mobilization of hematopoietic progenitor cells (HPCs) from the bone marrow into the periphery has been demonstrated in humans following major injury. Moore et al reported that following blunt trauma to the chest, circulating CFU-GM could be observed for up to 10 days after injury.⁹ Similar to our previous data, these patients were only studied at only one time-point following injury. Grzelak et al found a significant rise in circulating CD34+ HPC in 10 patients exposed to an open elective cholecystectomy. However, circulating HPCs essentially disappeared from the circulation by day seven.¹⁰ These data are in sharp contrast to our observation, where the rise in the number of circulating progenitor cells persisted for greater than 21 days post-injury. We believe that these differences may be explained in part by the degree of “surgical trauma”. An elective cholecystectomy induces a moderate degree of tissue injury that is a onetime event. In contrast, patients sustaining multiple or severe trauma admitted to the ICU have a markedly greater degree of tissue injury. More importantly, these traumatic injuries can result in shock and hypoperfusion, prolonged intubation and ventilatory support, multiple and sequential operative procedures as well as multiple blood transfusions. All of these factors lead to a persistent stress state and ongoing tissue injury. We hypothesize that this degree of sustained physiological stress contributes to a sustained release of HPC cells into the peripheral blood which in turn contributes to the prolonged disruption of BM function.

Our results also demonstrated more primitive progenitor cells (CFU-GEMM) as well as mesenchymal stem cells were present in higher numbers in the PB following major trauma. This suggests that this process is neither lineage specific nor restricted to only hematopoietic cells but represents an overall dysfunction at the bone marrow niche level. Widespread disruption of bone marrow architecture and would further contribute to the prolonged anemia observed in these patients. In a study of septic patients, Tsaganos et al found CD34+/CD45+ cells throughout their study period which was limited to seven days. The number of mobilized cells was proportionate to the degree of sepsis.¹¹

There was also a 50-fold increase in plasma G-CSF within the first 24 hours of injury compared to controls. A similar elevation of G-CSF was reported by Tanaka et al in a study of 19 trauma patients with increases in circulating G-CSF levels also demonstrated in burn and septic patients.¹²⁻¹⁴ Endogenous production of G-CSF and release from endothelium, macrophages and other immune cells is incompletely understood, but appears to be mediated by inflammatory markers such as IL-6 and TNF α . Traumatic shock appears to be the driving force in our observed increase. Patients presenting in shock (systolic blood pressure less than 90 mmHg) have a 75 fold increase in G-CSF compared to control. Interestingly, Tanaka demonstrated a significant correlation between injury severity score and G-CSF, whereas we found no similar correlation. While there is an association between increasing ISS and hemorrhagic shock, the correlation is imperfect and likely explains the disparate findings, especially if the sample size is small. Our findings indicate that G-CSF is more closely tied to degree of shock and rather than soft tissue injury. This observation is

supported by murine research. Hierholzer et al demonstrated G-CSF locally produced in liver and lung of hemorrhagic shock animals which appears to be mediated through NFkB activation.¹⁵ NFkB is also seen to be elevated early in polytrauma patients and is associated with the downregulation of the innate immune system.^{15,16} In all of our study patients, there is a dramatic drop in G-CSF level within the first 48 hours of injury, though patients sustaining shock maintain elevated plasma levels up to 2 weeks after injury. Our results correlate with similar data reported in burn patients. Finnerty et al describe a peak in circulating G-CSF at day two after severe burn, which remains elevated through 3 weeks of injury.¹⁴ Additionally, septic patients have G-CSF levels that remain elevated throughout the course of infection with a return to baseline after recovery of illness.¹² This supports the idea that severe trauma results in a prolonged stress response that sustains the release of HPC cells into the periphery. Induction of HPC mobilization by recombinant G-CSF administration results in a peak plasma concentration within 24 hours of dosing and a rise in peripheral HPCs in 4-6 days.¹⁷ Similar results were observed in our trauma patients, with an elevated and sustained number of circulating progenitors peaking at 5-8 days following trauma.

There was a strong correlation between initial G-CSF levels and resultant anemia, even out to 21 days after injury. Those with high G-CSF levels had, on average, one gram lower hemoglobin at days 7, 14 and 21. Additionally, these patients with high G-CSF required three units of packed red blood cell transfusions compared to one in the lower initial G-CSF group. We do not believe there was any treatment bias as the same group of trauma and critical care surgeons took care of these patients during the entire time period of the study. This group practices a restrictive transfusion policy as long as patients are without cardiovascular disease or any hemodynamic instability which routinely allows hemoglobin levels to drop to below 7 grams before instituting transfusion. In addition the treating physicians had no knowledge of the G-CSF levels. Patients with high G-CSF were more likely to develop a hospital acquired pneumonia or blood stream infection. To our knowledge, this is the first clinical report of an association with increased plasma G-CSF following severe injury and clinical outcomes, specifically anemia and infection. These findings are consistent with our overall observation that severe injury results in severe bone marrow dysfunction affecting many facets of bone marrow physiology.

Recombinant G-CSF is clinically used to mobilize and collect stem cells for bone marrow transplantation. While this medication and technique is safe and approved, there is a documented drop in hemoglobin among healthy patients, approximately 10%, which returns to baseline within a year.¹⁸ This observed association between G-CSF and anemia has also been investigated in animal models. While erythropoiesis may be maintained with high dose G-CSF in normal rats, there is resultant anemia in impaired animals.^{19,20} Van Os suggests that bone marrow has a limited reserve capacity and G-CSF may function to activate stem cells to differentiate at the expense of self-renewal which may ultimately cause a permanent loss of stem cells.²¹ In the rare patient, G-CSF administration has been reported to lead to myelodysplastic syndromes and chronic leukemias. These findings support our observation and strongly suggest a mechanistic connection between post-traumatic G-CSF release and resultant bone marrow dysfunction.

Conclusions

In summary, following trauma there is a significant increase in plasma G-CSF which is greater in patients who present in hemorrhagic shock. G-CSF peaks within 24 hours with a decline in plasma concentration over the first 2 weeks of hospital admission. The rise in G-CSF appears to induce widespread mobilization of bone marrow cells to the periphery which peak in circulating at 5-8 days following injury. Early high elevation of G-CSF following severe trauma is associated with the development of post-traumatic anemia, an increased

requirement of blood transfusion and higher rates of hospital-acquired infection. These data suggest that high and sustained G-CSF levels are at least partly responsible for the observed bone marrow cell mobilization and subsequent dysfunction. Plasma G-CSF levels may serve as a useful marker in the investigation of post-injury immune suppression and we postulate that modulation of G-CSF plasma levels, especially later in a patient's post-injury course, may have a salutary effect on the bone marrow function, anemia and infection.

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Figure 1.

After severe injury, there is an increasing number of circulating (A) granulocyte-macrophage (CFU-GM) and (B) erythroid lineage precursors (BFU-E) that peak at day 5-8 after injury and remain elevated up to 3 weeks after injury. (**p<0.01, *p<0.05.)

Figure 2.

After severe injury, there is a marked increase in early progenitor cells (CFU-GEMM) by day 2 and through 7 days after injury.

Figure 3.

(A) Plasma G-CSF rises 50 times greater than controls within 24 h after injury. (** $p < 0.001$, * $p < 0.05$.) Levels remain persistently elevated for the first week after injury. (B) Patients who present in shock (SBP < 90) have a more profound and sustained elevation of plasma G-CSF compared to normotensive patients.

Figure 4.

Patients who presented in shock, with lower base deficit and higher arterial lactate levels had a significantly higher plasma G-CSF level (* $p < 0.05$). G-CSF levels were not significantly affected by soft tissue injury as reported by ISS. Patients who were transfused blood within 24 h of admission had a significantly higher plasma G-CSF level, and those patients who were massively transfused (>10 U pRBC) had the highest G-CSF levels compared to those who required less blood.

Table 1**Patient Characteristics**

	Patients	Volunteers
Demographics		
n	83	18
Age, y	38±19	31±5
Sex, male, %	78	83
ISS	23±12	
Blunt: penetrating, %	52:48	
Initial hemoglobin	12.3±2.4	
Shock (SBP<90 mmHg), %	52	
Resuscitative blood transfusion (< 24 h) U pRBC	7 ±11	
Base deficit	-5.8±5.5	
Lactate	4.5±3.5	
Outcomes		
Mortality, %	7	
ICU LOS, d	11±13	
DOV	7±8.5	
Pneumonia, %	36%	
Blood stream infection, %	7%	
Blood transfusion after resuscitation (>24 h) U pRBC	2±3	

Data are mean±SD unless otherwise noted.

ISS, Injury Severity Score; SBP, systolic blood pressure; pRBC, packed red blood cells; ICU LOS, length of stay; DOV, days on ventilator.

Table 2

G-CSF Correlates with Anemia and Infection

	Int Hgb, mean±SD	Hgb D7, mean±SD	Hgb D14, mean±SD	Hgb D21, mean±SD	pRBC Tx p 24H, mean±SD	PNA, %	BSI, %
G-CSF 500 pg/mL	12.8±0.8	9.8±0.3	9.4±0.4	9.7±0.3	1.2±0.3	17	0
G-CSF >500 pg/mL	11.9±0.4	8.6±0.2 *	8.3±0.3 *	8.4±0.3 *	3.2±0.6 *	55 *	15 *

* p<0.05, ANOVA Tukey-Kramer.

Hgb, hemoglobin; PNA, pneumonia; BSI, blood stream infection.