Cervical Spinal Cord Injury Shows Markedly Lower than Predicted Mortality (>72 Hours After Multiple Trauma) From Sepsis and Multiple Organ Failure

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Abstract

Background: Sepsis and multiple organ failure (MOF) remain one of the main causes of death after multiple trauma. Trauma- and infection-associated immune reactions play an important role in the pathomechanism of MOF, but the exact pathways remain unknown. Spinal cord injury (SCI) may lead to an altered immune response, and some studies suggest a prognostic advantage for such patients having sepsis or multiple trauma. Yet these findings need to be evaluated in larger cohorts of trauma patients. Methods: Retrospective, multicenter study, using the data of the TraumaRegister DGU. Patients with and without SCI surviving the initial first 72 hours after trauma were matched according to injury pattern and age. Comparative analysis considered morbidity (sepsis, MOF) and hospital mortality. Results: The study population included 800 matched pairs. As intended by the matching process, patients with cervical SCI had an otherwise comparable injury pattern but a higher severity of trauma (mean Injury Severity Score: 36 vs 29, mean number of diagnosis: 5.6 vs 4.4). They had a higher rate of sepsis (15.9% vs 10.9%, P = .005) and MOF (35.9% vs 24.1%, P < .001) while mortality revealed no significant difference (9.5% vs 9.9%, P = .866). Conclusions: Cervical SCI leads to an increased rate of sepsis and MOF but appears to be favorable with respect to outcome of sepsis and MOF following multiple trauma. Further research should focus on the pathomechanisms and the possible arising therapeutic options.

Keywords

spinal cord injury, multiple organ failure, MOF, SIRS, septic inflammatory response syndrome, SCI-associated immune deficiency syndrome

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host immune response to an infectious cause.¹ Multiple studies showed that sepsis is a main cause for hospital and intensive care unit (ICU) admission and hospital mortality.²,³ Fleischmann et al showed that in Germany alone the incidence of sepsis rose to 335/100 000 cases per annum in 2013. Meanwhile, the mortality rate decreased from 27% to 24.3%.² Estimated costs for intensive care treatment are about €1.7 billion and indirect health costs and consecutive costs for the social systems rise to about €6.3 billion per year.⁴

Despite major research in the field, the pathophysiology of sepsis and trauma-induced multiple organ failure (MOF) is yet not precisely understood.

The changes in microcirculation and the abnormalities of coagulation may lead to multiple organ dysfunction syndrome (MODS). In an editorial published by Baue in 1975, MODS has been described for the first time.⁵ After several adjustments, the term MODS is currently used to describe a clinical syndrome characterized by the development of progressive and potentially reversible physiologic dysfunctions in 2 or more organs.

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or organ systems, induced by a variety of acute insults, including sepsis. Despite all efforts, MODS-related mortality remains high. Lobo et al identified MODS as the primary cause of death in high-risk patients after surgery. Risk factors, according to several studies, include high severity of illness, 2 or more acute organ failures, shock, and acidosis.

There is evidence that sepsis and MODS are induced by various pathways including spinal cord structures, especially the sympathetic nerve system. In spinal cord injury (SCI), stimulus conduction is impaired or completely interrupted and a spinal cord injury–induced immune deficiency syndrome (SCI-IDS) may occur. The SCI-IDS could lead to altered reactions of immune cells, for example, macrophages, natural killer cells, and T and B lymphocytes. This may ultimately result in an increased rate of infection and mortality following multiple trauma. However, a recent study by Bertling et al revealed a lower mortality rate for patients with SCI compared to a control group of multiple injured patients without SCI.

Different study groups tried to evaluate the influence of the sympathetic nervous system on the outcome after trauma and trauma-related sepsis or systemic inflammatory response syndrome (SIRS). Sympathetic mediators such as epinephrine and norepinephrine may induce increased cytokine release of immune cells and enhance migration of immune cells to inflammation sites as well as the degree of plasma extravasation.

Sympathetic blockage of the adrenal medulla by thoracic epidural anesthesia (TEA) decreases the plasma concentration of epinephrine and therefore may modulate the inflammation cascade, whereas effects on mortality remain unambiguous.

The aim of this study was to evaluate the impact of cervical SCI on mortality rate, sepsis, and MODS in patients with cervical SCI. Therefore, we analyzed the data of the TraumaRegister DGU.

Materials and Methods

The TraumaRegister DGU of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie [DGU]) was founded in 1993. The aim of this multicenter database is a pseudonymized and standardized documentation of severely injured patients.

Data are collected prospectively in 4 consecutive time phases from the site of the accident until discharge from hospital: (1) prehospital phase, (2) emergency department and initial surgery, (3) ICU, and (4) discharge. The documentation includes detailed information on demographics, injury pattern, comorbidities, pre- and in-hospital management, course on ICU, and relevant laboratory findings including data on transfusion and outcome of each individual. The inclusion criterion is admission to hospital via emergency department with subsequent intensive care unit or intermediate care station (ICU/IMC) care or reach the hospital with vital signs and die before admission to ICU.

The infrastructure of documentation, data management, and data analysis is provided by AUC—Academy for Trauma Surgery (AUC—Akademie der Unfallchirurgie GmbH), a company affiliated to the German Trauma Society. The scientific leadership is provided by the Committee on Emergency Medicine, Intensive Care, and Trauma Management (Sektion NIS) of the German Trauma Society. The participating hospitals submit their pseudonymized data into a central database via a web-based application. Scientific data analysis is approved according to a peer-review procedure established by Sektion NIS.

The participating hospitals are primarily located in Germany (90%), but a rising number of hospitals of other countries contribute data as well (at the moment from Austria, Belgium, China, Finland, Luxembourg, Slovenia, Switzerland, the Netherlands, and the United Arab Emirates). Currently, approximately 25,000 cases from more than 600 hospitals are entered into the database per year.

Participation in TraumaRegister DGU is voluntary. For hospitals associated with TraumaNetzwerk DGU, however, the entry of at least a basic data set is obligatory for the reasons of quality assurance.

The present study is in line with the publication guidelines of the TraumaRegister DGU and registered as TR-DGU project ID 2015-040. It has been approved by the ethics committee of the University of Bochum (Ruhr-Universität Bochum; approval number 16-5731-BR).

Patients

The present study includes patients from Germany with an Injury Severity Score (ISS) ≥16 and a maximum abbreviated injury scale (AIS) ≥4 which were entered into the TR-DGU between 2002 and 2014. In the TraumaRegister DGU, sepsis is defined as a SIRS with a positive blood culture. Multiple organ failure is defined as organ failure of 2 or more organs described by a score of 2 or more points per organ system using the Sequential Organ Failure Assessment score. Patients with isolated traumatic brain injury or isolated cervical spine injury and AIS of 6 were excluded. Furthermore, death within the initial 72 hours postadmission was defined as an additional exclusion criterion.

In order to determine the effect of an additional cervical SCI, patients with and without SCI were matched according to the following criteria:

1. Age group: 0 to 59, 60 to 69, 70 to 79, older than 79 years.
2. Head injury (without SCI): AIS 0 to 2/3/4/5 to 6
3. Thoracic injury: AIS 0 to 2/3/4/5 to 6
4. Abdominal injury: AIS 0 to 2/3/4/5 to 6
5. Injuries of the extremities: AIS 0 to 1/2 to 3/4 to 5

A matching that relies on total ISS only would disregard the injury pattern. Since cases with SCI receive points from that injury (when ISS is calculated), whereas the partner case needs to have more severe injuries in the rest of the body. This reduces the comparability of the pairs. The present matching considered 4 body regions and matches according to 4 severity levels in each region. However, SCIs were disregarded in the matching. This creates pairs of patients with a similar pattern of injury, except for cervical SCI. Thus, cervical SCI patients who did not have an additional head injury tend to have a higher ISS than their partner case. Table 1 shows the results of the matching process.
Primary outcome measures were hospital mortality, sepsis, and MOF. Secondary outcome was the length of ICU stay.

**Statistical Analysis**

Statistical analysis was carried out using SPSS (version 22, IBM, Armonk, New York). Categorical data were presented as percentage, and continuous data were presented as mean with standard deviation and median. The $\chi^2$ test was used for comparing frequencies, and the Mann-Whitney $U$ test was used for ordinal and continuous data. The level of significance was set to 5% ($P < .05$).

**Results**

Eight hundred multiple and severe injured cervical spinal cord injury (cSCI) patients were matched to 800 multiple injured non-SCI patients using data sets from TraumaRegister DGU. The SCI subgroup included 263 patients with neck AIS 4 (32.9%) and 537 patients with neck AIS 5 (67.1%). Details are provided in Table 2.

The mean age was slightly higher in cSCI group (45.7 vs 47.7 years). Mean ISS and the mean number of diagnoses were higher in cSCI group as expected by the matching process. The mean number of days on ICU was also higher in the cSCI group (13.9 vs 18.2 days), whereas the median days in hospital were comparable.

The incidence of sepsis was significantly higher in the cSCI group (10.9% vs 15.6%, $P < .001$) as well as the rate of MOF (24.1% vs 35.9%, $P < .001$). However, cSCI showed no effect on mortality as 79 patients died in the cSCI group versus 76 patients in the non-cSCI group. The average length of stay until death was 16.9 days (mean, median: 11 days) in the non-cSCI group and 23.6 days (mean, median: 13.5 days) in the cSCI patients.

Pulmonary organ failure (23.4% vs 36.8%) and duration of ventilation (8.6 vs 12.6 days) were significantly increased in the cSCI group. Details on other organ failure are shown in Table 3.

**Discussion**

After surviving the first 72 hours after trauma, patients with SCI showed an increased severity of injury as well as a higher incidence of sepsis and MOF. Patients were homogenous with respect to the matching criteria. Mean age was even higher in the cSCI patients, a factor predisposing to adverse outcome compared to controls. However, mortality rate of the cSCI patients was similar as in the control group. We hypothesized this apparent prognostic advantage for cSCI patients having sepsis and MOF to be partly explained by an impaired systemic inflammatory response after trauma or consecutive sepsis.
non-SCI patients deceased during hospitalization. Citak et al\textsuperscript{20} reported a lower mortality rate in patients with SCI and Fournier gangrene compared to the literature.

Brommer et al\textsuperscript{21} gave some insight in the interaction between the level of SCI and the systemic immune response. In a mouse model for SCIs, they investigated the differences in immune response according to the level of spinal cord lesion (Th3 vs Th9) to infections with \textit{Streptococcus pneumoniae}. They were able to provide evidence that a higher level of lesion is associated with significantly higher bacterial load 24 hours after infection. They concluded that the sympathetic immune system innervation based on their differential impact on secondary lymphoid organs, including the spleen is interrupted in mice with a higher lesion level. They described an SCI-associated immune deficiency syndrome which might also be responsible for the increased rate of sepsis and MOF in cSCI in the present study. These findings would help to explain, in addition to the higher overall injury severity of our cSCI patients, the higher rate of sepsis and MOF in this group of patients.

In our study, we could observe, however, that patients who became septic or developed MOF appeared to have a prognostic advantage. It can be hypothesized that this favorable course may also be caused by an altered immune response in the later phase after the trauma. Several studies focused on evaluating this effect either by medication or by TEA.

Animal studies (mice models) reported positive effects of propranolol, a $\beta$-adrenergic blocker, on systemic inflammation reaction in sepsis.\textsuperscript{22,23} Thus far, human studies of traumatic brain-injured patients suggest a positive effect of $\beta$ blockage regarding mortality.\textsuperscript{24-26}

Thoracic epidural anesthesia mimics the effects of SCI. In various experimental setups of systemic inflammation, TEA has shown beneficial effects on microvascular perfusion,\textsuperscript{27,28} regional blood flow\textsuperscript{17} and intestinal function.\textsuperscript{17,29-31}

Regarding trauma patients, TEA is well recommended in thoracic trauma to achieve analgesia and therefore improve prophylaxis of pneumonia and delir.\textsuperscript{32,33} Yet the general effects of TEA after multiple injury remain not well investigated.

### Limitation

This is a retrospective, matched pair analysis using homogeneous groups of patients. Nevertheless, there is a wide variety of factors that may influence our findings. First, we used the data of the TraumaRegister DGU, and as a general limitation, data quality of registries is considered less reliable to the data of prospective clinical trials. Furthermore, diagnoses are only identified by their AIS codes. Thus, no strict description of each individual patient’s injuries is provided. Sepsis is described according to the definition of 1992. In order to exclude patients who deceased early from hemorrhage or traumatic brain injury, only survivors of the first 72 hours were considered for analysis. Therefore, we were unable to provide standardized mortality ratios as there would have been a high level of confounding, considering only the survivors of the initial 72 hours posttrauma. However, the study was designed in order to reveal the effect of a systemic response to injury, sepsis, and MODS, which usually occurs later than 72 hours. In addition, we excluded all patients with cervical SCIs AIS 6 as the registry provides no data on end-of-life decision and discontinuation/interruption of therapy, which might be a large confounder regarding AIS 6 cSCI.

Still, the strength of our study is the large number of patients from multiple centers with a high level of matching in order to determine the influence of cSCI.

### Conclusion

This is a study of 800 matched pairs, extracted from a large multicenter database, comparing 2 subgroups of multiple injured patients with or without cervical SCI. After surviving the first 72 hours after trauma, patients with cSCI showed an equal mortality rate, although severity of trauma, incidence of sepsis, and MOF were significantly higher. Further experimental and clinical studies are required to investigate the distinct impact of spinal cord signal conduction, especially the effects on the sympathetic immune system during trauma or SIRS.

### Authors’ Note

Oliver Kamp, Rolf Lefering, Thomas A. Schildhauer, Christian Waydhas, Oliver Jansen, Renate Meindl, and Ume Hamsen designed the study. Oliver Kamp, Rolf Lefering, and Ume Hamsen were responsible for data collection and statistical analysis. Oliver Kamp, Ume Hamsen, and Oliver Jansen did the literature search. Oliver Kamp wrote the manuscript. All authors were involved in data interpretation and critical revision, and finally approved the manuscript. TraumaRegister DGU is a Committee on Emergency Medicine, Intensive Care, and Trauma Management (Sektion NIS) of the German Trauma Society (DGU).

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**Table 3. Incidence of Organ Failure.**

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Control Group, n = 800</th>
<th>SCI, n = 800</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>16.9%</td>
<td>22.0%</td>
<td>.010</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>23.4%</td>
<td>36.8%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal</td>
<td>6.1%</td>
<td>5.0%</td>
<td>.33</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2.9%</td>
<td>2.0%</td>
<td>.26</td>
</tr>
<tr>
<td>Coagulation</td>
<td>9.0%</td>
<td>10.6%</td>
<td>.28</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>24.5%</td>
<td>39.6%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: SCI, spinal cord injury.
References


