Research Article

Non-infectious Fever After Acute Spinal Cord Injury in the Intensive Care Unit

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Objective: The aim of the present study is to evaluate the frequency, etiology, risk factors and clinical outcomes in acute traumatic SCI patients who develop fever and to evaluate the relationship between fever and mortality.

Design: Retrospective data were collected between January 2007 and August 2016 from patients diagnosed with persistent fever from SCI cases observed in the ICU.

Participants: Among 5370 intensive care patients, 435 SCI patients were evaluated for the presence of fever. A total of 52 patients meeting the criteria were evaluated.

Outcome measures: Fever characteristics were evaluated by dividing the patients into two groups: infectious (group-1) and non-infectious (group-2) fever. Demographic and clinical data, ICU and hospital stay, and mortality were evaluated.

Results: In the patients with noninfectious fever, mortality was significantly higher compared to the group with infectious fever ($P < 0.001$). Of 52 acute SCI cases, 25 (48.1%) had neurogenic fever that did not respond to treatment in intensive care follow-up, and 22 (88%) of these patients died. Maximal fever was 39.10 ± 0.64 °C in Group-1 and 40.22 ± 1.10 °C in Group-2 ($P = 0.001$). There was a significant difference in the duration of ICU stay and hospital stay between the two groups ($P = 0.005$, $P = 0.001$, respectively), while there was no difference in the duration of mechanical ventilation between the groups ($P = 0.544$).

Conclusion: This study demonstrates that patients diagnosed with neurogenic fever following SCI had higher average body temperature and higher rates of mortality compared to patients diagnosed with infectious fever.

Keywords: ICU, mortality, neurogenic fever, non-infectious fever, spinal cord injury

Introduction

Spinal cord injuries (SCI) often affect young adults and have permanent and often devastating neurologic deficits and disability. These permanent impairments may occur despite early intervention, and are associated with dramatically elevated costs and a long rehabilitation process. Primary spinal cord injuries result from the immediate effects of trauma including compression, contusion, and lacerations.¹ Secondary progression occurs as a result of ischemia, hypoxia, inflammation, edema, excitotoxicity, disruption of ion homeostasis,

and apoptosis.²⁻⁴ Long-term maintenance of patients with SCI involves distinct early and late phases. Fever frequently occurs in patients with SCI, and may begin during hospitalization and continue during later stages, resulting in life-threatening clinical complications. Fever occurs in approximately 50% of all intensive care patients, and an increase in body temperature is often observed during clinical follow-up. Fever may also contribute to mortality in critical patients.⁵⁻⁹ Pyrexia, hyperthermia, and even hypothermia are commonly seen in SCI and may accompany infections. However, unidentified fever etiologies may also be the cause of increased body temperature.^{10,11} Perhaps the most important cause of non-infectious fever in patients with SCI is the loss of supra-spinal control of the sympathetic nervous system and defective thermoregulation

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Figure 1 Classification of fever cases.

due to loss of sensation. Given the complexity of SCI associated fever etiology and the potential effects on mortality risk, improved clinical understanding of this condition is essential.

The aim of this study is to measure the frequency of unexplained fever and identify the etiology (infectious / non-infectious), risk factors, and clinical outcomes in acute traumatic SCI patients. We will also discuss the relationship between fever and mortality.

Methods

Study Group

This retrospective study was performed on patients admitted with SCI to the 20 bed medical-surgical Intensive Care Unit (ICU) at the Ondokuz Mayıs University Hospital, in Samsun Turkey. The hospital records of 5370 patients admitted to the ICU from January 2007 through August 2016 were reviewed. The local ethics committee reviewed and approved the study protocol prior to the start of the investigation (2016/386). A total of 52 patients, who had been selected from 435 SCI patients observed in the intensive care unit for more than 48 hours and who had been diagnosed with high body temperature of $\geq 38.0^{\circ}\text{C}$ for

one or more measurements during two consecutive days were included in this study. Patients under the age of 18 years, patients with no fever during follow-up, or patients with fever of $< 38.0^{\circ}\text{C}$ were excluded from this study (Fig. 1).

Patient Data

The data were obtained retrospectively from intensive care unit patient follow-up charts, file records, and the hospital automation system. Data collection included demographic data, trauma etiology, level of neurological injury (cervical, thoracic, lumbar), and completeness of injury as defined by the American Spinal Injury Association Impairment Scale (ASIA). The patients were divided into 2 groups: complete (ASIA A) and incomplete (ASIA B-C-D) according to ASIA classification (Table 1).^{12,13}

Co-morbidities accompanying SCI was evaluated, including the presence of intracranial hemorrhage, head trauma, history of surgical operation, use of LMWH and vasopressor, mechanical ventilation, duration of intensive care and hospital stay, and mortality.

Patients were divided into 2 groups according to the fever etiology. Demographic data and other parameters

Table 1 American Spinal Injury Association Impairment Scale (ASIA)

Grade A
Complete lack of motor and sensory function below the level of injury (including the anal area)
Grade B
Some sensation below the level of the injury (including anal sensation)
Grade C
Some muscle movement is spared below the level of injury, but 50 percent of the muscles below the level of injury cannot move against gravity.
Grade D
Most (more than 50 percent) of the muscles that are spared below the level of injury are strong enough to move against gravity.
Grade E
All neurologic function has returned.

are given for each of the two groups: Group-1: Infectious fever, Group 2: Non-infectious fever.

Fever Definition

Fever was defined in intensive care patients as body temperature of $\geq 38.0^{\circ}\text{C}$ on at least one measurement during two consecutive days. The number of consecutive days over which this threshold value was exceeded was defined as the "duration of fever". Only patients with persistent fever were included in this study. "Persistent fever" was defined as continuous fever for more than 6 h over 2 or more consecutive days. All patients were followed for the duration of intensive care treatment. The first febrile episodes in this phase were evaluated according to their probable etiology. A febrile episode was defined as three consecutive days without fever. For the patients included in this study, the first day of fever detection, the duration of fever, the highest measured body temperature, and whether the fever was responsive to antipyretic-antibiotherapy and external cooling were documented on daily nursing vital sign 'charts'. The body temperature was measured continuously using axillary and tympanic probes and recorded on an hourly basis. Fever was treated with acetaminophen, metamizole, and external cooling (cooling blankets, ice packs).

The presence of an endotracheal tube, arterial or central venous catheter, ventriculostomy, or indwelling bladder catheter was recorded for determination of the etiology of fever. WBC counts, neutrophil percentage, CRP elevation (reference range 0–5 mg/dl), clinical infection criteria, radiologic imaging methods, and possible body regions of focus were also evaluated. Culture sampling (tracheal aspirate, blood, urine, catheter, void, wound location etc.) was performed for patients with symptoms in order to screen for infection. Urinary tract infections were diagnosed by a urine culture with $> 10,000$ colony-forming units (CFU) per mL. Respiratory infection was defined as an increase in sputum purulence and oxygen requirements within

48 hours from the onset of fever. Infiltration identified in chest X-rays were also taken into consideration. Empiric antibiotics were initiated in patients with fever to reduce potential infection risk until the culture samples were finalized. A regression in infective parameters (CRP, white blood cell (WBC), and neutrophil percentage), fever regression, and clinical improvement at 3rd day of treatment was considered an effective antibiotic response. Empirically initiated antibiotics were terminated rapidly in patients with culture negativity or in whom bacterial infection was not considered a factor.

Cases where the source of fever was considered to be infection were defined as "Group-1=Infectious fever"; patients in whom the focus of infection was not detected= were defined as "Group-2=Non-infectious fever". Although the inter-evaluator agreement for this classification system was substantial, cases in which there was no agreement were classified as "non-identified infectious fever". Non-infectious causes of fever were assessed with tests for the related organ and system (pulmonary emboli, DVT, gastrointestinal tract, drug etc.). Patients who had high and persistent fever, who were unresponsive to treatment, who had bacterial colonization, but in whom culture reproduction was not considered a fever factor were also included in the non-infectious fever group. Group-2 patients for whom the possible other non-infectious causes that may emerge secondary to SCI had been eliminated were classified as Neurogenic fever. These cases were further sub-divided according to early- or late-stage onset. Fever occurring during the first seven days of intensive care hospitalization were identified as "early onset fever" other cases were classified as "late onset fever". The classification of fever cases is summarized in Fig. 1.

Statistical Analysis

Data were analyzed using IBM SPSS V23 (Chicago, USA). The normality of data was assessed using the

Table 2 Classification according to ASIA score

	ASIA A	ASIA B	ASIA C	ASIA D	ASIA E	p
Fever early						
Yes (n=43)	15 (34.9)	11 (25.6)	5 (11.6)	7 (16.3)	5 (11.6)	0.425
No (n=9)	4 (44.4)	0 (0)	2 (22.2)	1 (11.1)	2 (22.2)	
Infection						
Yes (n=27)	11 (40.7)	8 (29.6)	2 (7.4)	2 (7.4)	4 (14.8)	0.191
No (n=25)	8 (32.0)	3 (12.0)	5 (20.0)	6 (24.0)	3 (12.0)	
Total (n=52)	19 (36.5)	11 (21.2)	7 (13.5)	8 (15.4)	7 (13.5)	

n (%), Abbreviations: ASIA: American Spinal Injury Association Impairment Scale

Shapiro Wilk test. The independent samples t test was used for the comparison of normally distributed data. The Mann Whitney U test was used in the analysis of non-normally distributed data. The Pearson Chi-square test was used to analyze categorical data. The results of quantitative data are presented as mean $\pm$ standard deviation and median (min-max). Qualitative data were presented as frequencies (percentage). A P-value of < 0.05 was considered to represent a statistically significant result.

Results

There were 41 (78.8%) males and 11 (21.2%) females in 52 (12.2%) SCI cases with persistent fever out of 425 SCI patients. A total of 35 (67.3%) out of 52 SCI cases had undergone surgery following trauma. Intracranial hemorrhage accompanying SCI was detected in 19 (36.5%) patients. A total of 27 patients (51.9%) died. Twelve (23.0%) patients died from sudden cardiac arrest after high fever, 7 (13.4%) patients with sepsis, 6 (11.5%) patients with malignant arrhythmia, and 2 (3.8%) patients with brain death. The ASIA scores of the patients and the fever-infection rates are summarized in [table 2](#).

The cause of fever was identified as infectious in 27 (51.9%) of 52 patients (Group-1), and as non-infectious in 25 (48.1%) patients (Group-2). Among all patients

with SCI, gram (-) organisms were detected in 26 (50%) patients, gram (+) organisms were found in 1 patient, and multiple bacterial infections were found in 3 (5.8%) patients. No bacteria or other infectious agent was identified for 22 (42.3%) patients. Among the 27 patients in Group-1, respiratory tract source was found in 13 (48.1%), blood focus in 4 (14.8%), and urinary tract source in 3 (11.1%). In 2 (11.1%) cases there were multiple sources. Among the 25 patients in Group-2 no bacterial factors were detected in 17 (68%) cases. In the remaining 8 patients, other bacterial species were cultured but were not considered to be factors in infection.

Empiric antibiotic treatment was initiated immediately in 45 of 52 patients due to high fever and infection findings. Antibiotic therapy was terminated due to negative culture results in 18 of these patients. Antibiotics were not used in 7 (41.9%) of the patients. A total of 27 patients died, 5 in (18.5%) Group-1 and 22 (81.5%) in Group-2. Group-1 and Group-2 patient data are given in [table 3](#) and [table 4](#).

The locations of additional trauma among the SCI patient group is as follows: thorax in 25 (48.1%) patients, extremities in 8 (15.4%) patients, abdomen in 5 (9.6%) patients, and pelvis in 5 (9.6%) patients. SCI affected the cervical spine in 33 (63.5%) patients, thoracic spine in 19 (36.5%) patients, and lumbar spine in

Table 3 Evaluation of Group-1 and Group-2 Patients

	Group-1 (Infectious) n=27	Group-2 (Non-Infectious) n=25	p
Maximal Fever*	39.10 (0.64)	40.22 (1.10)	0.001
Number of fever days**	7 (2–38)	5 (2–30)	0.250
WBC*	13.00 (6.8)	9.7 (4.3)	0.049
CRP **	72.8 (0–307)	18.5 (0–586)	0.822
Neutrophil**	86 (65–97)	84.4 (67–93)	0.161
MV/ Day**	6 (0–107)	7 (0–37)	0.544
ICU/ Day **	16 (2–151)	9 (2–37)	0.005
Stay in hospital / day**	28 (6–151)	9 (2–37)	0.001

*mean $\pm$ standard deviation, **median (min-max)

Abbreviations: WBC: White blood cells, MV: Mechanical ventilation, ICU: Intensive care unit, CRP:C-Reactive protein

8 (15.4%) patients; at least two spinal region traumas were present in 7 patients. A total of 14 (51.9%) of 27 patients with isolated cervical spinal trauma, 6 (46.2%) of 13 patients had with isolated thoracic spinal trauma, and 2 (40%) of 5 patients with isolated lumbar spinal trauma died. There was no difference in the mortality rate between patients with cervical trauma and with thoracic and lumbar trauma ($P = 0.864$). Considering the relationship between infection and trauma region, thorax trauma occurred at a similar frequency in both groups. Thorax trauma was observed in 11 (40.7%) of 27 patients in Group-1 and in 14 (56%) of 25 patients in Group-2.

Spinal trauma affected regions above T_6 level in 21 (77.8%) patients in Group-1 and 19 (76%) patients in Group-2 ($P > 0.05$).

The patients in Group-2 were evaluated for intracranial hemorrhage (ICH) due to the dual fever effect. ICH was present in 19 (36.5%) of the study group

patients, but only 9 of these patients were in Group-2. There was no difference between ICH and non-ICH subgroups in terms of maximum fever, total days of fever, or mortality in Group-2, but there was a statistical difference between these subgroups in terms of duration of mechanical ventilation and duration of intensive care stay. In Group-2 the duration of mechanical ventilation (MV) was 9 (5–37) days in SCI patients with ICH and 4 (0–23) days in SCI patients without ICH ($P = 0.035$). The duration of intensive care unit stay was 9 (7–37) days in ICH subgroup and 6.5 (2–28) days in non-ICH subgroup ($P = 0.049$).

There was no significant difference between groups when comparing all group data according to early and late onset fever. A total of 21 (48.8%) of 43 patients with early fever onset and 6 (66.7%) of 9 patients with late fever onset died ($P = 0.469$).

The duration of mechanical ventilation for all 52 patients was 6.0 (0–107) days, the duration of intensive

Table 4 Group1 and Group-2 Patient demographics and Clinical Findings

	Group-1 (Infectious) n=27	Group-2 (Non-Infectious) n=25	p
Sex			
Male (n=41)	21 (51.2)	20 (48.8)	1.000
Female (n=11)	6 (54.5)	5 (45.5)	
Spinal surgery			
Yes (n=22)	15 (68.2)	7 (31.8)	0.084
No (n=30)	12 (40.0)	18 (60.0)	
Intracranial hemorrhage			
Yes (n=19)	10 (52.6)	9 (47.4)	1.000
No (n=33)	17 (51.5)	16 (48.5)	
Fever			
Early (n=43)	25 (58.1)	18 (41.9)	0.071
Late (n=9)	2 (22.2)	7 (77.8)	
Active P.			
Yes (n=31)	22 (71.0)	9 (29.0)	0.002
No (n=21)	5 (23.8)	16 (76.2)	
Mortality			
Yes (n=27)	5 (18.5)	22 (81.5)	0.000
No (n=25)	22 (88.0)	3 (12.0)	
Cervical Spine Trauma			
Yes (n=33)	17 (51.5)	16 (48.5)	1.000
No (n=19)	10 (52.6)	9 (47.4)	
Thoracic spine trauma			
Yes (n=19)	7 (36.8)	12 (63.2)	0.173
No (n=33)	20 (60.6)	13 (39.4)	
Lumbar spine trauma			
Yes (n=8)	5 (62.5)	3 (37.5)	0.705
No (n=44)	22 (50)	22 (50)	
X-ray findings (48 hour)			
Yes (n=17)	15 (88.2)	2 (11.8)	0.000
No (n=35)	12 (34.3)	23 (65.7)	
Vasopressor Treatment			
Yes (n=25)	6 (24.0)	19 (76.0)	0.000
No (n=27)	21 (77.8)	6 (22.2)	

n (%), Abbreviations: Active P.: Active pathogen, whether the cultured pathogen is considered to be an active

care stay was 9 (2–151) days, and the duration of hospitalization was 17.5 (2–151) days. LMWH was used in 35 (67.3%) patients and mechanical thromboembolism prophylaxis was used in 17 (32.7%) patients for prevention of venous thromboembolism. A total of 34 (65.4%) of the patients underwent sedation, and vasopressor was used in 25 patients (48.1%). The rate of vasopressor use was higher in the non-infectious fever group ($P < 0.001$).

Discussion

Acute spinal cord trauma can produce a severe clinical fever response during intensive care follow-up as a result of both infectious and non-infectious etiologies and thermoregulatory dysfunction secondary to trauma. Another type of fever emerging in SCI patients is a clinical condition called "neurogenic fever", characterized by a high rate of fatality. In this study, 25 (48.1%) of 52 acute SCI patients were diagnosed with neurogenic fever during intensive care follow-up due to thermoregulation, absence of response to treatment. A total of 22 (88%) of these patients died with a mean temperature of 40.2 °C.

Fever is an adaptive response to physiological stress regulated tightly by endogenous pyrogenic and antipyretic mechanisms, and usually responds to antipyretic treatment. Although the mechanism of fever development after SCI is not fully understood, injury to the hypothalamus, the main center of the brain involved in thermoregulation, can cause thermoregulation and especially hyperthermia.¹¹ It was reported in animal studies that temperature-sensitive neurons in the spinal cord can also regulate temperature changes; therefore, nerve damage due to traumatic SCI results in neurogenic fever with thermoregulation independent of the sympathetic system.¹⁴ Cases of hyperthermia secondary to thermoregulation do not respond to antipyretic treatment and must be treated by cooling and distributing the produced heat.^{11,15,16} The elevated body temperature resulting from hyperthermia syndrome often exceeds 41.0 °C. Various conditions have been implicated as potential causes of hyperthermia syndrome: subarachnoid hemorrhage, acute neurological cases such as traumatic brain injury or intracerebral hemorrhage, drug-induced hyperthermia syndromes, malignant hyperthermia, neuroleptic malignant syndrome, thyrotoxicosis, pheochromocytoma, and others. In addition, the incidence deep vein thrombosis and non-infectious fever of unknown cause is also high in patients with central nervous system impairment.¹⁷ Is every non-infectious fever of unknown origin in SCI patients a "neurogenic fever"? This question is difficult to answer

in the absence of definitive criteria for neurogenic fever diagnosis. However, the incidence of neurogenic fever has been reported at 2.6% to 27.8% in many studies.^{11–13,15,18,19} Savage *et al.* identified "neurogenic fever" in approximately one out of every 20–25 patients.²⁰ The frequency of non-infectious fever among our patients was comparable to the rate reported by Savage *et al.*

There are many unspecified gaps in the diagnosis, frequency, treatment, and contribution to mortality of neurogenic fever emerging in SCI patients during both the acute care period and rehabilitation period. In spite of everything, fever etiology was noted as unknown in 29% of neurology intensive care patients.²¹ With the data obtained in this study, it is not possible to definitively state that the source of fever among the 25 patients diagnosed with non-infectious fever was due to thermoregulation secondary to SCI. A total of 22 (88%) of these patients died even when probable causes were eliminated. Different study groups have reached a variety of conclusions when reviewing early mortality among SCI patients.^{22,23} Neurogenic fever mortality in SCI has been diagnosed in case series and other small sample size studies.^{18,19,24}

Many episodes of recurrent fever are caused by infections in SCI patients. Infection was identified as a factor in 27 (51.9%) of 52 SCI patients in the study group. The infection source was most commonly identified as the respiratory tract ($N = 13$; 48.1%). Empiric antibiotics were initiated in the early phase of SCI in 45 (86.5%) patients due to fever and clinical and laboratory findings supporting infection, but antibiotic therapy was terminated immediately due to negative culture results in 18 of these patients. Although pneumonia and urinary tract infection are the most common sources of infection in SCI patients, other infection source can also be detected.^{25,26} It should be emphasized that patients are exposed to unnecessary antibiotic therapy due to the difficulty in diagnosing the cause of fever in SCI. There is a critical need for markers or criteria for early identification of non-infectious fever.

It has been shown in this study that early or late fever attacks, occurring in the acute stages of SCI, had a prolonged duration in cases where infection was suspected but tended to result in lower maximum body temperatures compared to non-infectious fever, (Table 2). The duration of intensive care and hospital stay was longer in the infectious group. The shorter average duration of intensive care and hospital stay in the non-infectious fever group occurred because 22 (81.5%) of the 27 patients, died due to persistent and unresponsive fever (Table 2).

Previous studies investigating thermoregulation in patients with traumatic brain injury (TBI) have reported that these patients can have high temperatures that last for weeks, bradycardia, lack of sweating, and flat plate temperature curves that resist antipyretic drugs.^{27–30} Similar clinical conditions occurred among the persistent fever group in our study. Vasopressor was used in 25 (48.1%) of the study group patients. Vasopressors were used intensively in the non-infectious group due to autonomic dysregulation, a complication that also occurred secondary to the development of sepsis in the infectious group (Table 3). Other investigators have hypothesized that the presence of blood in the cerebrospinal fluid, especially in the intraventricular areas, may lead to increased central nervous system temperature and fever. Neurotransmitter release, accelerated free radical production, increased intracellular glutamate concentration, and susceptibility of neurons to excitotoxic damage may also contribute to the increase in internal temperature. Fever in SCI patients is the result of a mechanism distinct from fever secondary to infection.^{10,31,32} However, it is difficult to distinguish the impact ICH accompanying SCI. In this study, 10 (52.6%) of 19 patients diagnosed with ICH had infectious fever, and 9 (47.4%) of these patients had non-infectious fever (Table 3). Moreover, there was no significant difference between ICH and non-ICH subgroups in terms of maximum fever, course of fever, duration of mechanical ventilation, and mortality in non-infectious fever group with SCI.

In cases of tetraplegia and injuries above T₆ in patients with SCI, the primary respiratory muscles and accessory muscles are affected resulting in suppression of cough reflexes, respiratory failure, and atelectasis.³³ Colachis and Otis *et al.* reported that autonomic dysregulation is more common in SCI cases affecting the spine above T₆, affecting thermoregulation and triggering anomalies.¹⁵ However, there was no statistically significant difference in the rate of neurogenic fevers among patients with injuries above T₆ level in our study. Attia *et al.* reported that thermoregulation is impaired paraplegic or tetraplegic patients.³⁴ However, there was no relationship between the severities of neurological damage (ASIA A group-complete, ASIA B-C-D group-incomplete) maximum body temperature in our study group patients (Table 1). Ülger *et al.* diagnosed fever in SCI patients diagnosed with ASIA A as fatal fever in their case series.²⁴

Other non-infectious causes of fever were evaluated in the present study. Deep vein thrombosis and pulmonary embolism were not diagnosed. LMWH was used in 35 (67.3%) patients and mechanical prophylaxis was used

in 17 (32.7%) patients for venous thromboembolism prophylaxis.

Our study has several limitations. The study was a retrospective analysis of a derivation cohort and will require prospective validation. The data were collected from nursing papers, hospital automation data systems, and patient files, and therefore loss of data is possible. Secondly, fever measurements were conducted as tympanic and axillary, and no single standardized method was used for fever measurements. Third, only the intensive care process was observed; per-hospitalization observation and post-discharge follow-ups were not possible.

Conclusion

In conclusion, this study demonstrates that neurogenic fever is accompanied by high mortality rates in SCI patients. It is not always possible to distinguish the effects neurogenic fever due to intracranial haemorrhage accompanying SCI from other fever etiologies. This study supports the hypothesis that other etiologies must be carefully examined in SCI patients with accompanying intracranial hemorrhage. It is clear that there is a need for laboratory analyses and further studies that can clarify the origin of thermoregulation in SCI and identify clinically relevant biomarkers. There are many dark sides and unknowns in the diagnosis of neurogenic fever and clinical follow-up in SCI patients, and further studies are necessary.

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