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Research Article

Risk and outcome of Sepsis Associated Encephalopathy after Acute Gastrointestinal Perforation

Abstract

Sepsis associated encephalopathy (SAE) is the most common encephalopathy in ICU and may contribute to a high mortality. Few data are available on the risk and outcome of SAE after patients with gastrointestinal (GI) perforation. We reviewed all patients admitted to our department of general surgery with GI perforation over a 3-year period. We used the sepsis-related organ failure criteria for diagnosis of SAE (GCS<13 score in absence of sedation). Exclusion criteria were present evidence of meningitis/encephalitis and other primary encephalopathy. Of 58 patients admitted for GI perforation during the study period, 22 patients (37.9%) developed sepsis. Of them, 9 (40.9%) patients (7 male, mean 79y) had SAE according to the inclusion/exclusion criteria. The presence of SAE was significantly associated with increased age (79.0 ± 11.3 vs. 59.6 ± 16.3 , $p=0.006$), lower mean arterial pressure (MAP) (70.7 ± 15.3 vs. 90.4 ± 16.8 , $p=0.000$), lower GCS score (9.7 ± 3.6 vs. 15 ± 0.0 , $p=0.000$), elevated SOFA score (8.9 ± 3.3 vs. 3.6 ± 1.6 , $p=0.000$) and qSOFA score (1.9 ± 0.3 vs. 0.4 ± 0.5 , $p=0.000$), and higher mortality at 30 days (66.7% vs. 7.7% , $P=0.000$). Nevertheless, in Cox regression analysis, only a lower MAP was associated with worse survival in SAE. Sepsis occurred in 37.9% of patients after GI perforation. These patients had more frequent SAE and needed more aggressive ICU therapy; a lower MAP is significantly influence outcome.

Introduction

There is increased recognition of sepsis in patients with guidelines, such as the First International Consensus Definition for sepsis (Sepsis I, in 1992) is a systemic inflammatory response caused by infection [1]; in 2003, the Sepsis II was further established the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) for the diagnosis of sepsis [2]. As a result, clinicians have been aware of the clinical manifestations of SIRS in sepsis, but for those without clinical manifestations of SIRS. Until 2015, Kaukonen et al. [3], published the SIRS criteria for the diagnosis of sepsis, which were clearly classified into two types of SIRS-positive and SIRS-negative sepsis. We hypothesized that patients with gastrointestinal (GI) perforation were at high risk of potentially sepsis and sepsis associated encephalopathy (SAE), which were more likely to increase hospital mortality [4]. Our study aimed at examining the effect of SAE on the outcomes of GI perforation at the time of discharge in a nationally representative sample of patients with GI perforation.

Material and Methods

We used the data files from our inpatient sample in the

department of general surgery from January, 2014 to April, 2017 for our analysis. A comprehensive synopsis on our inpatient sample data is available. We used the *International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM)* primary diagnosis codes K 31.8 and K 63.1 to identify the patients admitted with GI perforation. Recently, in the Sepsis-3, sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection [5]. We are using the following criteria for the diagnosis of SAE: (1) Eligible the Third International Consensus Definitions for sepsis-3 criteria; (2) present evidence of diffuse or multifocal cerebral dysfunction (from mental changes to severe lethargy or coma); (3) GCS<13 score in absence of sedation. The exclusion criteria were as follows: (1) presence of meningitis/ encephalitis; (2) present evidence of other primary encephalopathy; (3) present evidence of non-sepsis or non-septic shock. We divided GI perforation patients with sepsis into with and without SAE. Patients were followed for 30 days or until death.

The following criteria were used to define SIRS: (1) temperature greater than 38°C or less than 36°C; (2) heart rate greater than 90 beats per minute; (3) tachypnea >20 respirations per minute or $PCO_2 < 32$ mmHg; (4) white blood cell count greater than $12.0 \times 10^9/L$ or less than $4.0 \times 10^9/L$, or more than 10% band forms [2].

Organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score ≥ 2 for a particular organ after the onset of infection [6]. The following were considered to be equivalent to a SOFA score ≥ 2 for a particular organ (on a scale from 0–4, with higher scores indicating more severe organ failure): brain failure =GCS score <13 ; respiratory failure=bilateral infiltrates on chest thorax radiography and an arterial oxygen pressure/fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 or a need for supplemental oxygen to maintain $>90\%$ oxygen saturation; circulation failure =hypotension (systolic blood pressure (SBP) <90 mmHg, mean arterial pressure <65 mmHg or decrease of >40 mmHg in the systolic pressure);hepatic failure= total serum bilirubin >33 $\mu\text{mol/L}$; kidney failure=creatinine >171 $\mu\text{mol/L}$; GI failure = an abdominal rumbling sound disappearance or a high degree of abdominal distention; and blood failure=platelet count $\leq 100 \times 10^9/\text{L}$.

The following data were analyzed in patients with GI perforation with SAE events: age, sex, underlying disease, body temperature, blood pressure, heart rate, respiratory rate, creatinine, bilirubin, serum glucose, white blood cell (WBC) count, platelet count, SOFA score, qSOFA score, abdominal X-ray or CT scan, and body fluid cultures. We also recorded the GCS score, the onset-to-sepsis time, and the length of hospital stay. Outcomes were assessed at 30 days of follow-up.

Statistical methods

The results in each group are expressed as means \pm standard deviation (SD) or medians (IQR), and n (%) for qualitative values. Patients without awakening were compared with patients with awakening using univariate analysis. Fisher's exact test and the Mann-Whitney *U* test were used to examine the relationship between baseline patient variables. Continuous variables were compared using Student's *t* test. Multivariate Cox regression analysis was performed with age and sex adjustment. All *p*-values were 2-sided, and significance was set at $P < 0.05$. Statistical calculations were performed using a proprietary, computerized statistics package (SPSS 17.0.).

Results

Of 58 patients admitted for GI perforation during the study period, 22 patients (37.9%) developed sepsis. Of them, 9 patients (7 male, mean 79y) had SAE according to the inclusion/exclusion criteria. The clinical characteristics of GI perforation in patients with SAE were showed in the table 1. All of patients had intra-abdominal infection (including suspected infection), but SIRS was less common (1.2 ± 0.7). In-hospital organ failure, such as brain failure, septic shock, liver failure, gastrointestinal failure, were more common in patients with GI perforation with SAE.

The results of univariate analysis are shown in table 2. There was no difference in male gender, body temperature, heart rate, respiratory rate, leukocyte count, SIRS criteria, acute renal failure, and sepsis-related hepatic failure in subjects with SAE and non-SAE subjects ($p > 0.05$). The presence of SAE was significantly associated with increased age (79.0 ± 11.3 vs 59.6 ± 16.3 , $p = 0.006$), decreased MBP (70.7 ± 15.3 vs 90.4 ± 16.8 , $p = 0.000$), lower GCS score (9.7 ± 3.6 vs 15 ± 0.0 , $p = 0.000$), elevated SOFA score (8.9 ± 3.3 vs 3.6 ± 1.6 , $p = 0.000$) and qSOFA score (1.9 ± 0.3 vs 0.4 ± 0.5 , $p = 0.000$), and higher mortality at 30 days (66.7% vs 7.7% , $P = 0.000$).

Using Cox proportional analysis, the risk of worse survival in patient with GI perforation with SAE was significantly associated with lower MBP (RR, 0.6; 95% confidence interval, 0.406–0.993; $P < 0.05$) (Table 3).

Discussion

Chest infection is the first common source of sepsis [4–7]. The abdominal cavity is the second source of sepsis [4,8,9], and its most common cause is GI perforation [9]. In our current series, GI perforation prevalence accounted for 1.7% of the hospitalized patients, but GI perforation can cause deep retroperitoneal abscess or empyema, sepsis is up to 37.9%, lower than the other reports (43.5%) [10].

Incidence of SIRS-negative sepsis was 81.8% (18/22) in our study, which was higher compared with previous studies of patients with sepsis [3]. We do not have a satisfactory explanation for this phenomenon. Perhaps, because the GI tract is the largest immune organ in the body [11,12], patients with GI perforation can experience SIRS-negative sepsis in follow several ways: immunosuppression [13,14], immunodeficiency [12], or deep infection site[13].

Our current data showed that there was no significantly differences in SIRS met 0–1 criteria between septic patients with SAE and septic patients without sepsis, suggesting that

Table 1: Characteristics of GI perforation patients with SAE (n=9).

| Characteristics | Value |
|-------------------------------------------------------|-----------------|
| Male gender (%) | 7(77.8) |
| Age (years, mean \pm SD) | 79.0 \pm 11.3 |
| Location and cause of GI P (%) | |
| Gastric antrum ulcer (%) | 4(44.4) |
| Duodenal bulb ulcer n (%) | 2(22.2) |
| Small intestine (%) | 3(33.3) |
| Time from onset to ward, median (IQR),h | 10(7-17) |
| Confirmed infection, n (%) | 3(33.3) |
| Suspected infection, n (%) | 6(66.7) |
| Body temperature,($^{\circ}\text{C}$,mean \pm SD) | 36.5 \pm 0.9 |
| Heart rate,(beat/min, mean \pm SD) | 87.2 \pm 13.8 |
| Respiratory (breaths/min, mean \pm SD) | 19.8 \pm 1.2 |
| WBC, (mean \pm SD) | 14.1 \pm 5.6 |
| MAP, mmHg (mean \pm SD) | 70.7 \pm 15.3 |
| Blood glucose (mmol/l, mean \pm SD) | 7.4 \pm 3.2 |
| SIRS criteria, (mean \pm SD) | 1.2 \pm 0.7 |
| Sepsis-related acute organ failure | |
| Brain, n (%) | 9(100.0) |
| Septic shock, n (%) | 7(77.8) |
| Acute respiratory failure, n (%) | 1(11.1) |
| Acute renal failure, n (%) | 1(11.1) |
| Acute hepatic failure, n (%) | 2(22.2) |
| GI failure, n (%) | 4(44.4) |
| SOFA score (mean \pm SD) | 8.9 \pm 3.3 |
| qSOFA score (mean \pm SD) | 1.9 \pm 0.3 |
| GCS score (mean \pm SD) | 9.7 \pm 3.6 |
| Surgical treatment, n(%) | 14(63.6) |
| Length of ICU stay, median (IQR),d | 1(0-4) |
| Mortalityat 30 days, n (%) | 6(66.7) |

GI=gastrointestinal; SAE=sepsis-associated encephalopathy; MAP=mean arterial pressure; SIRS=systemic inflammatory response syndrome; SOFA=sequential organ failure assessment; qSOFA=quickly sequential organ function assessment; GCS=Glasgow Coma Scale.

Table 2: Univariate analyses of septic patients with and without SAE after GI perforation.

| Episodes | All (n=22) | With SAE (N=9) | Without SAE (N=13) | p |
|-----------------------------------------|------------|----------------|--------------------|-------|
| Male gender, n (%) | 17(77.3) | 7(77.8) | 10(76.9) | 1.000 |
| Age, (years, mean ±SD) | 67.5±17.2 | 79.0±11.3 | 59.6±16.3 | 0.006 |
| Body temperature, (°C) | 36.8±1.0 | 36.5±0.9 | 37.0±1.0 | 0.246 |
| Heart rate, (beats/min) | 85.7±11.0 | 87.2±13.8 | 84.7±9.3 | 0.612 |
| Respiratoryrate, (breaths/mim) | 19.9±3.2 | 19.8±1.2 | 19.9±4.1 | 0.920 |
| leukocyte count, (x10 ⁹ /l) | 11.8±5.6 | 14.1±5.6 | 10.1±5.2 | 0.103 |
| SIRS criteria, (mean±SD) | 1.0±0.9 | 1.2±0.7 | 0.9±1.0 | 0.456 |
| SIRS met 0-1 criteria, n (%) | 18(81.8) | 6(66.7) | 12(92.3) | 0.264 |
| SIRS met 2-4 criteria, n (%) | 4(18.2) | 3(3.3) | 1(7.7) | 0.264 |
| MAP, (mmHg, mean±SD) | 82.3±18.7 | 70.7±15.3 | 90.4±16.8 | 0.011 |
| Lactic acid,mmol/l (mean±SD) | 2.9±3.3 | 3.4±4.4 | 2.5±2.3 | 0.534 |
| GCS, (mean ±SD) | 12.6±3.6 | 9.7±3.6 | 15.0±0.0 | 0.000 |
| Acute respiratory failure, n (%) | 2(9.1) | 1(11.1) | 1(7.7) | 1.000 |
| Septic shock, n (%) | 11(50.0) | 7(77.8) | 4(30.8) | 0.080 |
| Acute renal failure, n (%) | 4(18.2) | 1(11.1) | 3(23.1) | 0.616 |
| Acute hepatic failure, n (%) | 9(40.9) | 2(22.2) | 7(53.8) | 0.203 |
| Acute GI failure, n (%) | 8(36.4) | 4(44.4) | 4(30.8) | 0.662 |
| SOFA, (mean±SD) | 5.8±3.6 | 8.9 ±3.3 | 3.6 ±1.8 | 0.000 |
| qSOFA, (mean±SD) | 1.0±0.9 | 1.9±0.3 | 0.4±0.5 | 0.000 |
| Surgical treatment, n (%) | 14(63.6) | 4(44.4) | 10(76.9) | 0.187 |
| Hospital length of stay,median (IQR), d | 8(3-13.3) | 6(3-6) | 10(3-29) | 0.094 |
| Mortality at 30 days, n (%) | 7(31.8) | 6(66.7) | 1(7.7) | 0.000 |

SAE=sepsis-associated encephalopathy; GI=gastrointestinal; MAP=mean arterial pressure; SIRS=systemic inflammatory response syndrome; SOFA=sequential organ failure assessment; qSOFA=quickly sequential organ function assessment; GCS=Glasgow Coma Scale.

Table 3: Multivariate Cox risk ratios for SAE in GI perforation.

| Variable | RR | 95%CI for RR | P Value |
|-------------|------|--------------|---------|
| Sex | 1.6 | 0.618-7.236 | 0.077 |
| Age | 1.1 | 0.990-1.295 | 0.069 |
| SOFA score | 0.6 | 0.280-1.647 | 0.392 |
| qSOFA score | 0.01 | 0.000-60.43 | 0.290 |
| MAP | 0.6 | 0.406-0.993 | 0.043 |

SAE=sepsis-associated encephalopathy; GI=gastrointestinal; MAP=mean arterial pressure; SIRS=systemic inflammatory response syndrome; SOFA=sequential organ failure assessment; qSOFA=quickly sequential organ function assessment.

SIRS met 0-1 criteria is unpredictable for sepsis, but SIRS-negative patients do not also exclude the diagnosis of sepsis/SAE.

Our study found that the mortality rate in patients with GI perforation secondary to SAE was significantly higher than those with no SAE (66.7% vs.7.7%). However, in our current study, Cox regression analysis revealed that independent risk factors for worse survival in SAE is a lower mean arterial pressure. Our study findings are strongly supporting that the Sepsis-3 criteria is a useful predictable tool for the outcomes of sepsis/SAE.

Some studies also demonstrated that septic shock was related to higher mortality (43%-57%) [15,16]. The mechanism of the higher rate of worse outcomes in patients with septic shock/SAE may be

associated with severe hypotension. Patients with septic shock have higher rates of severe cerebral microcirculatory disturbance, which can lead to extensive subcortical white matter damage, or cause multifocal necrotizing white matter encephalopathy [17,18]. In fact, this white matter encephalopathy is also a SAE. The mortality rate of SAE is as high as 63.0%-71.9% [19,20], which is similar to our current study. There is a possibility that sepsis directly contributes to worsening of neurological ischemic injury. However, published data from the recent studies suggest that SIRS-positive sepsis is more likely to have a vasogenic cerebral edema on brain imaging [21,22]. These findings show that the pathological changes may be differ between SIRS-negative SAE and SIRS-positive SAE, and this needs further study.

The limitations of this retrospective study are unavoidable. First, a brain imaging for GI perforation with SAE is important. However, in this study brain imaging was absent. In addition, this is only a single center study, and the sample size is not large. Therefore, although the information is useful, further research is needed.

In summary, the incidence of sepsis after GI perforation is as high as 37.9%. GI perforation patients are more likely to have a severe SAE and associated with higher mortality.

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