Clinical research

Prior aspirin and/or nonsteroidal anti-inflammatory drug use in sepsis patients is associated with reduced intensive care unit morbidity and mortality: retrospective study

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Abstract

Introduction: Sepsis is a life-threatening condition that is characterized by multi-organ dysfunction and a high mortality rate, and prevention may be cheaper and easier than treatment. The sequential organ failure assessment (SOFA) score is associated with mortality risk, and the Quick SOFA (qSOFA) is a shortened version. In this study, we examined whether there was any difference between the qSOFA and SOFA scores, procalcitonin and CRP levels, and mortality among patients with sepsis who either used or did not use aspirin and/or nonsteroidal anti-inflammatory drug (NSAID).
Material and methods: This study was designed as a retrospective analysis of 64 septic patients, 38 males and 26 females. SOFA, qSOFA and APACHE II scores, as well as gender, age, length of hospital stay, procalcitonin and CRP levels, blood culture results, mortality rates and the use of aspirin and/or NSAID were recorded from the files.
Results: The median age of aspirin and/or NSAID users was 63 years and of non-users was 55. There were significant differences in the SOFA scores and mortality rates between aspirin and/or NSAID users and non-NSAID/aspirin users ($p < 0.05$). There were no significant differences in the length of hospital stay or blood culture results ($p > 0.05$). There were also significant differences in CRP and procalcitonin values ($p < 0.05$).
Conclusions: In this study, patients that used aspirin and/or NSAID had lower SOFA, qSOFA and APACHE II scores and lower mortality rates. There have been recent studies on the prevention of sepsis in patients having already used these drugs before hospital admission, but there have been no publications in which sepsis is supported by SOFA and qSOFA scores with aspirin and/or NSAID users.

Key words: quick sequential organ failure assessment, sequential organ failure assessment, nonsteroidal anti-inflammatory drug, aspirin, mortality.

Introduction

Sepsis is a severe condition characterized by multi-organ dysfunction and a high mortality rate [1]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection [2]. It presents with a non-regulated immune re-

Table I. The Sequential Organ Failure Assessment (SOFA) score [2]

Parameter	SOFA score			
	1	2	3	4
PaO_2/FIO_2 [mm Hg]	< 400	< 300	< 220	< 100
SaO_2/FIO_2	221–301	142–220	67–141	< 67
Platelets [× 10^3/mm^3]	< 150	< 100	< 50	< 20
Bilirubin [mg/dl]	1.2–1.9	2.0–5.9	6.0–11.9	> 12.0
Hypotension	MAP < 70	Dopamine ≤ 5 or dobutamine (any)	Dopamine > 5 or norepinephrine ≤ 0.1	Dopamine > 15 or norepinephrine > 0.1
Glasgow Coma Score	13–14	10–12	6–9	< 6
Creatinine [mg/dl] or urine output [ml/day]	1.2–1.9	2.0–3.4	3.5–4.9 or < 500	> 5.0 or < 200

MAP – mean arterial pressure, CNS – central nervous system, SaO_2 – peripheral arterial oxygen saturation.

sponse to infection, with the most severe cases advancing to a critical and resistant state of septic shock. Biomarkers used in sepsis detection often have a low specificity and/or sensitivity. These biomarkers include the three most common for sepsis detection in clinical practice: procalcitonin (PCT), C-reactive protein (CRP) and lactate [3]. Besides these markers, there are some scoring systems used for understanding the severity of sepsis in intensive care units (ICUs). One of these scores is the sequential organ failure assessment (SOFA) score (Table I). Organ dysfunction has been defined as an increase in the SOFA score of ≥ 2, and this increase was associated with a 10% mortality risk [4]. Because taking the SOFA score requires laboratory values that may not be readily available in all situations, the Quick SOFA (qSOFA) was developed to provide a shortened version that can more easily be performed in a variety of settings [4]. The qSOFA score is recommended as a proxy for organ dysfunction measurements and may act as a risk predictor for patients with known or suspected infection, as well as a quick result for clinicians considering the diagnosis of sepsis [5].

In sepsis, there is inflammation and endothelial dysfunction [6]. While the role of the inflammatory cascade in the pathophysiology of sepsis is well defined, clinical trials studying the use of anti-inflammatory agents in the treatment of sepsis have not been clear [7]. Aspirin is a non-selective inhibitor of the enzyme cyclooxygenase (COX) and has previously been used in high doses for the treatment of rheumatic fever. Low-dose aspirin also continues to be used as a preventative in cardiovascular medicine. There are a lot of mechanisms in which aspirin can manipulate the processes involved in sepsis, such as through the inhibition of COX, the inhibition of nuclear factor κB [8], the production of nitric oxide (NO) [9] and lipoxin production [9, 10]. For these reasons, some authors have suggested that aspirin or NSAIDs could prevent patients from acquiring sepsis [6, 7].

The aim of this retrospective study was to compare any differences between the SOFA, qSOFA and APACHE II scores, procalcitonin and CRP levels, and mortality among patients with sepsis who used or did not use NSAIDs and/or aspirin prior to hospital admission.

Table II. qSOFA (Quick SOFA) criteria [2]

qSOFA (Quick SOFA)*
Respiratory rate ≥ 22/min
Altered mentation
Systolic blood pressure ≥ 100 mm Hg

**The score ranges from 0 to 3 points. The presence of 2 or more qSOFA points near the onset of infection was associated with a greater risk of death or prolonged intensive care unit stay.*

Material and methods

We performed a retrospective study on all the patients in the Anaesthesiology and Reanimation ICU between 1st June 2016 and 31st July 2017. A total of 64 septic patients were included in this study. Thirty-two used nonsteroid anti-inflammatory drugs (NSAIDs) or aspirin (group: NSAID/aspirin users) (use of NSAIDs or aspirin at least 1 year), and 32 did not use NSAIDs or aspirin (group: NSAID/aspirin not users) prior to admission. The patients in the NSAID/aspirin user group used 600 mg ibuprofen and/or 100 mg aspirin for at least 1 year. The exclusion criteria for the study included patients who were less than 18 years old or who had missing files.

In this study, NSAID/aspirin user and non-user groups were compared with SOFA (Table I), qSOFA (Table II) and APACHE II (Table III) scores, gender, age, length of ICU stay, procalcitonin and CRP levels, blood culture results and mortality rates. The data were recorded from the patients' files.

Table III. APACHE II score

Parameter	Physiological changes								
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature [rectal °C]	≥ 41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤ 29.9
Mean arterial pressure (MAP) [mm Hg]	≥ 160	130–159	110–129		70–109		50–69	40–54	≤ 49
Heart rate [/min]	≥ 180	140–179	110–139		70–109		55–69	40–54	≤ 39
Respiratory rate [/min]	≥ 50	35–49		25–34	12–24	10–11	6–9		≤ 5
Oxygenation									
If $FiO_2 \geq 0.5$: Alveolar arterial gradient DO_2	≥ 500	350–499	200–349		< 200				
If $FiO_2 < 0.5$: PaO_2					> 70	61–70		55–60	< 55
Arterial PH	≥ 7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	< 7.15
Venous HCO_3 [mEq/l]	≥ 52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	< 15
Sodium [mEq/l]	≥ 180	160–179	155–159	150–154	130–149		120–129	111–119	< 110
Potassium [mEq/l]	≥ 7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		< 2.5
Creatinine [mg/dl]	≥ 3.5	2–3.4	1.5–1.9		0.6–1.4		< 0.6		
Haematocrit (%)	≥ 60		50–50.9	46–49.9	30–45.9		20–29.9		< 20
Leukocyte [/mm^3 × 1000]	≥ 40		20–39.9	15–19.9	3–14.9		1.2–9		< 1
Glasgow Coma Score point: 15-real GCS									

Ethical approval for this study (No: 2016.27.31) was provided by the Ethical Committee Kanuni Sultan Suleyman Education and Training Hospital, Istanbul, Turkey, on 20 June 2016.

Statistical analysis

The SPSS statistical package, version 17.0 (SPSS Inc, Chicago, IL, USA) was used to analyse the statistics. The data were checked for a normal distribution using this package. Non-parametric tests (Mann-Whitney *U*-test and χ^2 test) were used for data that were not normally distributed. *P*-value < 0.05 was considered statistically significant.

Results

A total of 68 patient documents were initially collected. Four of the patients' documents were not filled out completely and were thus excluded. Finally, 64 patients, including 38 males and 26 females, were enrolled in this study. Thirty-two used NSAIDs or aspirin, and 32 did not use NSAIDs or aspirin prior to admission. The data from these patients are shown in Figure 1. The median age of

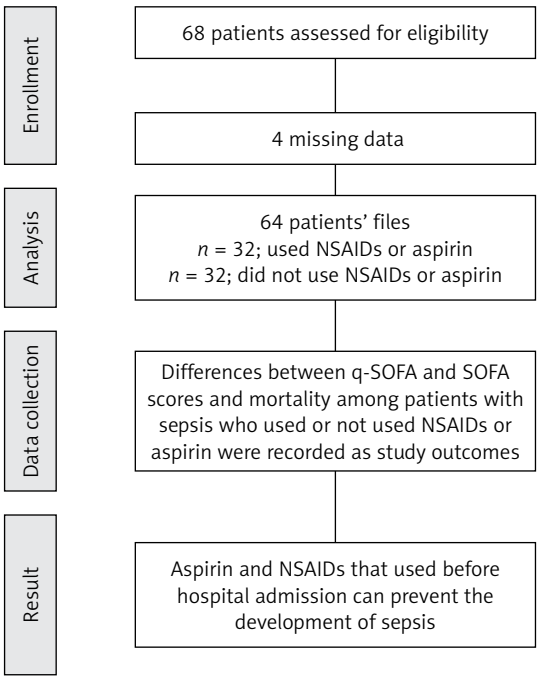

Figure 1. Flow diagram of the study

the NSAID/aspirin users was 63 years (range: 22–87) and that of non-users was 55 (range: 18–89).

The comparisons of the SOFA, qSOFA and APACHE II scores between the NSAID/aspirin users and non-NSAID/aspirin users are shown in Table IV. There were significant differences between SOFA scores of the NSAID/aspirin users and the non-NSAID/aspirin users ($p < 0.05$).

The difference between the median SOFA scores for the NSAID/aspirin users was 4.0, and for the non-users, it was 7.5, which was statistically significant ($p = 0.005$) (Table IV). There were also significant differences between the mortality rates ($p < 0.05$) (Table V). There were no significant differences between the qSOFA and APACHE II scores of the patients (Table IV), between the lengths of hospital stay ($p > 0.05$) (Table V). There were also significant differences between CRP and procalcitonin values ($p < 0.05$) (Table V). The difference in the blood culture results for the NSAID/aspirin users was 7 (21.9%) and for non-users was 11 (34.4%), which was not statistically significant ($p > 0.05$).

Among the patients in the NSAID/aspirin user group, 17 (53%) patients had hypertension, 13 (40%) patients had coronary artery disease, 10 (31%) patients had diabetes mellitus, 10 (31%) patients had cerebrovascular disease and 3 (9%) patients had peripheral arterial disease. In the NSAID/aspirin non-user group, 10 (31%) patients had hypertension, 8 (25%) patients had coronary artery disease, 6 (18%) patients had diabetes mellitus, 8 (25%) patients had cerebrovascular disease and 2 (6%) patients had peripheral arterial disease (Table VI).

Discussion

Sepsis is a condition with a high mortality rate in critically ill patients, and it presents many difficulties for both patients and the health care team in terms of equipment and staffing resources, treatment options and multiple organ failure. It may be cheaper and easier to prevent sepsis than to attempt to treat the disease after it occurs.

The SOFA score is a basic and efficient method for describing the level of organ dysfunction or failure in critically ill patients [11]. Periodic, recurrent scoring enables the patient condition and disease development to be monitored and better understood. During the first few days of ICU admission, SOFA is a good indicator of prognosis. Both the mean and highest SOFA scores are particularly useful predictors of patient outcome.

Table IV. Relationship between SOFA, qSOFA, APACHE II scores in patients with and without prior aspirin and/or NSAID use

Variable	Aspirin and/or NSAID users ($n = 32$)	Aspirin and/or NSAID non-users ($n = 32$)	*P*-value
SOFA	4.0 (1–9)	7.5 (0–14)	0.05
qSOFA	1.0 (0–3)	1.5 (0–3)	0.56
APACHE II	23.0 (6–41)	25.5 (7–80)	0.18

Table V. Relationship between mortality, hospital length of stay and CRP and procalcitonin values in patients with and without prior aspirin and/or NSAID use

Parameter	Aspirin and/or NSAID users ($n = 32$)	Aspirin and/or NSAID non-users ($n = 32$)	*P*-value
Mortality	22 (68.8%)	14 (43.8%)	0.044
Hospital length of stay	8 (1–59)	9 (1–38)	0.640
CRP	246.8 (9.5–397.6)	224.7 (24.2–3016)	0.697
Procalcitonin	17.1 (2.8–238.4)	14.7 (1.8–553.6)	0.577

Table VI. Percentages of accompanying diseases

Disease	Aspirin and/or NSAID users ($n = 32$)	Aspirin and/or NSAID non-users ($n = 32$)
Hypertension	17 (53%)	10 (31%)
Coronary artery disease	13 (40%)	8 (25%)
Diabetes mellitus	10 (31%)	6 (18%)
Cerebrovascular disease	10 (31%)	8 (25%)
Peripheral arterial disease	3 (9%)	2 (6%)

Irrespective of the initial score, an increase in the SOFA score during the first 48 h in the ICU also predicts a higher mortality rate.

There is a close relationship between the inflammatory cascade and the haemostatic system. Haemostasis plays a very important role in the natural immune system, successfully enveloping pathogens through the formation of fibrin, platelet and leucocyte clots [12]. While this occurrence may be evolutionarily advantageous, severe sepsis is characterised by the microvascular thrombosis that is caused by this haemostasis process, which can induce multi-organ dysfunction [13]. Like in our study, Toner *et al.* [14] suggested that aspirin can regulate various pathogenic mechanisms involved in the improvement of multiple organ failure in sepsis. This is probably because platelets play an important role in leucocyte recruitment, vascular permeability and the resultant oedema formation [14]. Platelet depletion resulted in a significant reduction in pulmonary oedemas in a transfusion-related model of acute lung injury without influencing neutrophil migration [15]. Platelet depletion not only inhibited platelet activation and aggregation, but also resulted in improved oxygenation, reduced pulmonary hypertension and fewer interstitial pulmonary oedemas [16].

Sepsis has multiple factors involved in its pathogenesis. Though the concept of aspirin use in sepsis appears exciting and new, an imbalance between pro- and anti-inflammatory molecules suggests that the use of aspirin to enhance the production of anti-inflammatory protectins and maresins might be more precautionary [17]. In one study, a combination of aspirin and arachidonic acid (AA) and eicosapentaenoic acid (EPA) was shown to be superior in the management of sepsis and acute respiratory distress syndrome (ARDS) compared to the use of aspirin alone [17]. Additionally, Richter *et al.* [18]. found that the risk was significantly reduced when patients were exposed to antirheumatic drugs at the time of sepsis and that treatment with any class of antirheumatic drugs had significant protective effects regarding mortality. In addition, O'Neal *et al.* [6]. suggested that the lowest rates of both severe sepsis and acute lung injury or ARDS were in patients who were taking both statins and aspirin prior to hospitalization and that mortality was also significantly lower in patients on both aspirin and statin therapy. Contrary to our study, they said that aspirin use alone did not have a significant association with development of severe sepsis. They did, however, suggest that aspirin might provide additional benefits and that further investigations should evaluate the possible additive effect of aspirin and statins on the prevention of sepsis.

The SOFA scores, CRP and procalcitonin values are the most popular and practicable scores and blood levels in ICU patients. We can use them to determine whether the patients are in sepsis. Procalcitonin is a peptide precursor of the hormone calcitonin. The level of PCT rises in response to a proinflammatory stimulus. It can, therefore, be used to monitor the course of systemic inflammation and guide the physician in therapeutic decision-making. Few studies have addressed serum procalcitonin levels in relation to hospital mortality [19]. Meng *et al.* reported that serum PCT levels > 10 ng/ml at the time of admission were associated with all-cause short-term mortality in the ICU [20]. In this study, both CRP and procalcitonin values were higher in aspirin and NSAID non-users.

Patients with different types of systemic diseases also have an increased risk of hospitalization [21]. In addition, mortality rate is an important indicator of successful intensive care follow-up. Although prehospital aspirin or NSAID use was associated with a decreased rate of diagnosis of sepsis [22], we detected differences in mortality between prehospital aspirin or NSAID users and nonusers, because in this study we defined such important predictors of mortality as scores like APACHE II or SOFA scores. In these scores we detected a lot of predictive levels and values of patients' condition such as temperature, mean arterial pressure, heart rate, oxygenation, platelets, bilirubin, etc. and appropriateness or timing of initial antibiotic therapy, respiratory rate, or underlying chronic medical conditions. In our study, mortality rate was higher in aspirin and/or NSAID non-users. The high mortality rate in the group without aspirin or NSAID is an expected result because the SOFA score is high in this group.

In conclusion, our study showed that patients using aspirin and/or NSAID drugs had lower SOFA scores and CRP and procalcitonin values. In addition, these patients had lower mortality rates. Although there are publications on how aspirin and NSAIDs help prevent sepsis, there are no publications in which the conclusions are supported by SOFA and qSOFA scores in these NSAID/aspirin users, which lends novelty to our study. Our results were intriguing enough that more studies should be done on this subject to help reduce sepsis in hospitals. Limitations of our study are that it was a retrospectively study and a small number of patients were included. The effect of prehospital use of NSAID/aspirin needs to be evaluated with prospective randomized intervention studies.

Conflict of interest

The authors declare no conflict of interest.

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