Observational Study

Medicine

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Pain management in surgical intensive care patients

A retrospective observational research

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Abstract

Sepsis and septic shock are the most common causes of death in non-cardiac surgical intensive care units (ICU). Adequate analgesia is essential to achieve positive outcomes. There were differences in pain management between patients with and without sepsis or septic shock. The release of inflammatory mediators, especially cytokines, in sepsis or septic shock decreases the pain threshold. Septic intensive care patients probably require higher doses of opioids than do non-septic patients. A retrospective observational study was carried out in an anesthesiologic intensive care unit from January 1, 2014 to June 30, 2016. Patients were divided into 4 groups according to the following criteria: sepsis ("yes/no" and communication ability "yes/no"). After adjusting for the number of cases using the pairing method, a total of 356 patients were recruited. The endpoint of our study was defined as the "total opioid dose". Statistical evaluations were performed using *t* tests and 2-factor analysis of variance. There was a significant difference in opioid doses between communicative and non-communicative ICU patients $F(1, 352) = 55.102$, $P < .001$). This effect was observed in the ICU patients with and without sepsis. The mean sufentanil dose was significantly higher in non-communicative patients than in communicative patients group ($E(1, 352) = 51.435$, $P < .001$, partial $\eta^2 = 0.144$). The effect of higher opioid- ($F(1, 352) = 1.941$, $P = .161$) and sufentanil ($F(1, 352) = 1.798$, $P = .342$) requirement was not statistically significant due to sepsis. The hypothesis that sepsis decreases the pain threshold could not be proven in this study. The effect of a higher opioid requirement is not directly caused by sepsis but by communication ability. Furthermore, we were able to show through our investigations and especially through the data of the pain recording instruments that the septic and non-septic intensive care patients receive sufficient pain therapy treatment in our ICU. Regular pain evaluations should be performed on patients in the ICUs who are able to communicate and those who are not.

Abbreviations: BPS = behavioral pain scale, Ca = communication ability, ICU = intensive care unit, NRS = numerical rating scale, SIRS = systemic inflammatory response syndrome.

Keywords: intensive care patients, opioids, pain management, pain threshold, sepsis

1. Introduction

Sepsis is a complex and severe condition. It is 1 of the most common causes of death in intensive care units.[1] The worldwide incidence of sepsis is approximately 19 million cases per year.[2] Even in high-income countries, the mortality rate is approximately 20% to 30%.[3,4] In Germany, almost 68,000 people died within 1 year of sepsis or as a result of septic shock.[5] According to the most recent studies, the mortality rate of sepsis in Germany was 27%. That of septic shock was 31%. In the case of septic shock, the 90-day mortality in Germany is 39%.[6]Thus, mortality in Germany has declined slightly in the recent years.[7–9] Sepsis is the third most common cause of death in the world. Both diagnosis and therapy are difficult to perform in clinical practice. Intensive care patients are often exposed to pain due to their illness and associated interventions. Sufficient analgesia is essential to achieve positive outcomes in intensive care unit (ICU) patients with sepsis or septic shock.[10,11] The pathogenesis of sepsis is complex and is a central component of sepsis research. This indicates that cytokines influence

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of the Faculty of Medicine of the Martin-Luther-University Halle-Wittenberg (approval number 2015-56.) Patients aged < 18 years were excluded from this study. The ethics committee of the Medical Faculty of Martin Luther University of Halle-Wittenberg works on the basis of German law and in accordance with the ICH-GCP guidelines (Good Clinical Practice). Therefore, the patient's consent was not required. This was because the retrospectively collected data were sufficiently anonymized as specified in the ICH-GCP guidelines. All methods were performed in accordance with ICH-GCP guidelines.

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nociception in sepsis.[12–14] Therefore, we hypothesized that ICU patients with sepsis would demonstrate a higher opioid requirement than non-septic patients. This may be an indirect indication of a lower pain threshold.

Opioids are a core component of analgesics for ICU patients. Internationally, there are certain differences in the preferences for individual substances.

Opioids are a group of substances that can be of natural origin (opiates) or are synthetically produced. Opioids can be classified according to their potency, duration of action, chemical properties, and receptor affinities. All opioids have a common effect on opioid receptors. A general distinction is made between μ-, δ-, and κ-receptor types, which mediate their individual effects via coupled G- proteins.[15–17] The specific mode of action of opioids is based on the interaction between their respective receptor types. Thus, the desired effects, such as analgesia, sedation, and anxiolysis, as well as undesirable side effects, such as respiratory depression, constipation, nausea, vomiting, and substance dependence, are observed.[18–20] Regarding the choice of opioids, the focus was on sufentanil, which is well established in intensive care.

Sufentanil is 1 of the synthetically produced opioids and the most potent opioid approved in Germany.[21] Sufentanil binds to both the μ- and the κ-receptor, but with a higher affinity to the μ-opioid receptor.[15,20,22] It is preferred in intensive care medicine because of its pronounced analgesia and sedation component, as well as its shorter context-sensitive half-life.[19] The classical and safest route of medication in intensive care patients is intravenous.

The aim of the present study was to assess pain management in patients receiving intensive care for sepsis and non-sepsis. This study focused on the total opioid dose in patients receiving intensive care. To check whether septic patients have a higher consumption of opioids than the non-septic patients, we calculated by a *T* test. A 2-factor analysis of variance was used to test whether sepsis and/or communication skills influence the mean opioid- and sufentanil dose.

Various studies have shown that sepsis influences the release of specific cytokines at the cellular level, which, in turn, affects nociception.[12,23,24] In their clinical trial, Goeij et al reported that an iatrogenic induced systemic infection influences the patient's pain threshold and causes it to drop.[25] Therefore, we hypothesized that ICU patients with sepsis or septic shock would require higher opioid doses than non-septic patients. This may be an indirect indication of a lower pain threshold. In addition, it should be investigated whether the regular use of the Behavioral Pain Scale (BPS) and Numerical Rating Scale (NRS) reflects sufficient pain therapy treatment in ICU patients.

2. Material and methods

This retrospective observational study was conducted in the anesthesiologic intensive care unit of University Hospital Halle (Saale). A total of 1995 patients were admitted to the intensive care unit during the study period from January 1, 2014 to June 30, 2016. A total of 638 patients from 1995 were recruited. Only patients with a minimum age of 18 years and a minimum length of stay of 3 calendar days were included in the study. This ensured that the patients were available for observation for exactly 24 hours on the second day after admission. They were divided into 4 different groups according to the criteria: Sepsis "yes/no" and communication ability (Ca) "yes/no".

The endpoint of our study was defined as the "total opioid dose". It included all parenteral opioids administered within 24 hours and was defined as a unit (mg/kg/24 hour). Individual opioid doses were divided by body weight and converted according to their respective morphine equivalent values.

To show the acuity of the disease, the Simplified Acute Physiology Score II was also determined in addition to the American Society of Anesthesiologistsclassification.

2.1. Inclusions

Sepsis criteria were developed using the surviving sepsis campaign of Dellinger et al (2013),[26] which was originally based on the Sepsis 2 definition.[27] This includes the systemic inflammatory response syndrome (SIRS) criteria for defining sepsis.[28] Patients diagnosed with sepsis, severe sepsis, or septic shock were included in the study. Patients who were unable to communicate were defined by the presence of disorders of consciousness (coma), neurological deficits, and mechanically controlled ventilation. Patients who needed ventilatory support by ventilation modes, such as non-invasive-ventilation continuous positive airway pressure, were recruited into the group that was able to communicate. Patients under additional sedation were included in this study.

2.2. Exclusions

Patients who experienced a change in consciousness during the 24-hour observation were excluded from the study. This included delirium, intubation, or extubation. These changes affect the status of the ability to communicate.

Patients who received ketamine or were supplemented with regional anesthesia, were excluded from the study. Further details are presented in Figure 1.

2.3. BPS and NRS

Pain intensity in the intensive care unit of the University Hospital Halle (Saale) was measured using BPS (Table 1) and NRS (Fig. 2). The BPS is used for pain assessment and objectification in patients who are unable to communicate. Thus, it is possible to assess the efficacy of pain therapy. This instrument contains 3 parameters, each of which is evaluated using a point system ranging from 1 to 4. A total value of a minimum of 3 and a maximum of 12 points was possible. The higher the total score, the greater is the pain experienced by the patient. The 3 parameters assess the facial expression, the upper extremity and additionally the adaptation to the ventilator.[29–31] For better illustration, the BPS is included in the Figure Legends as Figure 3. Statistical evaluation of the BPS values was performed descriptively. The NRS describes pain intensity on a scale of 0 to 10, with 0 representing no pain and 10 representing the worst pain. A descriptive statistical evaluation of the NRS values was performed. The results are shown in Figure 4.

The BPS and NRS were collected purely descriptively. They are intended to give an overview. No explorative calculation was made.

The NRS was used for awake, communicative patients, and BPS for non-communicative patients as is usual in everyday clinical practice.

The NRS was assessed by nursing every 2 to 4 hours. BPS was assessed every 6 hours. Table 2 presents the modal values and descriptive results of the study before matching. (Table 2)

2.4. Statistical analysis

To counteract a possible bias due to confounders and to ensure better comparability between the individual groups by adjusting the number of cases, the 4 groups were paired using the nearest neighbor method according to the following criteria: patient age, body size, severity of illness (American Society of Anesthesiologists classification), and degree of sedation (Richmond Agitation Sedation Scale). After the successful pairing

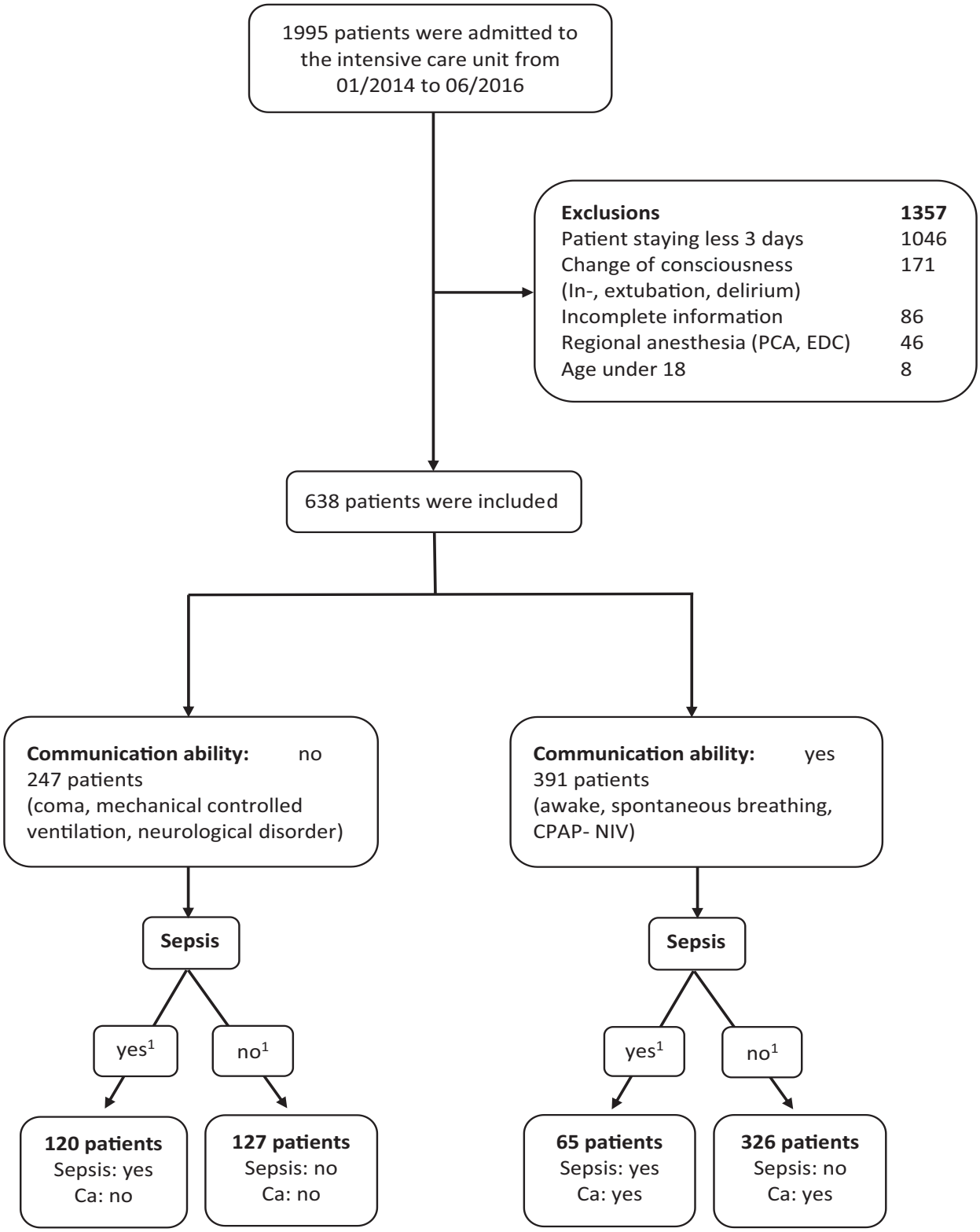

Figure 1. Flow chart of the study population.

of patient data using the statistical program "R", the number of cases decreased to 356. The data was not normally distributed. Therefore, a bootstrapping procedure was applied in each calculation, because the samples are sufficiently large enough.

The initial statistical evaluation was carried out using a t-test to determine whether septic intensive care patients received a higher opioid dose than non-septic patients did. Differentiation based on the ability to communicate was not initially performed. In further calculation by the 2-factorial analysis of variance, a differentiation of Ca was carried out. Statistical calculations were performed using SPSS from IBM.

Table 1

Behavioral pain scale.

	Description	Score
Facial expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

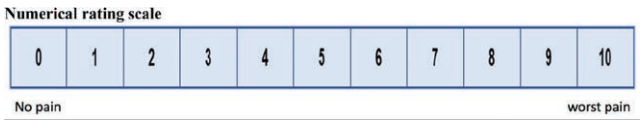

Figure 2. Numerical rating scale.

2.5. Limitations

Our study was limited by missing data on the use and dose of benzodiazepines and other sedatives such as propofol. In addition, no medication was documented in the data sets for NRS or BPS elevation, which resulted in pain reduction.

3. Results

3.1. Opioid doses

The initial calculation was performed without differentiation of the Ca. The descriptive data are shown in Table 3. Calculation of the opioid dose between septic and non-septic patients was performed using a *t* test. The results are presented in Figure 5 and Table 4. Initially, it could be shown that septic ICU patients received a significantly higher mean total opioid dose than non-septic patients by 0.726 mg/kg/24 hour, 95% Bca [−1.425; −0.002], $P = .045$. This was followed by differentiation according to Ca. All the data are summarized in Table 5. There were no major differences in the biometric data after matching (Table 5). The groups to be compared, sepsis "yes/no" and Ca "yes/no", are also almost homogeneous in terms of the number of cases. It became apparent that especially the opioids hydromorphone, piritramide and morphine were administered in a negligible dose.

The 2-factorial analysis of variance showed that the effect of higher opioid requirement was not statistically significant due to sepsis ($F(1, 352) = 1.941$ $P = .161$). The effect was based on the Ca factor, $F(1, 352) = 55.102$, $P < .001$, partial $\eta^2 = 0.144$). This effect was statistically significant (Table 6).

In addition, a review of individual analgesics showed that the sufentanil dose was significantly higher in the non-communicative group than in the communicative group ($E(1, 352) = 51.435$, $P < .001$, partial $\eta^2 = 0.144$) as the only analgesic. Sepsis had no significant effect on the sufentanil dose ($F(1, 352) = 1.798$, $P = .342$, partial $\eta^2 = 0.003$) (Table 6).

3.2. BPS and NRS survey

Table 2 shows the frequency of BPS and NRS use. This demonstrates that the frequency of the BPS survey differed between

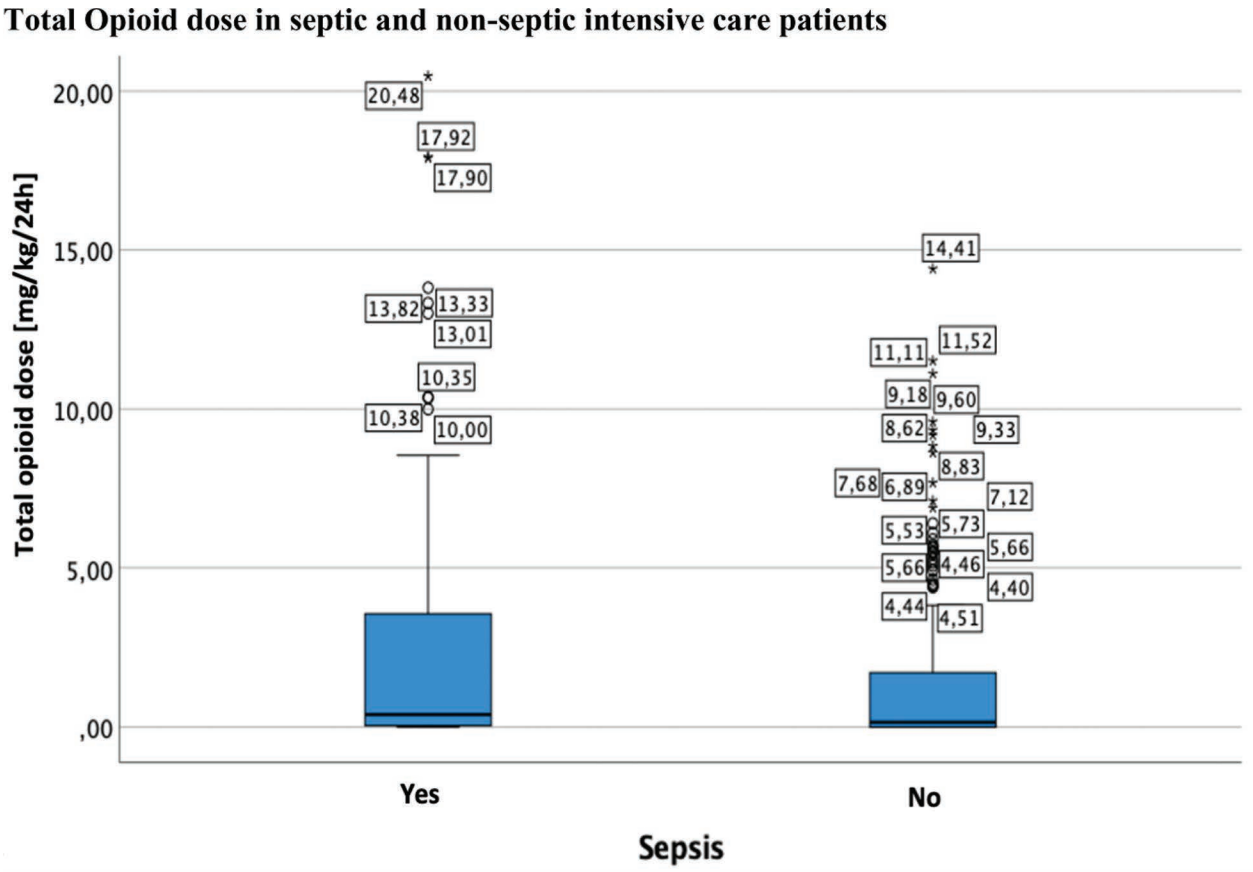

Figure 3. Opioid dose in septic and non-septic intensive care patients.

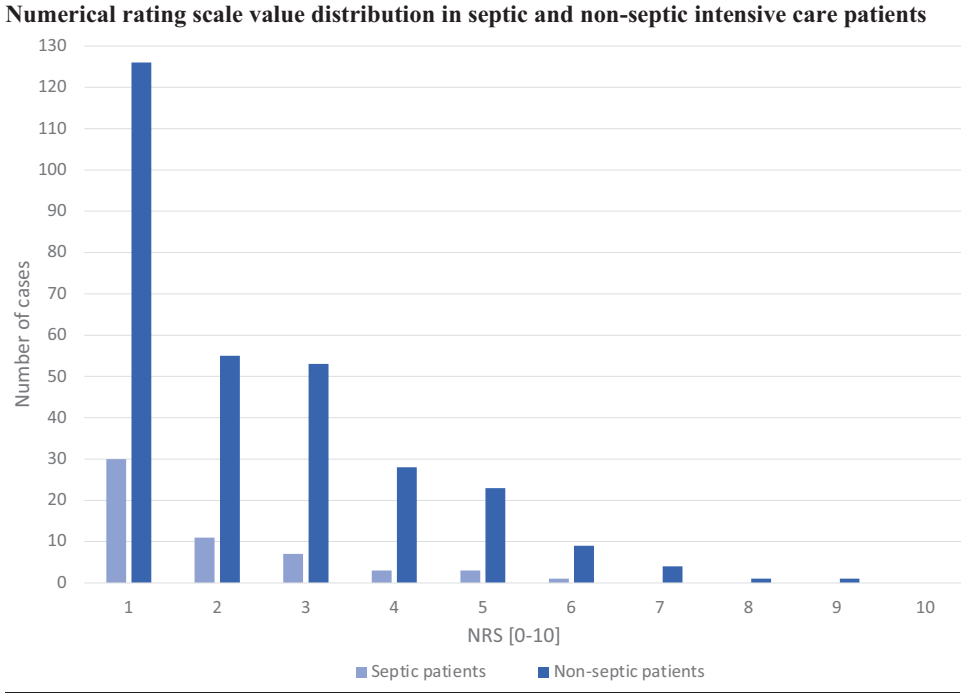

Figure 4. Numerical rating scale value distribution in septic and non-septic intensive care patients.

Table 2

Descriptive results of the study before matching.

	Communication ability			
	No		Yes	
	Sepsis		Sepsis	
n (%)	Yes 120 (19%)	No 127 (20%)	Yes 65 (10%)	No 326 (51%)
Age [yrs], M (SD)	65 (± 14,8)	65 (± 15,1)	68 (± 12,0)	67 (± 14,8)
Gender, female, n (%)	46 (38%)	42 (33%)	27 (42%)	129 (40%)
Weight [kg], M (SD)	84.5 (± 24.7)	86.8 (± 21.9)	78.3 (± 16.9)	78,3 (± 17.8)
Height [cm], M (SD)	173 (± 9.2)	173 (± 8.9)	170 (± 9.2)	171 (± 9.3)
BMI [kg/m^2], M (SD)	28.4 (± 8.6)	29.4 (± 7.4)	27.2 (± 5.6)	26.9 (± 6.0)
SAPS II, M (SD)	50.3 (± 14.6)	42.8 (± 11.8)	42.6 (± 13.7)	33.9 (± 12.1)
ASA [1 to 6], M (SD)	3.43 (± 0.56)	3.35 (± 0.67)	3.29 (± 0.58)	3.01 (± 0.54)
ASA [1 to 6], MV (min., max.)	3 (2 to 5)	3 (1 to 5)	3 (1 to 4)	3 (1 to 4)
RASS [–5 to 4], M (SD)	–3 (± 0.7)	- 3 (± 0.8)	0 (± 0.8)	0 (± 0.9)
RASS [–5 to 4], MV (min., max.)	–3 (–5 to 1)	–3 (–5 to 2)	0 (–3 to 1)	0 (–3 to 4)
Mechanical ventilation, n (%)	120 (100%)	124 (98%)	48 (74%)	198 (61%)
BPS [3 to 12], n (%)	58 (48%)	80 (63%)	20 (31%)	98 (30%)
BPS [3 to 12], MV (min., max.)	3 (3 to 5)	3 (3 to 7)	3 (3 to 5)	3 (3 to 6)
NRS [0 to 10], n (%)	4 (3%)	6 (5%)	55 (85%)	300 (92%)
NRS [0 to 10]], MV (min., max.)	0 (0 to 0)	0 (0 to 0)	0 (0 to 5)	0 (0 to 8)
Opioids [mg/kg/24 h], n (%)	120 (100%)	127 (100%)	65 (100%)	326 (100%)
M (SD)	3.62 (± 4.10)	2.84 (± 3.83)	0.56 (± 1.63)	0.30 (± 0.77)
Sufentanil [µg/kg/24 h], M (SD)	3.24 (± 0.45)	2.35 (± 3.81)	0.29 (± 0.19)	0.08 (± 0.39)
Hydromorphone [mg/kg/24 h], M (SD)	<0.01*	<0.01*	<0.01*	<0.01*
Piritramide [mg/kg/24 h], M (SD)	<0.01*	<0.01*	<0.01*	<0.01*
Morphine [mg/kg/24 h], M (SD)	<0.01*	<0.01*	<0.01*	<0.01*

* Displayed values are < 0.01 and are included for completeness.

ASA = ASA-classification (American Society of Anesthesiologists), BMI = body mass index, M = mean, max. = maximum, min. = minimum, MV = modal value, n = number of cases, NRS = numerical rating scale, RASS = Richmond agitation and sedation scale, SAPS = simplified acute physiology score, SD = standard deviation.

the septic and non-septic groups. The BPS was used in 63% of the non-septic ICU patients. In the septic patients, usable BPS were collected in 48% of all cases. In both groups, a modal value of 3 was chosen most frequently. The range of values in brackets differed minimally between the 2 groups. In non-septic patients, there was a discreetly widened spread of the BPS values (Table 2). It is noticeable that in the 2 columns of intensive care, patients who can communicate BPS values were also determined in the row of BPS frequencies. This is because the BPS was designed specifically for non-communicative patients.

To obtain a better overview of the distribution of the individual BPS values, Figure 5 was created.

Table 3

Descriptive results after matching without differentiation according to communication ability.

	Sepsis	
n (%)	**Yes 178 (50%)**	**No 178 (50%)**
Age [years], M (SD)	66 (± 14.0)	66 (± 14.3)
Gender, female, n (%)	73 (41%)	65 (36.5%)
Weight [kg], M (SD)	81.6 (± 22.0)	83.2 (± 21.1)
Height [cm], M (SD)	171 (± 9.4)	172 (± 9.4)
BMI [kg/m^2], M (SD)	27.7 (± 7.4)	28.1 (± 6.8)
ASA [1 to 6], M (SD)	3.38 (± 0.58)	3.35 (± 0.58)
RASS [−5 to 4], M (SD)	−2.13 (± 1.4)	−2.1 (± 1.5)
Opioids [mg/kg/24 h], n (%)	178 (100%)	178 (100%)
M (SD)	2.22 (± 3.63)	1.56 (± 3.10)
Sufentanil [µg/kg/24 h], M (SD)	2.08 (± 3.68)	1.41 (± 3.12)
Hydromorphone [mg/kg/24 h], M (SD)	<0.01*	<0.01*
Piritramide [mg/kg/24 h], M (SD)	<0.01*	<0.01*
Morphine [mg/kg/24 h], M (SD)	<0.01*	<0.01*

* Displayed values are < 0.01 and are included for completeness.

ASA = ASA-Classification (American Society of Anesthesiologists), BMI = body mass index, M = mean, n = number of cases, RASS = Richmond agitation and sedation scale, SD = standard deviation.

Figure 5 illustrates the value distribution of individual BPS data for non-communicative intensive care patients. A distinction was made between the septic and non-septic cases. Further scattering of the value distribution was recognizsable in patients without sepsis. Values from 3 to 7 were obtained for BPS. The sepsis group had values with a smaller spread of 3 to a maximum of 5.

NRS was documented in 85% of septic and communication patients. In the non-septic patients, it was documented in 92% (Table 2). In both groups, the modal value of zero was chosen most frequently. They differ in the dispersion of modal values. Patients without sepsis had a wider distribution of values than patients with sepsis. Figure 4 provides an overview of the individual values.

4. Discussion

Severe sepsis is the most common cause of death in non-cardiac and non-cardiac surgery intensive care units.[32] Adequate pain management can prevent the development of chronic pain and, above all, has a lasting impact on the quality of life even after discharge from the intensive care unit.[33]

Our results showed that septic ICU patients had a higher analgesic requirement than non-septic ICU patients did. This effect is consistent with the results of Goeij et al that septic patients may demonstrate a decreased severity threshold due to an increased need for opioids. In a study by Goeij et al, it was experimentally shown by quantitative sensory testing that intravenously injected endotoxin decreased the pain threshold compared to the control group. A limitation of the study by Goeij et al is that it was published before sepsis-3 definition. This is because the definition of sepsis in 2013 included, in a simplified form, 2 criteria SIRS and a proven infection.[34–36] Sepsis-3 definition describes sepsis as life-threatening organ dysfunction due to host dysregulation in response to infection.[28] Thus, SIRS is relegated to the background and is currently considered a separate entity. Goeij et al referreds to the clinical picture of SIRS, that is not explicitly related to sepsis. However, this clearly shows that the release of inflammatory mediators, especially cytokines decrease the pain threshold. Huang et al showed that in sepsis, there is also a pathophysiological increase in the release of inflammatory mediators and a cytokine storm at the cellular level.[13,23,37] These inflammatory mediators are partly identical to those reported by Goeij et al and the peripheral sensitization of nerve endings. This leads to a consecutive decrease in the stimulus threshold of the nociceptor, and thus, of the pain threshold.[38,39]

Sufentanil is the most commonly used opioid in non-communicative septic and non-septic ICU patients. We showed that the mean sufentanil dose was significantly higher in non-communicative ICU patients than in communicative ICU patients. This effect could be because sufentanil is used in intensive care both as an analgesic drug and as a sedative drug. The property of reduced context-sensitive half-life and the higher therapeutic breadth make sufentanil a preferred drug in the long-term ventilated and thus in non-communicative ICU patients.[20,40] In our study it was also evident that during the intensive care stay the opioids hydromorphone, piritramide and morphine were negligible in terms of frequency of use and dose. These data should be critically evaluated because zero values were included in the calculation of the opioid dose. Thus, the mean dose in each group was significantly reduced. Owing to the low average dose of the aforementioned opioids, further statistical evaluation was

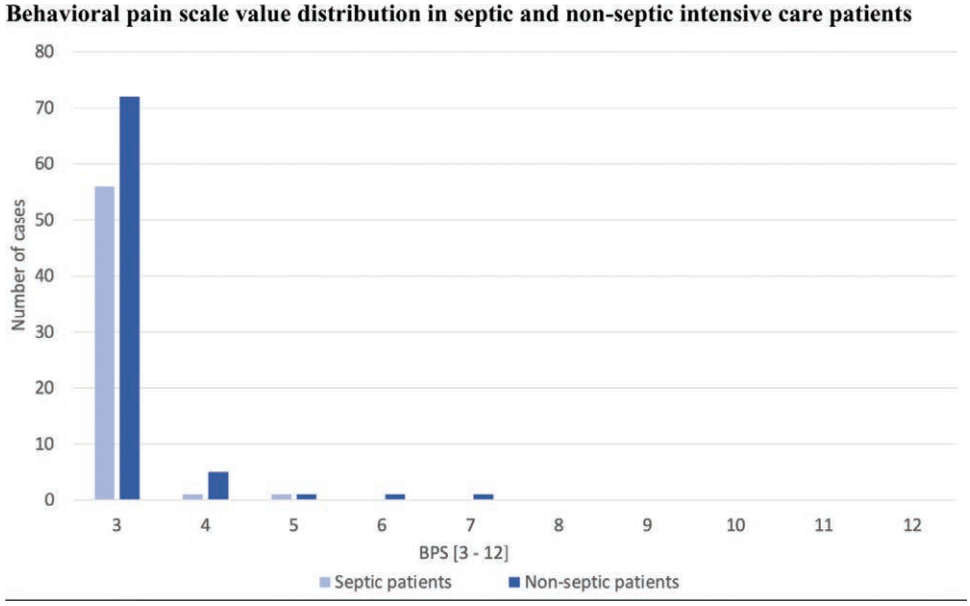

Figure 5. Behavioral pain scale value distribution in septic and non-septic intensive care patients.

Table 4

Results opioid dose in septic and non-septic patients after matching (t-test)[a].

							95% Confidence interval of difference	
		T	df	*P*-Value	Mean difference	Standard error of difference	Upper value	Lower value
Opioids [mg/kg/24 h]	Variances are equal	–1973	322	.045	–0.72611	0.36806	–1.45022	–0.00200
	Variances are not equal	–1973	297,432	.045	–0.72611	0.36806	–1.45045	–0.00177

[a]. Bootstrapped Welch-Test.

Table 5

Opioid dose requirement after matching and separation according to communication ability.

	Communication ability			
	No		Yes	
	Sepsis		Sepsis	
n (%)	Yes 117 (33%)	No 109 (31%)	Yes 61 (17%)	No 69 (19%)
Age [years], M (SD)	65 (± 14.8)	64 (± 14.9)	68 (± 11.9)	69 (± 13.8)
Gender, female, n (%)	46 (39%)	34 (31%)	27 (44%)	31 (45%)
Weight [kg], M (SD)	83.7 (± 24.1)	87.3 (± 21.2)	77.7 (± 16.7)	76.6 (± 19.1)
Height [cm], M (SD)	172 (± 9.1)	174 (± 8.5)	169 (± 9.4)	168 (± 9.6)
BMI [kg/m^2], M (SD)	28.1 (± 8.2)	28.8 (± 7.0)	27.0 (± 5.5)	27.0 (± 6.3)
SAPS II, M (SD)	50.3 (± 14.7)	42.4 (± 11.6)	42.7 (± 13.6)	34.2 (± 12.3)
ASA [1 to 6], M (SD)	3.43 (± 0.56)	3.36 (± 0.60)	3.30 (± 0.59)	3.33 (± 0.56)
ASA [1 to 6], MV (min., max.)	3 (2 to 5)	3 (1 to 5)	3 (1 to 4)	3 (1 to 4)
RASS [–5 to 4], M (SD)	– 3 (± 0.7)	– 3 (± 0.8)	0 (± 0.8)	0 (± 0.9)
RASS [–5 to 4], MV (min., max.)	–3 (–5 to 1)	–3 (–5 to 2)	0 (–3 to 1)	0 (–3 to 4)
Opioids [mg/kg/24 h], n (%)	117 (100%)	109 (100%)	61 (100%)	69 (100%)
M (SD)	3.18 (± 4.06)	2.47 (± 3.66)	0.38 (± 1.39)	0.18 (± 0.40)
Sufentanil [µg/kg/24 h], M (SD)	3.04 (± 0.38)	2.27 (± 3.74)	0.22 (± 0.18)	0.05 (± 0.38)
Hydromorphone [mg/kg/24 h], M (SD)	<0.01*	<0.01*	<0.01*	<0.01*
Piritramide [mg/kg/24 h], M (SD)	<0.01*	<0.01*	<0.01*	<0.01*
Morphine [mg/kg/24 h], M (SD)	<0.01*	<0.01*	<0.01*	<0.01*

* Displayed values are < 0.01 and are included for completeness.

ASA = ASA-classification (American Society of Anesthesiologists), BMI = body mass index, M = mean, max. = maximum, min. minimum, MV = modal value, n = number of cases, RASS = Richmond agitation and sedation scale, SAPS = simplified acute physiology score, SD = standard deviation.

Table 6

Results of opioid dose and sufentanil dose in septic and non-septic intensive care patients by 2-factorial analysis of variance.

Dependent variable	Opioids [mg/kg/24 h]		Opioids [mg/kg/24 h]			
Source	Sum of square	*df*	Mean square	Error	*P*-Value a	Partial $\eta 2$ [a]
Communication	545.698	1	545.698	55.102	<.001	0.144
Sepsis	19.224	1	19.224	1941	.161	0.006
Communication × Sepsis	4087	1	4087	0.415	.521	0.002
Error	3486.010	352	9903			
Total	5341.099	356				
Dependent variable	Sufentanil [µg/kg/24 h]		Sufentanil [µg/kg/24 h]			
Communication	524.909	1	524.909	51.435	<.001	0.114
Sepsis	18.352	1	18.352	1798	.342	0.003
Communication × Sepsis	7320	1	7320	0.717	.281	0.003
Error	3592.264	352	10.205			
Total	5242.895	356				

R-Square =.144 (corrected *R*-Quadrat =.137).

[a]. Determined from robust standard error using HC4-method.

not possible. Therefore, we could not prove the hypothesis of decreased pain threshold due to sepsis.

Further exploratory statistical evaluation according to the communication factor showed that the effect of the increased opioid dose was not due to sepsis, but rather to the communication factor. Sepsis had no direct effect on the total opioid dose when the communication factors were considered. This may be because sepsis is complex, severe, and not fully understood. Current studies are looking at a comprehensive pathophysiology, especially at the cellular level, to develop new therapeutic targets. In recent years, new biomarkers have been discovered that will, enable new therapeutic approaches in the future.

To ensure sufficient pain management in patients receiving intensive care for sepsis and non-sepsis, the establishment of pain assessment instruments is essential.

Our work also showed the successful implementation of BPS and NRS in non-communicative and communicative patients, respectively. The frequency of use was not 100% in all patients. Every patient received a value, but zero values were given, which were excluded from the descriptive analysis. When examining the individual distribution of values, an overall narrower distribution was apparent in patients with sepsis than in those non-septic ICU patients. This does not mean that septic cases have a lower pain intensity than non-septic cases. The BPS and NRS were only included for illustrative purposes and were statistically analyzed in a purely descriptive manner. In addition, the BPS survey must be carried out by a caregiver and not be actively determined by the patient. This could have led to subjective differences in

the collection of BPS values. Furthermore, clinical routines are subject to fluctuations among daily staff members. This can also lead to distortions in values. Overall, the modal values of the BPS reflect a very good pain therapy treatment for all intensive care patients who are unable to communicate. NRS also provides an overview of sufficient pain management in patients who can communicate.

5. Conclusion

Our study showed that there were differences in pain management between septic and non-septic intensive care patients in daily clinical practice. The initial calculation showed a higher opioid consumption in the septic group than in the non-septic group. There was a significant difference in opioid doses between the communicative and non-communicative ICU patients. The mean sufentanil dose was significantly higher in the non-communicative patients than in the communicative patients. The current body of evidence supports the hypothesis that sepsis affects the pain threshold. However, we were unable to prove this hypothesis in this retrospective study. This could be because our study was based on a retrospective design and only the dose of opioids was evaluated exploratively. Further prospective studies with specific analgesia in patients receiving septic intensive care should be conducted. In this study, we demonstrated that non-cardiac surgical intensive care patients at the University Hospital Halle (Saale) were treated sufficiently overall in terms of pain therapy. Pain-recording instruments have been successfully implemented.

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Author contributions

CMD helped manage patient data, helped with statistical evaluation, conducted background research, and wrote the manuscript. MB helped manage the patient data and write the manuscript. AMB helped write the manuscript. AC helped in writing the manuscript. LF helped write the manuscript. All the authors have read and approved the final manuscript.

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