

“Pain Management in Intensive Care Patients, a Retrospective Observational Research.”

Christoph Moritz Dinse (✉ C.Dinse@bgk-hamburg.de)

BG Klinikum Hamburg

Michael Bucher

University Hospital Halle (Saale)

Anna-Maria Burgdorff

Helios Kliniken Mansfeld-Südharz

Annett Christel

University Hospital Halle (Saale)

Lilit Flöther

University Hospital Halle (Saale)

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Abstract

Background

Sepsis and septic shock are the most common causes of death in non-cardiac surgery intensive care units. The treatment of sepsis is difficult. Adequate analgesia is essential for a positive outcome. There are differences in pain management between septic and non-septic patients. Septic ICU patients receive higher doses of opioids than non-septic ICU patients.

Methods

A retrospective observational study was carried out in an anesthesiological intensive care from 1.1.2014 to 30.6.2016. The cases were divided into four different groups according to the criteria: Sepsis "yes/no" and communication ability "yes/no". After adjusting the number of cases by pairing method, 356 cases were recruited. The endpoint of our study was defined as the "total opioid dose". A statistical evaluation was carried out by T-tests and two-factor variance analyses.

Results

There is a significant difference in opioid dose between communicative and non-communicative ICU patients. The mean sufentanil dose is significantly higher in the non-communicative patients than in the communicative patients. Sepsis has no significant effect on the dose of sufentanil.

Conclusion

The hypothesis that sepsis decreases the pain threshold could not be proven in this study. The effect of the higher opioid requirement is not directly caused by sepsis, but by the factor of 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.

Background

Sepsis is a complex and severe disease. It is one of the most common causes of death in intensive care medicine [1]. The worldwide incidence of sepsis is about 19 million in one year [2]. Even in high-income countries, the mortality rate is about 20%-30% [3, 4]. In Germany, almost 68,000 people died within one year from sepsis or as a result of septic shock [5]. The mortality rate in Germany of septic shock is between 38% and 59%[6]. According to the INSEP study, the ICU mortality rate is 44.3% [4, 7, 8]. This makes sepsis the third most common cause of death in this country. Both diagnosis and therapy are long and difficult in everyday clinical practice. Intensive care patients are often exposed to pain due to their

illness and the interventions associated with it. Sufficient analgesia is essential for a positive outcome for the septic ICU patients. Opioids are a core component of the analgesia concept in ICU patients. Internationally there are certain differences in the preference of individual substances.

Opioids are groups of substances that can be of natural origin (opiates) or synthetically produced. Opioids originate from opium, which is extracted from the opium poppy (*papaver somniferum*) [9, 10]. Opioids can be classified according to different categories such as potency, duration of action, chemical properties, and receptor affinity. All opioids have in common their effect on the opioid receptors. A general distinction is made between μ -, δ - and κ -receptor types, which mediate their individual effects via coupled G-proteins [11–13]. The specific mode of action of opioids is based on the interaction of the respective receptor type. Thus, both the desired effects such as analgesia, sedation and anxiolysis and the undesired side effects such as respiratory depression, constipation, nausea, vomiting and substance dependence are achieved [14–16]. Regarding the choice of opioids, the focus was placed on sufentanil, which is well established in intensive care medicine.

Sufentanil is one of the synthetically produced opioids and is the most potent opioid approved in Germany [17]. Sufentanil binds to both the μ - and the κ -receptor, but with a higher affinity to the μ -opioid receptor [11, 16, 18]. It is preferred in intensive care medicine because of its pronounced analgesia and sedation component, as well as its shorter context-sensitive half-life [15]. The classical and safest route of medication in intensive care patients is intravenous.

Pain intensity in the intensive care unit of the University Hospital Halle (Saale) is measured by using the Behavioral Pain Scale (BPS). The BPS is an instrument for pain assessment and objectification in patients who are unable to communicate. Hereby, it is possible to obtain an assessment of the sufficiency of pain therapy treatment. This instrument contains three parameters, each of them is evaluated with a point system from 1 to 4. A total value of a minimum of 3 and a maximum of 12 points is possible. The higher the total, the more pain the patient has. The 3 parameters assess the facial expression, the upper extremity and additionally the adaptation to the ventilator [19–21]. For better illustration, the BPS is included in the Figure Legends as Figure 2. A statistical evaluation of the BPS values was carried out purely descriptively.

The aim of the present study is to assess the pain management in septic and non-septic intensive care patients. The focus was placed on the total opioid dose of intensive care patients. Various studies show that sepsis influences the release of specific cytokines at the cellular level, which affects nociception [22–24]. In their clinical trial, *Goeij et al* describe that an iatrogenic induced systemic infection has an influence on the patient's pain threshold and causes it to drop [25]. Therefore, we generated the hypothesis that septic ICU patients demonstrate a higher opioid requirement than non-septic patients. This may be an indirect indication of the presence of a lowered pain threshold. In addition, it should be investigated whether the regular use of BPS reflects sufficient pain therapy treatment in ICU patients.

Methods

A retrospective observational study was carried out in the anesthesiological intensive care unit of the University Hospital Halle (Saale). During the study period from 1.1.2014 to 30.6.2016 638 cases out of 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 their admission. They were divided into four different groups according to the criteria: Sepsis "yes/no" and communication ability "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 with the unit (mg/kg/24h). The individual opioid doses were already divided by the individual bodyweight and converted according to the respective morphine equivalent value.

To counteract a possible bias due to confounders and to ensure better comparability between the individual groups by adjusting the number of cases the four groups were paired by the nearest neighbour method according to the following criteria: Patient age, body size, severity of illness (ASA classification) and degree of sedation (RASS). After successful pairing of the patient data by the statistical program "R", the number of cases decreased to 356. A statistical evaluation was then carried out by T-tests and two-factor variance analyses by the program SPSS from IBM.

Results

Opioids:

After matching, all data were summarized descriptively in a summary table for a better overview (Table 1). Table 1 shows that there are no major differences in the biometric data after matching. The groups to be compared, sepsis "yes/no" and communication ability "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.

Table 1
Opioid dose requirement after successful matching

n (%)	Communication ability			
	no		yes	
	Sepsis		Sepsis	
	yes	no	yes	no
	117 (33%)	109 (31%)	61 (17%)	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)
ASA [1–6], M (SD)	3,43 (± 0,56)	3,36 (± 0,60)	3,30 (± 0,59)	3,33 (± 0,56)
ASA [1–6], MV (min., max.)	3 (2 – 5)	3 (1 – 5)	3 (1 – 4)	3 (1 – 4)
RASS [-5 – 4], M (SD)	-3 (± 0,7)	-3 (± 0,8)	0 (± 0,8)	0 (± 0,9)
RASS [-5 – 4], MV (min., max.)	-3 (-5 – 1)	-3 (-5 – 2)	0 (-3 – 1)	0 (-3 – 4)
Opioids [mg/kg/24h], 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/24h], M (SD)	3,04 (± 0,38)	2,27 (± 3,74)	0,22 (± 0,18)	0,05 (± 0,38)
Hydromorphone [mg/kg/24h], M (SD)	<0,01*	<0,01*	<0,01*	<0,01*
Piritramide [mg/kg/24h], M (SD)	<0,01*	<0,01*	<0,01*	<0,01*
Morphine [mg/kg/24h], M (SD)	<0,01*	<0,01*	<0,01*	<0,01*

* Displayed values are <0,01 and are included for completeness.

M mean, MV modal value, n number of cases, min. minimum, max. maximum, SD standard deviation, BMI Body Mass Index, RASS Richmond Agitation and Sedation Scale, ASA ASA-Classification (American Society of Anesthesiologists)

Initially, it could be shown that septic ICU patients receive a significantly higher mean total opioid dose than non-septic patients by 0.726mg/kg/24h, 95%Bca [-1.425; -0.045], p= 0.045 (Figure 1).

The additional differentiation according to communication ability showed that the effect of the higher opioid requirement was not statistically significant due to sepsis (F(1, 352) = 1.941 p= 0.161). The effect is based on the factor of communication ability F(1, 352) = 55.102, p < 0.001, partial η^2 = 0.144). And this with a high effect size (Table 2).

Table 2
Results of the two-factorial analysis of variance

Dependent variable	Opioids [mg/kg/24h]		Opioids [mg/kg/24h]			
Source	Sum of square	df	Mean square	Err	P-Value ^a	Partial η^2 ^a
Communication	545,698	1	545,698	55,102	<0,001	0,144
Sepsis	19,224	1	19,224	1,941	0,161	0,006
Communication * Sepsis	4,087	1	4,087	0,415	0,521	0,002
Error	3486,010	352	9,903			
Total	5341,099	356				
R-Square = ,144 (corrected R-Quadrat = ,137);						
a. Determined from robust standard error using HC4-method.						

In addition, a review of the individual analgesics showed that the sufentanil dose was statistically significantly higher in the non-communicative groups compared to the communicative groups ($F(1, 352) = 51.435, p < 0.001, \text{partial } \eta^2 = 0.144$) as the only analgesic (Table 2). Sepsis had no significant effect on the dose of sufentanil ($F(1, 352) = 1.798, p = 0.342, \text{partial } \eta^2 = 0.003$).

BPS Survey:

Table 3 additionally shows the frequencies of the BPS usage. It demonstrates the frequencies of the BPS survey differ between the septic and non-septic groups. The BPS was used in 73% of the non-septic ICU patients. In the septic patients, usable BPS was collected in 50% of all cases. In both cohorts, the most collected value, i.e., the modal value (MV), is the lowest value of the BPS 3. The range of values in the brackets differs only minimally between the two groups. In non-septic patients, there is a discreetly widened spread of BPS values (Table 3).

Table 3
Overview of BPS usage

n (%)	Communication ability			
	no		yes	
	Sepsis		Sepsis	
	yes	no	yes	no
	117 (33%)	109 (31%)	61 (17%)	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)
BPS [3–12], n (%)	58 (50%)	80 (73%)	2 (3%)	3 (4%)
BPS [3–12], M (SD)	3 (3 - 5)	3 (3 - 7)	3 (3 - 5)	3 (3 - 6)
Opioids [mg/kg/24h], 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/24h], M (SD)	3,04 (± 0,38)	2,27 (± 3,74)	0,22 (± 0,18)	0,05 (± 0,38)
Hydromorphone [mg/kg/24h], M (SD)	<0,01*	<0,01*	<0,01*	<0,01*
Piritramide [mg/kg/24h], M (SD)	<0,01*	<0,01*	<0,01*	<0,01*
Morphine [mg/kg/24h], M (SD)	<0,01*	<0,01*	<0,01*	<0,01*
* Displayed values are <0,01 and are included for completeness.				
M mean, MV modal value, n number of cases, min. minimum, max. maximum, SD standard deviation, BMI Body Mass Index, BPS behavioral pain scale, RASS Richmond Agitation and Sedation Scale, ASA ASA-Classification (American Society of Anesthesiologists)				

Table 4
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

It is noticeable that in the two 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 get a better overview of the distribution of the individual BPS values, Figure 2 was created.

Figure 2 illustrates the value distribution of the individual BPS data of the non-communicative intensive care patients. A distinction is made between septic and non-septic cases. A further scattering of the value distribution is recognisable in the non-sepsis patients. Values from 3 to 7 are achieved on the BPS. The septic group shows values with a smaller spread of 3 to a maximum of 5.

Discussion

Severe sepsis is the most common cause of death in non-cardiac and non-cardiac surgery intensive care units [26]. 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 intensive care unit [27].

Our results show that the septic ICU patients have a higher analgesic requirement than the non-septic ICU patients. This effect is consistent with the study by *Goeij et. al* that the septic patients may demonstrate a decreased severity threshold due to an increased need for opioids. In the study by *Goeij et al*, it was experimentally shown by quantitative sensory testing that intravenously injected endotoxin decreased

pain threshold compared to the control group. A limitation of the study by *Goeij et al.* is that it was published before the sepsis-3 definition. This is because the definition of sepsis in 2013 included, in simplified form, two criteria of a systemic inflammatory response syndrome (SIRS) plus a proven infection [28–30]. The current Sepsis-3 definition describes sepsis as a life-threatening organ dysfunction due to host dysregulation in response to infection [31]. SIRS is thus relegated to the background and is currently counted as a separate entity. The study by *Goeij et al.* refers to the clinical picture of SIRS and not explicitly to sepsis. But it clearly shows that the release of inflammatory mediators and especially cytokines have a decreasing effect on the pain threshold. *Huang et al.* show that in sepsis there is also a pathophysiological increase in the release of inflammatory mediators and a so-called cytokine storm at the cellular level [22, 32, 33]. These inflammatory mediators are partly identical to those from *Goeij et al.* and cause a so-called peripheral sensitization of the nerve endings. This leads to a consecutive lowering of the stimulus threshold of the nociceptor and thus of the pain threshold [34, 35].

Sufentanil is the most used opioid in non-communicative septic and non-septic ICU patients. We could show that the mean sufentanil dose was significantly higher in the non-communicative ICU patients than in the 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 [16, 36]. 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 average dose of the respective group was significantly reduced. Due to the low average dose of the above-mentioned opioids, a further statistical evaluation was not possible. Therefore, we cannot prove the hypothesis of a decreasing pain threshold due to sepsis.

Further exploratory statistical evaluation according to the communication factor shows that the effect of the increased opioid dose is not due to the sepsis, but rather to the communication factor. Sepsis has no direct effect on the dose of total opioids once the communication factor is considered. This may be because sepsis is a complex, severe and still not fully understood condition. Current studies are looking at the comprehensive pathophysiology, especially at the cellular level, to develop new therapeutic targets. New biomarkers have been discovered in recent years that could enable new therapeutic approaches in the future.

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

Our work also shows the successful implementation of BPS in non-communicative patients. The frequency of use is not 100% of all patients. Every patient received a value, but values with zero were given, which were excluded in the descriptive analysis. When examining the individual distribution of values, overall narrower distribution of values was apparent in the septic than in the non-septic ICU patients. This does not mean that the septic cases have a lower pain intensity than the non-septic cases.

BPS was only included for illustrative purposes and statistically analyzed in a purely descriptive manner. In addition, the survey of BPS must be carried out by a caregiver and is not actively determined by the patient himself. This could lead to subjective differences in the collection of BPS values. Furthermore, the clinical routine is subject to daily staff fluctuations. This fact could also lead to distortions in the values. Overall, the modal values of the BPS reflect a very good pain therapy treatment of all intensive care patients who are unable to communicate.

Conclusion

We were able to show through our study that there are differences in pain management between septic and non-septic intensive care patients in everyday clinical practice. The initial calculation could show higher consumption of opioids in the septic compared to the non-septic patients. There is a significant difference in opioid dose between communicative and non-communicative ICU patients. The mean sufentanil dose is significantly higher in the non-communicative patients than in the communicative patients. The current body of evidence supports the hypothesis that sepsis has an impact on the pain threshold. We could not prove this hypothesis by our retrospective study. This could be due to the fact that our study was based on a retrospective design and only the dose of opioids was evaluated exploratively. Further prospective studies with the question of specific analgesia in septic intensive care patients should be conducted. We demonstrated in our work that the cardiac and non-cardiac surgery intensive care patients of the University Hospital Halle (Saale) are treated sufficiently overall in terms of pain therapy. There is a successful implementation of pain recording instruments for patients who are unable to communicate.

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BPS	Behavioral Pain Scale
ICU	Intensive Care Unit
INSEP	Incidence of severe sepsis and septic shock in German intensive care units
M	Mean
max.	Maximum
min.	Minimum
MV	Modal value

n	Number of cases
RASS	Richmond Agitation Sedation Scale
SD	Standard deviation

Declarations

Ethics approval and consent to participate: This study was approved by the ethics committee of the Faculty of Medicine of the Martin-Luther-University Halle-Wittenberg, with approval number 2015-56. Patients under 18 years of age were excluded from the study. The ethics committee of the Medical Faculty of the 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 consent was not necessary. Because the retrospectively collected data were sufficiently anonymised as specified in the ICH-GCP guidelines. All methods were carried out in accordance with the ICH-GCP Guidelines.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated and analysed during the current study are not publicly available due to data protection but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: CMD helped manage the patient data, helped statistical evaluation, conduct the background research and write the manuscript. MB helped manage the patient data and helped write the manuscript. AMB helped write the manuscript. AC helped write the manuscript. LF helped write the manuscript. All authors read and approved the final manuscript.

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Figures

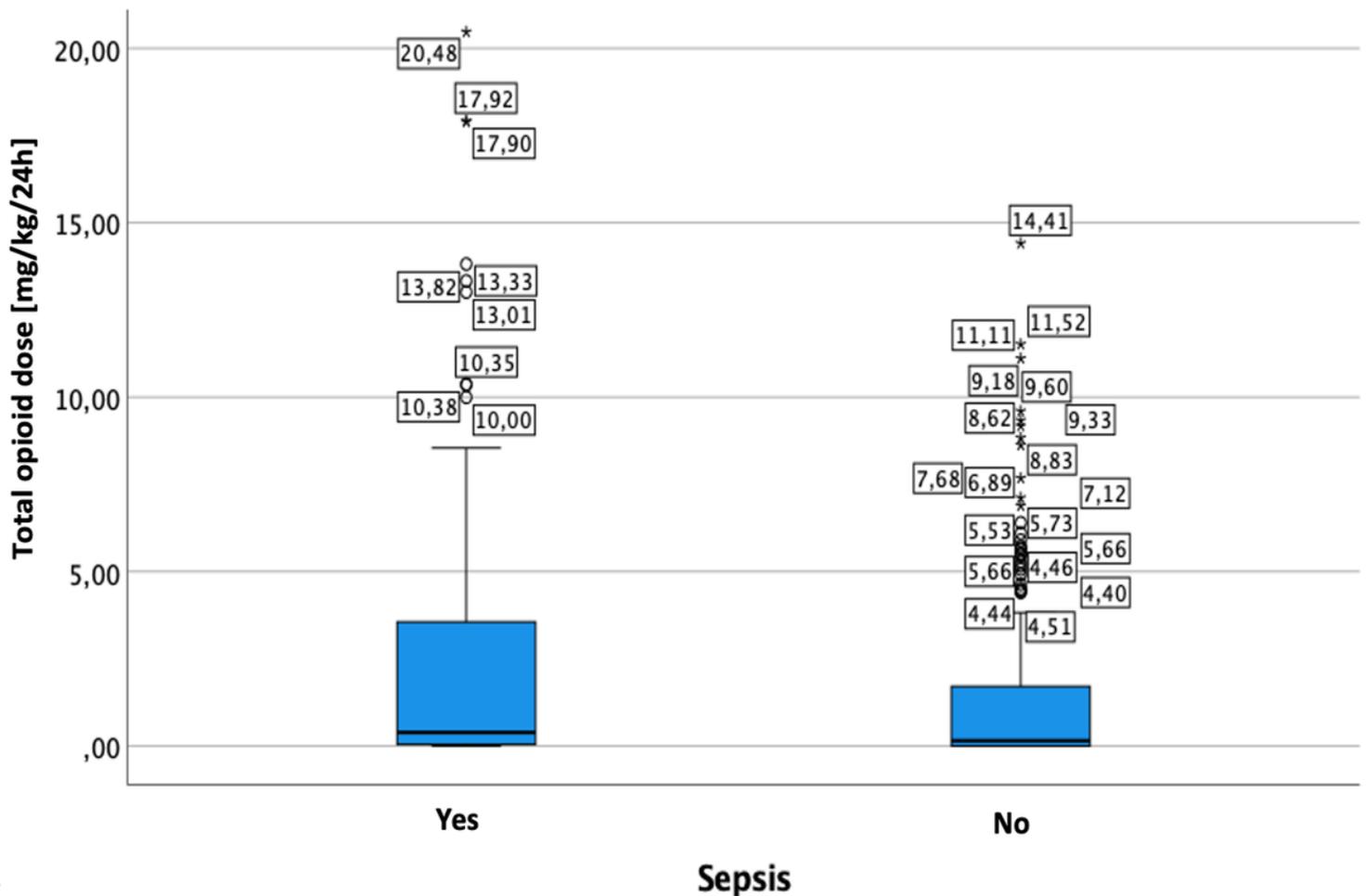


Figure 1

Opioid dose in septic and non-septic intensive care patients

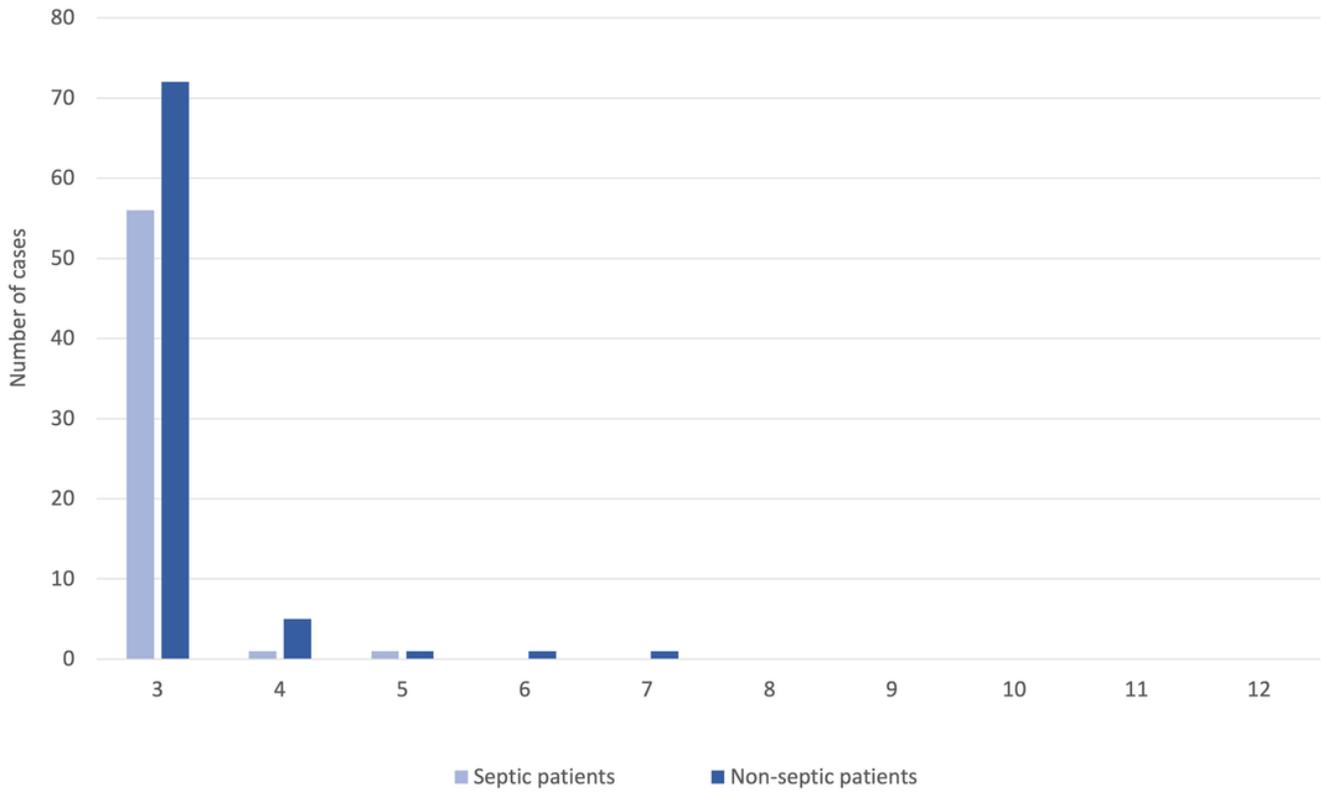


Figure 2

BPS value distribution in septic and non-septic intensive care patients