Association of opioid analgesics and sedation with inflammatory markers in critically ill patients: a retrospective descriptive exploratory study

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SUMMARY

- Medical care of critically ill patients is complex and resource intensive. Systemic inflammation is a usual problem among critically ill patients; however, the effects of common medications on inflammation has not been adequately studied.
- Aim: To explore associations between sedation and opioid analgesics with common inflammatory markers in critically ill patients treated in intensive care units (ICU).
- Methods: This is a retrospective descriptive correlational study. The study was conducted at the ICU of the biggest Cyprus general hospital and involved all patients hospitalized during the year 2013. Purposive sampling was used. Collection of data was carried out through the ICU electronic data.
- Results: There is no apparent association of opiate analgesics and suppressants with the CRP.
- Conclusion: There was no significant association between the use of opiate analgesics and sedatives and inflammatory indicators. There is a need for further research to investigate potential associations between pharmacotherapy and inflammatory markers in critically ill patients giving emphasis on confounding variables, such as patients' clinical characteristics and severity.

INTRODUCTION

Critically ill patients are those who are at high risk of actual or potential health problems that are considered life-threatening. Analgesia and sedation are integral components of the care of critically ill patients, as pain and agitation can lead to a number of side effects (Barr et al., 2013). Barr et al. (2013), recommend that the necessary central nervous system suppressants (sedatives) be administered in small doses, unless clinically contraindicated. The most commonly used opioid analgesics administered to critically ill patients, treated in intensive care units (ICUs), are fentanyl, remifentanyl and morphine, while sedatives include Propofol and midazolam, which are known to have a potential anti-Inflammatory effect and antioxidant activity (Kang 1998; Chen et al., 2005; Kim et al. 2006). In addition, Nelson (1997) and Salo (2001), report that morphine has a great effect on the immune response, during anaesthesia and surgery, including sedation and analgesia.

Propofol, in small dosages, can reduce the inflammatory response (Ma et al., 2010). The cytoprotective and immunosuppressive effects of propofol are a result of the reduction of nitric oxide biosynthesis to lipopolysaccharide (LPS) which activates macrophages (Chen et al., 2003). Propofol contains an additional 12 mg/ml of phospholipids, which C-reactive protein (CRP), has the ability to bind to, possibly presenting a falsely reduced value of the CRP, and, thus, concealing a possible inflammatory response.

CRP is an acute phase protein and is synthesized by hepatocytes in response to proinflammatory cytokines, in particular interleukin-6. (Shrivastava, 2015). It is one of the common test parameters used in clinical practice, to assess, diagnose, and prognosticate inflammation. However, the role of CRP in physiological processes is not clearly elucidated. CRP belongs to the pentraxin family of proteins and it increases in concentration during injury, inflammation or tissue death (Pepys and Hirschfield, 2003).

Despite its common clinical use, few studies have examined CRP levels as a biomarker of infection in critically ill patients, and the results have not been consistent (Sapin, 2017). Apart from CRP, other clinical inflammatory indicators are white blood cells (WBC) and their sub-populations, which play an important role in the assessment, diagnosis, and prognosis of inflammation in critically ill patients.

Through an extensive literature review, we were not able to identify any other study addressing correlations of analgesia and sedation with CRP and white blood cells, in critically ill patients. However, the concentration of Interleukin 6 (IL-6), which is also a key mediator of the patient's acute phase and the need for postoperative ventilation have been positively correlated with CRP (Ni Choileain & Redmond, 2006). Furthermore, in a randomized control trial, Vuori et al. (2004) compared the administration of three different kinds of analgesia (diclofenac, oxycodone (opioid), bupivacaine + fentanyl) and showed that a statistically significant difference in lymphocyte and C- reactive protein values existed in the group receiving opiates. Leucocytosis was of shorter duration in the opioid group than in the non-steroidal anti-inflammatory drug (NSAID) or epidural groups, and phytohemagglutinin (PHA)-induced lymphocyte proliferative responses were decreased in the opioid group, whereas the response was increased in the NSAID and epidural groups. In addition, from the 1st postoperative day and during the postoperative period, a decrease in lymphocyte values and an increase in CRP values was observed, in the opiates group.

Literature reports that the additional phospholipids contained in Propofol enhance the binding ability of CRP, and lead to a falsely

reduced CRP value that result in the concealment of a possible inflammatory reaction (Ma et al., 2010). If this occurs, there is a possibility of misguiding treatment that may lead to a worsening of patients' condition as well as to prolongation of their illness. Additionally, there is little information in the literature regarding research results associating with the above hypothesis.

Purpose and specific objectives

The purpose of the current study was to explore potential associations between dose of sedation and opioid analgesics with CRP levels and WBC counts in critically ill patients.

The specific objectives included:

- Investigation of the levels of inflammatory markers during the two-day-stay of critically ill patients in ICU
- Exploration of the association of the most widely used opioid analgesics and sedatives, CRP levels and WBC counts, and clinical characteristics (age, temperature).
- Exploration of the association between inflammatory biomarkers and patients' outcome (length of stay, length of mechanical ventilation).
- Comparisons of sedation and analgesia dosage and inflammatory biomarkers in patients who survived versus those who did not.

Ethics

The study was approved by the Cyprus University of Technology Ethics Committee and the Ministry of Health Ethics Committee according to the National law and conformed with the principles of the Declaration of Helsinki (World Medical Association, 2014).

METHODS

Study Design

We used a retrospective descriptive correlational design. This specific study design was chosen to explore correlations that occurred at a given period of time in the past.

Data collection

Sampling was purposeful and involved all patients admitted to the ICU of an academic general hospital in Nicosia, with capacity of 17 beds, during the year of 2013. Data collection was made retrospectively through the electronic hospital information system. The population of patients admitted during the selected period amounted to 807 people.

Participants

Eligibility criteria were: Age > 18 years, length of ICU stay > 48 hours, patients with duration of mechanical ventilation > 48 hours, patients who received analgesia and sedation for more than 48 hours, patients with initiation of analgesia, sedation, and mechanical ventilation in the first 6 hours after admission. Patients were excluded if they were re-admitted in the ICU and if they were immunosuppressed. These eligibility criteria were used to capture a sample of more severely ill patients, who would be more likely to experience systemic inflammation.

Sample size

Sample size calculation was performed by the G Power analysis software. A sample size of 160 patients was sufficient to identify an effect size of d = 7 (standardized mean differences) with a statistical power of 70%, at a 0.005 alpha level.

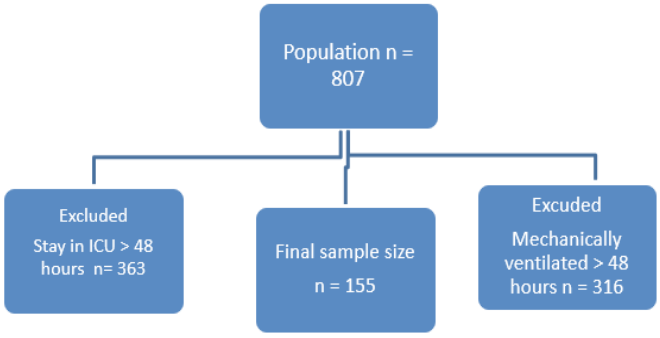

Figure 1. Flow diagram: sample size selection

Sample selection

The selection of the sample is shown in figure 1. Specifically, the number of critically ill patients admitted to the ICU, during the year 2013, was 807. Only 363 patients met the inclusion criterion regarding the duration of stay in ICU > 48 hours, of which only 316 patients had a duration of sedation > 48 hours. The final sample size according to the inclusion criteria was 155.

Data Identification

Data were collected during the first 2 days of patients' admission, since, according to WHO (2015), a patient may contract a nosocomial infection after 48 hours of stay in hospital. Data obtained from the electronic file were:

- Demographics (gender, age, weight)
- Patient's clinical outcome (mortality, length of ICU stay, Days of mechanical ventilation)
- Highest temperatures recorded during the first and the second day of admission
- Type of sedation
- The average daily dose of sedation, adjusted to mg/kg/h for the two days of follow-up.
- Type of Analgesia
- The average daily dose of analgesia, adjusted to mg/kg/h for the two days of follow-up
- Levels of CRP during the three measurements on admission and at the end of the first and the second day
- WBC counts on admission, at the end of the first and second day and from beginning of the sedation and the given analgesia.

Data analysis

Variable values are expressed as means and standard deviation (SD). Descriptive statistics were used to show the mean dose of medications, in the first two days of hospitalization. The normality of variable distributions was assessed by the Kolmogorov Smirnov criterion. To explore correlations between medication dosage and clinical markers we used Spearman Correlation Coefficient. Patients who survived and patients who died were compared by Student's t-test. Change over time was assessed by Wilks λ criterion.

RESULTS

Patient characteristics

Overall, 155 patients with a mean age 53.6 years (SD 19.2) and

			Propofol		Midazolam		Fentanyl		Remifentanyl		Morphine equanalgesic dose		Temperature		Days ventilated	Duration of nursing care	Age
			Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2			
CRP	Day 1	r	0.07		-0.011		0.03		-0.049		0.036		0.406		0.044	-0.077	0.03
		p	0.521		0.958		0.794		0.873		0.738		0		0.671	0.454	0.772
		N	86		26		78		13		91		97		97	97	97
	Day 2	r		-0.062		-0.385		-0.018		0.406		0.142		0.121	-0.039	-0.142	-0.15
		p		0.559		0.039		0.885		0.068		0.186		0.246	0.705	0.17	0.148
		N		90		29		70		21		88		94	95	95	95
WBC day 1 of medicine administration (ref 3.91-8.77)		r	0.031		-0.089		-0.048		0.31		0.02		0.213		0.094	0.097	-0.167
		p	0.718		0.596		0.622		0.15		0.819		0.009		0.257	0.244	0.043
		N	134		38		108		23		132		147		147	147	147
Neutrophils (ref 40.3-74.8%)		r	-0.01		0.001		-0.08		-0.066		-0.068		-0.214		-0.065	-0.081	0.033
		p	0.905		0.994		0.41		0.766		0.438		0.009		0.436	0.329	0.693
		N	134		38		108		23		132		147		147	147	147
Lymphocytes (ref 12.2-47.1%)		r	0.032		0.06		0.177		-0.063		0.118		0.203		0.095	0.108	-0.037
		p	0.713		0.72		0.067		0.774		0.179		0.013		0.254	0.191	0.659
		N	134		38		108		23		132		147		147	147	147
Monocytes (ref 4.4-12.3%)		r	-0.066		-0.1		-0.053		0.147		-0.032		0.121		0.034	0.04	-0.015
		p	0.447		0.55		0.587		0.502		0.717		0.145		0.687	0.627	0.857
		N	134		38		108		23		132		147		147	147	147
Eosinophils (ref 0-4.4%)		r	0.079		-0.043		0.066		0.501		0.116		0.095		0	0.036	0.053
		p	0.363		0.797		0.499		0.015		0.186		0.251		0.996	0.665	0.525
		N	134		38		108		23		132		147		147	147	147
Basophils (ref 0 -0.7%)		r	0.125		-0.062		0.193		0.15		0.161		0.096		0.105	0.063	0.125
		p	0.152		0.71		0.045		0.495		0.065		0.246		0.207	0.447	0.131
		N	134		38		108		23		132		147		147	147	147
WBC day 2 of medicine administration (ref 3.91-8.77)		r		0		-0.002		0.049		0.035		0.069	0.164	0.015	0.154	0.118	0.007
		p		0.996		0.986		0.605		0.855		0.421	0.042	0.859	0.057	0.146	0.936
		N		140		50		113		29		139	154	151	154	154	154
Neutrophils (ref 40.3-74.8%)		r		-0.07		-0.093		-0.022		0.147		0.07	-0.065	-0.264	0.01	0.013	0.133
		p		0.412		0.519		0.815		0.448		0.415	0.421	0.001	0.898	0.87	0.099
		N		140		50		113		29		139	154	151	154	154	154
Lymphocytes (ref 12.2-47.1%)		r		0.04		0.007		0.045		-0.109		-0.054	0.08	0.234	-0.03	-0.034	-0.197
		p		0.637		0.964		0.633		0.574		0.529	0.322	0.004	0.708	0.674	0.014
		N		140		50		113		29		139	154	151	154	154	154
Monocytes (Ref 4.4%-12.3%)		r		0.03		0.108		-0.057		-0.154		-0.075	0.01	0.225	0.05	0.066	0.027
		p		0.721		0.455		0.545		0.426		0.379	0.902	0.005	0.541	0.415	0.738
		N		140		50		113		29		139	154	151	154	154	154
Eosinophils (ref 0-4.4%)		r		0.175		0.216		0.194		-0.123		0.045	0.006	0.019	0.032	0.025	-0.268
		p		0.038		0.132		0.039		0.525		0.601	0.941	0.815	0.694	0.756	0.001
		N		140		50		113		29		139	154	151	154	154	154
Basophils (ref 0-0.7%)		r		0.087		0.135		0.073		0.07		0.066	0.065	0.177	0.04	0.026	-0.17
		p		0.307		0.351		0.443		0.718		0.437	0.424	0.03	0.625	0.753	0.035
		N		140		50		113		29		139	154	151	154	154	154

Table 1: Association between inflammatory biomarkers and opioid analgesics and sedatives. N = number, P = significance, r = Spearman correlation coefficient, WBC = white blood cells.

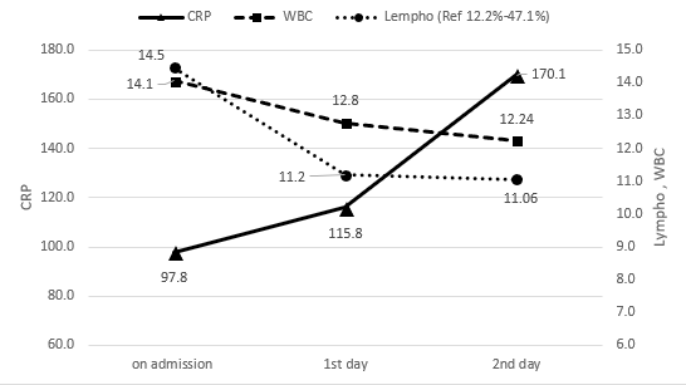

Figure 2: Mean levels of CRP, WBC and Lymphocyte counts during the first two days of hospitalization

mean weight 83.2 kg (SD 21.7) participated in this study. Forty-one (26.5%) of the total number of participants were women. The mortality rate was 21.3% (33 patients). The average length of stay in the intensive care unit was 16.3 days (SD 12.3), and the average duration of mechanical ventilation was 12.3 days (SD 10.2).

Levels of the inflammatory biomarkers during the two-day-stay

Figure 2 shows the course of CRP, WBC and lymphocyte count means from patients' admission to the 2nd day of their ICU stay. The mean of CRP on admission was 97.8 (SD 105) and it increased on the first day of hospitalization (115.8, SD 95.4) with an additional increase on the second day (170.1, SD 82.8) (Wilks λ = 0.683 p = 0.001). The mean of WBC was 14.1 (SD 7.2), on day 1 (12.8, SD 7.2) and on day 2 (12.24, SD 5.4) (Wilks λ = 0. 91 p = 0.002). Similarly, the mean level of lymphocytes on admission was 14.5 (SD 10.9), it decreased on the first day (11.2, SD 6.5), and was further decreased on the second day (11.06, SD 6.3) (Wilks λ = 0.904; p = 0.002).

Associations between sedatives and inflammatory biomarkers

Propofol and midazolam were the two sedative medications that were correlated with the clinical inflammatory markers. Results showed that Propofol was not associated with any inflammatory indicators on the first day. On the second day, the dose of Propofol had a weak positive correlation (r = 0.17 p = 0.04) with eosinophil counts. (Table 1). In addition, Midazolam was not found to be associated with any clinical signs of inflammation on the first day of hospitalization. On the second day, a small sample of 29 patients who received Midazolam showed a moderate negative correlation with CRP (r = -0.39 p = 0.04). (See Table 2)

Association between opioid analgesics and inflammatory biomarkers

Fentanyl was not associated with any biomarkers on the first day of hospitalization. The dose on day 2 had a low correlation with eosinophil counts (r = 0.19 p = 0.04 n = 113). The dose of Remifentanyl in 23 patients on day 1 showed a moderate to high correlation (r = 0.5; p = 0.015) with eosinophil levels. On the 2nd day, remifentanil dose had a weak correlation with neutrophil counts (r = 0.15; p = 0.49, n = 29) and a weak negative correlation with monocyte counts (r = -0.15 p = 0.43,

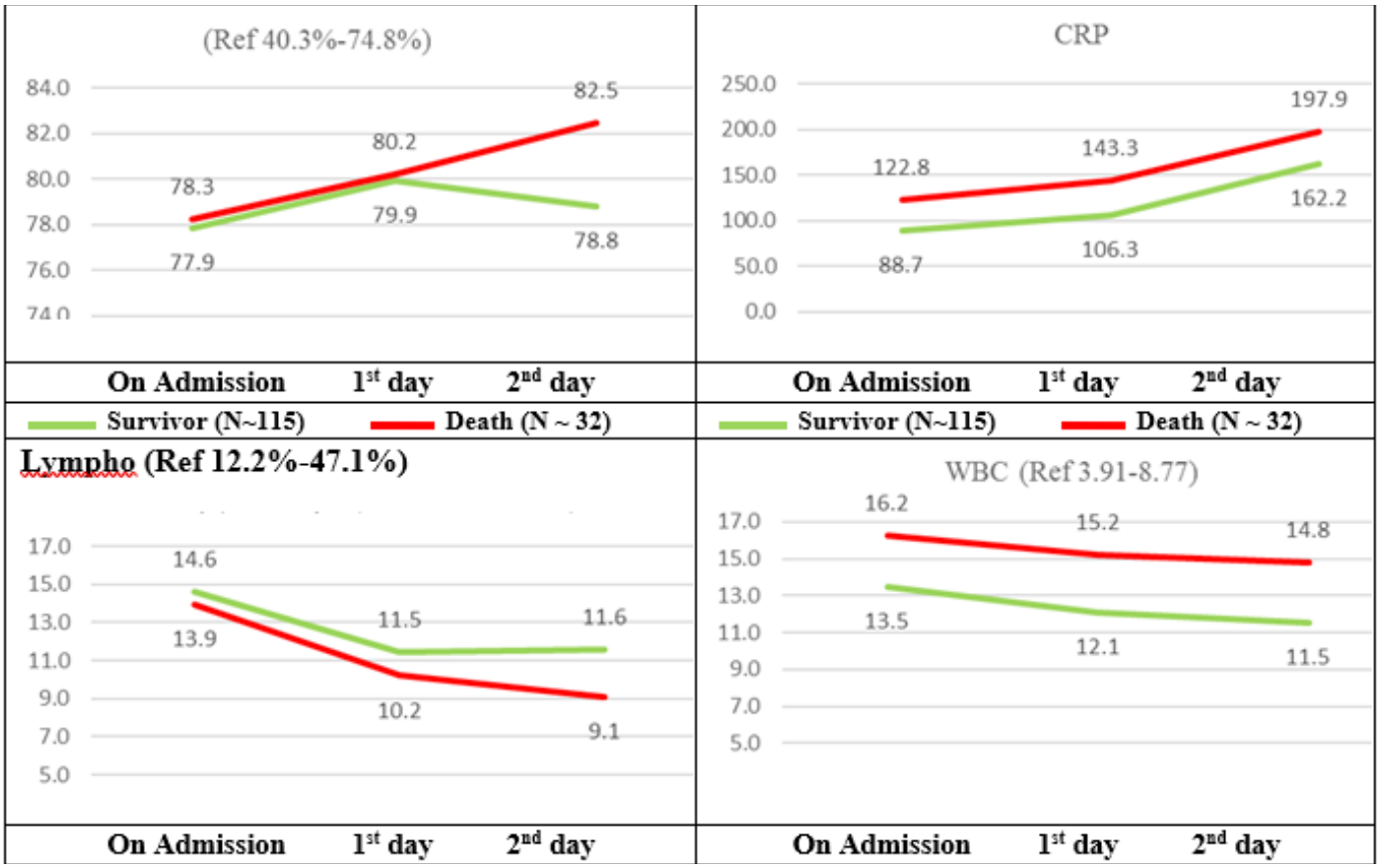

Figure 3. Patient outcome correlation with clinical measurements

		N	Mean	Median	SD	Minimum	Maximum
Propofol mg/kg/hr	Day 1	142	1.77	1.88	1.0	0.099	4.567
	Day 2	141	2.05	2.05	0.9	0.181	5.735
Midazolam mg/kg/hr	Day 1	41	0.12	0.12	0.073	0.0100	0.2990
	Day 2	51	0.14	0.13	0.073	0.0240	0.3410
Fentanyl mg/kg/hr	Day 1	114	0.0009	0.0010	0.0005	0.0001	0.0029
	Day 2	114	0.0011	0.0011	0.0005	0.0001	0.0027
Remifentanyl mg/kg/hr	Day 1	24	0.0008	0.0007	0.0005	0.0001	0.0018
	Day 2	29	0.0006	0.0006	0.0004	0.0001	0.0016
Morphine equanalgesic dose	Day 1	139	0.0894	0.0900	0.0510	0.0080	0.2850
	Day 2	140	0.1019	0.0990	0.0501	0.0090	0.2730
Temperature	Day 1	155	36.4	36.6	1.3	32.0	39.0
	Day 2	152	37.1	37.2	1.1	33.4	39.3
Clinical assessments							
CRP	Admission	56	97.8	42.2	105.0	0.3	397.0
	Day 1	97	115.8	79.0	95.4	1.8	367.8
	Day 2	95	170.1	173.6	82.8	6.5	360.8
Admission	WBC (ref 3.91-8.77)	145	14.1	12.5	7.2	2.3	50.8
	Neutrophils (ref 40.3-74.8%)	145	77.9	80.9	12.4	28.9	95.8
	Lymphocytes (ref 12.2-47.1%)	145	14.5	10.9	10.7	2.0	64.0
	Monocytes (ref 4.4-12.3%)	145	7.0	6.3	4.9	0.0	44.6
	Eosinophils (ref 0-4.4%)	145	0.5	0.1	0.8	0	3.9
	Basophils (ref 0 -0.7%)	145	0.2	0.1	0.2	0	1.2
Day 1	WBC (ref 3.91-8.77)	147	12.8	11.6	7.2	0.98	48.5
	Neutrophils (ref 40.3-74.8%)	147	80.0	81.6	10.4	16	98.0
	Lymphocytes (ref 12.2-47.1%)	147	11.2	9.8	6.5	1.7	33.1
	Monocytes (ref 4.4-12.3%)	147	8.3	7.7	6.6	0	76.0
	Eosinophils (ref 0-4.4%)	147	0.4	0.1	1.1	0	9.2
	Basophils (ref 0 -0.7%)	147	0.1	0.1	0.2	0	1.0
Day 2	WBC (ref 3.91-8.77)	154	12.24	11.54	5.4	3.1	32.2
	Neutrophils (ref 40.3-74.8%)	154	79.59	81.05	9.1	36.0	96.5
	Lymphocytes (ref 12.2-47.1%)	154	11.06	9.90	6.3	1.4	42.6
	Monocytes (ref 4.4-12.3%)	154	8.34	7.60	5.0	0.7	54.0
	Eosinophils (ref 0-4.4%)	154	0.85	0.30	1.2	0	7.3
	Basophils (ref 0 -0.7%)	154	0.16	0.10	0.3	0	3.2

Table 2: Descriptive drug treatment data and inflammation indicators. N = number, WBC = white blood cells

n = 29). The association of morphine with the inflammatory indicators was not possible, because of the small sample size (only 1 person received morphine). The total dose of morphine administered, on either day 1 or day 2, showed no correlation with any inflammatory indicators (see Table 1).

Associations between inflammatory biomarkers and patients' length of hospitalization, age and temperature

Findings support that the length of hospitalization had no correlation with CRP on admission (r = -0.03), neither on day 1 (r = -0.08) nor on day 2 (r = -0.14). In addition, there was no correlation between the number of days that patients were ventilated and CRP on admission (r = 0.05), on day 1 (r = 0.04) and on day 2 (r = -0.04) (see Table 1).

A slight positive correlation (r = 0.24, p = 0.076) was observed between patients' age and CRP, on admission. Older patients had a higher CRP on average (see Table 2). In addition, the temperature of the first day had a slight positive correlation (r = 0.21, p = 0.009) with WBC, a slight negative correlation with neutrophils levels (r = -0.21 p = 0.009) and a small positive correlation with lymphocyte levels (r = 0.2, p = 0.013).

Associations between inflammatory marker and patients' outcomes

Patients who eventually died, had a trend for increased CRP on admission (122.8, SD 113.5) compared to patients who survived (88.7, SD 101.6). This difference was also observed on the first and the second day (see Figure 2). The absence of a statistically significant difference might have been due to the small sample size, but also to the large variations in CRP measurements (see Table 3). A similar condition was also observed at WBC levels, where there was a parallel decrease in both groups. However, the group of patients who died had higher WBC than patients who survived, both on admission (p = 0.056) on the first day (p = 0.031) and on the second day (p = 0.002).

Neutrophils showed a correlation with patients' outcomes (Figure 2). In particular, there was a similar increase, on the first day of hospitalization, in the group of patients who died and in the surviving group. However, on the second day of hospitalization, survivors (78.8, SD 8.5) had lower neutrophil counts than those who died (82.5, SD 10.7) (p = 0.039). In addition, lymphocytes were decreased in both groups of patients, on the first day of hospitalization, but on the second day, the group of patients who survived (9.1, SD 5.2) had lower levels than the group who died (11.6, SD 6.5) (p = 0.044).

DISCUSSION

The present study explored the associations between sedation and opioid analgesics with common inflammatory markers in critically ill patients treated in the biggest ICU of Cyprus.

Regarding the investigation of the levels of inflammatory markers during the two-day-stay of critically ill patients in ICU, it was found that only CRP was increased during the three measurements (admission, 1st day and second day). The increase of CRP in ICU is supported by current literature and is strongly associated with critically ill patients (van Genderen et al., 2011). Furthermore, the findings of the present study do not support an association between the most widely used sedatives and inflammatory markers except for Propofol that had a weak positive correlation with eosinophils accounts.

The length of patients' hospitalisation and ventilation showed no association with inflammatory biomarkers. Instead, a slight correlation between inflammatory markers and patients age and temperature was observed. Finally, results showed that patients who died had a trend increased of CRP and WBC on admission compared to patients who survived.

Results showed that remifentanil had the higher correlation with eosinophils. Opiate analgesics, have been shown to play an important role in the outcome of critically ill patients (Vuory et al., 2004). Literature states that intravenous opioid administration is considered to be the first line of treatment of non-neuropathic pain in critically ill patients (Barr et al., 2013). Apart from Remifentanil, the most commonly used intravenous opioid analgesics studied in the present research were Fentanyl and Morphine which are known to have potential anti-inflammatory and antioxidant activity (Kang 1998; Chen et al., 2005; Kim et al., 2006), and which appear to be used widely in the study ICU. The rates of Fentanyl administered in the study ranged from 0.6 to 1.8 μg/kg/h, which is in accordance with the recommended dosage (Mirski et al., 2009).

In contrast, the mean dose of remifentanil given to the patients studied, in both days were lower from the recommended doses (3-12 μg/kg/h) (Mirsk et al., 2008, Rowe & Fletcher, 2008). This was probably due to the fact that remifentanil was often administered intermittently. At the same time, remifentanil was not administered in combination with other analgesics and sedatives. The hypothesis that the analgesia given could reduce the inflammation markers was not verified. Spierman's correlations for all administered opiates and inflammation markers (CRP, WBC) did not show any significant association.

The maintenance of low levels of sedation in adult ICU patients is associated with improved clinical outcomes, such as a reduction in the duration of mechanical ventilation and the patients' stay in the ICU (Barr et al., 2013). In this study, it was observed that the median dose of Midazolam in both days (n = 41), was low and more particularly it ranged from 0.12 to 0.6 mg/kg/h, compared to the recommended dosage, as supported by Mirski et al. (2009). Barr et al. (2013), recommend that the necessary sedatives be administered in small doses so as to achieve moderate sedation, unless clinically contraindicated (Pasero, 1999). In this study, a total of 28 patients on the first day and 36 patients on the second day received both sedative drugs at the same time, and therefore the mean dose of Midazolam was marginal at the lowest recommended levels.

The mean, as well as the median, value of CRP and white blood cell counts were high throughout the evaluation, indicating the increased severity of the disease and the presence of an inflammatory reaction. CRP levers increased on the first day of hospitalization and even more on the second day, as opposed to the white blood cell counts that declined. It appears that CRP is a more objective indicator than WBC in assessing inflammation.

Propofol did not show any significant association with any markers and specifically with the CRP and WBC inflammation markers. As it has been pointed out, Propofol can reduce the inflammatory response of the organism (Ma et al., 2010) but this does not seem to correlate with the existing inflammatory markers that have been evaluated in this study. Further investigation is warranted to explore these associations as they may potentially be very important for patients' outcomes. Midazolam was not associated with any clinical inflammation markers on the first day of hospitalization but on the second day, it showed a moderate negative correlation with CRP in a small sample of 29 patients.

On the first day temperature had a moderate positive correlation with CRP and a slight positive correlation with WBC. Literature supports this finding (Pepys & Hirschfield, 2003). CRP appeared to have some relation with the outcome of the patient. In particular, patients who died had an increased CRP on admission compared to that of the surviving patients. At the same time, there was a slight positive correlation of CRP with age on admission and it was found that older patients had a higher CRP. The fact that older people have other co-morbidities may give an explanation for this finding.

Limitations

This was a retrospective exploratory single-centre study, and has therefore many limitations, the most important being the absence of adjustment for confounding variables, such as the severity of the disease, age, type of admission diagnosis and depth of sedation. However, it provides preliminary evidence on associations that warrant further investigation.

CONCLUSIONS

In this exploratory retrospective not adjusted study, we observed no significant associations between opiate analgesics and sedatives, and CRP and WBC inflammation biomarkers. However, based on the limitations of this study, and the documented associations in the literature, these associations merit further investigation.

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