Opioids and immunosupression in oncological postoperative patients

José Luis Bonilla-García[1]*, Manuel Cortiñas-Sáenz[2], Esperanza del Pozo-Gavilán[3]

[1]FEA Anestesiología y Reanimación, Complejo Hospitalario Universitario de Huelva, Huelva, Spain
[2]FEA Anestesiología y Reanimación, Hospital Torrecárdenas, Almería, Spain
[3]Departamento de Farmacología e Instituto de Neurociencias, Facultad de Medicina, Universidad de Granada, Granada, Spain

Summary

Introduction: Recent animal studies demonstrated immunosuppressive effects of opioid withdrawal resulting in a higher risk of infection. The aim of this study was to determine the impact of remifentanil discontinuation on Post-Anesthesia Care Unit (PACU)-acquired infection after a schedule of sedoanalgesia of at least 6 days.
Method: All patients over 18 years of age with a unit admission of more than 4 days were consecutively selected. The study population was the one affected by surgical pathology of any origin where sedation was based on any hypnotic and the opioid remifentanil was used as analgesic for at least 96 hours in continuous perfusion. Patients who died during admission to the unit and those with combined analgesia (peripheral or neuroaxial blocks) were excluded. Bivariate analysis was performed to determine risk factors for infection acquired in the unit. A comparative study between periods of 6 days before and after the cessation of remifentanil was performed. Paired samples test and McNemar test was used for quantitative and categorical variables, respectively.
Results: There were 1,789 patients admitted to the PACU during the study and the population eligible was constituted for 102 patients. The incidence rate of PACU-acquired infection was 38 per 1,000 PACU days. Ventilator-associated pneumonia was the most frequently diagnosed PACU-acquired infection. *Pseudomona aeruginosa* was the most frequently isolated microorganism. Hospital mortality was 36.27%. No statistically significant differences were seen in the incidence of HAI in cancer patients in relation to discontinuation of remifentanil (p=0.068).
Conclusion: The baseline state of immunosuppression of cancer patients does not imply a higher incidence of HAI in relation to the interruption of remifentanil. It would be of interest to carry out a multicenter PACU study that included immunological patterns.

Keywords: remifentanil, morphine, opioid, healthcare-associated infections, unit-acquired infection, withdrawal, immunosuppression, critical care, mortality.

Study conducted at Hospital Torrecárdenas, Almería, Spain

Article received: 1/14/2017
Accepted for publication: 2/26/2017

***Correspondence:**
Address: Ronda exterior norte s/n
Huelva, Huelva – Spain
Postal code: 21005
joseluisbonilla86@gmail.com

http://dx.doi.org/10.1590/1806-9282.63.09.753

Introduction

Oncological pathology is a complex problem characterized by high prevalence and incidence. The use of the various opioid drugs has increased exponentially each year in chronic benign and malignant pain.[1] Many of its primary effects on organic systems are diverse, complex, and not fully known.[2]

Potential results and long-term effects of sedoanalgesia in the field of anesthesiology and critical medicine evoke increasing interest and importance, especially after the advent of oncologic surgery.[3,4] It is suggested that different anesthetic and/or analgesic techniques may influence the rates of surgical infection, cancer recurrence, post-surgical chronic pain, need for transfusion of blood products, episodes of cardiac ischemia, neurological ischemia and cognitive dysfunction in the elderly and neonates.[5] The possible mechanisms by which sedoanalgesia in critically ill patients favors the presence of healthcare-associated infections (HAI) in a classical way are a possible prolongation of the exposure to several risk factors, the presence of micro-aspirations, changes in microcirculation and in gastrointestinal motility.[3]

Sedoanalgesia modifies immune function, but its actual clinical importance is unknown. Studies by Helmy et al.[6] and Hermann et al.[7] show that different hypnotic drugs such as propofol, midazolam and sevoflurane can produce pro-inflammatory or anti-inflammatory immune changes. The antioxidant properties of propofol have been related to its anti-inflammatory effect and therefore are described as contributing to the alteration of neutrophil phagocytosis against certain bacteria.[8] As for midazolam, its role is described as a suppressor of the innate immune response.[8] Moreover, it is linked with the inhibition of the release of cytokines, and thus of interleukins (IL) 1 and IL-6 in the central nervous system.[9]

On the other hand, multiple investigations in animals and humans demonstrate the immunosuppressive effects of opioids[10] and, therefore, administration of these drugs has been associated with increased susceptibility to certain bacterial and viral infections.[11] Morphine is associated with decreased lymphoproliferative processes, natural killer (NK) lymphocyte activity, and interferon-γ and IL-2 production.[2]

The relation between opioids and impaired immune function is constantly referred to in the medical literature, and there is a consensus that opioids act in the modulation of the immune system. Currently, there is a growing interest in elucidating the possible influences of opioid use in the management of patients with pain.[2,12] Traditionally, as documented since the 9th century, there has been an increase in the incidence and severity of infections among opiate users. The potential target of the immunosuppressive effect of opiates is not fully understood, but different investigations appear to indicate bidirectional connections between the neural, endocrine and immune systems, placing it peripherally based on the expression of the MOP receptor on immune cells with implications at the central nervous system level.[12,13]

The administration of opioids affects the immune system in different degrees and manners.[2] The clinical relevance of this immunological role is not well-known. The mechanisms of immunomodulation of opioids may be in vitro or in vivo (Table 1). In the first case, there is a change in the phagocytic and chemotactic function of neutrophils and monocytes with increased apoptosis of lymphocytes and phagocytic cells.[14] In vivo investigations seem to relate changes in the downregulation of protein C, somatostatin and nitric oxide with a decline in NK cell function, suppression of inflammatory cytokines with a sympathetic nervous system activation that promotes high levels of norepinephrine and which could be related with immune suppression.[2,12,15]

There is a close relation between cancer, inflammation, sepsis and immunity.[16] This relationship is based on the interaction that is produced between the inflammatory cells in the presence of several cytokines. A state of immunosuppression may be influenced by the underlying disease itself, the surgical and anesthetic-analgesic techniques, chemo and radiotherapy employed.

There is a wide variety of opiates used by different routes, such as morphine, fentanyl, hydromorphone, oxycodone, tapentadol, buprenorphine, tramadol, codeine, alfentanil, sufentanil, remifentanil, etc.[17] Because of their widespread use, the immunological effects of opioid drugs receive considerable attention, knowing that the changes induced by these drugs in the immune system may affect surgical outcomes or a variety of chronic pathological processes. On the other hand, we are starting to learn and

TABLE 1 Main changes in NK cell immune function with different opiates.

Opiates	In vitro studies Cellular series		In vivo studies Cellular series			
	Animals	Humans	Animals		Humans	
			No Surgery	Yes Surgery	No Surgery	Yes Surgery
Morphine	=, ↓	=, ↓	=, ↓	↑,=, ↓	↑,=, ↓	=, ↓
Fentanyl	?	?	=, ↓	↓, ↑	=, ↑	=, ↓
Remifentanil	?	?	↓	?	=	?
Sufentanil	?	?	↓	?	?	↓
Meperidine	↓	?	?	?	?	=
Methadone	=, ↓	=, ↓	=, ↓	?	=, ↓	?
Buprenorphine	?	?	=, ↓	=, ↑	?	?
Tramadol	?	?	=, ↑	↑	?	↑

↑: Increase; ↓: Decrease; =: Neutral effects; ?: Data not available.

understand that not all opioid drugs have the same profile and therefore do not induce the same immunomodulatory effects (Table 1).[18] The clinical relevance of these effects is unknown and there are no recommendations for the use of opioids in various clinical situations regarding the immunological consequences of these drugs.

Animal studies suggest that opiates withdrawal induces a state of immunosuppression that would increase the risk of infections[19] and, thus, changes in immunomodulation caused by certain drugs may be responsible for a part of the HAI-related complications in critical medicine. Recently, it was reported that anesthetic techniques and different sedoanalgesia regimens could be an important confounding factor when comparing sepsis mortality investigations.[11] Therefore, due to the inconsistent results of investigations in animal and human models, the clinical relevance of the suppression of the immune system caused by hypnotics and opiates is unclear.[20]

The aim of our investigation was to assess the hypothesis that remifentanil discontinuation is associated with an increase in HAI rates in a subpopulation of critical post-surgical patients according to the etiology of the underlying disease.

Method

After approval by the Hospital Ethics Committee, a prospective and observational study of a historical cohort in a 6-bed Post-Anesthesia Care Unit (PACU) was conducted during the years 2010-2012.

All patients older than 18 years hospitalized at the unit for more than 4 days were consecutively selected. The investigated population included surgical patients of any origin sedated with any hypnotic and treated with remifentanil as analgesic opioid infused continuously for at least 96 hours. Patients who died during the stay in the unit and those under combined analgesia (peripheral or neuraxial blocks) were excluded.

Doses of midazolam, propofol and remifentanil are described in the unit's sedoanalgesia protocol (Figure 1) and are in accordance with the guidelines of the Society of Critical Care Medicine.[21] Withdrawal syndrome is treated following the strategy of sequential sedation.

The main variable in our investigation was the number of healthcare-associated infections acquired in the PACU during the days of hospitalization. We also considered the incidence density, defined as the number of infections acquired in the unit per 1,000 days of hospitalization.

The cutoff point for differentiating early and late HAIs was determined as 6 days before and after cessation of remifentanil.

There is a nosocomial infection surveillance system with systematic and routine detection of multiresistant microorganisms. Only the infections confirmed by the Microbiology Service were considered in our study. A number of nosocomial infections were defined according to the definitions adopted by the Centers for Disease Control and Prevention (CDC).[22]

Other variables included age; sex; APACHE II (Acute Physiology and Chronic Health Evaluation II) classification; ASA (American Society of Anesthesiologists) index; McCabe score; number and type of comorbidity; cause of hospitalization; number of surgical re-interventions; previous antibiotic treatment; length of stay in critical care; Ramsay scale; rate of central and arterial venous catheter usage; closed urinary catheters and mechanical ventilation; number of re-intubations; tracheotomy; duration and type of antimicrobial agent; dose of remifentanil, midazolam or propofol; use of neuromuscular blocking drugs; and mortality.

Recommendations based on the guidelines of the Sociedad Española de Anestesiología y Reanimación adapted to the local epidemiology of bacterial resistance of our critical care unit were adopted for the empirical treatment of infectious processes.[23]

In patients with sepsis at hospitalization, vigorous resuscitation with fluids and hemodynamic support measures were initiated, including vasopressors in case of hypotension or lactate > 4 mmol/L, low-dose corticosteroids in patients with septic shock, invasive mechanical ventilation for pulmonary protection, blood glucose control between 150-180 mg/dL, assessment of the need for surgical intervention or percutaneous drainage, bacterial cultures and introduction of empiric antimicrobial treatment, as advocated in the Surviving Sepsis Campaign.[24]

The data analysis was performed with Stata statistical software version 7.0. The results are presented as number, percentages for categorical variables, and mean with their standard deviation for the quantitative variables. Univariate analysis was used to determine the factors associated with nosocomial infection. Qualitative variables were compared using Pearson's Chi-square test or Fisher's exact test, as appropriate. Quantitative variables were compared using the Mann-Whitney test or Student's t-test. Statistical significance was defined as $p<0.05$. In patients with nosocomial infection, exposure to potential risk factors was taken into account until the onset of the last episode of infection. Patients with various infections were considered at risk until the last episode. A comparative study was carried out between 6 days before and

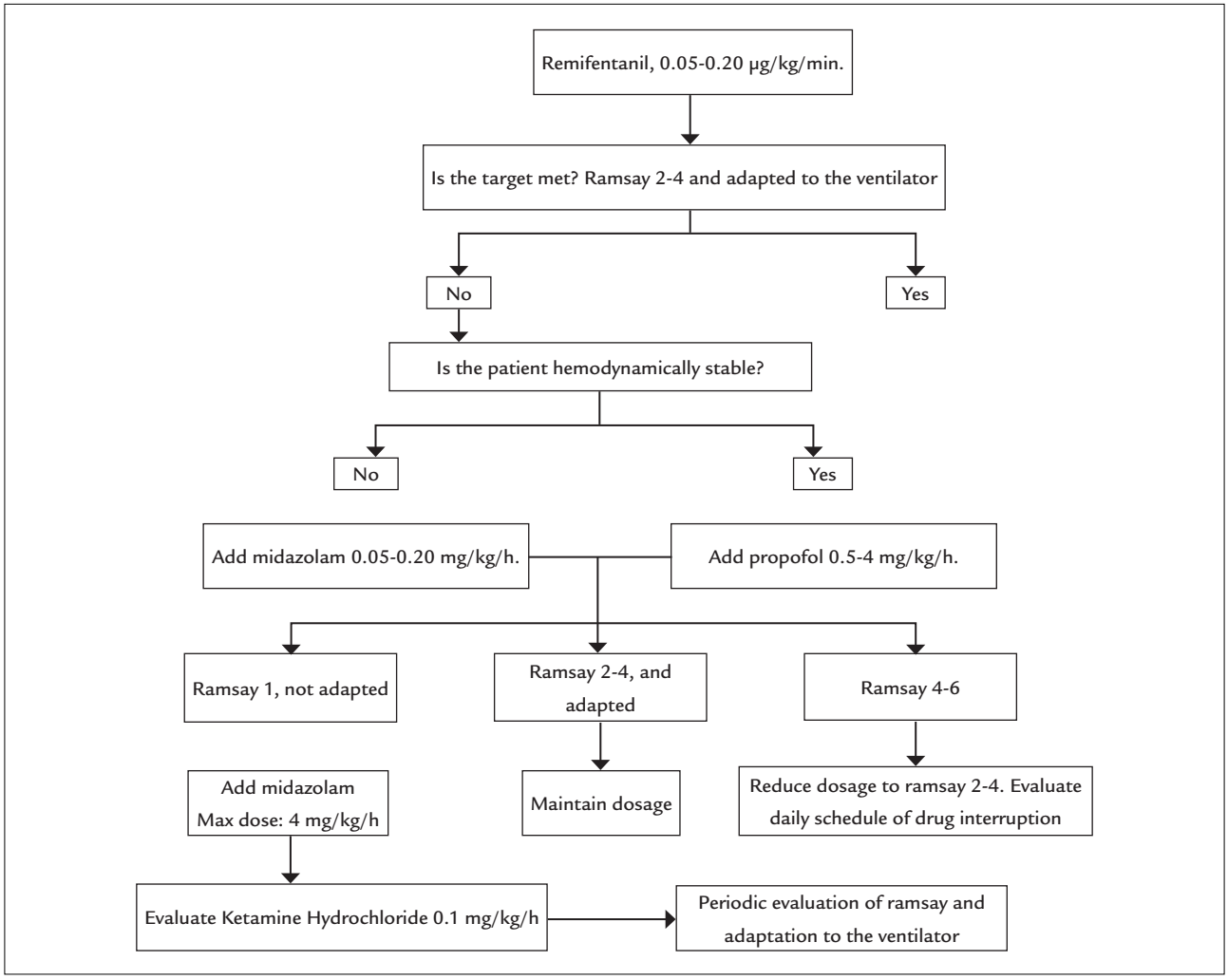

FIGURE 1 Unit's sedoanalgesia protocol.

after the cessation of remifentanil, the cutoff point being the day of cessation of this drug. For these comparisons, paired samples and the McNemar test were used for the quantitative and categorical variables, respectively.

Results

The number of patients who were admitted to the Post-Anesthesia Care Unit during the investigation period was 1,789. After applying the inclusion and exclusion criteria, the eligible population consisted of 102 patients whose analgesia protocol was the intravenous infusion of remifentanil for at least 96 hours. The hospital mortality of the cohort was 36.27%.

The demographic and prognostic characteristics of the population are summarized in Table 2 and the clinical variables in Table 3. Fifty-nine cases (59/57.84%) of hospitalizations at the unit were urgent. The main etiology for hospitalization was the occurrence of secondary peritonitis after urgent surgeries (23.52%).

Ninety percent (90%) of the patients were treated with simultaneous sedation with hypnotics, while the others did not receive sedative drugs. Remifentanil infusion during the investigation period was 11.45±11.57 days (Table 4).

The most frequent HAI was pneumonia associated with mechanical ventilation, and *Pseudomonas aeruginosa* was the most frequently isolated microorganism. The rate of use of medical devices in the investigated population admitted to PACU and treated with remifentanil for at least 96 hours is shown in Table 5.

Figures 2 and 3 show the number of HAI in a temporal relation with the administration and cessation of remifentanil according to the underlying disease (oncological and non-oncological patients of the cohort). There were no

TABLE 2 Demographic and prognostic characteristics of the cohort investigated.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
Age in years	65.57±12.03	63.89±10.31	0.236
Sex (male)	29	21	0.443
ASA > 2	41	21	0.132
McCabe Score			
Good prognosis	13	14	
Poor prognosis	20	15	0.129
Fatal prognosis	21	6	
Death expectations	9	4	
APACHE II	16.41±6.89	13.41±8.22	0.025
Underlying comorbidity			
Hemodynamic	34	19	0.606
Respiratory	24	20	0.191
Renal	17	9	0.660
Hepatic	9	7	0.621
Immunosuppression	27	15	0.661
Diabetes mellitus	34	4	<0.001
Number of comorbidities			
≤ 2	13	16	<0.001
> 2	50	23	

TABLE 3 Clinical characteristics of the cohort.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
Length of stay in PACU (days)	17.17±13.37	12±10.62	0.021
Length of hospital stay (days)			
Pre-PACU	4.28±3.88	3.25±2.35	0.069
Post-PACU	14.74±20.18	12.71±15.93	0.297
Global	36.36±24.93	27.94±22.70	0.044
Mortality			
PACU	17	8	0.460
Post-PACU	10	2	0.143
Type of urgent surgery	29	14	0.314
Reintubation	19	9	0.436

PACU: Post-Anesthesia Care Unit.

TABLE 4 Type of sedoanalgesia administered to the patients in the cohort.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
Remifentanil	5	3	0.657
Days of remifentanil	13.11±12.92	8.76±8.48	0.032
Midazolam and remifentanil	31	14	0.188
Days of midazolam	14.83±13.36	10.64±11.07	0.155
Propofol and remifentanil	27	22	0.183
Days of propofol	8.40±6.02	6.21±2.90	0.060

TABLE 5 Utilization rate of medical devices in the investigated population admitted to a post-surgical critical care unit (CCU) and treated with remifentanil for at least 96 hours.

Variables	Oncological patients (n=63)	Non-oncological patients (n=39)	p-value
CVC	63	38	-
Days of CVC	20.15±16.17	16.30±12.99	0.106
IMV	63	39	-
Days of IMV	12.09±8.34	7.94±5.47	0.003
Tracheotomy	20	5	0.031
Days of tracheostomy	9.8±3.42	11±6.22	0.342
UC	63	39	-
Days of UC	21.19±16.17	16.48±11.07	0.056

CVC: central venous catheter; IMV: invasive mechanical ventilation; UC: closed urinary catheter.

statistically significant differences in the incidence of HAI in the oncological patients regarding remifentanil cessation using the Mann-Whitney U test (p=0.068) (Table 6).

Discussion

Sepsis is a critical problem in all areas of clinical medicine.[25,26] New and complex immunological investigations conducted during sepsis suggest that immunosuppression is the determinant of mortality in severely ill patients.[27-29] A shift in the traditional sepsis paradigm focuses on immunostimulation to improve clinical outcomes as a key to new therapeutic options.

The main finding in our study is a quasi-significance and the existence of two temporal patterns of post-surgical patient behavior after opioid withdrawal according to the underlying disease or etiological diagnosis (Figures 2 and 3), which is why these patients should be monitored closely for the consequences of a delayed diagnosis.[30] We observed a high incidence of HAI within 6 days after the discontinuation of opioid analgesia (remifentanil) in the population of oncological patients, with an antagonistic pattern among non-oncological postoperative patients. This different pattern in cancer patients hospitalized in our unit has been described by other authors in relation to the use of opiates, as reported by Schwacha et al.[31] in burn patients and by Nseir et al.[32] in critically ill patients after a multivariate analysis.

Patient characteristics play a key role in the risk of infection,[33] while, in the surgical setting, duration of mechanical ventilation, patient severity based on the APACHE-II index, albuminemia, and time of hospitalization prior to intervention are known factors favoring HAI.

Analyzing the characteristics of our cohort, we observed a homogeneous distribution of the sample in both groups in terms of age and sex (oncological and non-oncological), although they are not fully comparable due to differences in severity at hospitalization, comorbidity number and days of stay in PACU, which are factors predisposing to nosocomial infection,[34] and which could partially justify the differences in the incidence of HAI between groups.

Severity at hospitalization, days of mechanical ventilation and patient immuno-depressive states were factors associated with HAI acquisition in our post-surgical critical care unit. These results are in agreement with the results obtained by Nserir et al of the risk factors for HAI acquisition in critically ill patients.[32]

In our series, the high utilization rate of intrinsic risk medical devices is characteristic. These devices, along with artificial nutrition and the use of immunosuppressive therapies, are identified as extrinsic risk factors for infection.[35] The justification for these high ranges of device use may be the generalized involvement of organs and systems that are produced in patients affected by severe infections and who will require ventilatory, hemodynamic and diuretic support, as well as continuous monitoring of body functions, to assess the effectiveness of the measures put in place for treatment. In the medical literature, intubation and presence of central vascular catheter are the most prevalent extrinsic risk factors in hospital acquired infection,[36] which coincides with our investigation.

Our study does not determine whether acute use and discontinuation of remifentanil are independent risk factors for nosocomial infection, unlike results reported by Nseir et al.[32] This study showed, after a logistic regression analysis, that there is a high incidence of nosocomial infection during the 4 days after cessation of remifentanil-based analgesia.

In this context, cancer is a pathology closely related to the immune system. Cancer generates a state of immunosuppression that causes the patient to present an

TABLE 6 Analysis of multiple non-parametric Mann-Whitney U-test for nosocomial infection in a post-surgical critical care unit.

Measures	6 days pre-remifentanil cessation	6 days post-remifentanil cessation	Type of patient
Mean±SD	4.00±1.27	7.00±2.78	Oncological patients
	6.00±1.23	1.14±1.07	Non-oncological
	10.00±1.67	6.86±2.85	Global
T mean at 5%	4.06	6.94	Oncological patients
	6.06	1.10	Non-oncological
	10	6.73	Global
95CI	2.67-5.33	4.44-9.56	Oncological patients
	4.67-7.33	0.15-2.15	Non-oncological
	8.24-11.76	4.22-9.50	Global
p-value	0.068		Oncological patients
	0.002		Non-oncological
	0.030		Global

TD: typical deviation; T mean: trimmed mean; CI: confidence interval.

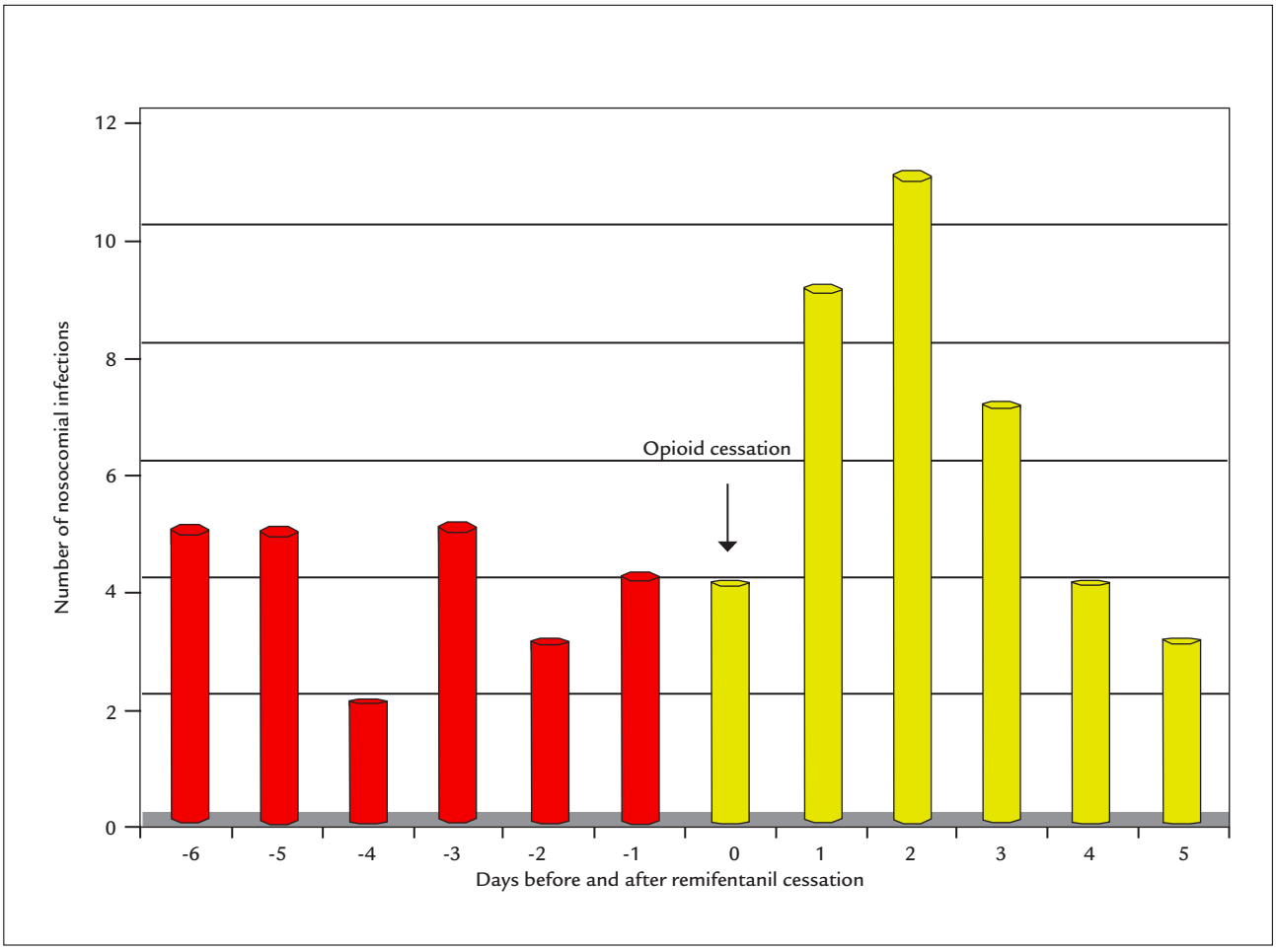

FIGURE 2 Time relation between healthcare-associated infections (HAI) and intravenous remifentanil analgesia in oncological patients in a Post-Anesthesia Care Unit (p=0.068).

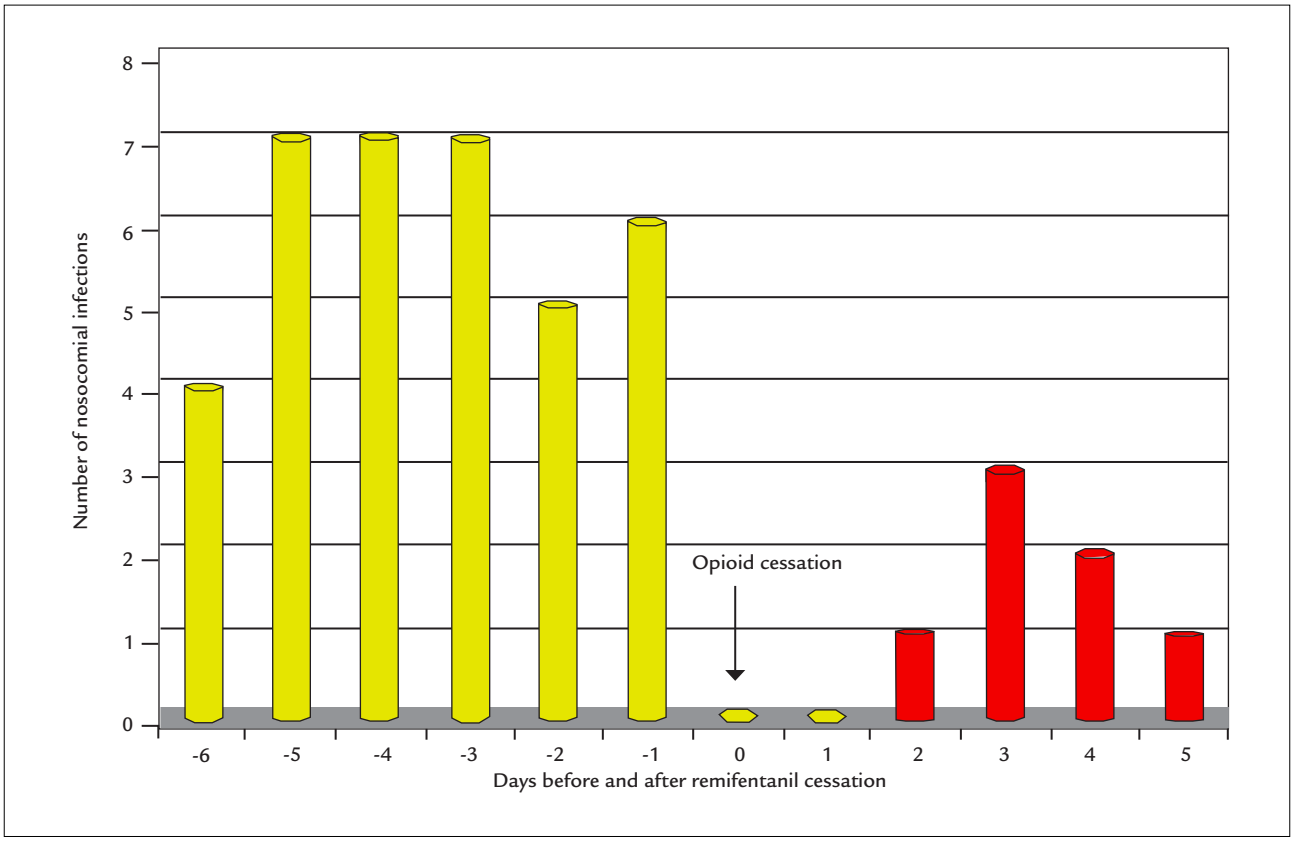

FIGURE 3 Time relation between healthcare-associated infections (HAI) and intravenous remifentanil analgesia in non-oncological patients in a Post-Anesthesia Care Unit (p=0.002).

increased risk of infectious disease. Likewise, there appears to be an inverse relationship in which immunosuppression would increase the risk of oncological pathology.[37] Several investigations clearly show contradictory data regarding the immunological action of opioids in the perioperative period.[38,39] A study by El Solh et al.[38] reveals that morphine administration in patients undergoing coronary revascularization is associated with an increased risk of nosocomial pneumonia. In contrast, Spies et al.[39] indicate that low doses of morphine protect against the development of nosocomial pneumonia after cancer surgery. Our results appear to be more in agreement with the first group cited.

Several investigations describe the immunomodulatory properties of opiates depending on the acute or chronic use and dosage.[7,40,41] Several other studies indicate that morphine is the opioid with the highest degree of impact on the immune system, which is transient with fentanyl and non-existent with tramadol and buprenorphine. As for remifentanil, the available studies show discordant results. Therefore, each substance appears to have a different effect and synthetic opioids appear to have less immunological impact due to weak interaction with leukocyte opioid receptors. This weak association described for synthetic opioids could also partially explain our results.

The use of potent immunosuppressive drugs or analgesia required by this type of patients, presented as the top rungs of the WHO analgesic ladder, may increase the risk of nosocomial infection.[42] On the other hand, many of them receive surgical treatment, which also presupposes an increase in the immunosuppression of the patient caused by both the surgery itself and the anesthesia used during the procedure, although in our investigation all patients were operated under general anesthesia, with no associated regional techniques.

Our sedation protocol is based on recommendations established in the literature. For both short-term sedation and prolonged sedation, it is recommended to use propofol for superficial sedation in hemodynamically stable patients, with special attention to triglyceridemia. Midazolam should be used in hemodynamically unstable patients with no need for frequent neurological assessment, while remifentanil and/or propofol are indicated for sequential and dynamic sedation, and ketamine is contraindicated as prolonged infusion.[43,44]

The use of the drugs is related to the modification of immune cellular functions through several mechanisms not yet fully known. In this sense, the investigation by Helmy et al.[6] shows that different hypnotic drugs can produce pro-inflammatory or anti-inflammatory immunological changes. This fact may suggest a bias in our analysis.

Although there is a change in immunity in patients treated with propofol[8] or midazolam[9] which might be biased in our investigation due to differences between these drugs, we have to say that in our cohort there are no differences in their use between oncological and non-oncological patient groups, although there may be a difference in the time of use.

In our cohort, as we indicated before, oncological and non-oncological patient groups are not fully comparable due to differences in severity at hospitalization, number of comorbidities and days of stay in the critical care unit, which are factors that predispose to infection[31] and may partially justify the differences in the incidence of nosocomial infection between groups. However, other immunomodulatory perioperative factors should be considered, such as hypothermia, pain, stress, steroid use, blood transfusion, etc., which may be associated with enhanced immunosuppression and function as confounding factors in the different human studies.[2,45] Immunosuppression presented by critical oncological patients is a complex multifactorial process that depends not only on the oncological disease itself, but also on the diagnostic and therapeutic measures used to solve or improve the patient's clinical condition, their genetic characteristics, comorbidities, multiorgan dysfunction, etc.

We can identify different limitations in our work, especially sample size and the fact that the study is being performed in a single critical care unit. Secondly, the possible occurrence of infra-sedation or over-sedation, with the possible immunological and infectious changes that this may cause, and which were not considered in the present investigation. Thirdly, there is no control group. Lastly, the lack of results for immunological markers related to cancer disease, which would allow us to better identify the relation between cancer, immunosuppression, remifentanil-related suppression, immunosuppression and healthcare-associated infection.

In conclusion, the baseline immunosuppression status of oncological patients does not lead to an increased incidence of HAI related to remifentanil discontinuation.

This is a fascinating topic, current in critical care medicine and with relevant grey areas, so it may be of interest to carry out a multicentric PACU investigation that includes immunological standards to confirm the results of studies that postulate a immunomodulatory, and not only immunosuppressive, effect of the different sedoanalgesia strategies in critical patients.

Acknowledgments

The results of this publication are part of the doctoral dissertation project of Dr. José Luis Bonilla García, titled: "Relación entre tasa de infección asociada a cuidados de salud en una Unidad de Críticos Postquirúrgica y suspensión del tratamiento con remifentanilo."

We thank the Andalusian Public Foundation for Biosanitary Research of Eastern Andalusia – Alejandro Otero de Almería for their invaluable help in the study and statistical analysis.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Opioides e imunossupressão em pacientes oncológicos pós-cirúrgicos

Introdução: Recentes pesquisas utilizando animais demonstraram efeitos imunossupressores depois da suspensão de opiáceos, associados a um maior risco de infecção nosocomial. O objetivo desta investigação foi determinar o impacto da interrupção do opioide remifentanilo em uma Unidade de Reanimação Pós-cirúrgica (URP) nas infecções associadas aos cuidados da saúde depois de uma pauta de sedoanalgesia de ao menos 6 dias.
Método: Foram relacionados de forma consecutiva todos os pacientes maiores de 18 anos com internação na unidade superior a 4 dias. A população investigada foi aquela afetada por patologia cirúrgica de qualquer origem, na qual a sedação esteve baseada em qualquer hipnótico e como analgésico, foi utilizado o opioide remifentanilo durante pelo menos 96 horas em perfusão contínua. Foram excluídos os pacientes que faleceram durante a internação na unidade e aqueles com analgesia combinada (bloqueios periféricos ou neuroaxiais). Foi realizada uma análise bivariante para determinar fatores de risco para a infecção adquirida na unidade. Foi realizada uma investigação comparativa entre períodos dos 6 dias anteriores e posteriores à interrupção de remifentanilo. Utilizamos o teste de amostras pareadas e a prova de McNemar para as variáveis quantitativas e categóricas, respectivamente.
Resultados: O número de pacientes internados na URP durante o período de investigação foi de 1.789. Depois

de aplicar os critérios de inclusão e exclusão, a população elegível ficou constituída por 102 pacientes. A densidade de incidência de infecção de forma global foi de 38 por cada 1.000 dias de internamento. A pneumonia associada à ventilação mecânica foi a infecção adquirida mais frequente e *Pseudomona aeruginosa*, o micro-organismo mais frequentemente isolado. A mortalidade hospitalar foi de 36,27%. Não foram observadas diferenças estatisticamente significativas na incidência de IACS em pacientes oncológicos em relação à descontinuação de remifentanilo (p=0,068).

Conclusão: O estado basal de imunossupressão dos pacientes oncológicos não implica uma maior incidência de IACS em relação à interrupção do remifentanilo. Seria interessante a realização de uma investigação multicêntrica de URP que incluísse padrões imunológicos.

Palavras-chave: remifentanilo, morfina, opiáceos, infecções nosocomiais, infecção associada aos cuidados da saúde, síndrome abstinência, imunossupressão, cuidados críticos, mortalidade.

References

1. Mowry J, Spyker D, Cantilena L, Bailey J, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol. 2013; 51(10):949-1229.
2. Santos JB, Guimarães de Melo M, Cristina M. Opioids and the immune system: clinical relevance. Rev Bras Anestesiol. 2012; 62(5):1-6
3. Hager DN, Dinglas VVD, Subhas S, Rowden AM, Neufeld KJ, Bienvenu OJ, et al. Reducing deep sedation and delirium in acute lung injury patients: a quality improvement project. Crit Care Med. 2013; 41(6):1435-2.
4. Snyder G, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth. 2010; 105(2):106-15.
5. Kavanagh T, Buggy D. Can anaesthetic technique effect postoperative outcome? Curr Opin Anesthesiol. 2012; 25(2):185-98.
6. Helmy S, Al-Attiyah RJ. The immunomodulatory effects of prolonged intravenous infusion of propofol versus midazolam in critically ill surgical patients. Anaesthesia. 2001; 56(1):4-8.
7. Herrmann IK, Castellon M, Schwartz DE, Hasler M, Urner M, Hu G, et al. Volatile anesthetics improve survival after cecal ligation and puncture. Anesthesiology. 2013; 119(4):901-6.
8. Sanders R, Hussell T, Maze M. Sedation & immunomodulation. Anesthesiol Clin. 2011; 29(4):687-706.
9. Lu HB, Jia YP, Liang ZH, Zhou R, Zheng JQ. Effect of continuous infusion of midazolam on immune function in pediatric patients after surgery. Genet Mol Res. 2015; 14(3):10007-14.
10. Eisenstein TK, Hilburger ME. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. J Neuroimmunol. 1998; 83(1-2):36-4.
11. Risdahl JM, Khanna KV, Peterson KW, Molitor TW. Opiates and infections. J Neuroimmunol. 1998; 83():4-18.
12. Sacerdote P. Opioids and the immune system. Palliat Med. 2006; 20(Suppl 1):S9-15.
13. Stein C, Schäfer M, Machelska H. Attacking pain at its source: new perspectives on opioids. Nat Med. 2003; 9(8):1003-8.
14. Singhal PC, Kapasi AA, Reddy K, Franki N, Gibbons N, Ding G. Morphine promotes apoptosis in Jurkat cells. J Leukoc Biol. 1999; 66(4):650-8.
15. Welters I. [Opioids and immunosuppression: clinical relevance?]. Anaesthetist. 2003; 52(5):442-52.
16. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010; 140(6):883-99.
17. Muellejans B, Matthey T, Scholpp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial. Crit Care. 2006; 10(3):R91.
18. Martucci C, Panerai AE, Sacerdote P. Chronic fentanyl or buprenorphine infusion in the mouse: similar analgesic profile but different effects on immune responses. Pain. 2004; 110(1-2):385-92.
19. Feng P, Wilson QM, Meissler JJ, Adler MW, Eisenstein TK. Increased sensitivity to Salmonella enterica serovar Typhimurium infection in mice undergoing withdrawal from morphine is associated with suppression of interleukin-12. Infect Immun. 2005; 73(12):7953-9.
20. Cronin AJ, Aucutt-Walter NM, Budinetz T, Bonafide CP, DiVittore NA, Gordin V, et al. Low-dose remifentanil infusion does not impair natural killer cell function in healthy volunteers. Br J Anaesth. 2003; 91(6):805-9.
21. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al.; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002; 30(1):119-41.
22. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988; 16(3):128-40.
23. Guirao X, Arias J, Badía JM, García-Rodríguez JA, Mensa J, Álvarez-Lerma F, et al. Recomendaciones en el tratamiento antibiótico empírico de la infección intraabdominal. Cir Esp. 2010; 87(2):63-81.
24. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al.; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock 2012. Crit Care Med. 2013; 41(2):580-37.
25. O'Leary C. Evidence-based management of sepsis. Clin J Oncol Nurs. 2014; 18(3):280-2.
26. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Intensive Care Med. 2014; 40(11):1623-33.
27. Schlegel N, Flemming S, Meir M, Germer CT. [Is a different view on the pathophysiology of sepsis the key for novel therapeutic options?]. Chirurg. 2014; 85(8):714-9.
28. Schefold JC, Hasper D, Volk HD, Reinke P. Sepsis: time has come to focus on the later stages. Med Hypotheses. 2008; 71(2):203-8.
29. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014; 384(9952):1455-65.
30. Miller A. Identifying sepsis too late. Nursing. 2014; 44(2):12-4.
31. Schwacha MG, McGwin G Jr, Hutchinson CB, Cross JM, Maclennan PA, Rue LW 3rd. The contribution of opiate analgesics to the development of infectious complications in burn patients. Am J Surg. 2006; 192(1):82-6.
32. Nseir S, Hoel J, Grailles G, Soury-Lavergne A, Pompeo C, Mathieu D, et al. Remifentanil discontinuation and subsequent intensive care unit-acquired infection: a cohort study. Crit Care. 2009; 13(2):R60.
33. Philippart F, Max A, Couzigou C, Misset B. Reanimación y prevención de las infecciones nosocomiales. EMC-Anestesia-Reanimación 2013; 39(1):1-13
34. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005; 171(4):388-416.
35. Corrales-Fernández MJ, Gea-Velázquez de Castro MT, Limón-Ramírez R, Miralles-Bueno JJ, Requena-Puche J, Aranaz-Andrés JM. Factores que contribuyen a la infección relacionada con la asistencia sanitaria: cómo evitarlos. Rev Calid Asist. 2011; 26(6):367-75.
36. Vaqué J, Grupo de Trabajo EPINE. Resultados del "Estudio de Prevalencia de las Infecciones Nosocomiales en España (EPINEEPPS 2012)", en el contexto del European Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use (EPPS). [cited 2016 Dec 14]. Available from: http://hws.vhebron.net/epine/Descargas/Resultados%20EPINE-EPPS%202012%20Resumen%20(v1_1).pdf.
37. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011; 331(6024):1565-70.

38. El Solh AA, Bhora M, Pineda L, Dhillon R. Nosocomial pneumonia in elderly patients following cardiac surgery. Resp Med. 2006; 100(4):729-36.
39. Spies C, Eggers V, Szabo G, Lau A, von Dossow V, Schoenfeld H, et al. Intervention at the level at the neuroendocrine- immune axis and postoperative pneumonia rate in long-term alcoholics. Am J Respir Crit Care Med. 2006; 174(4):408-14.
40. Sanders RD, Hussell T, Maze M. Sedation & immunomodulation. Crit Care Clin. 2009; 25(3):551-70.
41. Molina PE. Opioids and opiates: analgesia with cardiovascular, haemodynamic and immune implications in critical illness. J Intern Med. 2006; 259(2):138-54.
42. Fortún Abete J, Martín-Dávila P. La infección intraabdominal en el paciente inmunodeprimido. Enferm Infecc Microbiol Clin. 2010; 28(Suppl 2):11-7.
43. Estébanez-Montiel MB, Alonso-Fernández MA, Sandiumenge A, Jiménez-Martín MJ; Grupo de Trabajo de Analgesia y Sedación de la SEMICYUC. Sedación prolongada en unidades de cuidados intensivos. Med Intensiva. 2008; 32(Supl 1):19-30.
44. Riker RR, Fraser GL. Altering intensive care sedation paradigms to improve patient outcomes. Crit Care Clin. 2009; 25(3):527-38.
45. Juffermans N, Vlaar A, Prins D, Goslings J, Binnekade J. The age of red blood cells is associated with bacterial infections in critically ill trauma patients. Blood Transfus. 2012; 10(3):290-5.