Excerpta Medica

The American Journal of Surgery®

The American Journal of Surgery 192 (2006) 82–86
Scientific paper

The contribution of opiate analgesics to the development of infectious complications in burn patients

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Manuscript received August 22, 2005; revised manuscript January 1, 2006

Presented in part at the 24th annual meeting of the Surgical Infection Society, April 29–May 1, 2004, Indianapolis, IN

Abstract

Background: Immune and infectious complications are associated with burn injury. Opiate analgesics also can induce similar complications, however, their impact on postburn infectious complications is unknown.
Methods: A retrospective survey of records from 1997 to 2002 from an academic burn center was conducted. Information on all opiate analgesic use was obtained and expressed as opiate equivalents (OEs). Total OEs were summed for each patient and then compared between cases and controls.
Results: Patients who developed infections were more likely to be in the high OE group. This association was modified by burn severity. Patients with small burns and infection were more likely to be in the high OE group, whereas patients with moderate to large burns and infections were not associated significantly with opiate use.
Conclusions: The results of this preliminary study suggest that opiate analgesics can contribute to the development of postburn infectious complications when the burn injury is of a less severe nature.

Keywords: Morphine; Immunosuppression; Sepsis

Major thermal injury occurs with significant frequency in the United States with more than 1 million cases per year requiring medical attention. Despite advances in treatment and care, immunosuppression resulting in increased susceptibility to sepsis and multiple organ failure remains a major cause of burn morbidity and mortality [1–3]. Some of the causative factors for postburn morbidity and mortality may be related to therapeutic regimens used in the treatment of such patients. In this regard, opiate analgesics (ie, morphine and other opioid derivatives) are the preferred treatment for the management of patient pain associated with burn injury, major trauma, surgical trauma, and cancer [4,5]. Nonetheless, although these compounds have excellent analgesic efficacy, it also is well-documented that chronic or therapeutic use of opiates compromises a wide range of immune functional parameters and increases susceptibility to infection in animals [6–8]. The majority of burn patients receive opiate analgesics for the treatment of pain associated with the initial injury and postinjury procedures such as wound debridement and dressing changes [9–11]. Because opiates have profound immunomodulatory effects, it is likely that treatment of burn patients with these drugs alters their immune response to the injury.

Given that opiates cause suppressed immune function and that burn patients are already in an immunocompromised state, it is plausible that opiate analgesia might promote infectious complications in such patients. The goal of this study was to determine whether opiate analgesics contribute to the development of infectious complications in

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0002-9610/06/$ – see front matter
doi:10.1016/j.amjsurg.2006.01.001

patients admitted to a regional burn center in the United States between 1997 and 2002.

Methods

Study population

This study was approved by the Institutional Review Board of the University of Alabama at Birmingham. Informed consent was obtained as required. The University of Alabama at Birmingham Burn Center is an academic tertiary referral center for patients who sustain burn injuries across the state of Alabama and parts of Georgia, Tennessee, Mississippi, and Florida. Annual admissions are approximately 350 patients. All patients admitted to the University of Alabama at Birmingham Burn Center for at least 2 days between 1997 and 2002 were eligible for participation in this retrospective study.

Study design

A nested case-control design was used. With the nested case-control design, a case-control study is conducted within the context of a larger cohort of study participants. In the present context, the larger cohort was as described earlier. However, for the purposes of the current study, patients who sustained an inhalation injury were excluded. Cases were those patients who developed a complication of infectious etiology during the course of their hospital stay. Included among the potential infectious complications were cellulitis, pneumonia, fungal sepsis, necrotizing fasciitis, sepsis-like syndrome, septicemia, sinusitis, wound infection, yeast infection, urinary tract infection, and graft infection, among others. Although patients could develop more than 1 complication, such patients were eligible to be a case only once and only the first infectious complication was of interest for this study. Controls were selected using incidence density sampling. That is, 1 control was selected randomly from among those patients who had been in the hospital at least as long as the case yet had not developed an infectious complication. Controls also were matched to each case based on age ($<$1 year) and percent total body surface area (TBSA) (within 5%) burned. Comorbidity factors were not assessed in this retrospective study.

Characterization of opiate analgesic use

Information regarding all medications for all study subjects was obtained. Specifically, information regarding the name of the medication, quantity prescribed, and date ordered. For the purposes of this study, the only medications of interest were opiate analgesics. This included morphine SO_4 administered parenterally, morphine SO_4 orally, hydromorphone (Dilaudid; Abbott Pharmaceuticals, North Chicago, IL) parenterally, hydromorphone (Dilaudid) orally, and oxycodone (5 mg in 1 Percocet tablet; Endo Pharmaceuticals, Chadds Ford, PA) orally. Because we were interested in the role of opiate analgesics in the etiology of infectious complications, a summation of each case's opiate analgesic use was truncated to exclude use after the occurrence of their first complication. The exposure period of interest therefore was the time from admission to the date of the first infectious complication. By using the length of each case's exposure period, for the matched control, only those opiate analgesics ordered during the same length interval were considered in the analysis. Thus, for a case who developed the first infectious complication on the fourth day after admission we would use only information pertaining to those opiate analgesics ordered in the first 3 days. For this case's matched control, whose length of stay would have to have been at least 4 days, only those opiate analgesics ordered during the first 3 days would be used in the analysis. This technique ensures that both cases and controls had equivalent periods of time during which to use opiate analgesics. The primary variable of interest was cumulative opiate analgesic use during the exposure period.

It was necessary to express opiate analgesics using a common metric equivalent because of their varying strength. Each opiate analgesic was translated into units of opiate equivalents (OE) of 10 mg morphine SO_4 administered parenterally as previously described [10]. Other opiate dosages equal to 1 OE (10 mg morphine SO_4 parenterally) are 30 mg morphine SO_4 orally, 1.5 mg hydromorphone (Dilaudid) parenterally, 3.0 mg hydromorphone (Dilaudid) orally, and 30 mg oxycodone orally (5 mg in 1 Percocet tablet). To illustrate, 45 mg morphine SO_4 orally, 45 mg oxycodone orally, and 15 mg morphine SO_4 parenterally are each equal to 1.5 OE.

Statistical analysis

Cases and controls were compared with respect to demographic and clinical characteristics using *t* tests and chi-square tests for continuous and categoric variables, respectively. Because of the highly skewed distribution of OE values, the median cumulative OEs for cases and controls were compared using the Kruskal-Wallis test. This test is the nonparametric version of 1-way analysis of variance. Conditional logistic regression was used to compute odds ratios and 95% confidence intervals (CIs) for the association between OEs and the development of infectious complications. The conditional logistic model was used to account for the matched nature of the study design. Cumulative opiate analgesic use (expressed in OEs) was categorized into 2 groups using the 75th percentile of the overall distribution (ie, $\geq$34 OEs [high] vs $<$34 OEs [low]). As to why the 75th percentile was chosen, a series of categorizations were made and through a series of likelihood ratio tests it was determined that a binary variable at the 75th percentile provided the most appropriate fit to the data. *P* values of .05 or less (2-sided) were considered statistically significant.