

Original Article

The Safety and Effectiveness of Pharmacotherapy for Opioid-Overdose Induced Aspiration Pneumonia in a Referral Poisoning Management University Hospital in Iran

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INTRODUCTION

Opioid abuse is widespread throughout the world and is a serious medical problem for the health systems, especially in developing countries. Iran has a high rate of opioid addiction globally, and the most abused substances in this country are opioids.^[1]

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ABSTRACT **Objective:** Opioid abuse is widespread throughout the world. Aspiration pneumonia is a serious problem following opioid overdose and poisoning. This study aimed to evaluate the safety and effectiveness of antimicrobial management of opioid-overdose induced aspiration pneumonia in a referral poisoning management university hospital in Iran. **Methods:** In an observational cross-sectional study (September–March 2019), opioid poisoned patients diagnosed with aspiration pneumonia within a maximum of 48 h of their overdose were evaluated regarding several variables, including the level of consciousness on admission, drug regimen used for the treatment of aspiration pneumonia, and its appropriateness, and the correctness of the used antibiotics dose and the therapeutic outcome. **Findings:** During the study, 53 eligible patients were identified and included in the study. The most frequently abused opioids were methadone (60.4%) and opium (17%). “Ceftriaxone + Clindamycin” (54.7%) and “Meropenem + Vancomycin” (9.5%) were the most frequently administered regimens. Regarding treatment outcome, most cases ($n = 36$, 67.9%) were discharged with a stable and satisfying medical status, while 3.8% of the cases ($n = 2$) died. **Conclusion:** The use of antibiotics in the treatment of aspiration pneumonia in hospitalized patients with opioid overdose in our referral university hospital is associated with notable antibiotic regimen choice issues. The implementation of strategies for improving the pattern of antibiotic prescribing for these patients is necessary.

KEYWORDS: *Antibiotic regimen, aspiration pneumonia, opioid overdose, treatment*

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Aspiration pneumonia is a pulmonary event caused by the abnormal entry of fluid, fine particles from foreign matter, or internal secretions into the lower airways.^[2,3] Decreased consciousness weakens the cough reflex and prevents the glottis from closing, which may be seen in people who abuse illicit drugs, people under anesthesia, and in patients with generalized seizures, making them more susceptible to aspiration pneumonia.^[4] Aspiration pneumonia is one of the serious problems caused by opioid poisoning. Opioid use can reduce alertness and increase the risk of aspiration.^[5] Over time, opioid users develop a weakened immune system and an increased risk of aspiration pneumonia due to inhibition of the production of cytokines and natural killer cells and macrophages.^[6] Therefore, timely and immediate treatment of opioid overdose can result in a better prognosis for these patients.^[5]

The most common type of aspiration pneumonia is bacterial, caused by bacteria that live in the upper part of the airways or stomach. Bacterial aspiration pneumonia is usually caused by anaerobic bacteria, including *Fusobacterium nucleatum*, *Peptostreptococcus* spp., *Pretovella* spp., *Bacteroides melaninogenicus* that can also cause pulmonary abscess and empyema.^[7-9]

Gram-negative bacilli (49%), anaerobes (16%), and *Staphylococcus aureus* (12%) are the most common pathogens causing aspiration pneumonia.^[10]

The choice of antibiotic for the treatment of aspiration pneumonia depends on the origin of the infection (community, hospital, or care center) as well as the risk factors for infection with resistant pathogens (e.g., treatment with various antibiotics in the last 90 days and hospitalization for at least 5 days).^[4]

In community-induced aspiration pneumonia, anaerobic bacteria are the possible causative pathogens, and ampicillin/sulbactam (1.5–3 g IV every 6 h) is recommended for normal renal function people as the first line. Co-amoxiclav (875 mg twice daily) is a good alternative for patients who are not severely ill and can tolerate the oral diet. In penicillin-sensitive individuals who are able to use cephalosporins, a suitable alternative is to combine ceftriaxone (1 or 2 g IV daily) or cefotaxime (1 or 2 g IV every 8 h) with metronidazole.^[5] There are not enough studies on antibiotic therapy duration, but most patients' usual course of treatment usually lasts for 7 days. Patients with pulmonary abscess typically need a more extended treatment course until the symptoms and radiographic findings improve.^[5]

Different antibiotic regimens, even broad-spectrum antibiotics, are prescribed to treat opioid-poisoned

patients, increasing the risk of antibiotic resistance. Therefore, this study aimed to evaluate the pattern of treatment of aspiration pneumonia in patients with opioid overdose in our referral university hospital, which acts as the only poisoning control and treatment center in the central part of Iran (Isfahan), and to identify the existing defects and drug-related issues for the treatment.

METHODS

This cross-sectional study was performed for 6 months from September to March 2019 in the poisoning management ward and intensive care unit (ICU) of Khorshid University hospital, affiliated with Isfahan University of Medical Sciences (IUMS). The ethics committee approved the study protocol of IUMS with the ethics code IR.MUI.RESEARCH.REC.1398.432.

Table 1: Clinical characteristics of the study patients and their poisonings/overdose details

Variable	n (%)
Underlying pulmonary disorder	6 (11.3)
Underlying cardiovascular disorder	3 (5.7)
Chief complaint upon admission	
Low level of consciousness	44 (83)
Dyspnea	5 (9.4)
Low level of consciousness + dyspnea	2 (3.8)
Unreported	2 (3.8)
Overdose type	
Intentional	22 (41.5)
Unintentional	11 (20.8)
Opioid type	
Methadone	32 (60.4)
Opium	9 (17)
Heroin	5 (9.4)
Tramadol	2 (3.8)
Buprenorphine	1 (1.9)
Methadone + opium	1 (1.9)
Unreported	3 (5.7)
Concomitant drug use	
Yes	18 (34)
No	29 (54.7)
Unreported	6 (11.3)
Time of referral from overdose (h)	
<6	7 (13.2)
6–12	15 (28.3)
13–18	7 (13.2)
19–24	2 (3.8)
>24	2 (3.8)
Unreported	20 (37.7)
Duration of hospitalization (days)	
1–3	25 (47.2)
4–7	16 (30.2)
8–14	6 (11.3)
>14	6 (11.3)

The target population in this study were patients poisoned with any opioids who were admitted to the hospital during the study with a diagnosis of aspiration pneumonia. The inclusion criteria of patients were: (1) age >18 years; (2) having the clinical triad signs of opioid poisoning including central nervous system depression, respiratory depression, and miosis; and (3) being diagnosed with aspiration pneumonia within a maximum of 48 h after the opioid overdose or poisoning.

We recorded age, gender, the most probable abused opioid, type of overdose (intentional vs. accidental), use of other opioid-containing substances or drugs, chief complaint on admission, the level of patients' consciousness on admission, intubation status before pneumonia, history of underlying pulmonary or cardiovascular disease, the time elapsed from abuse to hospitalization, duration of hospitalization in ICU, the total duration of hospitalization, drug regimen used for the treatment of aspiration pneumonia and its appropriateness, and the correctness of dose of treatment regimens used in the treatment of aspiration pneumonia and therapeutic outcome. The treatment regimen's accuracy and the estimated amount of the abused drugs were investigated and documented based on reliable and accessible sources.^[11]

The source of data collection was patients' medical records. The treatment outcome was recorded in five forms: Discharge in good general condition, discharge with symptoms and laboratory information confirming aspiration pneumonia (fever, leukocytosis, and crackles), discharge with intubation, discharge with consent, and death.

We used SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) for the descriptive statistical analysis of our data.

RESULTS

In this study, 53 eligible patients were identified and included. The most frequently abused opioids were methadone (60.4%) and opium (17%). Furthermore, 34% of patients used concomitant drugs. The mean elapsed time from an overdose to the hospitalization in the studied patients was 10.79 ± 9.06 h. The most common complaint in patients was decreased level of consciousness (83%). The mean duration of hospital stay in the studied patients was 7.02 ± 9.71 days [Table 1].

The results of treatment variables in the studied patients are shown in Table 2. "Ceftriaxone + Clindamycin" was the most frequently administered regimen (54.7%)

Table 2: The type, characteristics, and the outcomes of treatment regimens in the study patients

Variable	n (%)
Antibiotic regimen	
Ceftriaxone + clindamycin	29 (54.7)
Ampicillin/sulbactam + meropenem	1 (1.9)
Ampicillin/sulbactam + levofloxacin	1 (1.9)
Ceftriaxone + levofloxacin	2 (3.8)
Ceftazidime + clindamycin	4 (7.6)
Levofloxacin	3 (5.7)
Meropenem + levofloxacin + vancomycin	1 (1.9)
Meropenem + clindamycin	1 (1.9)
Meropenem + levofloxacin + linezolid	1 (1.9)
Meropenem + linezolid	1 (1.9)
Meropenem + teicoplanin	1 (1.9)
Meropenem + vancomycin	5 (9.5)
Metronidazole + ampicillin	1 (1.9)
Piperacillin/tazobactam + levofloxacin	1 (1.9)
Piperacillin/tazobactam + levofloxacin + teicoplanin	1 (1.9)
The correctness of antibiotic regimen	36 (67.9)
The correctness of antibiotics dose	50 (94.3)
Treatment outcome	
Discharge with good state	36 (67.9)
Discharge with fever	3 (5.7)
Discharge with crackle and/or wheezing	3 (5.7)
Discharge with intubation	1 (1.9)
Discharge with bad state (personal consent)	8 (15.1)
Death	2 (3.8)

followed by "Meropenem + Vancomycin" (9.5%) and Ceftazidime + Clindamycin" (7.6%). The prescribed regimen was correct in 67.9% of patients ($n = 36$). Furthermore, the prescribed dose was correct in 93.4% of cases ($n = 50$). Regarding treatment outcome, most cases ($n = 36$, 67.9%) were discharged with good state, while 3.8% of cases ($n = 2$) died.

DISCUSSION

In our study, the most commonly used opioid was methadone, possibly due to its availability through the open market, pills, and syrups among methadone dosage forms, and consequently, greater ease of use in treating addicted patients maintenance treatment protocol. Hence, restricting access to methadone and preventing it from being sold in the open market can reduce methadone poisoning.

The most commonly prescribed antibiotic regimens in the patients were ceftriaxone + clindamycin (54.7%) and meropenem + vancomycin (9.5%). Furthermore, our study showed that in 32% of patients, the prescribed antibiotic regimen was incorrect according to the empiric therapy guideline for aspiration pneumonia and the outcomes of therapy. Therefore, appropriate

strategies, including educational programs, are necessary for our hospital to improve the rational use of antibiotics in treating opioid overdose patients with aspiration pneumonia.

Of note, similar studies have not been conducted to evaluate the status of drug treatments of aspiration pneumonia in patients poisoned with opioids and their treatment outcomes. However, in recent years, several studies have been performed on the epidemiological features and therapeutic outcomes in people with various poisonings, including opioids, regardless of the incidence of aspiration pneumonia. In a study conducted in 2016–2017 in the ICU of Noor and Ali Asghar (PBUH) hospital on 206 patients with drug intoxication,^[12] 104 patients had aspiration pneumonia, of whom 53% were referred to the hospital with a decrease in the level of consciousness upon arrival, which is much lower than the current study (92.5%). Besides, 21.4% had a history of lung disease, which is higher than the present study (11.3%), and 3.9% had a history of cardiovascular disease, which is slightly less than the current study (5.7%). The mean time interval elapsed from an overdose to the hospitalization in patients was 11.01 ± 9.55 h, which was slightly higher than our study (10.79 ± 9.06 h). In terms of treatment outcome, 10.6% died, which is more than the current study (3.8%) and 65.4% had uncomplicated recovery compared to the present study (67.9%) is slightly less, which is due to the difference between the criteria evaluated between the two studies because in the study of 2016–2017, the treatment outcomes studied were uncomplicated recovery, complication recovery, and death, which means complication. In this study, kidney disease, rhabdomyolysis, liver or other organ involvement, while the therapeutic outcome in the current study, discharge in good general condition, discharge with symptoms and laboratory information confirming aspiration pneumonia (fever, leukocytosis, and crackles), discharge with intubation has been discharged with consent and death.

In another study conducted in 2010–2012 in the poison ward of Noor and AS hospitals on 385 patients with methadone poisoning, regardless of aspiration pneumonia,^[13] 14.3% of patients received other drugs at the same time as methadone (Opioids) which is less than the present study (34%).

Deliberate poisoning was observed in 57.7% of patients, which is higher than the present study (41.5%). The mean time elapsed from opioid abuse to the hospitalization in patients was 7.3 ± 8.4 h, which is lower than our study's results (10.79 ± 9.06 h).

Moreover, 58.2% of the patients admitted to the hospital have a low level of consciousness, much less than the current study (92.5%). Since the present study only included patients with aspiration pneumonia and one of the important predisposing factors in aspiration pneumonia is a decreased consciousness level, this significant difference in the rate of this presenting symptom between the two studies can be justified.

In another study conducted in 2012–2013 in the same medical setting (poison management ward of Noor and Ali Asghar [PBUH] hospital) on 433 patients with methadone poisoning, regardless of aspiration pneumonia,^[14] 19.7% of patients used other concomitant drugs with methadone which is lower than our findings (34%). The mean duration from opioid abuse to the hospitalization in patients was 6.6 ± 1.1 h, which was less than the current study (10.79 ± 9.06 h).

In a 2010–2015 study of 234 patients with opioid poisoning aspiration pneumonia in Austria,^[15] morphine was the most commonly used opioid (85.5% of patients), while in our study, methadone was the most frequently abused opioid (60.4% of patients). Therefore, the most commonly used opioid may be different in various regions, with all types having the potential for causing aspiration pneumonia.

The most commonly prescribed antibiotic regimens were ceftriaxone + clindamycin and meropenem + vancomycin in the present study. Furthermore, the prescribed regimens were incorrect or ineffective in 32% of patients. Of note, as the patients included in our study had community-acquired aspiration pneumonia, considering that anaerobic bacteria are the predominant pathogens in this type of pneumonia,^[7-9] the use of meropenem in combination with other drugs such as vancomycin could be considered because vancomycin lacks appropriate coverage for anaerobic bacteria. Besides, since carbapenems are the last-line for therapy of infections in cases of treatment failure, unnecessary administration of these agents can increase the risk of microbial resistance; therefore, their use in patients with aspiration pneumonia should be limited to hospital-acquired infections, in which aerobic bacteria especially Gram-negative bacilli have a significant causative role. Another critical point finding in our study is the costliness of meropenem among the antibiotics with a similar antimicrobial spectrum, and in the case of irrational prescription, the cost of this drug will be imposed on the patient and the health system. One of the essential measures to improve antibiotics' rational use and reduce errors is training medical staff regarding therapeutic guidelines and protocols. A study in 2005–2006 evaluated the utilization

of three broad-spectrum antimicrobials cefepime, piperacillin-tazobactam, and meropenem, appropriate use of meropenem increased from 79% to 89% with a 1-month training program.^[16]

We conclude that empiric antibiotic therapy for the treatment of aspiration pneumonia in patients with opioid overdose hospitalized in our university hospital setting was not appropriate and rational and was associated with preventable drug issues regarding antibiotic regimen choice. Implementation of strategies for improving the pattern of antibiotic prescription for these patients is necessary.

AUTHORS' CONTRIBUTION

Ali Mohammad Sabzghabae, Gholamali Dorvashy, and Shiva Samsamshariat have conceptualized the idea for this drug utilization research, Mohammadreza Tabatabaei and Rokhsareh Meamar gathered the data, Rasoul Soltani analyzed the data and drafted the manuscript. All authors contributed to revising and approved the manuscript and are responsible for the research integrity.

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Conflicts of interest

There are no conflicts of interest.

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