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Research Paper: Ampicillin-Sulbactam for the Treatment of Aspiration Pneumonia in Patients with Opioid Overdose: A Randomized Controlled Clinical Trial

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ABSTRACT

Background: Aspiration pneumonia is among overdose complications, requiring timely appropriate treatment. The present study aimed to evaluate the effects of ampicillin-sulbactam, compared to our usual regimen ceftriaxone + clindamycin on aspiration pneumonia in opioid-poisoned patients.

Methods: In a randomized-controlled clinical trial, opioid-poisoned patients with aspiration pneumonia were randomly divided into the experimental and control groups to receive ampicillin-sulbactam 3 g Intravenously (IV) every 6 hours (experimental group) and ceftriaxone 1 g IV every 12 hours + clindamycin 600 mg IV every 8 hours (control group) followed by co-amoxiclav 625 mg orally every 8 hours and cefixime 400 mg once daily + clindamycin 600 mg orally every 8 hours in experimental and control groups, respectively, to complete a 7-day course of therapy. White blood cell count and temperature (axillary) at baseline and the third day of the intervention and the treatment outcome on the third day of the intervention, defined as either complete response, partial response, or failure, were evaluated and recorded for all patients.

Results: Except for the number of cases of leukocytosis on the third day of the intervention, i.e., lower in the control group (5 patients, 26.30%) than the experimental group (13 patients, 68.40%) (P=0.020), no significant difference was observed between the study groups regarding other outcome variables. Clinical response was similar between the study groups; so that, 10.50% and 63.20% of patients in the experimental group and 21.10% and 47.4% of patients in the control group presented complete and partial responses, respectively (P=0.550).

Conclusion: The obtained data suggested that ampicillin-sulbactam is an effective antibiotic for the treatment of aspiration pneumonia in patients with opioid overdose, in which case, it has the same efficacy as the two-drug regimen of ceftriaxone + clindamycin.

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1. Introduction

Aspiration pneumonia is a pulmonary disorder caused by the abnormal entry of fluid, fine particles from foreign matter, or internal secretions into the lower airways [1, 2].

Decreased level of consciousness impairs the cough reflex and prevents glottis closure, which may be observed in individuals who abuse illicit drugs, those under anesthesia, and in patients with generalized seizures, making them more prone to aspiration pneumonia [3]. Opioid poisoning, by reducing the level of consciousness, can increase the risk of aspiration and subsequent pneumonia [4]. Furthermore, opioid use increases the risk of aspiration pneumonia by weakening the immune system due to inhibiting the production of cytokines and natural killer cells and macrophages [5].

The most common type of aspiration pneumonia is an infection induced by bacteria living in the upper airways and stomach. Bacterial aspiration pneumonia usually occurs due to anaerobic bacteria such as *Fusobacterium nucleatum, Peptostreptococcus spp., Prevotella spp., Bacteroides melaninogenicus*, and other Bacteroides species [6-8]. However, gram-negative bacilli (49%) and *Staphylococcus aureus* (12%) are also common pathogens of aspiration pneumonia [9].

Timely and immediate treatment of aspiration pneumonia can help improve the prognosis of patients [10]. The primary therapy for infectious aspiration pneumonia is using antibiotics. Ampicillin-sulbactam is considered the first line of treatment for people with normal renal function. Other alternative regimens with limited clinical data include metronidazole with either penicillin G or ceftriaxone. Clindamycin is a good choice for individuals allergic to penicillin [10-12].

The usual regimen used in numerous medical centers, including our poisoning treatment center, is a combination of ceftriaxone and clindamycin [13]. Despite its advantages, such as low cost and availability and no need for dose adjustment in renal impairment, it has several disadvantages, including increased risk of drug side effects (e.g. pseudomembranous colitis) and the cost of managing these complications. Moreover, the efficacy of ampicillin-sulbactam in the treatment of aspiration pneumonia in patients with opioid overdose remains unevaluated. Therefore, this study aimed to assess the effects of ampicillin-sulbactam and compare it with ceftriaxone + clindamycin regimen in treating aspiration pneumonia in this group of patients.

2. Materials and Methods

This randomized controlled clinical trial with two parallel groups was performed from July 2019 to July 2020 in Khorshid Educational and Research Complex affiliated with Isfahan University of Medical Sciences in Isfahan City, Iran. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Code: IR.MUI.RESEARCH.REC.1398.432). In addition, the study was registered in the Iranian Registry of Clinical Trials (Code: IRCT20090808002306N5).

Patients were selected from those referred to the hospital poisoned patients ward. Informed written consent was obtained from all patients enrolled in the study. The inclusion criteria were age over 18 years; a diagnosis of opioid overdose based on the history and physical examination confirming three clinical signs of opioid poisoning (CNS depression, respiratory depression, and miosis). Respiratory rate <12/minute was highly predictive of response to naloxone in one series [14]; and the diagnosis of bacterial aspiration pneumonia in the first 48 hours of hospitalization. The diagnosis of aspiration pneumonia was based on the presence of infiltration in the chest radiograph, dullness to percussion of the chest, and rales in chest auscultation, with at least one of the following clinical criteria [15]: a) Fever (axillary temperature ≥37 °C), b) Leukocytosis determined by White Blood Cell (WBC) count >11000 cells/mm^3, and c) Purulent sputum or tracheal secretion.

The exclusion criteria were as follow: taking antibiotics or immunosuppressive drugs in the last two weeks; mechanical ventilation for >48 hours; pregnancy; breastfeeding; known allergy to the studied antibiotics; the diagnosis of nosocomial aspiration pneumonia; pulmonary abscess, and empyema.

Demographic and clinical information of all study patients, including age, gender, type of abused opioid, WBC count, and temperature were recorded. Of note, the baseline clinical characteristics were defined as the features at the time of diagnosis. The examined patients were randomly divided into experimental and control groups using Research randomizer software, i.e., available online (URL: www.randomizer.org).

Patients in the experimental group received ampicillin-sulbactam (Jaber-Ebne Hayyan Co., Iran) 3 g IV every 6 hours, while, the patients in the control group received ceftriaxone (Exir Co., Iran) 1 g IV every 12 hours with clindamycin (Caspian Co., Iran) 600 mg IV every 8 hours [10, 13]. In both groups, the patient was discharged in

case of improvement in the clinical status and fever relief for 24-48 hours. The treatment was changed to the oral regimen, including co-amoxiclav 625 mg every 8 hours and cefixime 400 mg once daily + clindamycin 600 mg every 8 hours in experimental and control groups, respectively, to complete a 7-day course of therapy. All supportive measures, including oxygen therapy, chest physiotherapy, hydration, nutritional support, and prevention of Deep Vein Thrombosis (DVT) and pulmonary emboli, were performed for both groups if indicated.

WBC count and temperature (axillary) at baseline and on the third day of the intervention and the outcome of treatment on the third day of the intervention, defined as either complete response, partial response, or failure, were evaluated in all patients. Complete response was defined as the resolution of clinical symptoms (the cessation of fever & the normalization of lung auscultation) and the elimination of leukocytosis (WBC count $\leq 11000/mm^3$), relative response as the reduction of WBC count, the cessation of fever, and the improvement of respiratory sounds in lung auscultation, and failure as persistent fever and leukocytosis and abnormal lung auscultation. The physician judged the therapeutic outcome. Possible adverse effects of treatments were also recorded during the study period. The primary outcome measures included the changes of WBC count and temperature on the third day of the intervention compared to baseline, the number of cases of leukocytosis and fever on the third day of treatment, and the number of partial and complete responses and failure on the third day. The secondary outcome measure included the number of deaths during the intervention.

Sample size estimation

We used Epi info 7.1.0.6 to estimate the required sample size for our study. To detect at least a 10% difference in the cure rate between the control group (ceftriaxone + clindamycin) and experimental group (ampicillin - sulbactam), assuming 70% cure rate in our usual regimen with an 80% power and a 5% type I error, 18 subjects were needed in each group (36 for both arms).

3. Results

In the current study, 86 patients were evaluated for eligibility to participate. Based on the inclusion and exclusion criteria, 56 patients were admitted to the study and randomly divided into two groups. During the study, 11 patients in the experimental group and 7 patients in the control group were excluded (Figure 1).

Table 1 suggests the patients' baseline demographic and clinical characteristics (at the time of diagnosis) in the two groups. As shown, there was no significant difference between the two groups regarding these characteristics.

Table 2 lists the comparison of the two groups in terms of outcome parameters. As per the table except for the number of cases of leukocytosis on the third day of the intervention, which was lower in the control group (5 patients, 26.30%) than the experimental group (13 patients, 68.40%) (P=0.020), no significant differences were observed between the study groups in other parameters. The mean length of hospital stay in the experimental group was shorter than that in the control group; however, this difference was not statistically significant. Furthermore, no deaths occurred in either group during the interventions.

Concerning adverse effects, only one case of creatinine rise was observed in the experimental group, which resolved after early discontinuation of the antibiotic and conversion to ceftriaxone + clindamycin antibiotic regimen. Of note, this patient was excluded from the study.

4. Discussion

The present study results indicated the good and similar effectiveness of ampicillin-sulbactam and ceftriaxone + clindamycin treatment regimens on managing aspiration pneumonia in patients with opioid overdose. This is the first clinical study comparing these two treatment regimens in this group of poisoned patients to the best of our knowledge. However, several studies were performed on other groups of patients.

In a study conducted in Germany on 95 patients with aspiration pneumonia and pulmonary abscess [16], two treatment regimens of ampicillin-sulbactam and clindamycin ± cephalosporin (cefotiam, cefuroxime, ceftazidime, cefotaxime, and ceftriaxone) were compared. Consistent with our results, it was reported that the two treatment regimens are not significantly different respecting effectiveness, including partial and complete response [16].

In another study conducted on 1274 patients with aspiration pneumonia in Japan, a comparison of two treatment regimens ampicillin-sulbactam, and ceftriaxone, revealed that the two treatment regimens were similarly effective concerning in-hospital mortality rate [17].

Table 1. Baseline demographic and clinical characteristics of the study patients

Characteristic	Mean±SD / No. (%)		P
	Case Group (n=19)	Control Group (n=19)	
Age (y)	39.11±12.52	42.61±28.16	0.470
Gender			
Male	18	16	0.600
Female	1	3	
Type of opioid			
Methadone	13	13	
Opium	2	2	
Heroin	2	2	
Tramadol	-	1	0.700
Methadone + Heroin	1	-	
Methadone + Opium	-	1	
Unknown	1	-	
WBC count (cells/mm^3)	12.76±4.85	12.28±4.27	0.750
Leukocytosis	13 (68.40)	13 (68.40)	1.000
Temperature (°C)	37.72±0.44	37.71±0.68	0.950
Fever	15 (78.90)	12 (63.20)	0.480

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In another study conducted on 100 elderly patients aged 71-94 years with aspiration pneumonia in Japan, the comparison of four antibiotic regimens, including ampicillin-sulbactam 3 g twice daily, ampicillin-sulbactam 1.5 g twice daily, clindamycin 600 mg twice daily, and panipenem-betamipron presented no significant difference in efficacy [18]. Another study, performed on 96 patients with aspiration pneumonia in Germany, compared ampicillin-sulbactam and moxifloxacin treatment regimens. The relevant results indicated that the two treatment regimens were not significantly different in clinical response [19].

In summary, the mentioned studies indicated that in treating patients with aspiration pneumonia, ampicillin-sulbactam has comparable efficacy with some other antibiotic regimens such as clindamycin ± cephalosporin, clindamycin monotherapy, and moxifloxacin monotherapy. Therefore, it is crucial to design cost-effectiveness studies to determine the best treatment option for this infectious disease.

The length of hospital stay in the experimental group (6.83±4.18 days) was shorter than the control group (8.44±8.0 days), although the difference was insignificant. Thus, increasing the follow-up duration of the study (e.g. up to 7 days) might show a more significant efficacy of ampicillin-sulbactam. We did not follow up the patients after discharge because of their non-compliance for coming back to the clinic, as the patients with substance use disorders tend to be less adherent to treatment measures [20].

Overall, this study demonstrated the non-inferiority of ampicillin-sulbactam to ceftriaxone/clindamycin regimen in treating opioid poisoning-induced aspiration pneumonia. Therefore, considering similar effectiveness, lower cost, more safety (e.g. lower rate of pseudomembranous colitis), and less burden of antibiotic vials for administration due to monotherapy (versus dual therapy), ampicillin-sulbactam could be a better choice for treatment of this severe complication of opioid-poisoned patients.

Table 2. The changes of evaluated parameters during the study in the patients and their comparison between the study groups

Parameter	Time	Mean±SD / No. (%)		P
		Case Group (n=19)	Control Group (n=19)	
WBC count (cells/mm³)	Baseline	12.76±4.85	12.28±4.27	0.750
	Day 3	10.70±2.94	9.21±3.38	0.160
	Discharge	9.47±2.49	7.66±2.88	0.110
Leukocytosis	Baseline	13 (68.40)	13 (68.40)	1.000
	Day 3	13 (68.40)	5 (26.30)	0.020
	Discharge	6 (31.46)	4 (21.10)	0.220
Temperature (°C)	Baseline	37.72±0.44	37.71±0.68	0.950
	Day 3	37.61±0.64	37.45±0.45	0.350
	Discharge	37.07±0.58	37.05±0.38	0.770
Fever	Baseline	15 (78.90)	12 (63.20)	0.480
	Day 3	12 (63.20)	12 (63.20)	1.000
	Discharge	4 (21.10)	4 (21.10)	1.000
Clinical response – Partial response	Day 3	12 (63.20)	9 (47.40)	
Clinical response – Complete response	Day 3	2 (10.50)	4 (21.10)	0.550
Clinical response – Failure	Day 3	5 (26.30)	6 (31.60)	
Duration of hospitalization (days)	-	6.83±4.18	8.44±8.50	0.470

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5. Conclusion

As a single-drug regimen, ampicillin-sulbactam is an effective and safe antibiotic for the treatment of aspiration pneumonia in patients with opioid overdose; in which case, it has the same efficacy as the two-drug regimen ceftriaxone + clindamycin. Further studies with larger sample sizes and longer durations are necessary to support this finding.

The main limitations of our study were the short duration of follow-up and low sample size, i.e., mainly due to the occurrence of Coronavirus Disease 2019 (COVID-19) pandemic during the research and the subsequent reduction of hospitalization for other indications in our hospitals. However, the present study has the advantage of being the first study evaluating such a severe clinical issue.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information. They were free to leave the study whenever they wished, and if desired, the research results would be available to them. Written consent has been obtained from the subjects. Principles of the Helsinki Convention were also observed. Also, the study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (Code: IR.MUI.RESEARCH.REC.1398.432).

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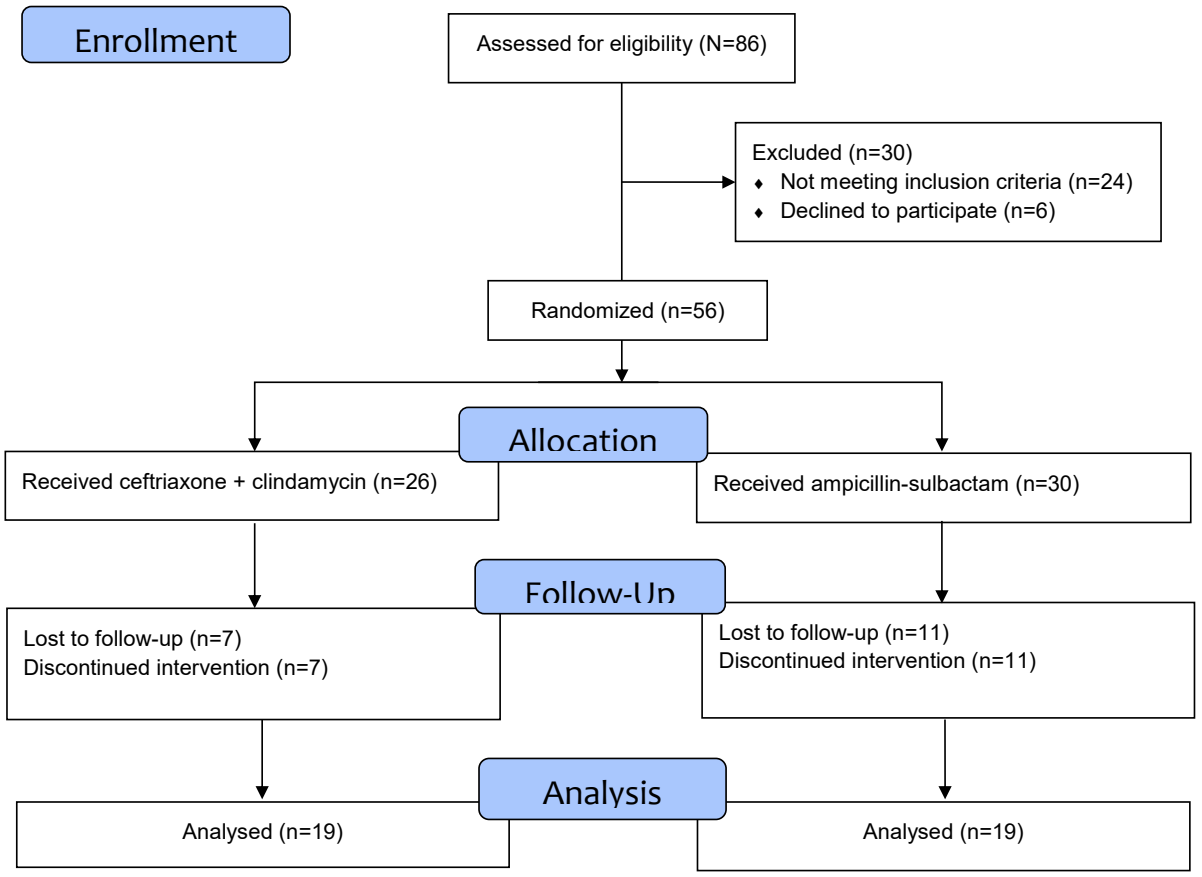

Figure 1. CONSORT Flow diagram of the study

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Author's contributions

Conceptualization and supervision: Rasool Soltani, Gholamali Dorooshi, and Ali Mohammad Sabzghabaee; Methodology: Rasool Soltani, Gholamali Dorooshi, Ali Mohammad Sabzghabaee, Shiva Samsamshariat, and Rokhsareh Meamar; Investigation, writing - original draft, and writing - review & editing: All authors; Data collection: Mohammadreza Tabatabaei; Data analysis: Rasool Soltani; Funding acquisition and resources: Ali Mohammad Sabzghabaee.

Conflict of interest

The authors declare no conflict of interest.

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