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Assessment of the efficacy of low dose hydrocortisone Infusion in severe community Acquired Pneumonia

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Abstract: Background: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide. Despite the developments in antibiotic therapy, no substantial progress has been made in the last decades. Additional therapeutic interventions along with antibiotics may help to improve outcome in patients with CAP. **Aim of the Work:** to assess the efficacy of low dose hydrocortisone Infusion in severe community-acquired pneumonia. The current study was conducted on 70 patients, attending Ain Shams University Hospital, with clinical or radiological findings of community-acquired pneumonia, they were assessed clinically, radiologically and haematologically. These hospitalized patients were classified into 2 groups: Control group included 35 patients with community acquired pneumonia receiving a placebo infusion (control group). Intervention group included 35 patients with community acquired pneumonia randomly receiving 200 mg hydrocortisone (2 hydrocortisone vials, 200 mg / 4 ml) intravenously for 7 days (intervention group). **Results:** In our study, there is statistically non-significant difference between the studied groups regarding age or gender. In the current study, there are statistically non-significant differences between the studied groups regarding respiratory rate, HCO_3, SpO_2, CRP and GCS at the first day. On the other hand, there are significant differences between both groups regarding respiratory rate, HCO_3, SpO_2, CRP and GCS on third and seventh day. On measuring change over time in each group, there are significant fluctuations in respiratory rate, HCO_3, SpO_2, CRP and GCS over time. On the other hand, there are significant differences between both groups regarding pulse, systolic blood pressure, pH, PCO_2 and TLC on the seventh day. On measuring change over time in each group, there are significant changes in pulse, systolic blood pressure and TLC over time and there is significant increase in pH and PCO_2 over time in the hydrocortisone group, while there are non-significant changes in pH and PCO_2 in placebo group. On measuring change over time in each group, there is significant fluctuation in diastolic blood pressure over time. There are statistically non-significant differences between the studied groups regarding temperature, random blood sugar and serum creatinine at the first, third or seventh day. On measuring change over time in each group, there are significant fluctuations in temperature, random blood sugar and serum creatinine over time. However, there are a significant difference between them regarding presence of pleural effusion on first day and a non-significant difference between them regarding pleural effusion on 7th day. Also, there are significant differences between the studied groups regarding percent change in respiratory rate, pulse, systolic, diastolic blood pressure, temperature, GCS, PCO_2, PCO_2, C-reactive protein, total leucocytic count, random blood sugar and serum creatinine. **Conclusion:** We found that in patients with severe community-acquired pneumonia, control of inflammation with prolonged low-dose hydrocortisone infusion hastens resolution of pneumonia and prevents the development of sepsis-related complications. A course of low-dose hydrocortisone infusion was associated with a significant reduction in duration of mechanical ventilation, hospital length of stay, and hospital mortality.

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Key words: low dose, hydrocortisone infusion, pneumonia

1. Introduction

Pneumonia is the most prevalent infectious respiratory disease. It entails high morbidity and mortality and large health care system expenses. Community-acquired pneumonia (CAP) is one of the 10 leading causes of death worldwide. Approximately 20% of CAP patients require hospitalization, 25% of whom are admitted to an intensive care unit (ICU) and have a mortality rate of 30–50%[(1)].

Despite progress in life-support measures and antimicrobial therapy, the mortality of severe pneumonia has not varied since the mid-1990s, suggesting that other factors are of crucial importance in the evolution of this respiratory infection [(2)].

Antimicrobial treatment has been acknowledged as the cornerstone of the management of patients with community-acquired pneumonia (CAP) [3].

Indeed, the case fatality of untreated bacteraemic pneumococcal pneumonia was initially ≥80%, while the introduction of antimicrobials led to a reduction of its associated mortality to 20%. Thus, guidelines on the management of CAP focus mainly on issues dealing with the administration of antimicrobial agents (namely, selection of the most appropriate regimen, timing, dosage, route and duration of its administration) [4].

However, even with the prescription of newer and more potent antimicrobial agents, the mortality due to CAP remains relatively constant [5].

A major role of aetiological testing in CAP is to enable the use of pathogen-directed therapy, and thus reduce the use of broad-spectrum antibiotics. As it is recommended that the antibiotic therapy should be started within 4 h of hospital admission [4, 6], rapid tests with a shorter analysis time can be used to influence the choice of first-line antibiotic therapy. Sputum Gram strain for respiratory pathogens is example of such rapid tests.

Less rapid tests, such as cultures for respiratory pathogens can provide useful information that may support ongoing antibiotic therapy, support narrowing of broad-spectrum therapy, and support therapy changes in case of treatment failure [7]. Culture of blood and respiratory specimens may be essential for the identification of unexpected or uncommon CAP aetiologies that the empirical treatment does not cover for, e.g., Pseudomonas spp., methicillin-resistant S. aureus, and other highly resistant pathogens. Culture remains a cornerstone of the diagnostic techniques, as it can provide information about antibiotic susceptibility.

In cases of therapy failure, when conventional methods have failed to identify the CAP aetiology, diagnostic bronchoscopy should be considered [8]. Cultures from tracheobronchial secretions, bronchoalveolar lavage (BAL), and mini-BAL are sensitive and specific methods [9]. Commonly used cut-offs for positive results are 10^4 CFU/mL for BAL fluid [10] [9] and 10^3 CFU/mL for mini-BAL [11].

Corticosteroids have been proved to block several arms of the inflammatory cascade. In detail, genes encoding proinflammatory proteins and those encoding anti-inflammatory mediators can be switched off and switched on, respectively by corticosteroids [14, 15].

Corticosteroids diminish plasma extravasation of mediators, inhibit the adhesion and migration of leucocytes across the capillary wall and prevent the release of proinflammatory mediators [16] Inpatients with severe CAP, a systemic inflammation can occur, and hence, administration of corticosteroids has been advocated for this purpose [17].

Monton, Ewig [16] reported that, among patients with severe community-acquired pneumonia requiring mechanical ventilation, those who received steroid had an attenuated systemic and pulmonary inflammatory response and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications and mortality.

Aim of the work

To evaluate the impact of hydrocortisone infusion as an adjuvant in community acquired pneumonia (CAP) on clinical recovery and hospital outcome. Also its role in attenuation of systemic inflammation and reduction of sepsis -related complications.

Patients and methods

Patients:

This randomized double-blinded placebo-controlled clinical trial included 70 patients, attending Ain Shams University Hospital, from November 2018 up to 6 months to one year or till the number required is achieved.

The study included patients with ages 18-80 years from both sexes with symptoms and signs of severe community-acquired pneumonia including: extent of infiltration on the chest X-ray examination → More than 2/3 area of one lung is infiltrated, body temperature → ≥38.6 °C, pulse rate → ≥130/minute., Respiratory rate → ≥30/minute., Dehydration → (+)., WBC → ≥ 20,000/mm^3 or<4,000/mm^3, CRP → ≥ 20 mg/dL, PaO2 → <60 Torr Spo2< 90%. Ratios of PaO2 to fraction of inspired oxygen (FiO2) (PaO2:FiO2) less than 250. Chest radiograph showing bilateral involvement or multi-lobar involvement.

While patinets with ages < 18 - > 80 years, nosocomial pneumonia, severe immuno-suppressed patients, acute burn injury, apreexisting medical condition with a life expectancy less than 3 months, pregnancy, patients with asthma, chronic chest problems, patients with hospital-acquired pneumonia and patients with TB pneumonia, a major gastrointestinal bleeding within 3 months of the current hospitalization and active gastrointestinal bleeding event requiring transfusion of five units Packed Red Blood Cells (PRBC) were excluded from the study.

Patients' classification:

These hospitalized patients, with clinical or radiological findings of community-acquired pneumonia (CAP) using standard clinical and radiological criteria, were classified into 2 groups: Control group included 35 patients with community acquired pneumonia receiving a placebo infusion (control group). Intervention group included 35 patients with community acquired pneumonia

randomly receiving 200 mg hydrocortisone (2 hydrocortisone vials, 200 mg / 4 ml) intravenously for 7 days (intervention group).

Methods:

Written informed consent for the study participation was obtained from legal guardians of the patient before recruitment. All studied patients in this study were subjected to the following: Full medical history: Personal history including age, sex and residence. Analysis of the present illness including symptoms of respiratory infection including: cough, dyspnea, and shortness of breath, etc……. History of previous pneumonia. History of other systemic diseases. Clinical examination: All patients included in this study were subjected to thorough general and local examination with special emphasis on:- Temperature.- Respiratory rate.- Retractions.- Auscultatory findings:* Air entry.* Grunting.* Cyanosis.* Chest wheezes.* Crepitations.- Signs of respiratory distress as tachypnea, working ala nasi and sub-costal and intercostal retractions. Local chest examination: Inspection: Shape of the chest, anteroposterior diameter, deformity, chest expansion, retractions and any visible pulsations. Palpation: Position of trachea, apex, assessment of respiratory movement and tactile vocal fremitus. Percussion: Assessment of the degree and equality of resonance Auscultation: Breath sounds as regards intensity, quality, prolongation of expiration and vocal resonance. Adventitious sounds as wheezes and crepitations. Radiological assessment: All patients included in the study were subjected to plain chest X-ray examination (postero-anterior view) on admission and follow-up X ray and to non-contrast head CT on admission, 24 hours or any time if deterioration occurs. Routine Laboratory assessment: Routine laboratory tests included complete blood count, WBC including total and differential counts and platelet count), CRP and PCT. Venous blood was taken through venipuncture to obtain blood sample once patients were admitted to the hospital and the sample taken on EDTA for complete blood picture. Treatment assignments: Patients were randomly assigned in a 1:1 manner to receive hydrocortisone infusion or placebo (sterile normal saline in a volume equal to the study drug). Hydrocortisone was given as an intravenous 200-mg loading bolus at a rate of 20 mg/hour for 7 days.

Method of treatment:

According to the Ain-shams ICU protocol for treatment of severe community-acquired pneumonia: Oxygenation: O2 supplementation (maintain PaO2 > 60 mmHg or SaO2 > 90%). Hemodynamic optimization: IV fluid (inotropic support) to maintain mean BP > 65 mmHg and UOP > 0.5-1 mL/Kg/hr. Nutritional therapy: Enteral nutrition preferred → preservation of immune function. Chest Physical Therapy (CPT): Aid sputum clearance and sample collection for further microbiology Corticosteroids: Corticosteroids may aid resolution and correct relative adrenocortical insufficiency in critically ill patients who require inotropic support for shock. Aerosol humidity: Mucolytic (e.g. N-acetylcysteine) can precipitate broncospasm. B2-agonists best reserved for patients with COPD or asthma. Antibiotic therapy: Initial therapyo Third-generation cephalosporin with macrolide (IV) oro Fluoroquinolone with third-generation cephalosporine When P.aeruginosa considered Antipseudomonal bete-lactam with antipseudomonal quinolone or aminoglycoside. Suspected MRSA Consider covering for community-acquired MRSA vancomycin. Ventilation support: Ventilatory support either invasive or Non-invasive in the following conditions: Persisting hypoxemia (PaO2<69mmHgdespite high FiO2). Progressive hypercapnia. Sever acidosis (pH<7.2). Shock. Depressed consciousness. Alveolar recruitment strategies using PEEP improve oxygenation (ventilator modes that avoid high Peak and alveolar hyperinflation are optimal).

Table (1) Comparison between the studied groups regarding special habits and past history

Special habits and past history	Study groups		Test	
	Hydrocortisone group N=35 (%)	Placebo group N=35 (%)	X^2/t	p
Smoking:				
No	7 (20)	14 (40)	3.333	0.068
Yes	28 (80)	21 (60)		
Drugs:				
No	28 (80)	33 (94.3)	Fisher	0.151
Yes	7 (20)	2 (5.7)		
Past history:				
Irrelevant	14 (40)	17 (48.6)	0.521	0.47
Relevant	21 (60)	18 (51.4)		

Primary endpoints: It is time to clinical stability, which is defined as follows: time (days) until stable vital signs for ≥ 24 hours: temperature ≤ 37.8°C without antipyretic agents, heart rate/minute ≤ 100, spontaneous respiratory rate ≤ 24 per minute, systolic blood pressure ≥ 90 mmHg (≥ 100 mmHg for patients diagnosed with hypertension) without vasopressor support, mental status back to level before CAP and adequate oxygenation on room air of oxygen therapy (PaO2 ≥ 60 mmHg or pulse oximetry ≥ 90%).

Secondary endpoints: We assessed the effect of adding a low dose corticosteroid within the test group against: Number of patients who need a mechanical ventilation. Duration of mechanical ventilation. Length of ICU stay. Mortality rate.

3. Results

There is statistically non-significant difference between the studied groups regarding smoking, drug abuse or past history of chest infection.

Table (2) Comparison between the studied groups regarding PH over time

PH	Study groups		Test	
	Hydrocortisone group	Placebo group	t	p
	Mean ± SD	Mean ± SD		
At first day	7.36 ± 0.12	7.35 ± 0.12	0.069	0.945
On the 3rd day	7.36 ± 0.09	7.34 ± 0.11	0.698	0.487
On the 7th day	7.38 ± 0.07	7.33 ± 0.13	2.704	0.009*
P (F)	0.001**	0.142		

There is statistically non-significant difference between the studied groups regarding PH at the first day and third day. On the other hand, there is significant difference between both groups regarding PH on the seventh day.

On measuring change over time in each group, there is significant increase in PH over time in the hydrocortisone group, while there is non-significant change in PH in placebo group.

Table (3) Comparison between the studied groups regarding PCO2 over time

PCO2	Study groups		Test	
	Hydrocortisone group	Placebo group	t	p
	Mean ± SD	Mean ± SD		
At first day	21 ± 6.19	22.57 ± 8.22	-0.904	0.369
On the 3rd day	24 ± 7.57	23.29 ± 8.09	0.381	0.704
On the 7th day	32.29 ± 5.23	24.86 ± 8.15	4.78	<0.001**
P (F)	<0.001**	0.108		

There is statistically non-significant difference between the studied groups regarding PCO2 at the first day and third day. On the other hand, there is significant difference between both groups regarding PCO2 on the seventh day.

On measuring change over time in each group, there is significant increase in PCO2 over time in the hydrocortisone group, while there is non-significant change in PCO2 in placebo group.

There is statistically non-significant difference between the studied groups regarding HCO3 at the first day. On the other hand, there is significant difference between both groups regarding HCO3 on third and seventh day.

On measuring change over time in each group, there is significant fluctuation in HCO3 over time.

Table (5) Comparison between the studied groups regarding CRP over time

CRP (mg/dl)	Study groups		Test	
	Hydrocortisone group	Placebo group	t	p
	Mean ± SD	Mean ± SD		
At first day	23.57 ± 3.53	24.2 ± 3.64	-0.733	0.466
On the 3rd day	18.8 ± 2.35	23.49 ± 4.21	-5.75	<0.001**
On the 7th day	15.54 ± 2.5	21.6 ± 4.95	-7.685	<0.001**
P (F)	<0.001**	<0.001**		

There is statistically non-significant difference between the studied groups regarding CRP at the first day while there is significant difference between them regarding CRP on third and seventh days. On measuring change over time in each group, there is significant decrease in CRP over time.

Table (6) Comparison between the studied groups regarding total leucocytic count over time

TLC (*10^3/dl)	Study groups		Test	
	Hydrocortisone group	Placebo group	Z	p
	Mean ± SD	Mean ± SD		
At first day	21.6 ± 4.95	27.09 ± 11.09	-1.041	0.298
On the 3rd day	17.2 ± 3.36	24.17 ± 11.36	-1.429	0.212
On the 7th day	15.4 ± 2.61	22.4 ± 12.36	-3.059	0.002*
P (F)	<0.001**	<0.001**		

There is statistically non-significant difference between the studied groups regarding TLC at the first or third day. On the other hand, there is significant difference between both groups regarding TLC on 7th day.

On measuring change over time in each group, there is significant decrease in TLC over time.

Table (7) Comparison between the studied groups regarding percent change in ABG parameters:

Percent change in ABG parameters	Study groups		Test	
	Hydrocortisone group	Placebo group	Z	p
	Median (range)	Median (range)		
PH	0.27 (-1.85 – 2.64)	0 (-2.74 – 1.39)	-1.836	0.066
PCO2	66.67 (3.23 – 181.25)	16.67 (-28.57 – 118.75)	-3.905	<0.001**
HCO3	0 (-21.43 – 76.47)	10 (-16.67 – 104.55)	-0.918	0.359
Oxygen saturation (SPO2)	6.25 (4.55 – 11.25)	3.53 (-7.14 – 11.25)	-3.671	<0.001**

There is significant difference between the studied groups regarding percent change in PCO2 and SPO2 while there is non-significant difference between them regarding, PH and HCO3.

4. Discussion

Pneumonia has been recognized as a global public health problem for many years. Despite advancing anatimicrobial therapy and supportive measures, mortality for patients with severe community-acquired pneumonia admitted to the ICU remains high; 22 to 54% [18].

Many efforts have been made in the past to distinguish viral and bacterial CAP by means of clinical signs, radiological findings or serum non-specific inflammatory markers. The main problems have been the lack of 'gold standard' methods for obtaining viral and bacterial etiology **Don et al.** [19].

Between 58 and 87% of patients with severe community-acquired pneumonia admitted to the ICU develop respiratory failure and require mechanical ventilation, a factor associated with a higher mortality. Irrespective of severity of initial presentation, the development of sepsis-related complications [delayed septic shock, Adult Respiratory Distress Syndrome (ARDS), and extrapulmonary organ dysfunction) during ICU stay is associated with a significantly higher ICU mortality (57-100%) [20].

Fernandez-Serrano et al. [13] have shown increased pulmonary and circulating inflammatory cytokine levels in patients with severe community-acquired pneumonia. Among patients admitted to the ICU, higher circulating inflammatory cytokine levels correlated with the presence of bilateral pneumonia, bacteremia, need for mechanical ventilation, and higher Acute Physiology and Chronic Health Evaluation (APACHE) II and Multiple Organ Dysfunction Syndrome (MODS) scores. Among patients with severe community-acquired pneumonia, non-survivors, unlike survivors, exhibit persistent elevation of plasma Interleukin (IL)-6 levels over time.

Meduri et al. [21] indicated that similar to patients with ARDS (8), degree and duration of the systemic inflammation have a strong effect on final outcome in patients with severe community-acquired pneumonia.

Glucocorticoids, the most important natural inhibitors of inflammation, are not always effective in suppressing life-threatening systemic inflammation. The presence of systemic inflammation-induced tissue resistance to glucocorticoids and/or inadequate adrenal output might explain why **Minneci, et al.** [22] found no efficacy with a time-limited course of massive doses of glucocorticoids, while **Keh et al.** [23] have shown efficacy and safety with prolonged glucocorticoid treatment in low to moderate doses in patients with catecholamine-dependent septic shock, severe pneumocystis pneumonia, and unresolving ARDS. Patients randomized to prolonged glucocorticoid treatment, in contrast to control subjects, had a significant reduction in circulating inflammatory cytokine levels over time.

We hypothesized that hydrocortisone administration initiated early in the course of severe community-acquired pneumonia attenuates pulmonary and systemic inflammation and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications and mortality. For these reasons, we assessed the efficacy of low dose hydrocortisone Infusion in sever community-acquired pneumonia. The current study was conducted on 70 patients, attending Ain Shams University Hospital, with clinical or radiological findings of community-acquired pneumonia, they were assessed clinically, radiologically and haematologically.

Confalonieri et al. [24] evaluated the efficacy and safety of prolonged hydrocortisone infusion in a trial of patients with severe community-acquired pneumonia admitted to the ICU. Patients admitted to the Intensive Care Unit (ICU) with severe community-acquired pneumonia received protocol-guided antibiotic treatment and were randomly assigned to hydrocortisone infusion or placebo. Hydrocortisone was given as an intravenous 200-mg bolus followed by infusion at a rate of 10 mg/hour for 7 days. They found that serum C-Reactive Protein (CRP) was higher in patients randomized to hydrocortisone at study entry. On study day 8, a greater than 50% reduction in CRP from study entry was observed in all but two patients in the hydrocortisone group and in only five patients in the control group. By study day 8, the 20 patients with persistent elevation in CRP levels had a higher incidence of delayed septic shock (9 versus 0). After randomization, a progressive reduction in CRP values was seen in the hydrocortisone group; a significant difference from the control group was seen on study day 8.

In accordance with our results **Glynn et al.** [25] found that patients with SIRS had significantly higher pulse rates and respiratory rates than patients without SIRS, but non-significantly higher temperatures and white cell counts.

Michelow, Olsen [153] concluded that the type of infection was not associated with significant change in total leucocytic count. A published literature review by **van der Meer et al.** [26] tried to evaluate the diagnostic accuracy of CRP in detecting radiologically proven pneumonia, They found that CRP was neither sufficiently sensitive to rule out, nor sufficiently specific to rule in, a bacterial etiology of pneumonia. This may be in part, due to the kinetics of CRP levels, as they rise early in the course of a bacterial illness, and then decrease, when acute inflammation subsides.

In our study, there are non-significant differences between the studied groups regarding presence of comorbid renal disease, CVS, congestive heart failure, liver disease, presence of ground glass appearance, consolidation, pH and HCO_3. However, there are a significant difference between them regarding presence of pleural effusion on first day and a non-significant difference between them regarding pleural effusion on 7th day. Also, there are significant differences between the studied groups regarding percent change in respiratory rate, pulse, systolic, diastolic blood pressure, temperature, GCS, PCO_2, PCO_2, C-reactive protein, total leucocytic count, random blood sugar and serum creatinine.

Confalonieri et al. [24] found 33 patients with comorbidities (20 versus 13). No significant difference was observed for type of underlying comorbidities (placebo versus hydrocortisone group); Hypertension (8 versus 4), ischemic heart disease (6 versus 4), diabetes mellitus (5 versus 3), alcohol abuse (4 versus 1), chronic liver disease (3 versus 1), COPD (1 versus 2), chronic renal insufficiency (0 versus 2), and others (5 versus 1). By study day 8, among survivors, the chest radiograph (placebo versus hydrocortisone) worsened in 13 (13 versus 0), did not change in 7 (5 versus 2), and improved in 26 (5 versus 21).

Little information is available on the effect of prolonged hydrocortisone administration in patients with severe community-acquired pneumonia. **Marik, et al.** [27] found that a single dose of hydrocortisone (10 mg/kg) before antibiotic administration had no effect on plasma TNF-α in patients with severe community-acquired pneumonia.

In a retrospective study, **Montón et al.** [28] reported that among patients with severe community-acquired pneumonia requiring mechanical ventilation, those who received methylprednisolone for 9 ± 7 days (most for bronchodilation) had an attenuated systemic and pulmonary inflammatory response and trended toward lower mortality (36 versus 67%). **Confalonieri et al.** [24] concluded that hydrocortisone treatment was associated with a significant reduction in length of hospital stay and mortality.

Conclusion

We found that in patients with severe community-acquired pneumonia, control of inflammation with prolonged low-dose hydrocortisone infusion hastens resolution of pneumonia and prevents the development of sepsis-related complications. A course of low-dose hydrocortisone infusion was associated with a significant reduction in duration of mechanical ventilation, hospital length of stay, and hospital mortality.

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