ORIGINAL ARTICLE

Adjuvant role of corticosteroids in the treatment of community-acquired pneumonia

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Abstract *Background:* 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.

Objective: To evaluate the impact of hydrocortisone infusion in community-acquired pneumonia (CAP) in the attenuation of systemic inflammation and reduction of sepsis-related complications.

Methods: The study enrolled 80 patients, clinically and radiolodically diagnosed as community-acquired pneumonia, admitted to Chest department, Respiratory Intensive Care Unit, General Medicine Department and General Medicine Intensive Care Unit of Zagazig University Hospitals. Sixty of them were randomized to receive hydrocortisone as a bolus dose of 200 mg intravenously once (only at day 1) then 10 mg/h IV infusion for 7 days and twenty received placebo, along with antibiotics according to IDSA/ATS 2007 guidelines which were given for both groups. The following parameters were compared in both groups; PaO_2 and PaO_2/FiO_2 ratio, length of hospital stay, duration of IV antibiotic treatment, duration of mechanical ventilation, weaning success from mechanical ventilation, pneumonia complication and hospital outcome.

Results: Hydrocortisone treated patients showed a significant improvement in PaO_2 and PaO_2/FiO_2 ratio, a significant reduction in White blood cell count, C-reactive protein levels, Erythrocyte sedimentation rate, a significant reduction in the duration of mechanical ventilation, duration of IV

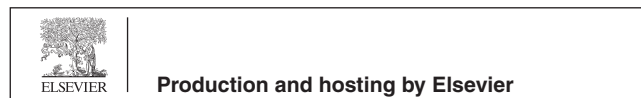* Corresponding author. Tel.: +20 01062248163.
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antibiotic treatment, pneumonia complications, and length of hospital stay. Also there was an improvement of hospital outcome, weaning success from mechanical ventilation and radiological resolution compared to the placebo group.

Conclusion: Adjunctive 7 day course of low dose hydrocortisone IV in patients with CAP hastens clinical recovery and prevents the development of sepsis-related complications with a significant reduction in the duration of mechanical ventilation, duration of IV antibiotics and length of hospital stay with the improvement in hospital outcome and weaning success from mechanical ventilation.

Introduction

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 bacteremic 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].

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 gluco-corticoids and/or inadequate adrenal output might explain why older clinical trials found no efficacy with a time limited course of massive doses of glucocorticoids [5], while recent randomized studies 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 [6]. Several studies demonstrated that the infusion of moderate doses of corticosteroids could blunt the systemic pro-inflammatory cytokine response in severe sepsis and the pulmonary inflammation in severe pneumonia and acute lung injury [7].

Aim of the work

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

Patients and methods

The study was conducted on eighty patients with community-acquired pneumonia (45 males and 35 females), their ages ranged from 18 to 65 years with a mean of (49.01 $\pm$ 13.33 years).

Patients were admitted to the Chest Department, Respiratory Intensive Care Unit, General Medicine Department and General Medicine Intensive Care Unit of the Zagazig University Hospitals, in the period from September 2010 to September 2012.

Patients:

The patients were enrolled in this study according to the following criteria:
Inclusion criteria:
1. Patients with clinical and radiographic evidence of CAP (pneumonia diagnosed by clinical signs and symptoms: cough with or without sputum, fever > 38.5, dyspnea, pleuritic chest pain or abnormal breath sounds, and radiographic pulmonary abnormalities that are at least segmental and are not due to preexisting or other known causes) which was acquired at the community or within the first 48 h of hospitalization according to (Fine et al.[8]).
2. Age 18 years or older.
- *Exclusion criteria:*
1– Nosocomial pneumonia or HCAP.
2– Severe immunosuppression (HIV, use of immuno-suppressant such as cytotoxic drugs, Cyclosporins, Monoclonal antibodies etc.).
3– Acute burn injury.
4– A preexisting medical condition with life expectancy less than 3 months (i.e., malignancy).
5– Pregnancy.
6– A major GIT bleeding within 3 months of the current hospitalization.
7– Acute asthma, chronic obstructive pulmonary disease or autoimmune disorders (COPD) (i.e., any condition requiring more than 0.5 mg/kg/day of prednisone equivalent).
8– Hepatic cirrhosis.

After diagnosis of CAP as described before in the inclusion criteria, then subgroup analysis of patients according to Pneumonia Severity Index (PSI) introduced by Fine et al. [8] was done. Patients were classified into mild, moderate and severe CAP.

Treatment Assignments

Each group of mild, moderate and severe CAP patients were randomly divided into hydrocortisone group (H group) &

Table 1 Demographic and clinical data of patients at study entry.

Parameter	Hydrocortisone		Placebo		t	P
Age(mean ± SD)	50.1 ± 13.3		45.8 ± 13.1		1.269	NS
	N.	%	N.	%	X^2	P
Sex					0.8	NS
Male	32	53.3	13	65		
Female	28	46.7	7	35		
Smoking habit					3.2	NS
Cigg.	23	38.33	5	25		
Goza	17	28.33	5	25		
Combined	6	10	5	25		
Non smokers	14	23.33	5	25		
Clinical data						
Confusion	9	15%	4	20%	0.276	NS
	Mean ± SD		Mean ± SD		t	p
H.R.(b/min)	122.1 ± 11.6	123.7 ± 9.8	−0.54	NS		
R.R.(/min)	27.18 ± 6.55	28.7 ± 4.3	−0.966	NS		
Systolic bl.p.(mmHg)	105.8 ± 11.8	101.75 ± 13.8	1.28	NS		
Diastolic bl.p (mmHg)	71.2 ± 8.3	70.3 ± 8.8	0.42	NS		
Temperature (°C)	39 ± 0.7	39.2 ± 0.8	−0.669	NS		

χ^2: Chi- square test, P: P-value, N.: Number, t: t test, HR: heart rate, R.R: respiratory rate, Bl.p: blood pressure, NS: non significant, t: t- test, SD: standard deviation.

Table 2 Laboratory investigations in both hydrocortisone and placebo groups.

Variables	Hydrocortisone group (N. 60) Mean ± SD	Placebo group (N. 20) Mean ± SD	t	P
CBC				
WBC(×10³/cm)	17.8 ± 4.5	17 ± 4.5	0.661	NS
Hct.%	30 ± 4.2	28.9 ± 2.7	1.09	NS
PLT. (×10³/cm)	249.56 ± 120.3	300.4 ± 92.8	−1.72	NS
BUN mg/dl	31.6 ± 14.2	41.8 ± 19.5	−2.156	NS
Creatinine mg/dl	1.14 ± 0.5	1.5 ± 0.8	−1.892	NS
CRP mg/l	91.3 ± 39.96	95.4 ± 45.64	−0.381	NS
ESR mm/hr	79.9 ± 9.7	81.7 ± 6	−0.981	NS
Glucose level mg/dl	195.3 ± 85.1	211.4 ± 94.9	−0.674	NS
Electrolyte				
Na level mEq/L	131.9 ± 6	130.1 ± 3.71	1.284 NS	NS
K level mEq/L	3.6 ± 0.46	3.63 ± 0.44	−0.343 NS	NS
PaO₂/FiO₂ ratio	343.9 ± 51.6	319.4 ± 54.3	1.814 NS	NS
Cortisol level (ug/ml)	18.38 ± 7.8	22.3 ± 10.2	−1.79 NS	NS

P: P-value, N.: Number, t: t test, NS: non significant, CBC: Complete blood cell count, WBC: White blood cell count, Hct: Hematocrit value, PLT: Platelet count.
BUN: Blood urea nitrogen, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Na: sodium level, K: potassium level, t: t test, SD: standard deviation, PaO_2/FiO_2: Arterial oxygen tension/Inspired oxygen fraction.

placebo or control group (P group) in a 3:1 single – blind manner. Placebo group (20 patients) received sterile normal saline in a volume equal to the study drug. Hydrocortisone group (60 patients) was given an intravenous 200-mg hydro-cortisone loading bolus dose followed by an infusion of hydrocortisone 240 mg in 500 cc 0.9% saline at a rate of 10 mg/hour for 7 days according to Emad Eldin et al. [9].

Initial antibiotic therapy followed the 2007 Infectious Diseases Society of America/ American Thoracic Society Consensus Guidelines for the initial management of adults with community-acquired pneumonia [4], then after that pathogen-directed therapy was given.

Methods:

Patients who had met the inclusion criteria of this work were subjected to the following:

1. Thorough medical history taking from patients or their relatives in mechanically ventilated patients.
2. Full clinical examination, including general and local chest examinations. Detection of improvement was assessed by comparison of vital signs in day 1 andday 7.
3. Laboratory investigations included: Complete blood count, Kidney function tests, Liver function tests, Serum sodium

Table 3 Clinical & laboratory data of both hydrocortisone and placebo groups after 7 days of treatment.

Variables	Hydrocortisone group	Placebo group	χ^2	P
Consciousness N. of improved cases/total number of cases with impaired conscious level (%)	7/9 (77.8%)	0/4 (0%)	15	<0.001
Mean ± SD	Mean ± SD		t	P
HR(b/min)	105.4 ± 11	113.9 ± 11.8	−2.921	<0.05
Systolic Bl.p mmHg	109.92 ± 10.8	102.75 ± 16.5	2.24	<0.05
Diastolic Bl.p mmHg	75 ± 6.64	68.3 ± 11	3.29	<0.05
R.R(/min)	20.7 ± 3.94	27.5 ± 4	−6.71	<0.001
Temperature(°C)	37.7 ± 0.6	38.2 ± 0.99	−2.91	<0.05
II. Investigations				
CBC:				
WBC (x10^3/cm)	9.2 ± 3.6	11.96 ± 5.5	−2.57	<0.05
Hct%	32.6 ± 3.97	31.1 ± 3.79	1.527	NS
Glucose level mg/dl	194.8 ± 105.6	202 ± 85.3	−0.307	NS
CRP mg/L	16.3 ± 18.9	43.7 ± 46.2	−3.77	<0.001
ESR mm/hr	10.1 ± 12.2	38.7 ± 32.2	−5.79	<0.001
Creatinine mg/dl	1.15 ± 0.54	1.7 ± 0.96	−1.156	NS
BUN mg/dl	28.95 ± 12.99	42.8 ± 17.82	−2.892	NS
Electrolyte				
Na mEq/l	138.1 ± 2.4	134.6 ± 4.7	4.37	<0.00
K mE/l	3.37 ± 0.4	3.6 ± 0.4	2.73	<0.05
Cortisol level (μg/ml)	21.7 ± 7.3	24.6 ± 10.2	−1.38	NS
PaO$_2$/FiO$_2$ ratio	365.5 ± 61.4	321.5 ± 101.9	2.32	<0.05

N.: Number, t: t-test, χ^2: Chi- square test, HR: heart rate, RR: respiratory rate.Bl.p: blood pressure, WBC: White blood cell count, Hct: Hematocrit value.CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Na: sodium level,K: potassium level, PaO$_2$/FiO$_2$: Arterial oxygen tension/inspired oxygen fraction.

and potassium, Blood glucose level, Erythrocyte sedimentation rate, C-reactive protein (CRP) and Serum Cortisol level.

4. Radiological investigations included: Plain Chest X- ray on day 1, 4 and day 7, Chest Computed Tomography (C.T) that was done for non responding patients to confirm the diagnosis of pneumonia and direct CT guided biopsy. Chest Ultrasonography (U.S) was done for all cases to confirm or exclude the presence of parapneumonic pleural effusion.

5. Bacteriological investigations included: Gram stain of sputum and pleural fluid, sputum culture and sensitivity, Blood culture, pleural fluid culture &sensitivity, Quantitative culture of C.T guided biopsy, Quantitative culture and gram stain of tracheobronchial secretions obtained by tracheal aspirate in intubated patients and bronchoscopic BAL and mini BAL in non intubated patients.

Statistical analysis

All data were collected, tabulated and reformed for statistical analysis using Statistical Package for Social Science (SPSS version 19; SPSS, Inc., Chicago, IL). The results of this work were analyzed and presented as numbers and percentage or mean ± standard deviation(SD). Student's "t" test, analysis of variance (ANOVA) and Chi-square (χ^2 test or Fisher's exact test) were used for comparison between groups. A P-value <0.05 was considered significant and P-value <0.001 was considered highly significant .

Results

After analysis of data from 80 patients (60 CAP patients in hydrocortisone group and 20 CAP patients in placebo group),

demographic and clinical data of patients did not differ between the two groups (Table 1), this means that the two groups were matched.

Table 2 shows that the laboratory investigations that were done to both groups (hydrocortisone and placebo) (CBC, BUN, Creatinine, CRP, ESR, glucose level, Na, K, PaO$_2$/FiO$_2$ ratio and cortisol level) at the study entry were also matched.

Table 3 shows the follow up of clinical and laboratory data of patients of both group after 7 days, which proved that there were a non significant difference between both hydrocortisone and placebo groups in the improvement of Creatinine, BUN, cortisol level, Hct value and glucose level. As regards improvement of clinical data in the hydrocortisone versus placebo group, there was a statistically significant improvement in the hydrocortisone group regarding: conscious level, mean heart rate, mean respiratory rate, mean systolic blood pressure, mean diastolic blood pressure and mean temperature readings. As regards other laboratory investigations: WBC, CRP, ESR, Na level, K level and PaO$_2$/FiO$_2$ ratio, there was a statistically significant improvement in the hydrocortisone group except for the serum K level.

As regards complications that occurred during the study in both CAP groups (Table 4); less pneumonia complications (septic shock or ARDS) occurred in the hydrocortisone versus placebo groups (6.7% vs 30%), complications of steroids during the study were statistically non significant between both groups except hypokalemia which was more in the hydrocortisone group versus placebo group (58.3% vs 25%) and this was a correctable side effect.

As regards mechanical ventilation of severe CAP patients in both groups (Table 5); there was a non significant difference between both groups in the need for mechanical ventilation

Table 4 Complications that occurred during the study in both CAP groups.

Variables	Hydrocortisone group (N. 60)		Placebo group (N. 20)		χ^2	P
	N.	%	N.	%		
Pneumonia complications (Septic shock or ARDS)	4	6.7	6	30	7.4	< 0.05
Drug complications						
*GIT bleeding	1	1.6	1	5	8.6	NS
*hypokalemia	35	58.3	5	25	7.3	< 0.05
*Uncontrolled DM (glucose > 250 mg/dl)	19	31.7	8	40	8.5	NS

χ^2: Chi-square test, N.: Number, NS: non significant, P: P-value, SD: standard deviation, t: t-test.

Table 5 Need, duration and weaning success of mechanical ventilation of severe CAP patients in both groups.

Variables	Hydrocortisone group (N. 60)		Placebo group (N. 20)		χ^2	P
	N.	%	N.	%		
Need for mechanical ventilation	8	13.3	5	25	1.5	NS
Weaning success	7	87.5	1	20	0.74	< 0.05
					t	P
Duration of mechanical ventilation range	5–24 days		12–22 days		−2.375	< 0.05
Mean ± SD	1.2 ± 3.75 days		4.3 ± 7.83 days			

χ^2: Chi-square test, N.: Number, NS: non significant, P: P-value, SD: standard deviation, t: t-test.

Table 6 Duration of IV antibiotics, radiological resolution, and LOS and hospital outcome after 7 days in both groups of CAP.

Variables	Hydrocortisone group (N. 60)		Placebo group (N. 20)		χ^2	P
	N.	%	N.	%		
CXR improvement	56	93.3	14	70	7.5	< 0.05
Hospital outcome						
No. Of Improved Cases	56	93.3	13	68.4	8.1	< 0.05
No. Of Deaths	4	6.7	6	31.6	7.83	< 0.05
	Mean ± SD		Mean ± SD		t	P
LOS						
In ICU	3.1 ± 4.9		6.3 ± 8.2		−2.124	< 0.05
In Ward	6.2 ± 3.7		0.2 ± 7.8		−3.09	< 0.05
Total hospital stay	9.27 ± 2.4		16.5 ± 2.24		−11.8	< 0.05
Duration of IV AB	7.45 ± 2.6		13.9 ± 2.98		−9.223	< 0.001

χ^2: Chi- square test, P: P-value, N.: Number, t: t-test, SD: standard deviation.
CXR: Chest x ray, LOS: length of hospital stay, ICU: intensive care unit.
IV: intravenous, AB: antibiotic, MV: mechanical ventilation.

while more successful weaning from mechanical ventilation in the hydrocortisone group than the placebo group was observed (87.5% vs 20%). The duration of mechanical ventilation ranged from 5–24 days with a mean of (1.2 ± 3.75 days) in the hydrocortisone group versus 12–22 days with a mean of (4.3 ± 7.83 days) in the placebo group.

Table 6 shows duration of IV antibiotics, radiological resolution, length of hospital stay and hospital outcome after 7 days in both groups; CXR clearance was significantly more frequent in the hydrocortisone group versus the placebo group, hospital outcome showed a statistically significantly greater number of improved cases and lesser number of deaths (6.7% vs 31.6%)in the hydrocortisone group, Total length of hospital stay and duration of IV antibiotics were less in the hydrocortisone group and the difference was statistically significant.

Discussion

Despite steady improvement in antibiotic therapy and intensive care management during the past decade, mortality from severe community-acquired pneumonia has remained high; a fact that has continued to stimulate interest in pharmacological agents that might reduce morbidity and mortality. It has been recently hypothesized that hydrocortisone administration initiated early in the course of severe CAP alters pulmonary and systemic responses and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications and mortality [10].

In this study and after 7 days follow up of both hydrocortisone and placebo groups, pneumonia complications (septic shock, ARDS); were less in the hydrocortisone group when compared with the placebo. As regards the most common side

effects that occur with steroid therapy, there was non significant difference in both GIT bleeding and uncontrolled diabetes mellitus, while there was a significant difference in hypokalemia which was more in the hydrocortisone group (58.3%) (Table 4) which was a correctable side effect and this was attributed to the mineralocorticoid action of hydrocortisone. So this study confirmed that the use of hydrocortisone in a low dose for a short period had a protective effect against pneumonia complications with less steroid side effects. This was in agreement with Confalonieri et al. [10], Rhen & Cidlowski [12] and Emad Eldin et al. [9] while Meduri and colleagues [13] found no effect of methylprednisolone infusion in decreasing pneumonia complications, in contrast there was an increase in the occurrence of delayed septic shock in the steroid group. Corticosteroids are very potent inhibitors of inflammation [12]. They switch off genes that encode proinflammatory cytokines and switch on genes that encode anti-inflammatory cytokines. Treatment with low dose corticosteroids down regulates proinflammatory cytokine transcription, which prevents an extended cytokine response and might accelerate the resolution of systemic and pulmonary inflammation in the early phase of community-acquired pneumonia [15]. In this study, there was a non significant difference in the need of mechanical ventilation in both hydrocortisone and placebo groups (matching in both groups), while there was a significant difference between weaning success which was more in the hydrocortisone group (87.5%) than the placebo group (20%). Regarding the duration of mechanical ventilation, the mean duration of mechanical ventilation was significantly shorter in the hydrocortisone group (1.2 ± 3.75 days) in comparison to the placebo group (4.3 ± 7.83 days) (Table 5). This is in agreement with Confalonieri et al. [10], El-Ghamrawy et al. [11], Emad-Eldin Omar et al. [9] and Meijvis et al. [15] who postulated that adjunctive treatment of community acquired pneumonia with intravenous dexamethasone changed the immune response and reduced morbidity, leading to a decrease in patients' length of stay in hospital. They illustrated that dexamethasone has potent anti-inflammatory effects and weak mineralocorticoid effects compared with other corticosteroids, thus avoiding interference with sodium reabsorption and water balance. Moreover, dexamethasone has a long-lasting effect, allowing for once-a-day regimen. In this study and as regards the clinical and laboratory variables of the follow up that was done at the 7th day of the study; there were highly significant differences in the improvement of conscious level, CRP, ESR, Na level, RR ($P < 0.001$) which improved more in the hydrocortisone group .The observation of a more reduction of CRP in the hydrocortisone group after the course of therapy is in agreement with the result reported by Confalonieri et al. [10] and Meijvis et al. [15]. CRP has been effectively used as a marker for pulmonary and systemic inflammation. Cortico-steroids could reduce the exaggerated inflammatory response in severe infection. In the present study there was significant difference in the improvement of: HR, Bl.p, temperature, WBCs count & PaO_2/FiO_2 ratio which improved more in the hydro-cortisone group. This finding that the hydrocortisone group showed more improvement in pulmonary oxygenation parameters following the treatment course as compared with placebo group, is in accordance with that of El-Ghamrawy et al. [11] who reported that patients randomized to a 7-day hydro-cortisone infusion had a significant improvement in PaO_2/FiO_2. In this study, there was non

significant difference in blood glucose level, serum cortisol level and Hct value in both hydrocortisone and placebo groups (Table 3). As regards other improvement parameters, there was a significant difference in CXR resolution, pneumonia and drug complications, both ICU and ward length of stay and hospital outcome (number of deaths and number of improved cases) in both the hydrocortisone and the placebo groups (as the improvement was more in the hydrocortisone group), also there was a highly significant difference ($P < 0.001$) in the total length of stay and duration of mechanical ventilation in both groups (being less in the hydro-cortisone group) (Table 6). These results are in agreement with other studies that suggested that patients with severe community-acquired pneumonia who were treated with systemic cortico-steroids had a reduced risk of mortality compared with patients who were not given adjunctive corticosteroids [10,16,15]. They also hypothesized that if these potential benefits of such relatively cheap treatment proved, this would decrease economic and social burdens and allow for better allocation of hospital resources; while Salluh et al. [17] showed that corticosteroids did not improve hospital mortality rates or survival, also Polverino et al. [18] studied patients with community-acquired pneumonia of any severity and compared prednisolone for 3 days with the placebo and reported a non-significant reduction in hospital stay from 16 to 11 days ($p = 0.182$). However, this study used a shorter duration of steroid therapy and this could explain their poor results. Also the study of Mikami et al. [14] who assessed the role of prednisolone (40 mg once per day for 7 days) in community-acquired pneumonia of any severity showed neither beneficial effects of adjunctive corticosteroids on clinical cure at day 7 or effects on the length of stay. A possible explanation for the absence of effects compared with our study was the use of prednisolone once a day, which might not have been sufficient to achieve effective serum concentrations during the course of 24 h. Furthermore, this study was not powered to show differences in the length of hospital stay.

In conclusion: adjunctive 7 day course of low dose hydrocortisone IV in patients with CAP fastens recovery and prevents the development of sepsis-related complications with a significant reduction in the duration of mechanical ventilation, duration of IV antibiotic treatment and length of hospital stay with improvement of hospital outcome and weaning success from mechanical ventilation.

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