Original Article

Outcome of Severe Pneumonia with Adjunct Corticosteroid Therapy at a Tertiary Care Teaching Hospital in Nepal

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Abstract

Introduction: Severe pneumonia is a major cause of Emergency Room (ER) admission and morbidity and mortality worldwide. Early identification and adequate resuscitation in the initial hours after severe pneumonia is the challenge today for a better outcome. It is not clear whether corticosteroid (CS) as adjunct therapy in severe pneumonia improves the outcome. Therefore, this study was done to assess the benefit of adjunct CS therapy in the treatment of severe community acquired pneumonia (CAP).

Methods: This was a prospective, randomized controlled trial (RCT) conducted from May 2017 to April 2018 (12 months) in the ER, Intensive Care Unit (ICU), Intensive Critical Care Unit (ICCU), and Medical Intensive Care Unit (MICU) of Tribhuvan University Teaching hospital (TUTH) in patients with severe CAP {(Pneumonia Severity Index (PSI) grade IV and V)} in two groups of patients (with and without steroid as adjunct therapy).

Results: Clinical cure at 5 days in the steroid and no steroid group was 43.2% and 54.1% respectively (P =0.696); clinical cure at 28 days in the steroid and no steroid group was 75.9% and 79.3% (P = 0.753) respectively. Treatment failure was comparable in the steroid and no steroid group (45.9 % Vs 37.8 %; P = 0.696). Overall mortality in steroid and no steroid group was 32.5% and 27.5% respectively (Chi square = 0.238, p=0.626).There was no statistically significant difference in the time to clinical stability (ttcs) between steroid and no steroid group (mean ttcs: 5.22 days Vs 5.78 days, SD: 3.106 Vs 3.671, p value: 0.521). The mean length of stay (LOS) in hospital for steroid group: 10.26 days, mean LOS for no steroid group: 11.26 days; p value: 0.438).

Conclusion: Among patients with severe pneumonia, adjunct corticosteroid therapy did not result in lower 48 hours, 5 days, and 28-days mortality. Hence, it was found that adjunct corticosteroid therapy is not beneficial in patients with severe pneumonia.

Keywords: severe pneumonia, corticosteroid, outcome

Introduction

Community-acquired pneumonia (CAP) remains a common and serious illness despite the availability of potent new anti-microbials and effective vaccines, as BA Shah et al discuss the research work of Garibaldi.[1,2] It is a major cause of morbidity and mortality, the Asian subcontinent contributing as a major cause of adult mortality,[3] with an incidence of 20-30% in the developing countries and 3-4% in developed countries.[4] CAP is associated with a high rate of infection, emerging antibiotic resistance, with significant impact on health-related quality of life, and high medical healthcare costs, as per the evaluation of a recent meta – analysis done by Charles Feldman and Ronald Anderson, who quoted the work of Steel.[5,6]

CAP is also the leading cause of sepsis and acute lung injury (ALI), and community acquired infection requiring

ICU admission.[7] Identification and resuscitation in the initial hours after severe pneumonia are likely to influence the outcome.[8] management in the emergency plays a pivotal role regarding this. Even though early prediction of the severity is crucial in decreasing mortality and improving survival rate, improving the outcome is an ongoing challenge, even in the setting of significant advances in antimicrobial chemotherapy and critical care, as irrespective of the severity of initial presentation, the development of sepsis-related complications during ICU stay is associated with a significantly higher ICU mortality (57-100%).[9]

Recognition of the underlying involvement of inflammation-mediated organ dysfunction as a determinant of adverse outcomes in CAP has aroused intense interest in the protective potential of adjunctive anti-inflammatory therapies in CAP, particularly the role of CS.[10] Despite the use of adjunctive CSs as an appealing option for CAP treatment and evaluation in many RCTs for decades, the role of steroids as an adjunct therapy in severe CAP still remains controversial, with some studies showing a benefit in clinical outcomes, [11,12,13,14] and another study showing no effect.[15]

Although steroids have been variably effective in some conditions, particularly where adrenal replacement is necessary, few studies have been done solely on pneumonia. Currently there is inadequate data outlining the incidence, prevalence, predicting factors and mortality from severe pneumonia alone in developing countries, especially in Nepal, [16]where pneumonia is one of the commonest causes of emergency service visits and ICU admissions, as well as mortality; here lies the importance of this study.

Pneumonia Severity Index: The PSI is a prognostic prediction rule that defines the severity of pneumonia based on predicted risk of mortality at 30 days.[4] It is calculated by using 21 prognostic variables to stratify the risk of death due to CAP into five classes; the mortality risk increases with the increase in class, ranging from 0.4% in class I to 31% with class V, and categorised into severe pneumonia (risk class IV and V) if they have a PSI score of in between 91 – 130, and > 130 respectively. In this study, PSI has been used as an independent predictor of severity in patients with severe pneumonia, who have been randomized to adjunct CS (glucocorticoid) treatment, in contrast to control subjects, to determine the outcome.

It is hypothesized in this study that CS treatment is not beneficial in the treatment of patients with severe pneumonia.

Methods

This was a RCT and open labelled study done in 80 adult patients presenting to TUTH emergency service with severe pneumonia (PSI grade IV and V). It was done at ER, ICCU, MICU and ICU of TUTH, from May 2017 to April 2018 (12 months).

Those patients who were pregnant, patients with suspected and known pulmonary tuberculosis and bronchiectasis, diabetes mellitus (DM), recent upper GI bleeding and immunosuppression were excluded from the study. Matching of patients regarding variables e.g. age, co – morbidities was done after patients fulfilled criteria for enrollment and in those who gave written consent to participate in the study.

In this study, patients were randomly assigned into two groups, with and without steroid and received protocol-guided antibiotic treatment. A five-day treatment course of intravenous (iv) hydrocortisone, which was given as an iv 200-mg bolus followed by 100 mg twice daily (BD) for 5 days. Primary end-point of the study was clinical outcome at 48 hours, 5 days and 28 days, and, decrease in mortality, and secondary end points were decrease in the length of stay (LOS) in hospital, and time to clinical stability (ttcs). Patients were followed up and assessed 48 hours, 5 days, and 28 days later in the admitted units/ wards, ICU, ICCU and MICU, medical ward (MW).

Results

In this study among 184 patients, 80 patients underwent randomization. There were a total 40 patients in each group. Mean age was 65.78, SD: 14.45 (steroid group); mean age: 58.33, SD: 20.07 (no steroid group); t value: 1.91, p value: 0.061.

Table 1 Demographic data: Age wise distribution. (N=80)

Age	S(n)	S(%)	No Steroid(n)	No Steroid (%)	Chi square	*P*
18-49	5	12.5	14	35.9	5.94	0.053
50-64	9	22.5	6	15.4		
>=65	26	65	20	48.7		
	40	100	40	100		

*S= steroid, NS= no steroid, n= number of patients

Above table shows no statistical significance in difference in between steroid and no steroid group in different age groups.

Table 2 Demographic data: Gender wise Distribution (N=80)

Gender	S (n)	S (%)	NS (n)	NS (%)	Chi square/ Fisher exact value	*P* value
F	28	70	25	62.5	0.503	0.478
M	12	30	15	37.5		
	40	100	40	100		

*F= female, M= male, S= steroid, NS= no steroid, n= number of patients

Above table shows no statistical significance in between steroid and no steroid group in male and female gender.

Table 3 Demographic, clinical and labdata of patients at study entry (N=80)

	Steroid	Mean	SD	t	P
Age	Yes	64.82	14.30	1.62	0.10
	No	58.72	19.03		
pulse	Yes	110.2	17.47	1.39	0.16
	No	104.45	19.46		
SBP	Yes	105.49	29.56	-0.65	0.51
	No	110.49	36.45		
DBP	Yes	55.384	17.29	0.23	0.81
	No	54.3514	20.81		
RR	Yes	29.15	6.51	0.77	0.43
	No	28.2	4.14		
Temp	Yes	37.22	1.14	0.33	0.73
	No	37.12	1.34		
PCV	Yes	41.15	9.67	3.16	0.002
	No	35.03	7.43		
RBS	Yes	144.62	71.68	-1.35	0.17
	No	169.28	89.98		
Na	Yes	131.69	7.77	-0.01	0.99
	No	131.71	7.54		
BUN (Urea)	Yes	31.96	14.14	-0.79	0.43
	No	36.05	29.51		
pH	Yes	7.312	0.09	-0.86	0.38
	No	7.33	0.12		
p02	Yes	64.94	11.98	2.61	0.01
	No	58.34	10.47		
PSI score	Yes	143.68	27.72	1.08	0.28
	No	136.3	32.77		
PSI Grade	Yes	4.62	0.49	1.57	0.11
	No	4.45	0.50		
LOS	Yes	10.26	7.33	-0.77	0.43
	No	11.66	8.24		

Above table shows statistically significant difference in the mean value of PCV and p02 in between steroid and no steroid group. Other parameters do not show a statistically significant difference in the mean value in between both groups.

Table 4 Clinical outcome analysis at 48 hrs, 5 days and 28 days (N=80)

Outcome at 48 hrs.	**S (n)**	**S (%)**	**NS (n)**	**NS (%)**	**fisher exact**	***P***
Improved	7	17.5	2	5.1	3.29	0.197
not improved	30	75	36	89.7		
mortality	3	7.5	2	5.1		
	40	100	40	100		
Outcome at 5 days	**S (n)**	**S (%)**	**NS(n)**	**NS(%)**	**fisher exact**	***P***
Cured	16	43.2	20	54.1	0.934	0.696
Treatment failure	17	45.9	14	37.8		
mortality	4	10.8	3	8.1		
	37	100	37	100		
Outcome at 28 days	**S (n)**	**S (%)**	**NS (n)**	**NS (%)**	**chi square**	**P**
Cured	22	75.9	23	79.3	0.099	0.753
mortality	7	24.1	5	20.7		
	29	100	29	100		

*not improved- no improvement in symptoms and signs

*clinical cure -resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative therapy

*treatment failure - persistence or progression of all signs and symptoms that developed during the acute disease episode after randomization, or the development of a new pulmonary or extrapulmonary infection, or the deterioration of chest radiography after randomization

*improved - improvement in symptoms and signs

*S= steroid, NS= no steroid, n= number of patients

Clinical outcome analysis at 48 hrs, 5 days and 28 days was not statistically significant in between steroid and no steroid groups.

Table 5 Comparison of overall mortality in between steroid and no steroid group (N=80)

		S (n)	S (%)	NS (n)	NS (%)	Total (n)	Total (%)	Chi square	p
Mortality	No	27		29		56		0.238	0.626
			67.5		72.5		70		
	Yes	13		11		24			
			32.5		27.5		30		
	Total	**40**	**100**	**40**	**100**	**80**	**100**		

There is no significant difference in the overall mortality in between the steroid and the no steroid group.

Table 6 Subgroup analysis using mortality as dependent variable

			95% CI for OR	
	P value	OR	Lower	Upper
steroid(S)	0.185	2.608	0.632	10.768
No steroids (reference)				
Age group (18-49)	0.083	0.227	0.042	1.213
Age group (50-64)	0.222	0.366	0.073	1.839
Age group >65(reference)				

Patients in the steroid group are 2.6 times more likely for mortality as compared to no steroid group. Patients in the age group less than 65 years are less likely to have mortality than those compared to more than 65 years of age.

There was no statistically significant difference in the time to clinical stability between steroid and no steroid group (mean ttcs: 5.22 days Vs 5.78 days, SD: 3.106 Vs 3.671, t test: -0.645, *p* value: 0.521).

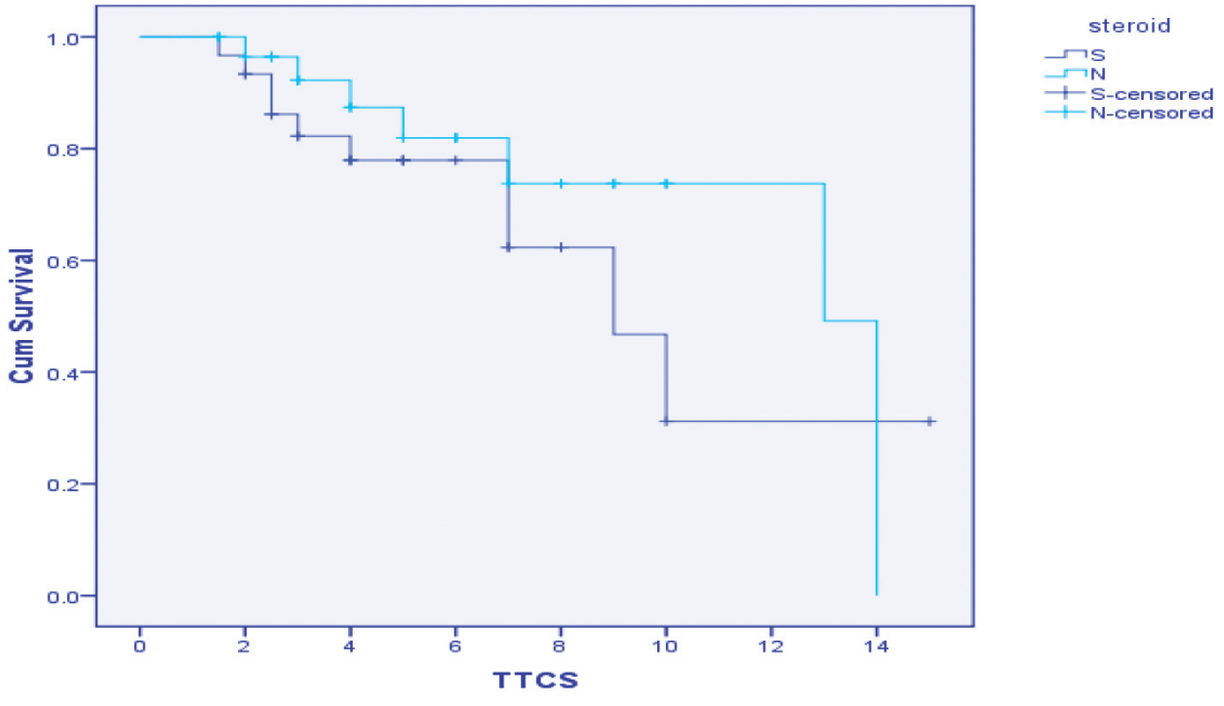

Fig.1Kaplan-Meier analysis of the Effect of Steroid on Time to Clinical Stability

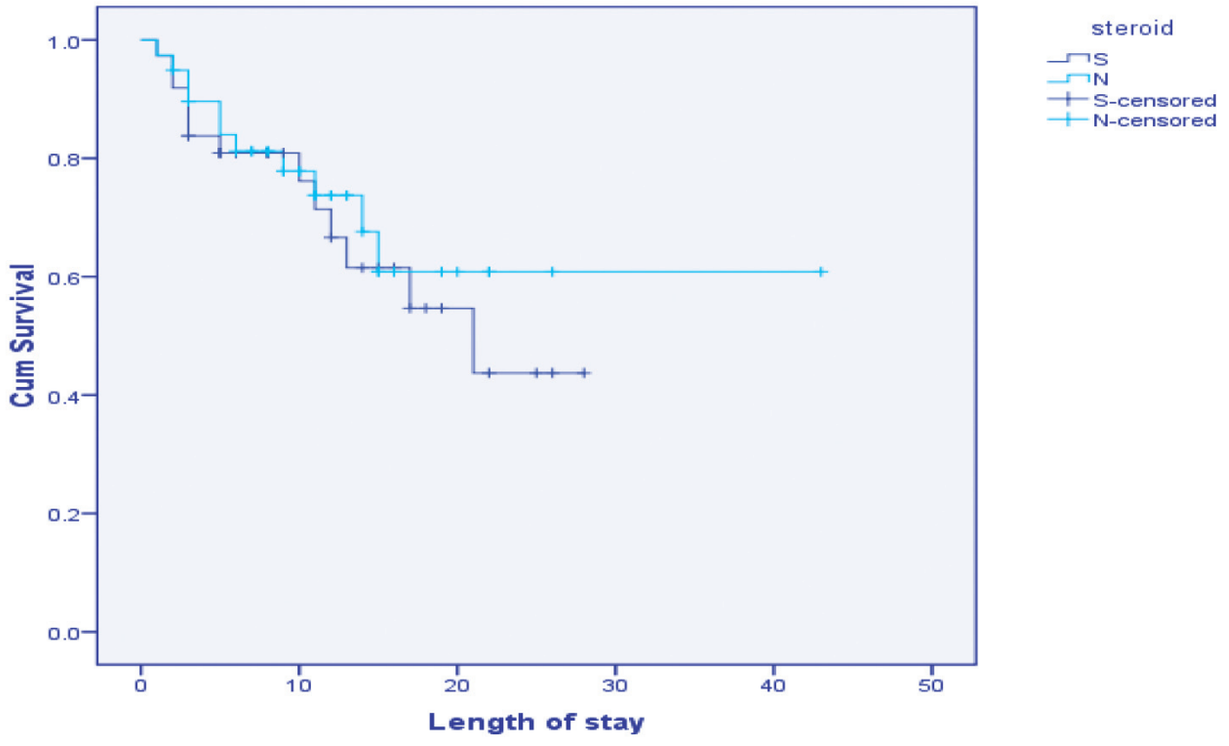

Fig. 2 Kaplan Meier analysis of the Effect of Steroid on Length of (hospital) Stay

The mean LOS: 10.26, SD: 7.333 (steroid group); mean LOS: 11.26, SD: 8.244 (no steroid groups); t test: -0.779, *p* value: 0.438)

Discussion

In this study, number of improved and not improved cases, with mortality was comparable at 48 hours. There was no statistically significant difference between clinical cure, treatment failure, and mortality in between both groups at Day 5 and 28, though percentage of mortality was found to be comparatively higher in the steroid group.

The overall clinical cure rate at 5 days and at 28 days is in concordance with the study done by Dominic Snijders et al (2010).[17] In contrast, in the study done by Torres A. et al (2015),[18] there was less treatment failure among patients from the steroid group compared with the placebo group; steroid treatment reduced the risk of treatment failure and a lower inflammatory response in this study, as documented by lower CRP levels. Markers of inflammation were not measured in our study, hence inflammatory response could not be assessed. Also, the anti-inflammatory effects of hydrocortisone did not lead to a significant shorter LOS in our study, as LOS decreased by only 1 day in our study. The ttcs was similar between the two groups in our study, which was similar to the study done by Snijder and colleagues.[17] In a study by Mikami and colleagues [19] the authors concluded that CSs in patients with CAP hastens symptom resolution and shortens the duration of treatment with iv antibiotics. No effect on LOS was observed in this study, but a small number of patients were included with an open-labelled design, which is very similar to our study. In this study, CS was given once daily for 3 days, which did not match with our study, in which it was given for 5 days. In a recent meta analysis,[20] adjunct corticosteroids for patients hospitalized with CAP reduced ttcs and LOS by approximately 1 day without a significant effect on overall mortality.

Our definition of severe CAP was based on the PSI score, not the modified American Thoracic Society (ATS) criteria, as used by Confalonieri and colleagues,[21] hence there is difficulty comparing the two studies.

A Spanish retrospective study also found a reduced mortality in patients treated with corticosteroids.[12] This study included patients only with severe CAP, who are more likely to benefit from CSs, which is comparable to our study. A possible rationale for the use of CSs is due to the relative adrenal insufficiency found in severe

CAP.[22] In the study done by Confalonieri et al,[21] it was concluded that, given the lack of proven benefit on clinically meaningful endpoints and adverse events, CSs cannot be recommended for adjunctive treatment of severe CAP, which is very similar to our study. In this study, CS was given by continuous infusion for 7 day, which was not comparable with our study, in which CS was given as a bolus dose, followed by intermittent doses for 5 days. In the study done by Torres et al,[18]in-hospital mortality did not differ between the two groups, which is similar to our study, though there was comparatively higher mortality in the steroid group in our study. As mentioned above, as inflammatory markers were not measured in our study, it is difficult to explain the increased mortality in the steroid group, though statistically insignificant. The total duration of steroid administration in this study was 5 days, which is also similar to our study.

The CORTICUS-study failed to show mortality reduction with hydrocortisone in patients with sepsis; only faster reversal of shock was observed,[23] with no better outcomes in patients who were non-responders to a corticotrophin test, which was not done in our study. Gotoh and colleagues[24] examined adrenal insufficiency in 64 patients hospitalized with CAP and found a low incidence of adrenal insufficiency in this population. As our study included only patients with severe pneumonia, and adrenal insufficiency was not assessed in our study, both these studies cannot be compared.

In our study, steroid was used in a twice-daily dosage rather than four times a day dosage (for practical reasons), which may be sufficient for establishing effective serum levels during 24 hours. This limits the comparison with studies using hydrocortisone by continuous infusion (Confalionneri et al, 2008),[21] and differs from the study by Snijders et at (2010),[17] in which once – daily dose was used.

Overall, as the sample size in our study was small, this probably explains the insignificant results in our study; the small sample size further limits the comparison with trials done on large scales.

Conclusion

Adjunct corticosteroid therapy did not result in lower 48 hours, 5 days, and 28-day mortality in patients with severe pneumonia. There was no statistically significant difference in the length of stay in hospital and time to clinical stability between steroid and no steroid group. Hence, it is found that adjunct corticosteroid therapy is not beneficial in patients with severe pneumonia.

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Conflict of interest: None declared

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