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Original Research Article

Dexamethasone in treatment of community acquired pneumonia in children: a randomised control trial

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ABSTRACT

Background: An inflammatory response is a two edge sword in pneumonia as reasonable inflammatory response is required for microorganism clearance but excessive inflammation can cause on-going local and systemic damage. Because of this, despite appropriate antibiotic therapy, adjuvant therapy that can positively modify the immune response has become a relevant approach to improve pneumonia prognosis. The objectives of this study was to document the beneficial effects of adjunctive dexamethasone therapy in patients admitted with community-acquired pneumonia (in terms of length of hospital stay) and to study what patients admitted with CAP benefit most from dexamethasone therapy, based on predefined subgroup of disease severity (PSI 1-5) and C-reactive protein level at admission as well to evaluate utility of CRP in monitoring resolution of CAP.
Methods: In this prospective case-control trial, 100 children aged 1 to 14 years were enrolled randomly with confirmed community-acquired pneumonia, who presented to emergency department of paediatrics PMCH Patna. We randomly allocated patients on a one-to-one basis to adjuvant dexamethasone with antibiotics and antibiotics alone groups by drawing lots.
Results: The median length of hospital-stay in both the adjuvant dexamethasone group and antibiotics alone group was 7 days with IQR in adjuvant dexamethasone group of 6.0-8.0 days and antibiotics group of 7.0-9.0 days (95% CI of difference in means 0.3-1.2 days; $p = 0.001931$ and was significant at p value of ≤ 0.01). There was a positive correlation between length of hospital-stay and CRP at the time of admission in adjuvant dexamethasone and antibiotics alone group with R value = 0.0261 and 0.3541 respectively. There also exist a positive correlation between length of hospital-stay and PSI at admission in adjuvant dexamethasone and antibiotics alone group with R value = 0.3555 and 0.1196 respectively. Median length of hospital-stay in those admitted with high PSI (PSI 4-5) and high CRP were 8.0 days in antibiotics alone group compared to 7.0 days in adjuvant dexamethasone group. The mean CRP on day 1, 3 and 5 was 7.734 (SEM 0.664), 3.974 (SEM 0.412) and 1.440 (SEM 0.133) respectively.
Conclusions: There was no significant difference in length of hospital-stay in CAP patient treated with adjuvant dexamethasone with antibiotics and antibiotics alone. However it is clearly evident from this study that using adjuvant dexamethasone reduced the length of hospital-stay in those who admitted with higher PSI as well as higher CRP compared to antibiotics alone group. Moreover there was a definite decremental relationship between CRP and resolution of CAP. So use of adjuvant dexamethasone in those presenting with high PSI and high CRP can be consider. Since the sample size of our study was small, further evaluation is warranted.

Keywords: Community-acquired pneumonia, C-reactive protein, Dexamethasone, Immune-compromised, PSI

INTRODUCTION

An inflammatory response is a two edge sword in pneumonia as reasonable inflammatory response is required for microorganism clearance but excessive inflammation can cause ongoing local and systemic damage. Because of this, despite appropriate antibiotic therapy, adjuvant therapy that can positively modify the immune response has become a relevant approach to improve pneumonia prognosis.

Community-acquired pneumonia (CAP) is a common disease, which causes considerable morbidity and mortality worldwide.[1] Despite the availability of effective antibiotics, pneumonia remains the leading cause of death from infectious diseases and mortality from CAP and has not decreased in the last decades.

To ultimately improve outcome of lower respiratory tract infections, new (non-antibiotic) treatment strategies are therefore urgently needed. Whatever clinical trials was done till now have yielded conflicting results regarding benifits of corticosteroids in CAP. In a double-blind, placebo-controlled trial, they found median length of stay was 6.5 days (IQR 5.0-9.0) in the dexamethasone group compared with 7.5 days (5.3-11.5) in the placebo group (95% CI of difference in medians 0-2 days; p = 0.0480).[2] In another double-blind, multicentre, randomised, placebo-controlled trial it was found that Prednisone treatment for 7 days in patients with community-acquired pneumonia admitted to hospital shortens time to clinical stability.[3] In a systematic MEDLINE, Cochrane database, and CINAHL search (1966 to November 2007) to identify full-text publications that evaluated the use of corticosteroids in CAP. On the basis of their results, the use of corticosteroids as adjunctive therapy in severe CAP should be categorized as a weak recommendation (two studies) and a strong recommendation (two studies) with either low- or moderate-quality evidence and according to the GRADE system, available studies do not support the recommendation of corticosteroids as a standard of care for patients with severe CAP so they recommend further randomized controlled trials with this aim should be conducted.[4]

In this study, we intend to assess, whether addition of corticosteroids to antibiotic treatment benefits patients with community-acquired pneumonia who are not in intensive care units, as from whatever previous study has been done it is unclear yet.[1-3] We aimed to assess effect of addition of dexamethasone on length of stay in this group, which might result in earlier resolution of pneumonia through dampening of systemic inflammation. We additionally aimed at assessing which patient benefited most from dexamethasone treatment, based on predefined subgroup analysis with, disease severity score (PSI 1-5) , C-reactive protein level at admission. We also aimed to assess role of CRP in monitoring resolution of CAP.

METHODS

In this prospective case-control trial, 100 children aged 1 to 14 years were enrolled randomly with confirmed community-acquired pneumonia, who presented to emergency department of paediatrics PMCH Patna during a period of 2 years from September 2014 to September 2016. We randomly allocated patients on a one-to-one basis to adjuvant dexamethasone with antibiotics and antibiotics alone groups by drawing lots. Control was children not receiving 4 days TDS dexamethasone (0.3 mg/kg/dose).

Sample size was 100 (50 Adjuvant dexamethasone with antibiotics group and 50 Antibiotics alone group). At two-sided significance level (1-alpha) of 90, power (1-beta, % chance of detecting) of 70, Ratio of sample size, unexposed/exposed is 1, percent of unexposed with outcome is 5, percent of exposed with outcome is 19, odds ratio of 4.5, risk/prevalence ratio is 3.8, risk/prevalence difference is 14, the sample size of case and control of 48 each and total sample size of 98 is required.

Inclusion criteria

- Patient aged 1 to 14 years
- In combination with two of the following findings:
- Chest radiograph showing new opacities.
- Production of sputum
- Cough
- Audible abnormalities by chest examination compatible with pneumonia
- Leukocytosis, leftward shift (>10%) or leucopenia (<4000 cells/mm3)
- Temp >38.0°C or <36.0°C

Exclusion criteria

- C-reactive protein > 15 mg/l (three fold higher than the upper limit of normal)
- Immune-compromised patient defined by:
- Patients who received corticosteroids in the last 6 weeks
- Patients who received chemotherapy less than 6 weeks ago
- Patients with a known congenital or acquired immunodeficiency
- Patients with dexamethasone intolerance
- Patients with chronic obstructive pulmonary disease who are on systemic corticosteroids
- Patients who received immunosuppressive medication in the last 6 weeks (e.g. cyclosporin, cyclophosphamide, azathioprine)

Length of hospital stay defined by time frame from hospital admission (= day 1 = time point at which patient presents in hospital) until hospital discharge, days of hospital stay on basis of social indication were excluded.

Median length of stay in an earlier CAP study performed in the St. Antonius Hospital in Nieuwegein was 6.5 days, thus patients were followed during an expected average of 1 week.[5] Patients with clinical features of CAP were enrolled after obtaining informed /written consent from parents/guardians. A complete clinical examination was carried out and relevant investigations done and documented in the performa on the day of admission. The patients were followed for a period of 1 week or so. Complete clinical examination and relevant investigations were done on day 3 and day 5 as well and were documented in performa.

RESULTS

From September 2014 to September 2016 we enrolled 100 patients and randomly allocated 50 to antibiotics alone group and 50 to adjuvant dexamethasone treatment group.

Demographic profile based on PSI subgroup and CRP level at admission

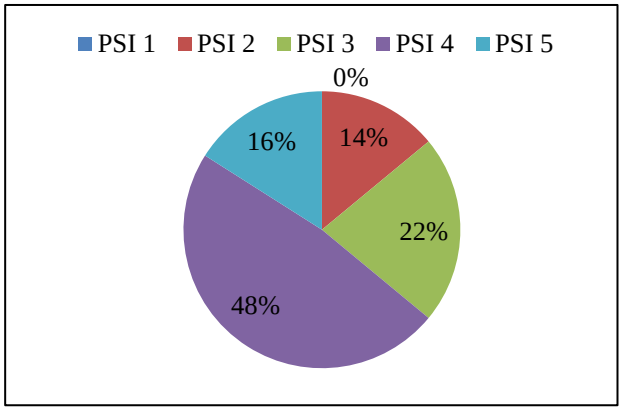

Figure1: Percentage of patient in different subgroup based on PSI of adjuvant dexamethasone group at admission.

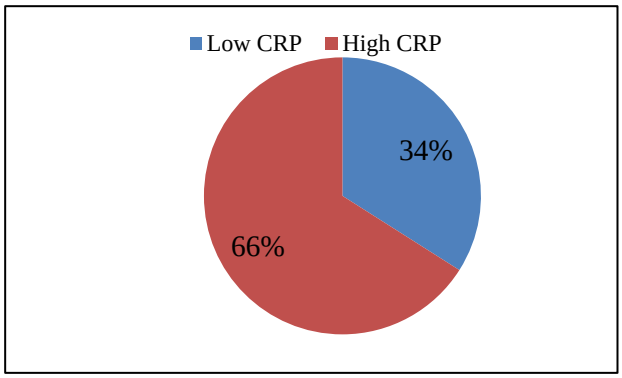

Figure 2: Percentage of patient in different subgroup based on CRP levels of adjuvant dexamethasone group at admission.

Out of 100 patient enrolled 67 had pneumonia of pneumonia severity index class 4-5 32 (64%) patient in adjuvant dexamethasone group and 35 (70%) in antibiotics alone group). Out of 100 patient 68 had high CRP at the time of admission 33 (66%) patient in adjuvant dexamethasone group 35 (70%) in antibiotics alone group) (Figure 1, 2, 3, 4).

Primary outcome (length of hospital stay)

The median length of hospital-stay in both the adjuvant dexamethasone group and antibiotics alone group was 7 days with IQR in adjuvant dexamethasone group of 6.0-8.0 days and antibiotics group of 7.0-9.0 days (95% CI of difference in means 0.3-1.2 days; p=0.001931 and was significant at p value of ≤0.01) (Table 1).

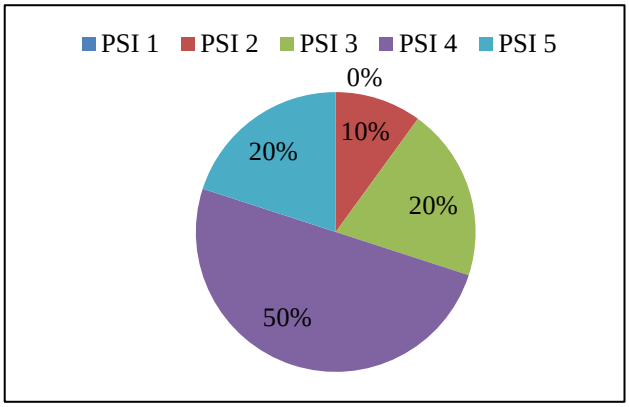

Figure 3: Percentage of patient in different subgroup based on PSI of antibiotics alone group at admission.

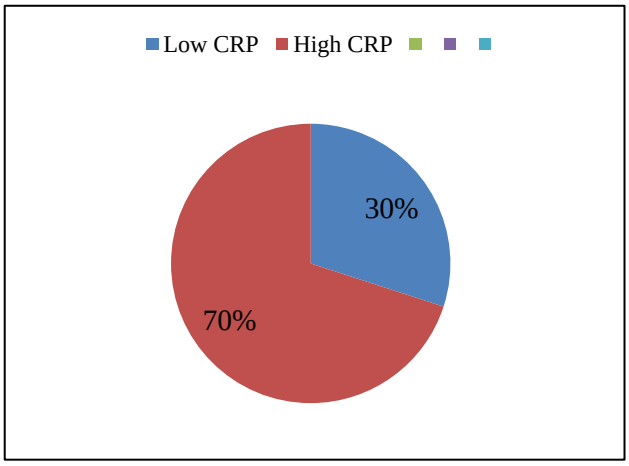

Figure 4: Percentage of patient in different subgroup based on CRP level of antibiotics alone group at admission.

Secondary outcome (subgroup analysis based on PSI and CRP level at admission)

There was a positive correlation between length of hospital-stay and CRP at the time of admission in adjuvant dexamethasone and antibiotics alone group with R value = 0.0261 (P value 0.857) and 0.3541 (P value 0.011) respectively. There also exist a positive

correlation between length of hospital-stay and PSI at admission in adjuvant dexamethasone and antibiotics alone group with R value = 0.3555 (P value 0.0112) and 0.1196 (P value 0.408) respectively (Table 2).

Moreover median length of hospital-stay in those admitted with high PSI (PSI 4-5) and high CRP were 8.0 days in antibiotics alone group compared to 7.0 days in adjuvant dexamethasone group (Table 3, 4).

Table 1: Median length of hospital stay in dexamethasone and antibiotics alone group.

	Dexamethasone group n = 50 (IQR)	Antibiotics alone group n = 50 (IQR)	P-value
Median length of hospital-stay	7 (6.0-8.0)	7 (7.0-9.0)	0.00193 (S)

S- Significant, IQR- Interquartile range

Table 2: Correlation between length of hospital-stay with PSI and CRP at the time of admission in adjuvant dexamethasone and antibiotics alone group.

Groups	Subgroups	Pearson correlation coefficient (R)	P-value
Adjuvant dexamethasone	PSI at admission	0.3555	0.0112 (S)
	CRP at admission	0.0261	0.857 (NS)
Antibiotics alone	PSI at admission	0.1196	0.408(NS)
	CRP at admission	0.3541	0.011(S)

S- Significant, NS- Non significant

Table 3: Median length of hospital-stay in different subgroup based on PSI at admission.

		Low PSI (1-3)	High PSI (4-5)
Median length of hospital-stay	Dexamethasone group	7	7
	Antibiotics alone group	7	8

Table 4: Median length of hospital-stay in different subgroup based on CRP level at admission.

		Low CRP	High CRP
Median length of hospital-stay	Dexamethasone group	7	7
	Antibiotics alone group	7	8

Tertiary outcome (role of CRP in monitoring resolution of pneumonia)

The mean CRP on day 1, 3 and 5 was 7.734 (SEM 0.664), 3.974 (SEM 0.412) and 1.440 (SEM 0.133) respectively.

DISCUSSION

This was a hospital based prospective case-control study with intention to treat, conducted in the department of paediatrics of Patna Medical College and Hospital, Patna, India from September 2014 to September 2016. In this study 100 children aged 1 to 14 years were enrolled randomly with confirmed community-acquired pneumonia further We randomly allocated patients on a one-to-one basis to adjuvant dexamethasone with antibiotics and antibiotics alone groups by drawing lots. In this study we aimed to assess whether using dexamethasone as an adjuvant with antibiotics has any effect on length of hospital-stay, which might result in earlier resolution of pneumonia due to damping effect of dexamethasone on systemic inflammation. We additionally aimed at assessing which patient benefited most from dexamethasone treatment, based on predefined subgroup analysis with, disease severity score (PSI 1-5), C-reactive protein level at admission. We also aimed to assess role of CRP in monitoring resolution of CAP.

In our study out of 100 patient enrolled 67 had pneumonia of pneumonia severity index class 4-5 (32 (64%) patient in adjuvant dexamethasone group and 35 (70%) in antibiotics alone group). Out of 100 patient 68 had high CRP at the time of admission (33 (66%) patient in adjuvant dexamethasone group 35 (70%) in antibiotics alone group) (Figure 1-4).

Which is almost similar to the double-blind, placebo-controlled trial done by Meijvis SC et al where they found 143 (47%) of 304 enrolled patients had pneumonia of pneumonia severity index class 4-5 (79 (52%) patients in the dexamethasone group and 64 (42%) controls).[1]

The number of patient presented with high CRP is almost equal to the patient with high PSI (PSI4-5) class (Figure1-4). There was also a trend of an association between the level of CRP on admission and high PSI class (PSI 4-5) with the R value of 0.5418. Thus CRP may be valuable to assess the disease severity, and can be

regarded as complementary to the assessment of the PSI, which is consistent with the retrospective case note review carried out by Smith RP, Lipworth BJ, where they also found Serum CRP may be a useful adjunctive test in pneumonia, both in terms of distinguishing parenchymal from endobronchial infection, as well as being a marker of treatment response.[6,7]

The median length of hospital-stay in both the adjuvant dexamethasone group and antibiotics alone group was 7 days with IQR in adjuvant dexamethasone group of 6.0-8.0 days and antibiotics group of 7.0-9.0 days (95% CI of difference in means 0.3-1.2 days; p = 0.001931 and was significant at p value of ≤ 0.01) (Table 1). There was no significant difference in length of hospital-stay in CAP patient treated with adjuvant dexamethasone with antibiotics and antibiotics alone. Which is Consistent with the systematic MEDLINE, Cochrane database, and CINAHL search (1966 to November 2007) done to identify full-text publications that evaluated the use of corticosteroids in CAP.

On the basis of their results also, the use of corticosteroids as adjunctive therapy in severe CAP is categorized as a weak recommendation (two studies) and a strong recommendation (two studies) with either low- or moderate-quality evidence and according to the GRADE system, available studies do not support the recommendation of corticosteroids as a standard of care for patients with severe CAP.[3] However there was a positive correlation between length of hospital-stay and CRP at the time of admission in adjuvant dexamethasone and antibiotics alone group with R value = 0.0261 and 0.3541 respectively. There also exist a positive correlation between length of hospital-stay and PSI at admission in adjuvant dexamethasone and antibiotics alone group with R value = 0.3555 and 0.1196 respectively and moreover the median length of hospital-stay in those admitted with high PSI (PSI 4-5) and high CRP were 8.0 days in antibiotics alone group compared to 7.0 days in adjuvant dexamethasone group (Table 1, 2).

It is clearly evident from this study that using adjuvant dexamethasone reduced the length of hospital-stay in those who admitted with higher PSI as well as higher CRP compared to antibiotics alone group. Which is similar to the result of a meta-analysis done by including all the randomized controlled trials (RCTs) which used corticosteroids as adjunctive therapy, to examine the benefits and risks of corticosteroids in the treatment of CAP, where they found in the subgroup analysis by the severity, a survival benefit among severe CAP patients (Peto OR 0.26, 95% CI 0.11-0.64; P = 0.003).[8] So use of adjuvant dexamethasone in those presenting with high PSI and high CRP can be consider.

The mean CRP on day 1, 3 and 5 was 7.734 (SEM 0.664), 3.974 (SEM 0.412) and 1.440 (SEM 0.133) respectively. There was a definite decremental relationship between CRP and resolution of CAP. So CRP can be used as tool for monitoring resolution of pneumonia.[7,9]

Limitations of this study were that the sample size of this study was small and the sensitivity and specificity of pneumonia severity index (PSI) has not been studied in children.

CONCLUSION

There was no significant difference in length of hospital-stay in CAP patient treated with adjuvant dexamethasone with antibiotics and antibiotics alone. However it is clearly evident from this study that using adjuvant dexamethasone reduced the length of hospital-stay in those who admitted with higher PSI as well as higher CRP compared to antibiotics alone group.

Also evident from this study that CRP may be valuable to assess the disease severity, and can be regarded as complementary to the assessment of the PSI. Moreover there was a definite decremental relationship between CRP and resolution of CAP. So use of adjuvant dexamethasone in those presenting with high PSI and high CRP can be consider. Since the sample size of this study was small further evaluation is warranted.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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