Original Article

Oral amoxicillin versus intravenous ampicillin for chest indrawing pneumonia in children aged 3–59 months: A randomized control trial

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ABSTRACT

Background: Pneumonia is one of the leading causes of under-five mortality. There is lack of consistency in treatment guidelines issued by various organizations. **Objective:** The primary objective of the study was to compare the efficacy of oral amoxicillin against intravenous (IV) ampicillin in children aged 3–59 months with chest retraction pneumonia. The secondary objective was to identify the risk factors associated with the absence of clinical improvement at the end of 48 h of treatment. **Materials and Methods:** This was a non-blinded randomized controlled, non-inferiority trial of oral amoxicillin 80 mg/kg/day in two divided doses and IV ampicillin 200 mg/kg/day in three divided doses in children aged 3–59 months with chest retraction pneumonia. The study was conducted in the pediatric wards of a tertiary care facility from November 2016 to September 2017. The children were followed up after 48 h and 5 days for the clinical improvement. The primary outcome considered was absence of improvement or deterioration in the study children at the end of 48 h of initiation of therapy and was expressed as risk difference between the two treatment groups. Multivariate regression analysis was performed to determine the predictors of poor outcome of the disease. **Results:** Risk difference of treatment failure between both groups was -3.7% (95% confidence interval [CI] −16.8%–9.4%). The presence of wheeze and X-ray findings of pneumonia was significant independent risk factors for poor outcome at the end of 48 h. **Conclusion:** Oral amoxicillin is not inferior to IV penicillin in the treatment of chest retraction pneumonia in children aged 3–59 months. The presence of wheeze and X-ray findings suggestive of pneumonia can be used as prognostic indicators in children.

Key words: Chest retraction pneumonia, Intravenous ampicillin, Oral amoxicillin

Pneumonia is one of the leading causes of morbidity and mortality in children under-5 years of age in developing countries. Globally, pneumonia accounted for approximately 16% of 5.6 million under-five deaths, killing around 880,000 children in 2016 [1]. In India, 158,000 under-five children died of pneumonia in the same year accounting for nearly 18% of global burden.

Bacterial infection has a far greater role as a cause of pneumonia in children, especially in developing countries. Researchers have identified *Streptococcus pneumoniae* and *Haemophilus influenzae* as the common etiological agents of pneumonia in developing countries [2]. These organisms respond to semi-synthetic penicillin [3].

The diagnosis of pneumonia is purely clinical, based on the presence of fast breathing, while chest retraction and general danger signs are used to classify the disease severity [4].

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There is lack of consistency in treatment guidelines issued by various organizations. As per IMNCI and INDIACLEN task force on pneumonia, the presence of chest retractions implies severe pneumonia which has to be managed with intravenous (IV) antibiotics [4,5]. On the contrary, as per the WHO guidelines, presences of chest retractions signify non-severe pneumonia managed with oral antibiotics alone [6].

This study was a non-inferiority study, with the primary objective to compare the efficacy of oral amoxicillin against IV ampicillin in children aged 3–59 months with chest retraction pneumonia. The secondary objective was to identify the risk factors associated with the absence of clinical improvement in these children at the end of 48 h of treatment.

MATERIALS AND METHODS

We undertook a non-blinded randomized controlled, non-inferiority trial of oral amoxicillin and IV ampicillin in children aged 3–59 months with chest retraction pneumonia, in the

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pediatric wards of a tertiary care facility in South India from November 2016 to September 2017. Children of age 3–59 months who presented to the facility with a history of cough and cold with/without fever, fast breathing (respiratory rate more than 50/min in infants and more than 40/min in children), and chest retractions were included in the study.

Children with a history of cough/difficulty in breathing for more than 2 weeks, children who had antibiotics for more than 48 h for the current illness, known cases of immunodeficiency, asthma, whose lower chest retractions responded to nebulization, those with severe acute malnutrition, congenital heart disease, those with general danger signs, and those who did not give consent were excluded from the study. A convenient sample size of 100 was chosen. The study was commenced after obtaining approval from the Institutional Ethical Committee.

After obtaining informed consent from parents, eligible children were recruited in the study. The baseline characteristics of the child such as name, age in months, and sex were noted. Duration of the presence of symptoms such as cough and cold, fever, fast breathing, noisy breathing, and any other symptoms was also noted. Anthropometric measurements of the child were made. The length of the children <2 years was measured using an infantometer, while the height of those more than 2 years was measured using stadiometer without shoes, with head, shoulders, buttocks, and heels touching the board. Weight of the children was measured using an electronic weighing scale. Weight for age, height for age, and weight for length/height were plotted using the WHO growth charts.

Clinical data of the children such as temperature, heart rate, respiratory rate, presence of retractions, and any added sounds were noted at the time of admission. Axillary temperature of the children was recorded at admission using a digital thermometer. Temperature more than 37°C was taken as fever. Heart rate was auscultated for 1 min. Standard age-wise cutoff values were used to classify normal heart rate and tachycardia. The child was undressed up to the waist and seated in a non-threatening position (preferably on mother's lap) to count respiratory rate. It was counted by placing hand on the chest and the respiratory movements were counted for 1 min. The presence of added sounds and type of added sounds (creps, wheeze, or both) were also documented.

The children were randomized in the ratio of 1:1 using online randomization codes (seed 12201) with the block size of 10. Random sequence was generated by one of the investigators and placed in serially numbered opaque sealed envelopes for allocation concealment. The children were assigned to treatment by another investigator using consecutive envelopes. The oral group children were given oral amoxicillin 80 mg/kg/day in two divided doses for 5 days and IV group, ampicillin 200 mg/kg/day in three divided doses was given for 5 days. These children were also subjected to blood and radiological investigations as per the unit protocol.

The children were followed up after 48 h and 5 days for the clinical improvement. Data such as temperature, respiratory rate, heart rate, added sounds, and persistence of retractions after 48 h were noted. Any development of danger signs, other new symptoms, and adverse reactions to the drug were also recorded. The supportive measures given to the child such as antipyretics and nebulization were taken into account. Any deterioration after 48 h was noted and time taken for the discharge of the study children was documented. All the children were followed up till discharge/death. The primary outcome of the study was taken as absence of improvement in terms of respiratory rate/chest retractions or deterioration in terms of respiratory rate, heart rate, chest retractions, or appearance of any general danger sign warranting escalation of antibiotics in either arm at the end of 48 h of initiation of therapy.

Statistical analysis of the data was performed by SPSS software version 21. Baseline characteristics of two groups were compared using Chi-square test for categorical variables and Student's t-test for numerical variables. The primary outcome was measured in both the limbs and expressed as risk difference between the two treatment groups. Non-inferiority between amoxicillin and ampicillin was defined a priori as a risk difference of treatment failure and associated upper bound of the 95% confidence interval (CI) of <10%. This definition is comparable to those of previous studies on childhood pneumonia [7,8]. We planned to undertake both intention-to-treat and per-protocol analyses for the primary outcome. Multivariate regression analysis was performed to determine the predictors of poor outcome of the disease. $p<0.05$ was considered statistically significant.

RESULTS

A total of 100 children of age 3–59 months with chest indrawing pneumonia were included in the study. A brief summary of patient flow is depicted in Fig. 1.

As much as 34% of them were infants, while the rest 66% were children aged 1–5 years. Median (IQR) age of the study population was 15.5 (11–25.5) months. Sex ratio was 1.56:1 (male:female). Most of the children presented with fever, cough, cold, and breathlessness of variable duration. Mean (SD) duration of cough and cold was 4.86 (1.975) days. Fever was present in 85% of children. The mean (SD) duration of fever was 4.47 (2.129) days. Median (IQR) duration of fast breathing was 2.5 (2–3) days. Some children also had other symptoms such as vomiting (5%) and loose stools (3%). A total of 40 children had chest X-ray findings suggestive of pneumonia; 28 children had bilateral patchy infiltrates involving more than 1 lobe while 12 of them had lobar consolidation. Baseline characteristics of the study children were comparable between both amoxicillin and ampicillin groups (Table 1).

One child was lost to follow up at the end of 48 h and the rest 99 patients were available for the assessment of primary outcome. Protocol violation was not observed in any participant. The risk of treatment failure was 16.3% in oral amoxicillin group and 20% in IV ampicillin group at 48 h. Risk difference was −3.7%, the 95% CI being −16.8%–9.4%indicating non-inferiority within the specified margin of 10%. None of the children recruited for the study expired during the study period.

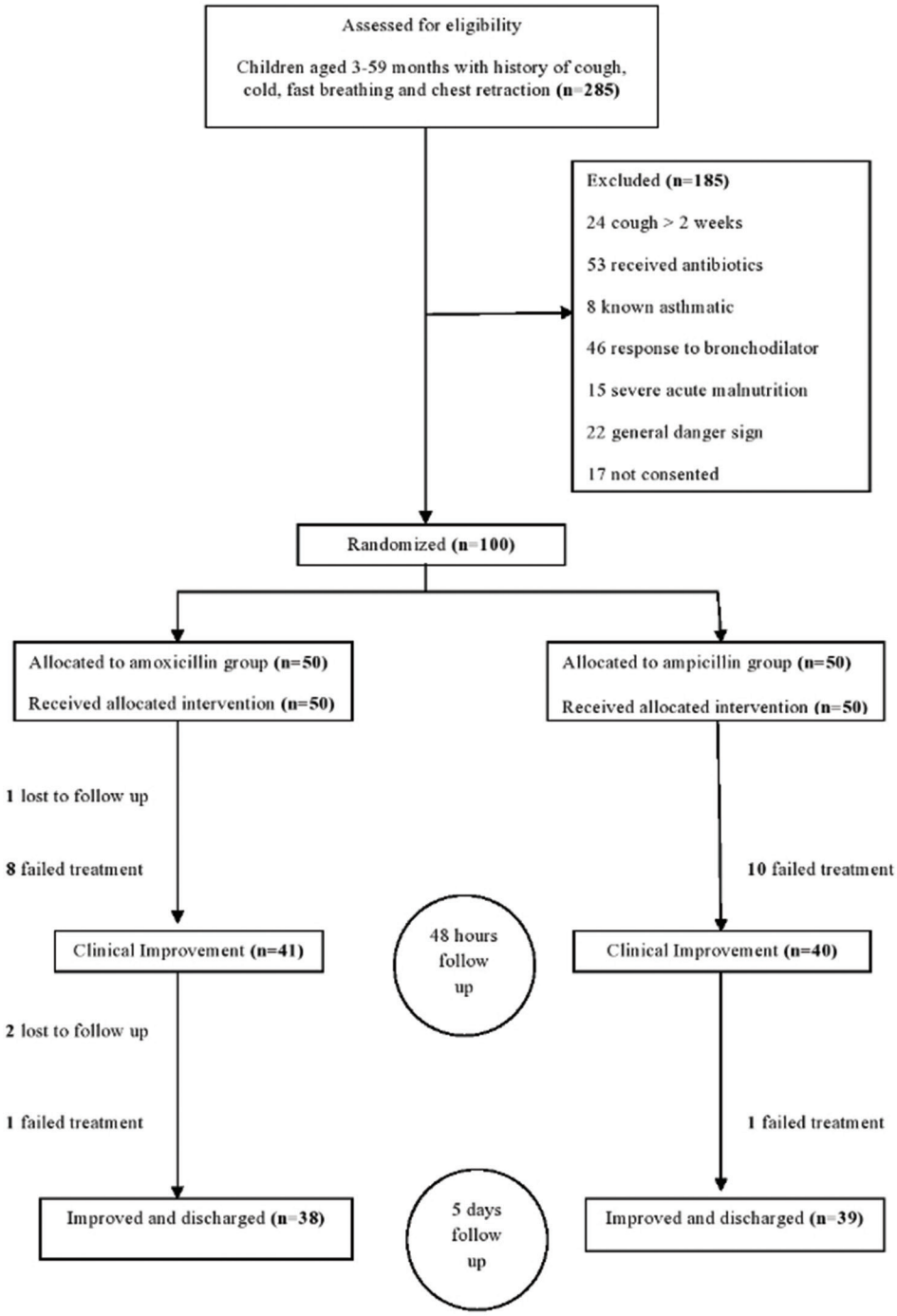

Figure 1: Patient flow in trial

There were no adverse reactions reported during this study. Children who failed initial therapy were started on the second line antibiotics and eventually improved and were discharged after a maximum of 10 days.

Further analysis was done to identify the individual parameters that can affect the outcome of the disease in the children. Age of the child (infancy), duration of symptoms (cough, cold, and fever), chest X-ray findings, presence of wheeze in the child, and nutritional status were the factors considered (Table 2).

Univariate analysis was performed followed by logistic regression to identify independent predictors of poor outcome. The presence of wheeze (adjusted OR 4.9 [95% CI 1.18–20.40]) and X-ray findings of pneumonia (adjusted OR 5.7 [95% CI 1.76–18.77]) emerged as significant independent risk factors for poor outcome at the end of 48 h.

DISCUSSION

This study has proved that oral amoxicillin is not inferior to IV ampicillin in the treatment of chest retraction pneumonia in children aged 3–59 months. Further, it was found that the presence of wheeze on examination and chest X-ray features suggestive of pneumonia were independent predictors of non-improvement with first line antibiotics at the end of 48 h of treatment.

Table 1: Comparison of baseline parameters

S. No.	Parameter	Amoxicillin group	Ampicillin group	p value
1	Age (infancy)	18/50	16/50	0.153
2	Cough, cold duration*	4.74 (1.50)	4.98 (1.96)	0.541
3	Fever	42/50	43/50	1.000
4	Nutritional status (MAM)	23/50	16/50	0.352
5	Wheeze	6/50	6/50	1.000
6	Abnormal CXR	22/50	18/50	0.414
7	CRP positivity	39/50	39/50	1.000

***mean (standard deviation). CRP: C-reactive protein, CXR: Chest X-ray, MAM: Moderate acute malnutrition**

Table 2: Univariate analysis of factors affecting outcome at 48 h

S. No.	Parameter	Category	Not improved n (%)	Improved n (%)	p value
1	Age	Infancy	8 (23.5)	26 (76.5)	0.318
		>1 year	10 (15.4)	55 (84.6)	
2	Cough, cold	Mean (SD)	5.44 (2.09)	4.7 (1.93)	0.152
3	Fever	Present	16 (18.8)	69 (81.2)	1.000
		Absent	2 (14.3)	12 (85.7)	
4	Wheeze	Present	5 (41.7)	7 (58.3)	0.024
		Absent	13 (14.9)	74 (85.1)	
5	MAM*	Present	9 (23.1)	30 (76.9)	0.309
		Absent	9 (15)	51 (85)	
6	CXR pneumonia	Present	13 (32.5)	27 (67.5)	0.002
		Absent	5 (8.5)	54 (91.5)	

***Moderate acute malnutrition. CXR: Chest X-ray, MAM: Moderate acute malnutrition**

The finding of our study is in concurrence with previous other randomized control trials done on under-five children which have demonstrated the non-inferiority of oral amoxicillin over IV penicillin [7-9]. Few other studies by Bari *et al*. and Soofi *et al*. demonstrated the superiority of oral amoxicillin over cotrimoxazole [10,11]. A study by Patel *et al*. proved oral amoxicillin to be effective in the management of chest retraction pneumonia in under-five children with cost-effectiveness, when administered as domiciliary therapy [12]. A total of two systematic reviews concluded oral amoxicillin to be effective in the treatment of chest indrawing pneumonia [13,14]. In addition, a Cochrane review by Kabra *et al*. stated similar failure rates of injectable penicillin and oral amoxicillin [3].

Amoxicillin and ampicillin belong to same group of penicillins (aminopenicillins) with similar half-life and pharmacokinetics. Hence, oral amoxicillin is as effective as IV ampicillin in the management of pneumonia. The key implication of this finding is the cost-effectiveness and prevention of nosocomial infections and other issues related to hospitalization.

The previous studies have identified infancy and poor nutritional status as risk factors of poor outcome which is in contrast to the finding of our study [8,9]. The presence of wheeze was associated with less chance of treatment failure in a previous study by Agweyu *et al.* which was in sharp contrast with ours [9]. Wheeze when present is mostly a feature of viral pneumonia and could possibly delay improvement in these children. A previous study by Kelly et al identified chest X-ray findings of pneumonia to be associated with increased risk of treatment failure at 48 h, in line with our study [15]. Although the WHO does not include chest radiograph to diagnose or classify pneumonia, the current finding implies its use to prognosticate pneumonia.

This was a meticulously planned and rigorously executed randomized controlled trial which potentially created strong evidence. The main limitation of the study is the small sample size that is responsible for the wide 95% CI of risk difference. In spite of this, the 95% confidence limits were less than the non-inferiority margin of 10% proving non-inferiority of the intervention. Due to the nature of the interventions, blinding is not possible and hence could not be done. This could have resulted in observer bias.

CONCLUSION

Oral amoxicillin is not inferior to IV penicillin in the treatment of chest retraction pneumonia in children aged 3–59 months. The presence of wheeze and X-ray findings suggestive of pneumonia can be used as prognostic indicators in children.

AUTHORS' CONTRIBUTIONS

All authors were involved in conceptualization of the study, SAN generated the randomization sequence, MG recruited the patients, MG and NSB collected data, SAN and DP analyzed the data, MG and SAN prepared the manuscript, and all four authors were involved in revising the manuscript and final approval of manuscript sent for publication.

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