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Amoxicillin plus Clavulanic Acid Vs Amoxicillin in the Treatment of Community Acquired Pneumonia in Children: A Double-Blind, Randomized, Controlled Trial

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ABSTRACT

WHO recommendations for the management of Community Acquired Pneumonia (CAP) have been revised since 2014, amoxicillin is recommended as first choice for oral antibiotic therapy in domiciliary treatment of children. This study was planned to compare cure rate of oral amoxicillin plus clavulanic acid vs oral amoxicillin in children with CAP.

Children aged 6- 36 mo, presenting with the clinical features consistent with the diagnosis of CAP were enrolled. Patients were given oral amoxicillin or amoxycillin plus clavulanic acid for 5 d and followed at 48h, 5th d and 2 mo. The cure rate, adverse reactions and recurrence were assessed and analysed for these two drugs.

The cure rate of CAP in amoxicillin plus clavulanic acid group was significantly higher as compared to amoxicillin group (93.88% vs 79.17%, p 0.013). The chances of cure rate increased by 15.3% for children receiving oral amoxicillin plus clavulanic acid. Only mild side effects like diarrhea (22.1%), nausea (9.6%), vomiting (5.7%), and maculo-papular rash (2.9%) were observed in both the groups. All the cured children were followed up to 2 mo and none had recurrence of symptoms.

KEYWORDS: Community Acquired Pneumonia (CAP); Amoxycillin; Amoxycillin plus Clavulanic acid; Amoxyclav

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INTRODUCTION

Infectious diseases remain a leading cause of under-five deaths. Pneumonia (18·7%), diarrhoea (15·7%), malaria (15·8%) comprise majority of under-five deaths in the world. India accounted for 783314 under-five deaths in 2020 with mortality rate of 33 deaths per 1000 live births [1]. In fact, this number adds to approximately 14 children dying of pneumonia every hour.

Malnutrition, low birth weight and non-exclusive breastfeeding increase the incidence of pneumonia in developing countries. Symptoms of viral and bacterial pneumonia are similar. The diagnosis of pneumonia can be made by proper history and physical examination. The clinical setting and the severity of the illness define the diagnostic approach. The diagnosis of pneumonia is considered in infants and children who present with respiratory complaints viz cough, tachypnea, retractions, and abnormal lung examination in community practice; when in doubt diagnosis can be confirmed on chest radiographs or lung ultrasonography. In most clinical settings, the diagnosis of pneumonia can be made without a radiograph [2].

WHO (2014) recommended management of pneumonia by classifying into three categories. Category "no pneumonia" includes children with cough and cold, category "pneumonia" is when child is having fast breathing and/or chest in-drawing. When children have general danger signs (not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition) along with fast breathing with or without chest retractions are classified as category "severe pneumonia or very severe pneumonia". The WHO advises domiciliary treatment for category "pneumonia" with oral amoxicillin. [3]

MATERIAL AND METHODS

A double-blind randomized control trial was conducted in a tertiary care teaching hospital from January 2019 to May 2020. The study was a randomized (1:1) double-blind controlled trial based on PICO (population, intervention, comparator, outcome) framework.

Population- children aged 6 - 36 mo, presenting with the clinical features consistent with the diagnosis of CAP with 'pneumonia' category.

Intervention- Oral administration of Amoxicillin plus Clavulanic Acid (Treatment group)

Comparator- Oral administration of Amoxicillin alone (Control group).

Outcome- To compare cure rate of children with CAP in the 2 groups.

Sample size was calculated on the basis of odds ratio of cure rates for the two drugs under study with values provided by Jibril et al [4] using the formula of sample size for relative risk estimation provided by A. Indrayan, Basic Methods of Medical Research. After taking odds ratio 10.44 (given in the reference study) under research hypothesis with 95% confidence level and 90% power of study, the sample size was estimated to be 47 in each group (total of 94) and after considering 10% attrition final sample size was 52 subjects in each group (total of 104). Children aged 6 – 36 mo presenting to Pediatric outpatient or Emergency room with fast breathing for age (WHO defined (<50 breaths/min for ages 2–11 mo and <40 breaths/min for ages 12–59 mo) and/or chest indrawing were enrolled in the study. Children with severe acute malnutrition, or in a clinically immunocompromised state, foreign body ingestion, sickle cell anaemia with acute chest syndrome, or having received treatment 48 h prior to hospital visit were excluded.

For this research work the ethical clearance from the institutional committee and written informed consent was taken from the parents. Patients were divided by random numbers and allocation was done by serially numbered opaque sealed envelope (SNOSE) technique to receive either of the two drugs.

Details of history, examination and demography were filled in the predesigned proforma. Respiration rate was observed in calm, afebrile child. Parents were explained and counselled about the study and written consent was taken. On admission child's complete blood count, chest X-ray and CRP (if possible) were done.

The medications were of identical in packing (packed into white opaque box with name hidden by white opaque paper) and concentration. Oral amoxicillin was procured as CIPLA NOVAMOX and oral amoxycillin plus clavulanic acid was procured as ALKEM CLAVAM both IP 125mg/5ml (equivalent of amoxicillin). It was procured from different companies as similar concentration of the drugs were not available in the market from the same company. Dose of drug was calculated using the amoxicillin component as 40mg/kg/dose twice daily for 5 d.

Drug bottles with other supportive care treatment were handed to the caregiver with instructions for use and return after 48 h for reassessment. At 48 h if improvement (when respiratory rate decreases by ≥ 5/min or disappearance of in drawing with/without improvement in respiratory rate) [5] was seen further drug was dispensed and followed until 5th d. Children improved on 5th d were considered cured (defined as return of respiratory rate to age specific normal range) [5] and treatment was discontinued. They were followed in the out-patient department or on phone for 2 mo for any recurrence of CAP symptoms. Those children who did not improve by 72h or treatment failure by 5th d (includes development of signs of severe pneumonia or persistently raised respiratory rate for age on 5th d) [3] were excluded from the study and treated under hospital policy (all children were admitted, investigations were done including hemogram, CRP, blood culture and chest X-ray, and parenteral antibiotic was given, after sensitivity report). The adverse effects like nausea, vomiting, diarrhoea, rash or itching were observed during treatment. The data was analysed by using the statistical package for social sciences (SPSS 23.0) software.

RESULTS

Patients in two groups were comparable for age, gender, weight, immunization status and clinical profile (number of illness days, respiratory rate and presence of chest in drawing). After 48 h of treatment 45 children (86.5%) in each group showed improvement in signs and symptoms of CAP. In each group, 6 children (11.5%) did not improve at 48 h and 1 child did not report. At 72 h, in the treatment group, 4 children (66.67%) showed improvement, whereas in control group, 3 children (50%) improved. In all 4 children who did not show improvement were excluded from the study and treated as per hospital policy.

On 5th d of treatment, 49 children (94.2%) and 48 children (92.3%) in the treatment and control groups, respectively, who had shown improvement at 72 h were followed. In treatment group, 46 children (93.88%) were cured and in 1 child (2.04%) symptoms persisted designated as treatment failure and 2 children (4.08%) did not turn up. In control group, 38 children (79.17%) were cured and in 8 children (16.67%) symptoms persisted designated as treatment failure and 2 children (4.17%) did not turn up.

On d 5, the cure rate of CAP in treatment group was significantly higher as compared to control group (93.88% vs 79.17%, p 0.013). The chances of cure were increased by 15.3% for children receiving oral amoxicillin plus clavulanic acid. The data were also analysed on intention-to-treat basis and still the cure rate of CAP in treatment group was significantly higher as compared to control group (88.46% vs 73.10%, p 0.047).

Side effects of treatment were mild and comparable among both the groups i.e. nausea (6, 11.5% vs 4, 7.7%), vomiting (4, 7.7% vs 2, 3.8%), diarrhea (10, 19.2% vs 13, 25%), rash (1, 1.9% vs 2, 3.8%).

Table – 1: Comparison of cure rate in CAP category "pneumonia" with oral Amoxyclav vs oral Amoxy alone.

Condition		Amoxyclav Group (n=52)		Amoxy Group (n=52)		chi sq.	p-value
		No	%	No	%		
At 48 h (n=52)	Improved	45	86.50%	45	86.50%	0	1
	Not Improved	6	11.50%	6	11.50%		
	Did not Turn up#	1	1.90%	1	1.90%		
At 72 h (n=6)	Improved	4	66.67%	3	50.00%	0.13	0.936
	Not Improved$	2	33.33%	2	33.33%		
	Didn't turn up#	0	0.00%	1	16.67%		
Total improve at 72 h		49	94.23%	48	92.31%		
At 5th d	Cured	46	93.88%	38	79.17%	6.2	**0.013**
	Treatment Failure$	1	2.04%	8	16.67%		
	Did not Turn up#	2	4.08%	2	4.17%		
Total		49	100%	48	100%		
With Intention to Treat							
At 5th d	Cured	46	88.46%	38	73.10%	3.96	**0.047**
	Treatment Failure@	6	11.54%	14	26.90%		
Total		52	100%	52	100%		

*AR: Attributable risk (Risk difference), Amoxyclav Group= oral amoxicillin plus clavulanic acid, Amoxy Group= oral amoxicillin, wrt= with respect to @This include children who had no improvement by 72 hrs$, or were treatment failure by 5thd$, or didn't turn up# on 48hrs, 72h hrs and on 5thd (In Amoxyclav group= 2,1,1,0,2 and In Amoxy group= 2,8,1,1,2 respectively) $ Excluded from the study and treated with unit protocol # On telephonic contact parents reported consultation by another paediatrician as there was no improvement. Opted out.

DISCUSSION

Children suffering from "pneumonia" category of CAP, as per the revised WHO recommendations, were randomised into two groups (1:1) in this PICO designed study. It was noted that proportion of cured children was significantly higher (p 0.013), and cure rate increased by 15.3% for children receiving oral amoxicillin plus clavulanic acid compared to amoxicillin alone.

The WHO advises domiciliary treatment for category "pneumonia" with oral amoxicillin. The alternative antibiotics for the treatment of CAP are co-amoxyclav, cefpodoxime, cefaclor, cefuroxime, erythromycin, azithromycin, clarithromycin, chloramphenicol and levofloxacin [6,7].

To best of our knowledge there is only one study comparing amoxicillin plus clavulanic acid with amoxicillin in the treatment of pneumonia [3]. Many studies compared amoxicillin plus clavulanic with other antimicrobials like azithromycin, cefpodoxime, cefotaxime-sulbactam, levofloxacin, erythromycin, cefuroxime and clarithromycin and showed similar cure rate [6].

The limitation of our study was that we neither isolated the organisms responsible for CAP nor carried out any sensitivity study for the antibiotics. The strength of the study remains the

PICO designed double blinded randomized study with follow up of 98.9% by 5th d and long follow up to 2 mo (88.1%).

CONCLUSION

This study showed that cure rate of CAP in "pneumonia" category in children aged 6 mo to 36 mo with amoxicillin plus clavulanic acid was higher being 97.8%, increased by 15.3%, as compared to amoxicillin alone. There were no serious side effects of amoxicillin plus clavulanic acid compared to amoxycillin alone.

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Authors contribution

AA: protocol, data collection, research analysis, preparation of initial manuscript

MF: study designing, interpretation of data, research analysis, writing final manuscript, approve discussion

SS: supervise, literature search, data collection, manuscript writing

SK: radiological analysis

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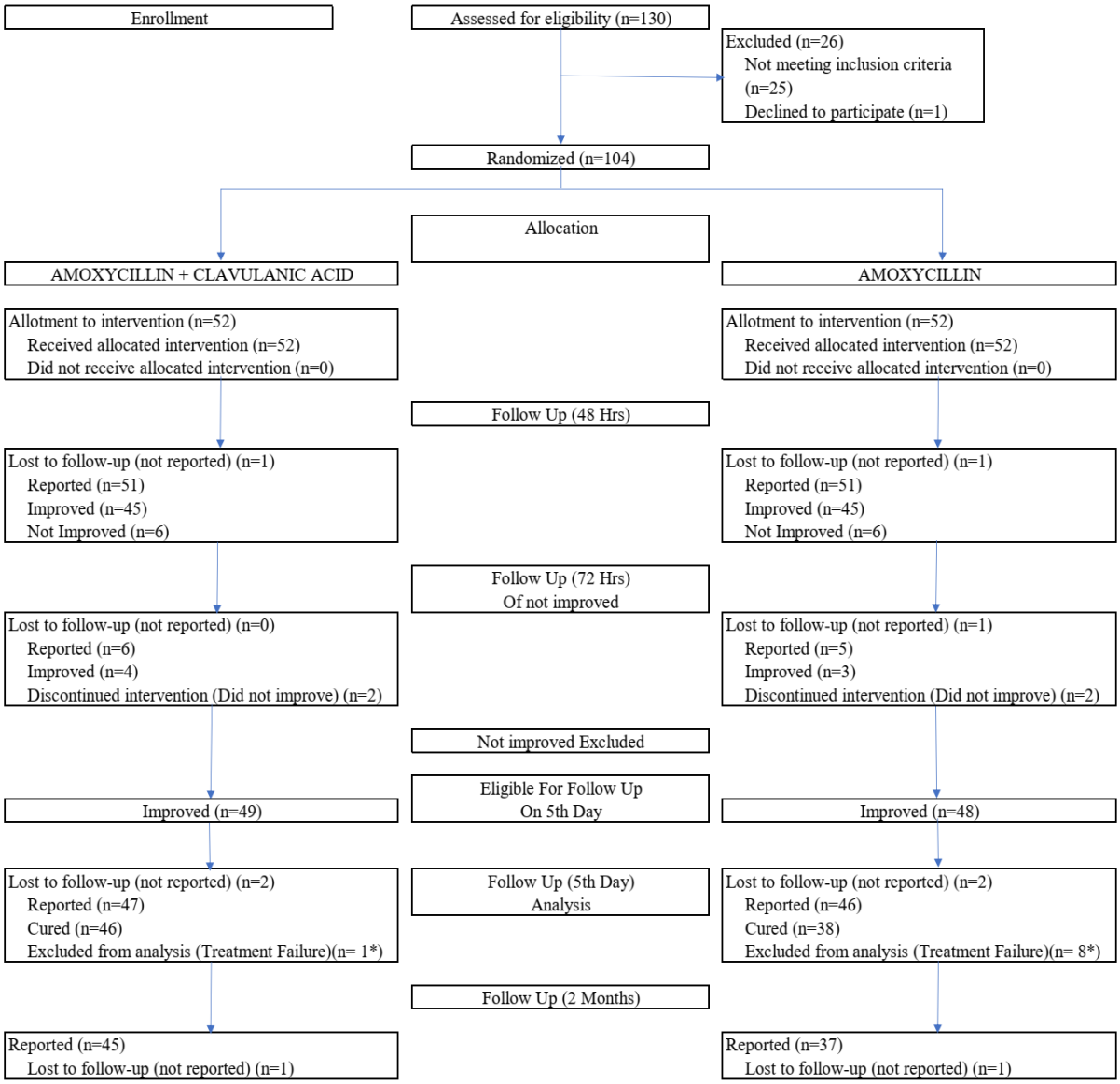
Fig 1: CONSORT Flow Diagram



*AGE SPECIFIC RESPIRATORY RATE NOT ACHIEVED