Original Articles

EFFECTIVENESS OF AMPICILLIN AND COMBINATION OF PENICILLIN AND CHLORAMPHENICOL IN THE TREATMENT OF PNEUMONIAS: RANDOMIZED CONTROLLED TRIAL

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Objective: *To assess the effectiveness of ampicillin and a combination of benzyl penicillin and chloramphenicol in the treatment of pneumonias.* ***Design:*** *Randomized controlled trial.* ***Setting:*** *Tertiary care hospital.* ***Subjects:*** *Patients 5 months to 4 years old with pneumonias of < 2 weeks duration. Exclusion criteria included acute bronchiolitis, allergy to penicillin, post-measles pneumonia or prior administration of trial antibiotics in full dose for more than 2 days.* ***Intervention:*** *Patients were randomized to receive either ampicillin (100 mg/kg/day) or combination of benzyl penicillin (100,000 units/kg/day) and chloramphenicol (100 mg/kg/day). The outcome measure was cure rate.* ***Results:*** *There were 52 and 49 patients in the ampicillin and the combination groups, respectively. There was no significant difference in the baseline characteristics between groups except, nasal flare and cyanosis which were less in benzyl penicillin plus chloramphenicol group. There was also no difference either in the primary outcome, cure rate or secondary outcomes (days for cure, duration of tachypnea, fever and grunt) in the two.* ***Conclusion:*** *Considering the potential toxicity of chloramphenicol and the number of, injections and doses to be given for the combination, ampicillin as a single drug could be preferred for the treatment of pneumonias, in this part of the country.*

Key words: *Pneumonia, Ampicillin, Chloramphenicol, Acute respiratory infections.*

AMONG the pediatric outpatients, 20 to 30% come to the hospital for acute respiratory infection(l). Considerable proportions are of severe ARI who need admission (25-40% of the hospital admissions). It has been reported earlier that pneumonia alone accounts for about 75% of all deaths due to acute respiratory infections(l,2). Even though the etiology is often undetermined in a clinical situation, the most frequent agents causing pneumonia in children are *S. pneumoniae, H. influenzae* and to some extent *S. aureaus.* Evidence for this emerges from using culture of lung aspirate, counterimmunoelectrophoresis, blood and pus culture(3-7). In deciding about treatment for pneumonias it is not always possible to confirm the etiological agent. So it is important to prescribe antimicrobials which would cover most of the organisms attributed for bacterial pneumonias(8). Parenteral penicillin is suggested as the drug of choice for the initial treatment of pneumonias, especially in developing countries, because of its

effectivenes in a high proportion of cases and low cost(2). However, pneumonias may be caused by *H. influenzae* strains which are resistant to penicillin necessitating addition of a second drug like chloramphenicol. The latter is cheap, well absorbed and penetrates into almost all tissues of the body. Ampicillin possesses a spectrum of activity against the common organisms mentioned above. The present study was designed to evaluate the relative effectiveness of ampicillin and a combination of benzyl penicillin and chloramphenicol in the treatment of pneumonia.

Subjects and Methods

This randomized controlled trial was conducted in 1992 and 1993 at Institute of Child Health and Hospital for Children, Madras. The study was approved by the Hospital Scientific Committee. Patients between 5 months and 4 years of age with pneumonia of acute onset of < 2 weeks duration, diagnosed clinically and radiologically, from two medical units were included in the study. The exclusion criteria were: *(i)* acute bronchiolitis, *(ii)* allergy to penicillin, *(iii)* post-measles pneumonia, *(iv)* receipt of antibiotics of the trial in full dose for more than 2 days, or *(v)* decision of attending physician to use drugs other than those under trial. Those who were subsequently proved to be tubercular in etiology were withdrawn from the study. The estimated sample size for a 10% difference in cure rate, assuming the combination of drugs having a cure rate of 95%, alpha 0.05, power of study 80%, was 138 per group. However, the sample size available was only adequate to detect a difference in cure rate of 26%.

Recruitment, data collection, monitoring and follow-up was done by the research officer. Patients were randomized using computer generated random numbers to receive either ampicillin (100 mg/ kg/day in 4 divided doses IV/IM) (Group A) or benzyl penicillin (100,000 units/kg/ day in 4 divided doses IV/IM) and chloramphenicol (100 mg/kg/day in 4 divided doses IV/oral) (Group B). The attending physician was responsible for the overall management of the child. The drug administration was done by the ward nursing staff and was supervised by the research officer. All the drugs were given intravenously for 48 hours followed by intramuscular injection and/or oral therapy during the rest of the treatment period. Supportive treatment was uniform in all patients.

The primary outcome measure was the cure rate. Other outcome measures were the duration taken for fever and tachypnea to come to normal range. Children were monitored for adverse reactions. Those who did not show clinical improvement with regard to fever, tachypnea and chest findings by 72 hours were considered as treatment failure and managed appropriately. X-ray was repeated at the time of discharge or on the 8th day of the therapy. Pneumonia was considered to have cleared if all the lung signs had cleared. Patients were followed for four weeks after discharge. Analysis was done using SPSS pc+ software. Chi square, Fisher exact and Student 't' tests were used.

Results

The total number of patients recruited was 115; 60 in Group A and 55 in Group B of which 5 and 4, respectively were withdrawn, as per protocol (tubercular bronchopneumonia). None of the patients were excluded on the criteria of the attending physician not wanting to prescribe drugs under trial. There were 5 dropouts, 3 in Group A and 2 in Group B. Analysis was done including and excluding the drop outs. There was no

difference in the baseline characteristics or the results of outcome between the above two types of analyses. There was no statistically significant difference in baseline characteristics between the groups except nasal flare and cyanosis which were less in Group B *(fable I).* The outcome measures are compared in *Table II.* There was no significant difference between the groups either in the primary outcome (cure rate) or secondary outcomes (days for cure, duration of tachypnea, fever or grunt). There was also no difference in the cure rate for pneumonia or bronchopneumonia. No side effects or reaction to drugs were documented in either group. One of the worst outcome in dropouts could be treatment failure. Analysis was done considering dropouts as failures and there was no significant difference between the groups.

Discussion

Though the Institute of Child Health is a tertiary care hospital, the study population is that of primary care setting, mostly urban, as the patients are brought directly to the hospital for this illness. Our study shows that ampicillin and a combination of benzyl penicillin and chloramphenicol are equally effective for the treatment of pneumonia of acute onset in the age group of 5 months to 4 years. An *in vitro* study documented resistant strains of *S. pneumonia* and *H. influenzae* for all these three drugs especially in urban population(9). In another report, chloramphenicol alone proved as effective as a combination of chloramphenicol and penicillin for the treatment of pneumonia but the dropout rate was high(10). Also chlorampheniol is suggested to be the preferred drug for treatment of pneumonia caused by *H. infuenzae(A).*

TABLE I–*Comparison of Baseline Characteristics.*

Characteristics	Ampicillin (Group A) (n=52)		Penicillin & Chloramphenicol (Group B) (n=49)		p value
Age (mo; mean ± SD)	14.21 ± 9.16		15.89 ± 10.47		0.39
Sex (Male : Female)	26:36		26:13		0.03
Hurried breathing	48	(92)	45	(92)	0.61
Poor feeding	28	(54)	34	(69)	0.16
Nutritional status:					
Normal & grade I	26	(50)	23	(47)	
Grade II - IV	26	(50)	26	(53)	0.91
Grunt	10	(19)	13	(27)	0.52
Nasal flare	50	(96)	41	(84)	0.03
Cyanosis	49	(94)	40	(82)	0.04
Intercostal & subcostal recession	51	(98)	48	(98)	0.73
Respiratory rate (mean ± SD)	58 ± 11		59 ± 12		0.94
Pneumonia (lobar)	37	(71)	27	(55)	
Bronchopneumonia	15	(29)	22	(45)	0.14

Figures in parentheses indicate percentages.

TABLE II–*Comparison of Outcome Measures.*

Outcome measures	Ampicillin (Group A) (n=52)	Penicillin & Chloramphenicol (Group B) (n=49)
Pneumonia*		
Cure (%)	42 (81)	44 (90)
Failure (%)	10 (19)	5 (10)
Days taken for Clinical cure	5.64 ± 3.5	5.78 ± 2.38
Duration of tachypnea	3.81 ± 2.7	3.52 ± 2.55
Duration of grunt	3.2 ± 2.7	2.44 ± 2.0
Disappearancy of intercostal & subcostal recession	2.31 ± 1.54	2.37 ± 1.68
Duration of fever	4.48 ± 2.69	4.71 ± 2.57
Duration of poor feeding	3.62 ± 2.58	4.19 ± 2.46
Hospital stay	6.19 ± 2.78	6.29 ± 2.15
Lobar pneumonia*		
Cure (%)	31 (84)	23 (85)
Failure (%)	6 (!6)	4 (15)
Bronchopneumonia*		
Cure (%)	11 (!6)	21 (95)
Failure (%)	4 (27)	1 (5)

There were no drug reactions or mortality in either group.

None of the differences between the two groups were significant ($p > 0.05$).

Except for *, values denote mean ± SD of outcome measure in days.

Considering the potential toxicity of chloramphenicol and the number of injections and doses to be given for the combination, ampicillin as a single drug could be preferred for the treatment of pneumonias, atleast in this part of the country. Since the response to the first line of drugs, penicillin or ampicillin is good, we feel that initially there is no need to go in for cephalosporines or wider spectrum of antimicrobials.

REFERENCES

1. Kumar V. Acute respiratory infections: Need for a national control programme.Indian J Pediatr 1987, 54:145-148.
2. Clinical management of acute respiratory infections in children: A WHO memorandum. Bull WHO 1981,59: 707-716.
3. Kumar L, Ayyagiri A. The etiology of lobar pneumonia and empyema thoracis in children. Indian Pediatr 1984, 21:133-138.
4. Kumar L. Severe acute lower respiratory infection: Etiology and management. Indian J Pediatr 1987, 54:189-198.
5. Kalra SK, Sasidharan T, Vatwani VK, *et al.* Lung puncture: A diagnostic aid in the childhood pneumonia. Indian Pediatr 1981,18: 727-730.
6. Bajaj S, Chowdhary JR, Vaishnava S, *et al.*An evaluation of techniques employed in the bacteriological diagnosis of pneumonia. Indian Pediatr 1974,11:111-114.
7. Sakunthala SKV, Mallikarjuna Rao, Urmila S. Diagnostic lung puncture aspiration in acute pneumonia of newborn.Indian Pediatr 1978,15: 39-44.
8. Guidelines for research on acute respiratory infections. Memorandum from a WHO meeting. Bull WHO 1992, 60: 521-533.
9. Mastro TD. Use of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Hemophilus influenzae* from children in Pakistan for surveillance for antimicrobial resistance. J Pediatr Infect Dis 1993, 12: 824-830.
10. Shann F, Barker J, Poore P. Chloramphenicol alone versus Chloramphenicol plus benzyl penicillin for severe pneumonia in children. Lancet 1985, ii: 684-686.