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Safety Profile of Ciprofloxacin used for Neonatal Septicemia

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We conducted a case matched control study to observe the adverse effects of ciprofloxacin used in neonatal septicemia We enrolled 30 neonates with multidrug-resistant septicemia who were treated with intravenous ciprofloxacin for 14 days. Thirty matched neonates with septicemia treated with other antibiotics were enrolled as controls There was no difference in the mean serum electrolytes, hepatic, renal and hematologic parameters of the two groups. Serial ultrasonographic measurements of the cartilage of the knee after 1 and 6 months showed no difference in the two groups. The femoral cartilage showed an increase of 78.8% in the mean longitudinal area after 6 months in the study group. In the control group, the femoral cartilage showed a 78.4% increase after 6 months. Similarly, the tibial cartilage showed no difference in the percentage increase in size of the study and control group at the end of 6 months. When controlled for birth weight and gestation, cartilage size was not affected by ciprofloxacin.

Key words: *Arthropathy, Ciprofloxacin, Newborn.*

Ciprofloxacin is an antibacterial agent with a broad spectrum of activity, effective against various pathogens like *Pseudomonas aeruginosa* and *Klebsiella pneumoniae.* Notwithstanding its immense potential as a "life saving" drug, its use is restricted in neonates and children due to its adverse effects, especially on the joints and growing cartilage(1).

Septicemia is one of the commonest causes of mortality in the Neonatal Intensive Care Units (NICU) in India(2) and multidrug resistant *Klebsiella pneumoniae* is the commonest offending bacterial agent.

Ciprofloxacin was used by us in the treatment of multi-drug resistant septicemia on a compassionate basis as a "life saving" drug. The main aim of this prospective study was to observe the adverse effects of ciprofloxacin - hepatic, renal, hematological and ocular dysfunction, and especially its arthropathogenic effect by doing serial measurements of the cartilage using ultrasonography.

Subjects and Methods

This study was conducted in the Neonatal Intensive Care Unit and "High Risk" follow up Clinic of Department of Pediatrics, King Edward Memorial Hospital, Pune in 1999-2000. Thirty neonates with septicemia who were already on other antibiotics, but had shown clinical deterioration and the blood culture had grown multi-drug resistant organisms sensitive to ciprofloxacin were selected for the study. Ciprofloxacin was given in a dose of 20 mg/kg in two divided doses as a slow intravenous infusion over a period of 30 minutes, for a period of 14 days. Informed consent of the parents was taken before starting this treatment. Clearance from the ethical committee of the hospital for use of ciprofloxacin was obtained before starting this study.

Thirty neonates with septicemia matched for gender, gestational age, birth weight, and risk factors who were being treated with other antibiotics (cefotaxime, amikacin), formed the control group. The infants on ciprofloxacin were scrutinized every day for objective evidence of arthropathy in the form of swelling or tenderness over the joint, decreased spontaneous movements or restriction and painful movements of the joints.

Serum electrolytes, blood urea nitrogen, serum creatinine, serum bilirubin, SGPT and alkaline phosphatase were evaluated at the beginning and end of the treatment. Similarly, a hemogram with peripheral blood smear and platelet count, prothrombin time and partial thromboplastin time was done at the beginning and end of the treatment.

Ultrasonography evaluation of the right knee joint was done at the end of the treatment (day 15) by a trained Ultrasonologist who was blinded to the group allocation, using Ultramark 9 machine (Phillips, Bothell) with high frequency broadband linear transducer. The following observations were made on examination of the right knee joint (*i*) anteroposterior, cranicaudal and transverse diameter and longitudinal and transverse area of the lower end of femur and upper end of tibia; (*ii*) "two layer" appearance of the cartilage which separates the epiphyseal and articular cartilage, the articular cartilage being less echogenic; (*iii*) fluid in the suprapatellar bursa; and (*iv*) contour of the epiphyses. These observations were recorded at the end of ciprofloxacin therapy, and 1 month and 6 months after completion of therapy.

Anthropometry was recorded at birth and at the 6 month visit. An *X*-ray of the right knee joint, anteroposterior and lateral views, was also taken at 6 months. An ophthalmic check up was done to look for lenticular opacities and cataract.

The means were compared using the unpaired 't' test. A multiple linear regression analysis was done using cartilage size as the outcome variable and birthweight, gestational age and ciprofloxacin as co-variates.

Results

Thirty neonates treated for septicemia with ciprofloxacin were followed up along with 30 neonates with septicemia treated with other antibiotics. Both the study and control group had 24 preterm and 6 full term neonates with

17 males and 13 females each. The birth weight in the ciprofloxacin group ranged between 900-3400 g with a mean of 1688 ± 122 g, whereas the mean birthweight was 1699 ± 105 g in the control group (range 980-3360 g). The mean gestational age of the ciprofloxacin group was 33.2 ± 3.83 weeks and that of the control group was 33.6 ± 3.43 weeks (range 28 to 40 weeks).

The organisms isolated from the blood culture of the ciprofloxacin group were *Klebsiella pneumoniae* in 20 (66.6%), *Pseudomonas aeruoginosa* in 5 (16.6%), coagulase negative *Staphylococci* in 2 (6.6%) and gamma hemolytic *Streptococci* in 1 (3.3%) neonate. The isolates were more diverse in the control group with *Klebsiella* in 10 (33%), *Pseudomonas* in 5 (16.6%), coagulase negative *Staphylococci* in 4 (13.3%), gamma hemolytic *Streptococcus* and *Enterococci* in 3 (10%) each and *Streptococcus pneumoniae* and *Salmonella worthington* in 1 case each.

Treatment with ciprofloxacin was started between 5th to 13th day of life with a mean of 8.06 days. Except for serum bilirubin, all the biochemical and hematological parameters were comparable between the two groups at the end of therapy (*Table I*). Daily examination of the joints showed no swelling, tenderness or restricted movements. *Table II* shows that there was no significant difference between the measurements of the lower femoral cartilages in the ciprofloxacin and control group. Percentage increase in mean longitudinal area of the lower femoral and upper tibial cartilage over 6 months was similar in the two groups (*Fig. 1*). Ultrasonography of the right knee showed no effusion, a normal "two layer" appearance at all the three examinations. There was no difference between the cartilage size and growth of the cartilage in male and female infants. A multiple linear regression analysis showed that ciprofloxacin did not affect cartilage size, when controlled for birth weight and gestation. *X*-ray of the knee joint (anteroposterior and lateral view) taken at 6 months, showed no abnormality in any of the infants.

The length (height) velocity was calculated for the first 6 months of life. This was 2.57 cm (SD = 0.53) in the study group compared to 2.36 cm (SD = 0.35) in the control group ($p > 0.05$). An ophthalmic check up revealed no lenticular opacities or cataracts.

Discussion

Ciprofloxacin is used for a variety of infections in adults. It has a broad antimicrobial spectrum, marked bactericidal activity and favorable pharmacokinetics, features which have made it a popular antibiotic in adult practice. However, like other quinolones, it has not been approved for use in children, primarily because of its potentiality to cause irreversible damage to growing cartilage in weight bearing joints in immature animals(3,4).

Ciprofloxacin was used on a compassionate basis in children. Chysky, *et al.* used it in 634 adolescents and found it to be safe(5). They concluded that the safety profile in children was no different from that in adults. Bethell, *et al.*(6) used it in Vietnam to treat 137 children with *Salmonella* infections and found no joint symptoms and no alteration of growth. Martell, *et al.*(7) treated 7 preterm infants with sepsis and found no evidence of joint involvement or growth failure. Pradhan, *et al.*(8) did measurements of linear growth in addition to MRI scans in children and found no cartilage toxicity. Gurpinar, *et al.*(9) followed up 9 neonates upto the age of 2.5 years and found normal growth and no

Key Messages

- Ciprofloxacin did not show any adverse effects, especially arthropathogenic toxicity, when used in neonates with septicemia.
- Ciprofloxain may be used with caution to treat multi-drug resistant septicemia in neonates.

osteoarticular problems.

Serial measurements of the cartilage by ultrasonography did not show any adverse effects of ciprofloxacin on the growing cartilage or any involvement of the joints in our study. No other untoward adverse effects were detected in this small series of neonates treated with ciprofloxacin. The main limitations of this study are the small sample size and the short follow up. However, since maximum growth of the cartilage and epiphysis occurs during the first six months, we feel that no arthropathogenic effects would manifest after this age. Hence ciprofloxacin may be used with discretion to treat multi-drug resistant septicemia in neonates, as a "life saving drug".

Contributors: SC conceived the project. selected the cases and matched controls and supervised the project, wrote the manuscript. PS collected the data. SA and MC did ultrasonography. AK supervised ultrasonography. SC will act as guarantor for the paper.

TABLE I–*Comparison of Biochemical and Hematologic Parameters of Study and Control Group.*

Parameters	Units	Day 1			Day 15		
		Study group Mean (SD)	Control group Mean (SD)	p value	Study group Mean (SD)	Control group Mean (SD)	p value
Sodium	meq/L	131.66 (3.28)	130.73 (2.03)	0.540	131.83 (3.29)	132.66 (2.94)	0.305
Potassium	meq/L	4.12 (0.53)	4.15 (0.45)	0.815	3.97 (0.51)	4.12 (0.39)	0.200
Blood urea	mg/dL	6.20 (1.10)	6.7 (1.8)	0.676	5.9 (2.2)	6.1 (1.6)	0.977
Creatinine	mg/dL	0.55 (0.24)	0.49 (0.2)	0.307	0.50 (0.25)	0.46 (0.12)	0.245
SGPT	U/L	18.40 (6.60)	18.86 (8.23)	0.810	18.10 (7.99)	16.66 (8.31)	0.499
Bilirubin	mg/dL	8.85 (4.7)	8.56 (5.4)	0.828	2.3 (2.0)	1.25 (0.90)	0.011
Alkaline phospatase	U/L	401 (22.12)	396 (18.1)	0.449	390 (17.13)	387 (15.2)	0.166
Platelet count	$\times 10^4$/cmm	1.28 (0.39)	1.46 (0.47)	0.121	1.51 (0.44)	1.74 (0.33)	0.27
Prothrombin time	second difference from control	2.40 (2.02)	2.86 (2.77)	0.460	1.36 (0.96)	1.56 (1.00)	0.435
Partial thromboplastin time	second difference from control	6.30 (2.95)	6.73 (4.63)	0.667	2.43 (0.97)	2.46 (1.00)	0.897

TABLE II–*Measurements of the Cartilage of Lower End of Femur.*

Femur (Dimensions)	Measurements	Study group Mean (SD)	Controls Mean (SD)	P value
Anteroposterior diameter (cm)	Baseline	1.60 (0.25)	1.57 (0.26)	0.59
	After 1 month	1.83 (0.22)	1.77 (0.20)	0.31
	After 6 months	2.29 (0.39)	2.15 (0.28)	0.12
Craniocaudal diameter (cm)	Baseline	1.04 (0.27)	1.02 (0.26)	0.84
	After 1 month	1.02 (0.26)	1.19 (0.22)	0.60
	After 6 months	1.53 (0.27)	1.49 (0.25)	0.52
Transverse diameter (cm)	Baseline	2.36 (0.51)	2.22 (0.41)	0.26
	After 1 month	2.77 (0.67)	2.59 (0.57)	0.27
	After 6 months	3.69 (0.75)	3.45 (0.11)	0.18
Longitudinal area (sq cm)	Baseline	1.53 (0.36)	1.47 (0.33)	0.53
	After 1 month	1.88 (0.44)	1.79 (0.36)	0.37
	After 6 months	2.71 (0.72)	2.60 (0.69)	0.54
Transverse area (sq cm)	Baseline	2.78 (0.62)	2.71 (0.66)	0.68
	After 1 month	3.37 (0.73)	3.36 (0.73)	0.92
	After 6 months	5.12 (0.83)	4.93 (0.68)	0.33

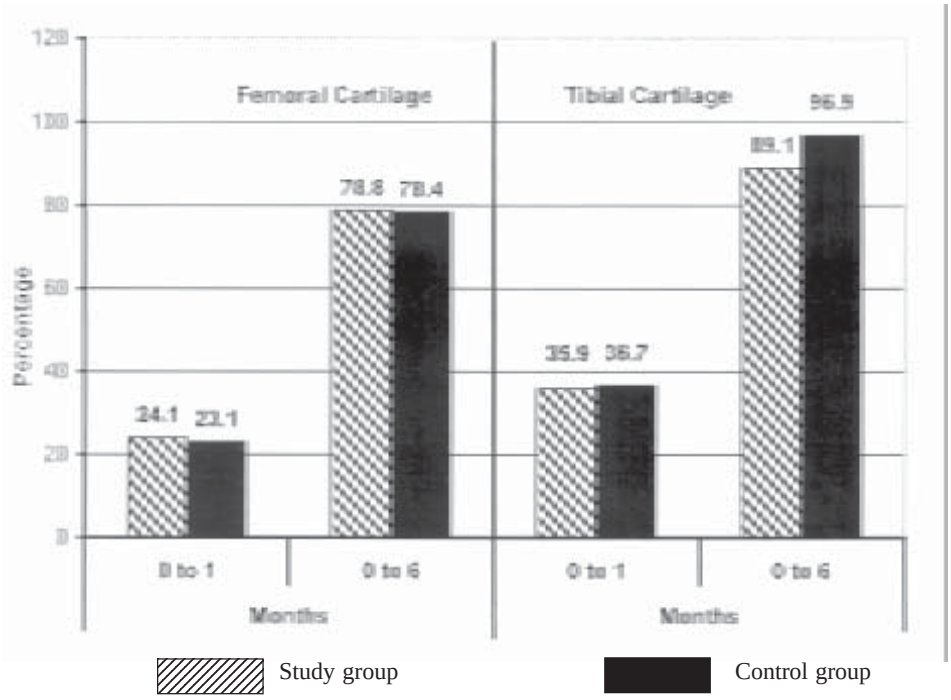

Fig. 1. Percentage increase in longitudinal area (mean) of femoral and tibial cartilage.

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