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Original Article

Neonatal septic arthritis: Clinical profile and predictors of outcome

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ABSTRACT

Background: Neonatal septic arthritis deserves a special attention due to its subtle signs and symptoms and catastrophic consequences. There is paucity of literature regarding the clinical profile and predictors of outcome in neonatal septic arthritis. **Objectives:** The objective was to study the clinical profile of neonates admitted with septic arthritis, their clinical and radiological outcomes on follow-up, and factors that predict outcomes. **Methodology:** Neonates with septic arthritis as assessed by retrospective case sheet review were included. Prospective data collection of clinical and radiological outcomes was done during follow-up visits. Children with good outcomes (controls) were compared to those with poor outcomes (cases) subsequently to identify the predictors of outcomes using a nested case–control design. **Results:** Data of 70 neonates admitted with septic arthritis were collected. Single joint involvement was common (75.8%), and hip joint was the most common joint involved. Gram-negative organisms were predominant (72%), and *Klebsiella* was the most common organism isolated from joint aspirate (36%), followed by *Escherichia coli* and *Staphylococcus aureus*. Of 52 babies who turned for follow-up, half had poor outcomes. In univariate analysis, multiple joint involvement (odds ratio [OR] 4.79, [confidence interval (CI): 1.14-20.21]), pre-intervention period ≥7 days (OR 92, [CI: 14.06-601.9]), culture positive joint aspirate (OR 3.70, [CI: 1.55-11.86]), and restricted range of joint movements at discharge (OR 83.3, [CI: 9.2-749.9]) were significantly associated with poor outcomes. Pre-intervention period ≥7 days (adjusted OR 107.99, [CI: 5.16-2258.8]) and restricted joint mobility at discharge (adjusted OR 139.53, [CI: 9.03-2154.04]) were the independent predictors of poor overall outcome by logistic regression analysis. **Conclusions:** Long pre-intervention period and restricted joint mobility at discharge were independent predictors of poor outcome in neonatal septic arthritis. We emphasize the importance of early diagnosis, prompt referral to tertiary centers, timely surgical intervention, appropriate measures to ensure good joint mobility, and regular follow-up in these neonates to achieve best outcomes.

Key words: *Nested case–control study, Newborn, Outcomes, Predictors, Septic arthritis*

Septic arthritis is one of the most seriously disabling conditions in all age groups. The incidence of septic arthritis is more in infancy and childhood because of their innate deficiencies and inabilities in defense mechanisms. Bone and joint infections, though uncommon in neonatal sepsis, contribute to a significant number of cases in developing countries. The incidence of septic arthritis and osteomyelitis is 1 in 1500 among inborn neonates in India compared to 1 in 5000 (U.K) to 1 in 15,000 (U.S.A) in the western world [1]. Diagnosis and management of neonatal septic arthritis possess significant challenges to clinicians. Diagnosis is hindered and may be difficult to establish because the physical signs are frequently minimal, laboratory findings are often normal, and initial roentgenographic appearance is often unhelpful or difficult to interpret as joint structures are primarily cartilaginous. If not identified early and treated adequately, the condition might lead to long-term osteoskeletal handicaps.

A number of studies document poor outcomes highlighting the potential to cause permanent sequelae even with modern treatment facilities [2,3]. Neonatal septic arthritis can lead to permanent joint disabilities or disturbances in skeletal growth secondary to damage to the cartilaginous growth plate. These include arthritis, decreased range of motion, limb-length discrepancy, and gait abnormalities. The reported incidence of permanent sequelae varies from 6% to 50% [4]. Among multiple risk factors proposed to be associated with sequelae, identification of significant factors leading to adverse outcomes seems clinically important. These factors may help us decide on the type and timing of therapeutic interventions, duration of antimicrobial therapy, to predict the occurrence of adverse sequelae and thereby prevent them. The scanty literature evidence available from developing countries throws little light, especially on these factors which predict poor long-term outcomes [4,5]. Hence, we studied the clinical and bacteriological profile, risk factors of neonatal septic arthritis, and factors which predict poor outcomes on long-term follow-up.

METHODOLOGY

We undertook an ambidirectional cohort study with a nested case–control analytic component. We did this study at a tertiary neonatal care teaching hospital in South India. We reviewed

the medical records and radiographs of all patients diagnosed with septic arthritis from June 2013 to August 2015. We collected data from their inpatient records, and follow-up visits were planned until May 2016. The study was approved by the Institutional Ethics Committee. Informed consent was obtained from parents for data collection during follow-up visits. We assigned a diagnosis of septic arthritis when a patient had a positive culture in aspirated joint fluid. If culture was negative, we presumed a diagnosis of septic arthritis when Morrey's criteria were satisfied with at least 2 of major criteria, namely, pus aspirated from the joint, marked elevation of erythrocyte sedimentation rate, specific roentgenographic changes in the involved site, and at least 5 of the minor criteria such as fever greater than 38.3°C, pain (localized to the joint) made worse by gentle passive motion, swelling of the involved joint, systemic symptoms of lethargy, malaise, irritability, no other demonstrable pathological process, satisfactory response to antibiotic therapy, and supportive evidence of ultrasound showing joint fluid collection [6].

We studied their clinical profile and assessed clinical and radiological outcomes during follow-up. We defined poor outcomes when there was limb length discrepancy of more than 1 cm or restricted joint mobility on clinical examination and/or radiological findings such as absence of epiphyseal ossification, presence of small epiphysis, metaphyseal widening, dislocation or subluxation noted on follow-up. We analyzed factors associated with poor clinical and radiological outcomes at follow-up by comparing cases (children with poor clinical/radiological outcome) and controls (those with normal outcome) in a nested case–control design.

We used descriptive statistics to describe baseline variables. We compared categorical outcome variables by Chi-square test or Fisher's exact test; normally distributed variables by Student's *t*-test, variables with skewed distribution by Mann–Whitney *U*-test. Individual predictors for poor clinical and radiological outcomes were determined by inferential univariate analysis. Multiple logistic regression analysis was used to identify independent predictors of outcome. $p < 0.05$ was considered statistically significant. We used Statistical Software Package SPSS version 13.0 for analysis.

RESULTS

We assembled a cohort of 70 babies diagnosed with neonatal septic arthritis from existent medical records. Of these 70 neonates, 52 were available for follow-up. One infant died during its hospital stay and 2 infants expired after discharge. We followed up these 52 infants, subjected them to clinical examination and radiological investigations and recorded their findings (Figure 1).

The mean (standard deviation [SD]) gestational age at birth and birth weight of our study group were 38.41 (2.04) weeks and 2.64 (0.59) kg, respectively. Low birth weight neonates constituted one-thirds of the population. Primary reason for admission was septic arthritis in 62 neonates. Septic arthritis was diagnosed during their hospital stay in remaining 8 infants. The mean (SD) age of onset of symptoms was 18.8 (7.19) days and mean duration of symptoms before intervention was 5.4 (3.5) days. 50 neonates (71.4%) had a history of hospitalization previously for other illnesses. In 53 (75.7%) neonates, their venous lines either peripheral or central had been accessed during their previous hospitalization. Significant comorbidities such as hypoxic ischemic encephalopathy (HIE), patent ductus arteriosus, neonatal jaundice, congenital heart disease, and portal vein thrombosis were present in 13(18.5%) neonates. Six neonates had undergone invasive procedures such as mechanical ventilation and exchange transfusions (Table 1).

A total of 88 joints were involved in our 70 infants. Multiple joint involvements were seen in 17 (24.2%) neonates and 76% had single joint involvement. Hip joint was involved in 40% cases, followed by shoulder (15.7%) and knee (15.7%). Infants had bilateral hip joint involvement in 12.8% of cases. Associated osteomyelitis was found in 19 infants (27.1%). Joint effusion was present in all the cases (Table 2). The joint fluid showed positive growth in 25 (35.7%) infants. Most common organism in the cultures was *Klebsiella* (9 cultures), followed by *Escherichia coli* (8), *S. aureus* (7), Candida non albicans (2), and Pseudomonas (1). Multiple growths were present in 2 infants' cultures (*E. coli*, *Klebsiella*, and *S. aureus*). The blood culture taken at admission grew organism only in 8 (11.4%) infants. *S. aureus* was the predominant organism in blood culture (7 infants) and 1 had *E. coli.* Among the 70 babies, both pus and blood showed bacterial growth in only 4 infants with one infant showing same organism (staphylococcal) growth in both.

47 infants (67.1%) had undergone arthrotomy and needle aspiration was done in 23 (32.8%) infants. There was a need for a repeat procedure in 11 (15.7%) neonates. The infants were treated with antibiotics for a mean (SD) duration of 5 (0.94) weeks, of which antibiotics were administered intravenously for 2.7 (0.6) weeks. At the time of discharge, 32 infants (45.7%) had

Table 1: Baseline characteristics of the study subjects

Variables	Infants n=70 (%)
Male	38 (54.3)
Birth weight (kg)*	2.64±0.59
Gestational age (weeks)*	38.41±2.04
Age at presentation (days)*	18.8±7.19
Pre-intervention period from onset of symptoms (days)*	13.7±3.8
Comorbidities	13 (18.5)
Previous hospitalization	50 (71.4)
Risk factors in subjects with previous admission (n=50) duration of previous hospitalization (days)*	11.18±6.47
Duration of IV antibiotics before intervention (days)*	10.9±6.5
Exchange transfusion	3 (4.2)
History of previous surgery	1 (2)
Mechanical ventilation	2 (4)

***Values are represented as mean±SD. IV: Intravenous**

restricted range of movements in the involved joints and were discharged on spica (hip)/cast. All these children were enrolled in occupational therapy/physiotherapy clinics and were advised follow-up both with us and orthopedics.

Of the 70 infants, the mean (SD) age of the 52 infants (74.2%) who came for follow-up was 15.3 (10.3) months. The follow-up group had an average of 2 follow-up visits. On clinical examination, we found that 19 infants (36.5%) had poor clinical outcomes-length discrepancy (15.3%) and restricted range of movements (30.7%). We found that 22 (42.3%) infants had poor radiological outcomes-small epiphysis (21.1%), no epiphyseal ossification (7.6%), dislocation (1.9%), subluxation (3.8%), metaphyseal widening (5.7%), and chronic osteomyelitis (1.9%). Seven (13.4%) infants had abnormal outcomes on X-rays but were normal clinically.

On univariate analysis, we identified multiple joint involvement (odds ratio [OR] 4.792, [confidence interval (CI): 1.136-20.21]), pre-intervention period ≥7 days (OR 92, [CI: 14.06-601.9]), positive joint fluid culture (OR 3.701, [CI: 1.55-11.86]), and restricted joint movements at discharge (OR 83.3, [CI: 9.2-749.9]) as significant predictors for poor overall outcomes. No particular joint involvement or particular organism was associated with increased risk on univariate analysis (Table 3). On multivariate logistic regression, pre-intervention period ≥7 days (OR 107.99, [CI: 5.16-2258.8]) and restricted joint movements at discharge (OR 139.53, [CI: 9.03-2154.04]) were found to be independent predictors for overall poor outcome (Table 4).

Table 2: Clinical profile of the study infants

Variables	Infants n=70 (%)
Joint distribution	
Hip	28 (40)
Shoulder	11 (15.7)
Knee	11 (15.7)
Elbow	3 (4.2)
Multiple	17 (24.2)
Radiological findings of joint	
Soft tissue swelling	29 (41.4)
Increased joint space	22 (31.4)
Osteomyelitis	19 (27.1)
Ultrasound findings of joint	
Effusion	70 (100)
Effusion and dislocation	7 (10)
Effusion and subluxation	2 (2.9)
Type of surgical intervention	
Arthrotomy	47 (67.1)
Needle aspiration	23 (32.9)
Need for repeat procedure	11 (15.7)
Total leukocyte count (cells/mm^3)*	14817±4596
Positive joint aspirate culture	25 (35.7)
Positive blood culture	8 (11.4)
Infants with restricted movements at discharge	35 (50)

*Values are represented as mean±SD

DISCUSSION

Our study throws light on clinical profile and predictors of outcome in neonatal septic arthritis that might help us in implementing preventive measures and assess prognosis. Our study population was predominantly term neonates (63%) who were referred to our institute from peripheries. Babies were symptomatic after the 2nd week of life after getting exposed to many risk factors for bloodstream infections either during prior hospitalization or from the community. Many of them had monoarticular involvement, and hip joint was the most common. Gram-negative organisms

Table 3: Predictors of overall outcome in septic arthritis

Characteristics	Poor outcome n=26 (%)	Good outcome n=26 (%)	OR (95% CI)	p value
Male	14 (53.8)	14 (53.8)	1.00 (0.33-2.97)	1.00
Gestational age (weeks)*	38.36±2.3	38.4±2.2	1.03 (0.80-1.32)	0.80
Prematurity	3 (11.5)	3 (11.5)	1.00 (0.18-5.47)	1.00
Previous hospitalization	20 (76.9)	19 (73.1)	1.22 (0.34-4.32)	0.74
Comorbidities	7 (26.9)	5 (19.2)	1.54 (0.42-5.7)	0.51
Pre-intervention period (≥7 days)	24 (92.3)	3 (11.5)	92 (14.06-601)	<0.001**
Multiple joint involvement	10 (38.5)	3 (11.5)	4.79 (1.13-20.21)	0.03**
Hip joint involvement	9 (34.6)	12 (46.2)	0.61 (0.20-1.88)	0.39
Osteomyelitis	6 (23.1)	8 (30.8)	0.67 (0.19-2.32)	0.53
Nature of surgical intervention arthrotomy	20 (76.9)	16 (61.5)	2.08 (0.62-6.95)	0.23
Needle aspiration	6 (23.1)	10 (38.5)	0.48 (0.14-1.60)	
Positive joint aspirate culture	15 (57.7)	7 (26.9)	3.70 (1.15-11.86)	0.02**
Type of organism - *Klebsiella*	4 (15.4)	3 (11.5)	1.39 (0.27-6.95)	0.68
Positive blood culture	2 (7.7)	3 (11.5)	0.63 (0.09-4.1)	0.64
Restriction of movements at discharge	25 (96.2)	6 (23.1)	83.3 (9.2-749.9)	0.001**
Number of follow-ups	16 (61.5)	21 (81.8)	0.38 (0.10-1.33)	0.13
Infants<1 year at follow-up	12 (46.2)	12 (46.2)	0.95 (0.3-2.8)	1

*Values are represented in mean±SD. **Statistical significance was considered when the p value was<0.05. OR: Odds ratio, CI: Confidence interval

Table 4: Independent predictors of outcome in septic arthritis

Predictor	OR	Adjusted OR	CI	p value
Pre-intervention period (≥7 days)	92	107.99	(5.16-2258.8)	0.003**
Multiple joint involvement	4.79	0.99	(0.094-10.66)	0.99
Positive joint aspirate culture	3.7	8.620	(0.773-96.07)	0.08
Restriction of movements at discharge	83.3	139.53	(9.03-2154.0)	<0.001**

**Statistical significance was considered when the p value was<0.05. OR: Odds ratio, CI: Confidence interval

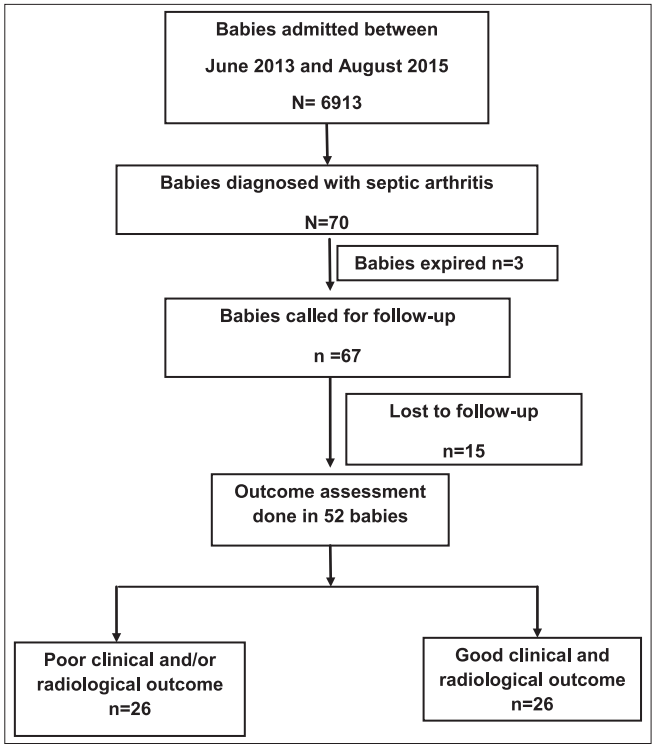

Figure 1: Flow diagram of the study outline

dominated the profile suggesting a nosocomial origin from their previous hospitalization.

Most of the recent literature on neonatal septic arthritis deals with preterm infants admitted in intramural nurseries [1,4,7], except the study by Berberian et al. which was done in a tertiary care extramural nursery like ours [8]. Risk factors such as prior hospitalization and peripheral venous access were high in our neonates (70%) suggesting a nosocomial etiology similar to the Berberian's study. In the past studies, risk factors such as umbilical vessel catheterization, presence of central venous catheters, and femoral vessel blood sampling were also identified [9-12]. In our study, history of umbilical venous catheterization was present in 3 babies.

In our study, 24% of babies had multiple joint involvements, which is comparable to Berberian's study. The high incidence seen in other studies by Narang et al. (32%) and Frederiksen et al. (35%) could be due to the immune handicaps of the preterm population in their study [1,4]. An increased coexistence of osteomyelitis and septic arthritis is appreciated predominantly in neonatal population compared to pediatrics. This can be explained by the peculiar nature of neonate's osteal blood supply where the communication between the metaphyseal and the epiphyseal vessels facilitates the rapid spread of infection, thus offering a route of infection into the joint [13-15]. Osteomyelitis was present in 27% of babies along with septic arthritis.

Joint fluid culture was positive in 35.7% of babies and blood culture was positive in 11.4% of babies. Increased yield from joint culture can be explained by the increased concentration of organism in the site of infection compared to blood. The joint culture positivity was low when compared to other studies by Narang et al. (48%), Frederiksen et al. (68%), Deshpande et al. (60%), and Berberian et al. (82%) [1,4,7,8]. In addition, our blood culture positivity was also lower when compared to these studies. These low yields can be explained by prolonged antibiotics received even before admission (mean of 10 days). Organisms were predominantly Gram-negative organisms, *Klebsiella* being the most common. Most of the post-millennium studies reported Gram-negative organisms predominantly. There is a paradigm shift from the predominance of Gram-positive organisms observed in pre-millennium studies [16].

Our mean age of follow-up was 15 months. However, a higher proportion of neonates (36.5%) had poor clinical outcomes compared to Lee et al.'s study (16.1%). In this study, a prognostic factor for outcome in septic arthritis of hip joint alone was followed up [5]. Majority of our study subjects also had hip joint involvement. Neonatal septic arthritis, in particular, septic arthritis of hip can lead to serious musculoskeletal sequelae [8] and this would have contributed to the poor outcome in our study population. The poor radiological outcome was seen in 42% of our follow-up babies. In Berberian's study, 37% had evidence of radiological damage but this was at the initial presentation, and the babies were not followed up for sequelae. In Lee's study on septic arthritis of hip, 16% had poor radiological prognosis [5]. There is paucity of studies on long-term follow-up of septic arthritis babies for sequelae.

Our mean pre-intervention period was 13 days compared to other studies where pre-intervention period was shorter (2-3 days). The sequelae were significantly more in babies who had long pre-intervention periods. Long pre-intervention period is found to be a risk factor in other studies as well [4,17,18]. Wilson and Di Paola have advocated a minimum waiting period of 4 days with interim intravenous antibiotics and aspiration, before a decision of arthrotomy is made [19]. Despite having received intravenous antibiotics before referral, the long pre-intervention period in our study reflecting a delay in the surgical intervention (arthrotomy) might have led to higher rate of sequelae. Whenever multiple joints were involved or restriction of joint mobility was present at the time of discharge, there was a significant chance of poor outcome on follow-up indicating that

an initial severe illness predisposes to osteoskeletal handicaps later. Although the type of intervention did not influence the outcome of the disease in our study, a delay in intervention seems to have a greater impact on the later outcomes prompting earlier intervention to prevent sequelae. Our study brings out the importance of clinical examination in a symptomatic child at the time of admission as well as discharge by showing pre-intervention period ≥7 days and restricted joint mobility at discharge as independent prognosticating factors for poor outcome.

The strength of the study is that it was a study with large number of neonates with a good follow-up from the developing part of the world even though it was a retrospectively planned one. We focused on determining the predictors of outcomes using robust statistical methods and our results have good validity. The study is limited by its high chance of selection bias, being a referral hospital-based study, as the participants are neonates in whom illness severity is expected to be more with a significant delay in intervention due to late referrals. There is scope for information bias because of the retrospective design, but we attempted to keep it minimal using data from documented information in the case sheets and then applying standard criteria for diagnosis. Our study was a cross-sectional analysis of outcomes of follow-up subjects at various ages. Prospective follow-up at predefined time intervals would have improved the validity. Factors such as compliance of oral antibiotics post-discharge and comorbidities such as HIE influencing the restriction of joint mobility could not be accounted for in our study either due to lack of data or due to small numbers.

CONCLUSION

Most neonates with septic arthritis have a monoarticular involvement with hip being the most common joint involved in it. Ultrasound seems to be a very reliable tool as it detects effusion in all cases. The bacteriological profile is still dominated by Gram-negative organisms, especially *Klebsiella*. Apart from initiating intravenous antibiotics, we should focus on early referral to tertiary care centers, timely surgical intervention, and measures to ensure good joint mobility at the time of discharge. These factors are shown to be important predictors of outcomes in neonates with septic arthritis.

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