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Original Research Article

A Comparative Study of Etiopathological Profile and Outcome in Acute Kidney Injury in Inborn and Outborn Neonates: A Cross Sectional Observational Study in Central India

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Abstract

Background: Acute kidney injury (AKI) is a common occurrence in the neonatal intensive care unit (NICU) as has been shown to be associated with adverse outcomes including increased length of mechanical ventilation, prolonged length of stay, and rise in mortality. Neonatal modified Kidney Disease: Improving Global Outcomes (KDIGO) criteria is applied as the standard definition for neonatal AKI for clinical and research purpose.

Aim: To study and compare etiopathological profile and outcome of acute kidney injury in outborn and inborn neonates**,** estimate incidence of AKI and compare outcome of acute kidney injury in outborn and inborn neonate

Methods: A cross-sectional study was done at tertiary centre from December 2021 to May 2022 for duration of 6 months in which neonates with AKI were admitted in inborn and outborn unit respectively and were analysed in detail and outcome was studied.

Results: There was preponderance of AKI in term neonates in outborn newborns (55%) as compared to more preterm neonates in inborn unit (60%). More number of neonates with AKI was admitted during summer months (i.e. April, May). Among outborn neonates the most common risk factor associated with developing AKI was sepsis, followed by perinatal asphyxia and shock. Out of 20 outborn neonates who had AKI, nine (45%) expired and eleven (55%) were successfully discharged with complete recovery of renal functions, while out of ten inborn neonates who had AKI, two (20%) expired and six (60%) were successfully discharged with complete recovery while two were discharged with residual kidney disease and called for further follow up.

Conclusion: The results show better outcome in inborn unit patients as were discharged with complete recovery and are maintained on follow up. The study emphasises on proper antenatal and perinatal management with postnatal monitoring of newborn to prevent AKI and also for the early diagnosis and management in patients with risk factors to avoid morbidity and mortality due to acute kidney injury.

Keywords: Acute kidney injury, Neonate, Etiopathogenesis, Outcome

Background

Acute kidney injury (AKI) is a common occurrence in the neonatal intensive care unit (NICU. Neonates with AKI are also at higher risk of chronic kidney disease (CKD). In the past, AKI had been defined multiple ways but now Neonatal modified kidney disease: Improving Global Outcomes (KDIGO) criteria is applied as the standard definition for neonatal AKI for clinical and research purpose. AKI has been defined as an abrupt (within 48 hours) reduction in kidney function, i.e., an absolute increase in serum creatinine of >/= 0.3mg/dl, % increase in serum creatinine of >/= 50% (1.5 folds from baseline) or a reduction in urine output/ oligouria of <0.5ml/kg/hour for >6hours [1,2].

As the impacts of neonatal AKI have become clear, a shift in efforts toward identifying those at highest risk, protocolizing AKI surveillance, improving prevention and diagnosis, definitive treatment can be provided to minimise mortality. Different retrospective studies have shown higher incidence of mortality due to AKI in extremely low birth weight (ELBW), very low birth weight (VLBW), asphyxia, sepsis, and newborn with other congenital malformations/ syndromes.

The serum creatinine level is the simplest and most commonly used indicator of neonatal kidney function. In general, each doubling of the serum creatinine level represents a 50% reduction in GFR and for the sake of uniformity for different gestational age of neonates we have taken ≥1.5mg/dl creatinine value as AKI [3-7].

In this comprehensive review we will provide an overview of recent work and advances in the field of neonatal AKI. This research article will include a detailed study of the etiopathogenesis, risk factors, management and outcomes associated with neonatal AKI with comparison between inborn and outborn units.

Materials and Methods

A cross-sectional study was done at tertiary centre from December 2021 to May 2022 for duration of 6 months in which neonates with AKI were admitted in inborn and outborn unit respectively and were analysed in detail and outcome was studied. A retrospective cross- sectional study was conducted on 100 neonates admitted and diagnosed with AKI, in the outborn and inborn NICU units of ABV Government Medical College and Hospital Vidisha from December 2021- May 2022, total duration of 6 months.

Inclusion criteria

1. Neonates diagnosed with AKI (serum creatinine>1.5mg/dl) at any point during NICU stay.
2. Neonates referred from other centers or peripheral health facilities who either had AKI or developed AKI at any point of NICU stay
3. Newborns with antenatal investigations suggestive of renal or other congenital anomalies.

Exclusion criteria

1. Newborns who left against medical advice (LAMA)
2. Inborn neonates who died within 24hours of delivery

Signed informed consent was taken from parents. A detailed history and clinical examination was done and relevant clinical and laboratory findings, demographic features, gestational age (term or preterm), birth weight/weight on admission, antenatal, perinatal history was recorded along with any associated contributing conditions including signs and symptoms of hypoxic ischaemic encephalopathy, sepsis, respiratory distress syndrome, dehydration, heart failure, meconium aspiration syndrome.

In all neonates with AKI relevant investigations like blood urea, serum creatinine, serum electrolytes (sodium and potassium), urine output, urine

examination were performed on every day until renal parameters became normal or the patient became unavailable for follow up. Oliguria was defined as urine output <1.0 ml/kg/hour and anuria are defined as absence of any urine output within 24 hours after birth [8]. Twenty-four hours urine output was measured by collecting urine in baby urobags. An ultrasound imaging of kidney was done, after stabilising the neonate, for size, echo-texture and cortico - medullary differentiation, any congenital malformation and/or abnormality of urinary tract.

Observation chart

Table 1: Distribution of neonatal AKI as per gender

Gender	Outborn n=20	Inborn n=10
Male	13 (65%)	07 (70%)
Female	07 (35%)	03 (30%)

Table 2: Distribution of cases in relation to the type of delivery

Type of delivery	Outborn n=20	Inborn	p-value
Caesarean section	05(25%)	07(70%)	0.017706
Vaginal delivery	15(75%)	03(30%)	

Table 3: Distribution of cases as gestational age

Gestational age	Outborn n=20	Inborn n=10	p-value
Preterm (<37 weeks)	09(45%)	06(60%)	0.438578
Term (=/>37 weeks)	11(55%)	04(40%)	

Table 4: Distribution of cases as per birth weight/ admission weight

Birth weight	Outborn n=20	Inborn n=10	p-value
>/= 2.5kg	09 (45%)	02(20%)	0.319635
LBW	08 (40%)	07(70%)	
VLBW	02 (10%)	01(10%)	
ELBW	01 (5%)	00	

Table 5: Etiology/ risk factors for neonatal AKI

Risk factors	Outborn	Inborn	p-value
Perinatal asphyxia	14 (87.5%)	02 (12.5%)	0.009661
Use of nephrotoxic drugs	20 (66.6%)	05 (16.6%)	0.090969
Mechanical ventilation	13 (86.6%)	02 (13.3%)	0.020137
Congenital anomalies/ syndromic child	02 (50%)	02(50%)	0.447521
Dehydration	10 (100%)	01	0.009181
Sepsis	20 (66.6%)	10 (33.3%)	0.196706
Shock	15 (100%)	01	0.000768
Cardiac failure/ congenital heart disease	02 (100%)	-	

Table 6: Management of neonatal AKI

Management/ treatment given	Outbornn=20	Inborn n=10	p-value
Appropriate fluid therapy	25 (12.5%)	05(50%)	0.03676
Furosemide/ diuretics	05 (100%)	01	0.332922
Inotropic support	25 (12.5%)	05 (50%)	0.003676
Use of non-nephrotoxic therapy	16 (80%)	02 (20%)	0.001565
Peritoneal dialysis	unavailable	unavailable	
Renal replacement therapy	unavailable	unavailable	

Table 7: Serum creatinine in neonatal AKI

Serum creatinine	Outbornn=20	Inborn=10	p-value
=/> 1.5mg/dl in consecutive samples	14	02	
Reduction (< 1.5mg/dl)in consecutive samples	6	08	0.009661

Table 8: Urine output in neonatal AKI

Urine output	Outbornn=20	Inborn n=10	p-value
<0.5ml/kg/hour for 6-12 hours	10(50%)	03(30%)	
>1ml/kg/hour	10(50%)	07(70%)	0.297365

Table 9: Distribution of cases as per outcome in neonatal AKI

Outcome	Outborn	Inborn	p- value
Discharged with complete recovery	10 (45%)	06 (60%)	
Discharged with residual kidney disease		02 (20%)	
Death	11 (55%)	02 (20%)	0.087648

Results

Out of 175 NICU admissions meeting the inclusion criteria, 113 were admitted in outborn unit (65%) and 62 in inborn unit (35%). 110 (63%) were males and 65 were females (37%). Out of 113 outbornneonates, 70 were males (62%) and 43 were females (38%). In inborn unit out of 62 admissions, 28 were females (45%) and 34 were males (54%). There is a major difference between outborn and inborn admissions as the study centre is a tertiary health care centre which has sick neonates being referred from all peripheral areas.

Out of the total cases majority were delivered by vaginal route (18 out of total 30) and the remaining were caesarean delivered overall. The inborn deliveries were caesarean in majority cases as most of the mothers were referred from peripheral centres with pre-existing maternal risk factors. The p-value in this distribution taking into consideration the mode of delivery comes out to be 0.017 (significant) When the results were analysed in terms of distribution as per gestational age, it was found that there was preponderance of AKI in term neonates in outborn newborns (55%) as compared to more preterm neonates in inborn unit (60%). More number of neonates with AKI were admitted during summer months (i.e. April, May) Out of the total 30 neonates developing AKI, the maximum number was seen in newborns with birth weight; 2.5 Kg, and those that were LBW babies cumulatively, in both inborn and outborn units. The cases in VLBW and ELBW were less reported.

In current study, among outborn neonates the most common risk factor associated with developing AKI was sepsis, followed by perinatal asphyxia and shock. Use of nephrotoxic drugs played a major role. Dose modifications and change of drug as per need in renal toxicity were done but

still due to ongoing severe septicaemia complete avoidance of nephrotoxic drugs could not be feasible. In inborn neonates most common risk factor associated with AKI was again sepsis followed by other risk factors considered in the study. Majority of newborns in inborn unit were LBW babies more likely to be predisposed to sepsis.

All the different treatment modalities applied during treatment of admitted cases with AKI were analysed in terms of results and included appropriate fluid therapy given to majority of patients, especially in the outborn unit (20/20) as most out born patients were received in dehydrated state. Many of the newborns also required inotropic support. Use of non-nephrotoxic drug therapy was meticulously followed, wherever permissible as per patient's clinical condition. Due to non-availability of RRT at our centre and majority of patients being unaffordable in a government set up, renal replacement therapy could not be done.

The major criteria for analysis and diagnosis of AKI were kept as serum creatinine 1.5mg/dL to maintain uniformity. In serial creatinine samples a reduction in creatinine values were seen in majority of cases both in outborn (55% cases) and inborn (60% cases) units. This helped predict the prognosis better.Urine output was monitored in all the admitted cases with AKI as per KDIGO definition. Urine output was found to be vital contributory factor for assessment of AKI in inborn units as there was a clear predisposition of newborns with output over 1ml/kg/hr, making serum creatinine values more important for diagnosis and prognosis. Out of 20 outborn neonates who had AKI, nine (45%) expired and eleven (55%) were successfully discharged with complete recovery of renal functions, while out of ten inborn neonates who had AKI, two (20%) expired and six (60%) were successfully discharged with complete recovery while two were discharged with residual kidney disease and called for further follow up.

Statistical Analysis

The collected data was summarized by using frequency, percentage, mean & S.D. To compare the qualitative outcome measures Chi-square test or Fisher's exact test was used. To compare the quantitative outcome measures Independent t test was used. If data was not following normal distribution, Mann Whitney U test was used. SPSS version 22 software was used to analyse the collected data. p value of <0.05 was considered to be statistically significant.

Discussion

Increased incidence of survival of newborns with AKI in intensive care units has been attributed to improve resuscitative and ventilatory support, increased use of non- nephrotoxic drugs, also for sepsis. There is higher risk of renal failure in premature neonates due to physiological immaturity of renal function. The early recognition of renal dysfunction is important in critically sick neonates because it facilitates appropriate fluid and electrolyte management and modification in drug dosage if required.

This study was conducted with the objectives to know determine and compare the etiological profile of renal failure in newborns and its associated risk factors for developing AKI, and to determine outcome of patient with AKI in outborn and inborn neonates with a view to help in early identification of the disease & avoidance of risk factors to improve prognosis in future cases. We provided a descriptive overview of AKI in newborns that were admitted to inborn & outborn units of NICU. The incidence of AKI in our unit was 17.1 % during the study period. There have been two recent studies in similar population (critically ill neonates); one using urine output with serum creatinine as the criteria and the other one only using serum creatinine. The

incidence of AKI was 20% and 6.3% respectively, highlighting the importance of having fixed definitions of AKI [9,10].

In present study total 30 neonates who were diagnosed as AKI admitted in inborn & outborn units of NICU of the study center. We found that most of cases (20) were outborn neonates whereas 10 cases were inborn neonates. Similarly, Airede *et al* studied 43 neonates with AKI and revealed majority (27) of neonates was outborn [11]. Low proportion of AKI amongst newborns of inborn NICU might be explained by the fact that these neonates were delivered within our hospital, picked up at an early stage of disease and managed appropriately that must have taken care of hypoperfusion.

In present study 20 male and 10 female neonates were diagnosed as AKI. In current study, we observed predominance of male newborns (n= 61; 82.4%) in the AKI group, in accordance with previous study [12]. Another recent NICU study although reported higher prevalence of AKI among females [13]. Higher number of male neonates in the study might be explained by overall higher male admissions in the NICU owing probably to a significant social and cultural bias against the female child in community in general. This study revealed that 18 neonates out of 30 cases with AKI were delivered by normal vaginal delivery in comparison to 12 neonates with AKI were delivered by caesarean section. This can be attributed to multiple factors like higher antenatal risk factors such as fetal distress, prolonged hospitalization and more occurrence of dehydration due to ineffective lactation. Yaseen H *et al* (2004) had reported that dehydration fever was associated with caesarean section [14] and dehydration being a risk factor leading to AKI.

Amongst term and preterm neonates in both inborn and outborn units, much difference was not noted with AKI having similar incidence in term and preterm at our center as per results of this study. This may be explained by immaturity of the renal system in preterm newborns whereas in term neonates this may be attributed to complications like birth asphyxia and septicemia.

We observed higher occurrence of AKI in LBW babies and those with birth weight >2.5Kg as compared to VLBW and ELBW neonates. The results were similar in inborn and outborn units. A previous study from India showed similar results to our study in which the percentage of babies with birth weight of <2500 gm in AKI group was higher than in healthy neonates [15].

In present study, in outborn neonates causative risk factors associated with AKI were dehydration, sepsis, shock, perinatal asphyxia, RDS and mechanical ventilation and congenital anomalies, while in inborn neonates most common risk factor associated with AKI were perinatal asphyxia followed by sepsis. Coincidentally there were equal number of neonates (2 each) admitted with congenital malformations, in inborn as well as outborn units. Kapil *et al* observed that in outborn neonates, neonatal sepsis was the commonest cause of AKI followed by perinatal asphyxia, respiratory distress syndrome and use of mechanical ventilation [16].

Sepsis came out to be a major risk factor predisposing to AKI in our study. Sepsis has been consistently associated as a risk factor for development of AKI in various studies conducted around the world, contributing to as high as 78% cases in some neonatal studies [10,13,17]. Another study from India by Mathur NB *et al*., shows that out of 200 newborns with sepsis, 26% developed AKI [6].

The newborns with sepsis are thought to be predisposed for AKI as a result of hypotension secondarily to sepsis and a direct damaging effect on renal microvasculature. Several previous studies

have found birth asphyxia to be a common cause of AKI of neonatal period [18,19,20]. Perinatal asphyxia is associated with acute tubular injury which is the most common cause of intrinsic AKI. Two recent studies reported an association between asphyxia and AKI using modern definition for AKI [8,20]. Prolonged ventilation leads to compromised renal blood flow because of hypercapnia or hypoxemia; and barotrauma induced pulmonary inflammatory reaction leading to secondary systemic inflammatory reaction [17,21,22].

Appropriate fluid therapy with inotropic support was given in almost all outborn neonates with AKI. Nephrotoxic drugs were either shifted to non-nephrotoxic drugs or dosing were adjusted as per GFR which is similar to all the recent studies. Renal replacement modalities including peritoneal dialysis becomes a crucial invasive procedure for management, which was unavailable at our centre, is different from the study done by Aslihan *et al* [23]. Serum creatinine was serially done to assess the improvement. There was significant reduction in serum creatinine over 24-48 hours of treatment, 55% in outborn unit and 60% in inborn unit whereas 13 patients did not show any improvement despite all treatment which is in contrast to the study done by Nayan *et al* [24]. The urine output also showed improvement upon adequate fluid therapy as severe dehydration was seen in 50% of outborn neonates.There was a significant difference in mortality between outborn and inborn neonates. 20% in inborn and 55% in outborn neonates could not be saved despite all treatment, total 43% which is similar to, Norman and Asadi *et al* [25] and contrary to Nayan *et al*. 45% neonates from outborn unit and 60% neonates from inborn were discharged with full recovery.

Conclusion

- Incidence of neonatal AKI was found to be 17%
- Incidence was more in out born unit as many antenatal factors go mismanaged at peripheral health centres.
- Sepsis was found to be the most common cause of AKI in both inborn and out born units due to which higher antibiotic were prescribed which in turn cause more damage to neonatal kidneys. Other important causes include perinatal asphyxia, prolonged ventilation and dehydration.
- Serum creatinine and urine output was found to be the most convenient and economic investigation for monitoring AKI.

Limitation of the study

- Antenatal factors like oligohydramnios or polyhydramnios could not be assessed because of unavailability of documents in referred patients.
- Unavailability of investigations like arterial blood gas, urinary electrolyes and advanced modalities like peritoneal dialysis.
- Many patients were unavailable for follow up due to poor transport facilities in rural areas.

Declarations

Funding: None Conflicts of interest/Competing interests: None Availability of data and material: Department of Paediatrics Atal Bihari Vajpayee Governement Medical College Vidisha Code availability: Not applicable Consent to participate: Consent taken Ethical Consideration: There are no ethical conflicts related to this study. Consent for publication: Consent taken

What this study add to existing knowledge

The study also emphasises on the importance of proper antenatal management, institutional deliveries to avoid perinatal asphyxia, post natal neonatal monitoring for urine output,

feeding. Requirement of tertiary care centres at peripheral/rural areas so that referral can be minimised. Promoting advanced neonatal care including bed side sonogram, renal replacement therapy like peritoneal dialysis and haemodialysis to reduce mortality.

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