STUDY OF GLOMERULAR FUNCTIONS IN NEONATES

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ABSTRACT

Glomerular function of neonates (25 full term and equal number of preterm neonates) at birth, on day seven and day fourteen were estimated by endogenous Creatinine clearance (CCr). The Preterm were divided into three groups viz. Group I (Gestation age (GA) 30-32 weeks), Group II (GA 33-34 weeks) and Group III (GA 35-36 weeks). Group IV consisted of 25 term neonates. Serum creatinine (in mg/dl) in all the groups of preterm ranged from 0.92 ± 0.153 to 1.204 ± 0.154 and in term neonate from 0.562 ± 0.175 to 1.148 ± 0.247 showing that the levels were inversely proportional to the period of gestation. Besides the Serum Creatinine levels in all groups of Preterm as well as term neonates were found to fall significantly ($p < 0.001$) during the first and second week. Glomerular filtration rate (GFR) in Group I were 16.603 ± 2.519 , 19.786 ± 2.078 and 23.720 ± 2.320 on day one, seven and fourteen respectively showing progressive improvement during the first two weeks. The GFRs were also found to be directly proportional to the GA. In addition the levels of GFR were found increasing significantly during the second week compared to that on day seven in all the groups of preterm neonates. GFR's in Group I & II on all the three occasions were significantly lower ($p < 0.001$) than those of term counterparts, however the GFR on the first day in Group III neonates was lower than group IV, the difference was insignificant ($p > 0.05$). The increase in GFR in Group I on the three occasions was linear but insignificant ($p > 0.05$). The rise was more rapid & significant ($p < 0.001$) during the second week in Groups II & III. On the contrary the rate of improvement of GFR in full terms was quite rapid during the first week and gradual over the second week of life.

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Introduction

For the maintenance of normal homeostasis, intact renal functions are of paramount importance. The complex structure of nephrons and their accompanying blood vessels help regulate homeostasis of body water and electrolyte metabolism as well as acid base regulation.

The early nephrons are formed by 11-12 weeks from the ampulla of the ureteric bud arising out of the mesonephros [1,2]. By 22 weeks all nephrons are juxtamedullary [3]. The formation of new glomerulus ceases when the foetus weighs between 2100-2500 gms and by 35 weeks nephrogenesis is complete [4]. The kidney of the newborns consists of approximately one million nephrons [4].

Renal blood flow (RBF), Glomerular filtration rate (GFR) and tubular functions are not that manifest in utero since the secretory or regulatory functions of foetal kidneys are limited [1]. Foetal kidneys receive 2-4% of the combined ventricular output during the last trimester may be due to high renovascular resistance and the filtration fraction compared to full term newborns [1]. RBF following 24 hours after birth progressively increases to almost 12 fold with precipitous fall in renovascular resistance attributable to decrease

in level of vasoconstrictor agents, viz. catecholamines, vasopressors, angiotensin and increase in the level of vasodilator prostaglandins [2].

The intrarenal blood flow is evenly distributed during foetal life. After birth, the perfusion in the outermost cortical nephrons is only one fifth of medullary nephrons. But by six weeks, the perfusion in the superficial nephrons increases to five fold higher than that of deep medullary nephrons [1].

GFR in neonates and infants is low compared to adults and it is also directly related to increasing gestational or conceptional age [4]. It has also been generally agreed that preterms have a lower rate of improvement of GFR till about 34-36 weeks of gestation age and then the rise is significant as seen in the first week of life in term neonates [4]. Thus the GFR corrected for body surface area doubles from birth to two weeks of age, rises to more than half adult levels by two months of age and reaches maturity by about two years of age [4].

Problems of fluid and electrolyte, acid base balance are frequent in early neonatal period & more so in sick and preterm neonates [1]. Many substances like Inulin, ^{99m}Tc , DTPA, Cr_{51} and poly fructosan have been used to assess GFR. However endogenous creatinine

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clearance measurements approximate the GFR in term/preterm newborns as well as compromised sick neonates [5]. There has been scanty literature in our country on this account. Hence it is desired to study the glomerular function of the preterm & term neonate by estimation of the GFR by creatinine clearance at birth, first week & second week of life. This would enable to study the degree of maturity and correlation of the GFR in the two groups and to note the difference, if any, in the progressive improvement of GFR in both preterm & term neonates during the first and subsequent weeks of life.

Material and Methods

Fifty newborns, twenty five term babies (gestation age between 37-40 weeks) and twenty five preterm babies whose gestation age varied between 30-36 weeks were the subjects of the study. Neonates born with congenital anomalies, suspected sepsis, cardiovascular, central nervous system & gastrointestinal anomalies were excluded. Gestational age was calculated from the maternal history of the last menstrual period, obstetrical record and by clinical assessment of physical & neurological maturation as described by Dubowitz et al [6]. All the preterm babies were admitted to the nursery for two weeks or more. Term babies born of Caesarean deliveries also stayed in the hospital for a week or more and those born of normal vaginal delivery were studied on the first day while in hospital. Caesarean babies and normal vaginal delivery were recalled on day 7 and 14 and detained for 24 hours for conducting the study.

Informed consent was taken from the parents before starting the study. Since clean and accurate urinary collection was not possible in the female neonates only male neonates were included in the study. All infants were exclusively breast fed or given EBM only. The quantity of EBM was adjusted as per the schedule of the nursery based on the body weight and post-natal age. Preterm neonates weighing less than 1500 gms were put on 10% dextrose IV on the first day of life. Endogenous CCr was taken as function for assessing GFR. Urine was collected by means of condom drainage. Condoms were placed immediately after birth and on the first day of life and subsequently on the 7 & 14 day around 8 to 9 A.M. To ensure that the last aliquot of urine was also collected manual compression of bladder was done without undue discomfort to the baby. 3 ml of venous blood was collected from the peripheral vein one hour prior to the removal of condom. Samples were immediately transferred to the biochemistry laboratory.

Estimation of Serum Creatinine:

Serum Creatinine was estimated by the alkaline picrate method of Brod & Sirota [7]. The test & standard readings are taken set-

ting the blank to zero. The readings are taken at 520 nm wavelength in a photocolormeter. 24 hours urinary creatinine was determined by the same methodology as serum creatinine but urine was made into 1 : 100 dilution.

Calculation

Estimation of CCr (ml/min/1.73m².)

$CCr = U \times V / P \times 1.73 / SA$

Where U= Conc. of Creatinine in urine

V= Volume of urine in ml/min

P= Conc. of creatinine in blood in mg/dl

SA= Surface area of the neonate in sq.m

Observations and Results

For the relative comparison of GFR the preterm neonates were divided into gestational age groups of 30-32 weeks, 33-34 weeks, and 35-36 weeks (Table 1)

TABLE 1
Distribution of cases

Group	Gestation age (weeks)	Number of cases
Group I	30-32	06
Group II	33-34	11
Group III	35-36	08
Group IV	37-40	25

Serum Creatinine (P) and Urinary Creatinine (U)

In both preterm & term neonates the values of P & U exhibited gradual significant decrease ($p < 0.001$) on day 1, 7, and 14. (Table 2). Serum Creatinine (P) was found to be significantly high ($p < 0.001$) in preterm infants on day 7 & 14 when compared to those of term neonates but showed no significant difference ($p > 0.05$) on day one (Table 2)

Group I-Gestation age (GA) 30-32 Weeks

Mean GFR (ml/min/1.73 sq.m) $\pm$ 1 SD in this age group on day 1, 7, and 14 were 16.603 ± 2.519 , 19.786 ± 2.078 and 23.720 ± 2.320 respectively, showing progressive improvement. However no statistically significant increase was noticed between day 1 and 7 ($p > 0.05$) as well as over the second week between day 7 & 14. (Table 3). The values were also significantly lower ($p < 0.001$) than their term counterparts when compared on all three occasions i.e. at birth and over the first and second week (Table 3).

Group II (GA 33-34 weeks)

GFR in this group indicates progressive increase on day 1 and 7 which is of statistical significance ($p < 0.01$). However the in-

TABLE 2

Serum creatinine and urinary creatinine in preterm and term neonates

	Gestation age (weeks)	Day 1		Day 7		Day 14	
Serum creatinine	< 37 (n=25)	1.204	$\pm$ 0.154	0.92	$\pm$ 0.153*	0.788	$\pm$ 0.127**
	> 37 (n=25)	1.148	$\pm$ 0.247	0.712	$\pm$ 0.174*	0.562	$\pm$ 0.175
Urinary creatinine	< 37 (n=25)	44.92	$\pm$ 11.372	26.0	$\pm$ 8.23*	19.08	$\pm$ 5.88**
	> 37 (n=25)	44.6	$\pm$ 10.368	25.12	$\pm$ 10.187*	23.16	$\pm$ 7.4

* $p < 0.001$ Significant difference with the previous week in the same age group; ** $p < 0.001$ Significant difference with term age group.

TABLE 3

Glomerular filtration rate

Group and GA (in weeks)	Day 1		GFR in ml/min/1.73 sq.m Day 7		Day 14	
Group I (GA- 30-32 weeks)	16.603	± 2.519#	19.786	± 2.078#*	23.720	± 2.320#
Group II (GA- 33-34 weeks)	17.592	± 1.667#	20.334	± 1.878#	24.693	± 2.368#\$
Group III (GA 35-36 weeks)	22.034	± 1.955	28.892	± 2.508*#	29.038	± 2.368*#\$
Group IV (Term neonates)	24.888	± 3.070	46.026	± 5.036*\$	60.555	± 3.190**

* $P = < 0.001$ significant difference between the previous age group

$p = < 0.001$ significant difference with term neonates

\$ $p = < 0.001$ significant difference with the levels of previous week in the particular group

** Gradual but significant increase over the levels of the previous week in that group

crease was observed to be more rapid and more significant ($p < 0.001$) during the second week but was still less compared to the term babies. (Table 2).

Group III (GA 35-36 weeks)

The values of the mean GFR $\pm$ 1SD on day 7 and 14 showed statistically significant ($p < 0.001$) increase over on day 1. (Table 3).

Group IV (GA > 37 weeks)

The mean GFR was found to be 24.88 ± 3.07 , 46.02 ± 5.30 and 60.55 ± 3.19 on day 1, 7 & 14 respectively (Table 2).

There was statistically significant increase ($p < 0.001$) over the first two weeks i.e. between day 1 and 7 and between day 7 and 14. When compared with each group of preterm neonates, GFR was significantly more on all three occasions ($p < 0.001$) except in group III (GA 35-36 weeks) where no statistical significant difference ($p > 0.05$) was noticed on GFR of day 1 (Table 3 and Fig 1).

Discussion

The abruptness, with which placental function is terminated makes it necessary for the kidneys nearly dormant in utero to respond to the functional demands of extra uterine life [8]. Estimation of GFR in relation to adult body surface area by endogenous CCr method has been used as the most practical method for detecting renal disease in sick neonates as well as to evalu-

ate the renal functions (normal) of neonatal kidney [9]. The population of the neonates taken in this study was heterogeneous and the same babies were followed up on subsequent days over the 1st and 2nd week.

Serum Creatinine levels observed in this study, in general agree with those of Gordani and co-workers [10] showing rapid significant fall during the first and second week of birth both in the term and the preterm neonates (Table 2). Whereas there was no significant difference in the levels at birth in the two groups. It is attributed that the levels at birth correlate with the maternal levels and progressive decrease in these levels is due to the increase in RBF and redistribution of intra renal pattern of Glomerular blood flow [8]. Contrary to our study, the levels of serum creatinine by others [7,11] were lower, may be due to different method of estimation. In the present study it was found that the increase of GFR in the first 2 weeks in group I showed no statistically significant difference and the increase is linear (Table 3). In groups 2 and 3, significant increase in GFR was seen over the first week as well as second week and the increase was more significant in group 2.

However there was no significant difference in GFR from birth till 2 weeks of postnatal age when group I (GA30-32 weeks) and group 2 (33-34 weeks) are compared with each other (Table 3). Significant difference was noticed in all the three occasions between GFR of those born before 35 weeks (Group 1 & 2) and those born at or after 35 weeks (Group 3 and 4), GFR showed significant improvement over the first two weeks in term neonates (Table 3). More aggressive increase in values were demonstrated in the term neonates (Group 4) compared to the other groups during the first and second weeks of life (Table 3). This study tends to agree with the fact that at birth GFR is significantly lower in the preterm neonates born before 35 weeks of gestation as compared to those born after 35 weeks of GA. This is in agree-

Fig. 1: GFR vs Postnatal age in preterm and term infants.

ment with observation made by others [8, 12]. However Aperia and co-workers [9], Nair et al [13] have failed to demonstrate any significant difference in GFRs of term and preterm neonates at birth, may be because of limited number of preterm neonates in their studies.

The progressive increase in GFR from birth to 2 weeks, in the three groups of preterm neonates, and term neonates may be a reflection of more rapid development of function in the relatively more mature neonates compared to the preterm counterparts. The reason, for low GFR noted at birth between the three groups of preterm & term babies may be due to the difference in the rapidity with which circulatory changes take place after birth [1,4,14]. Other factors that may be operating after 34 weeks, could be the completion of nephrogenesis at 35 weeks [4].

The very rapid increase in GFR observed after 34 weeks (Group 3) and term neonates (Group 4) may also be due to increase in RBF and redistribution of intrarenal pattern of glomerular blood flow [8] which results in recruitment of superficial cortical nephrons [15]. Besides changes in hydraulic permeability [16,17] and increase in glomerular surface area [8,18] would play role in rapid increase of the GFR.

Drug dosage for preterm neonates are presently calculated with the assumption of improvement in renal function in about two weeks of age. This study shows that glomerular functions in preterm, specially those born before 35 weeks of GA, lag far behind term neonates. Thus drugs like aminoglycosides used in the treatment of neonates, specially in preterm neonates below 35 weeks, need to be monitored and dose adjusted as per glomerular functions.

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