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USE OF CLOFIBRATE UNCONJUGATED HYPERBILIRUBINEMIA IN NEONATES

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Conflicts of Interest: Nil
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Abstract:

INTRODUCTION: Hyperbilirubinaemia is a common problem in the neonatal period, occurring in around 60% of newborns. The treatment for for severe jaundice is exchange transfusion and phototherapy, but the need for exchange transfusion has markedly decreased because of the availability of effective phototherapy, and however a small proportion of infants with severe hyperbilirubinemia need exchange transfusion, which leads to increased risk of infections and death. Clofibrate increases the activity of extrahepatic lipoprotein lipase thereby increasing lipoprotein triglyceride lipolysis. This is accompanied by a slight increase in secretion of lipids into the bile and ultimately the intestine.

MATERIAL AND METHODS: This was a randomised control trial performed on 64 neonates admitted in the hospital during study period. Term neonate in which gestational age between 38-41 weeks, Weight ranging between 2500-4000 grams, age of the neonate between 2-7 days, Serum total bilirubin level between 17-26 mg/dl with priority of unconjugated bilirubin was included in the study. Case group were treated by clofibrate and phototherapy, while control group treated only with intense phototherapy. Clofibrate was administered as a single dose of 100 mg/kg. Phototherapy was discontinued when serum bilirubin level is lower than 10mg/dl.

RESULTS: In case group (clofibrate and intense phototherapy) there were 16 (50%) male and 16(50%) female while in control group there were 18 (56.3%) male and 14 (43.8%) female. No statistically significant difference was observed between the cases and control group in terms of mean age, weight, total serum bilirubin and serum conjugated bilirubin. At 48 hours Serum bilirubin levels in case group was 7.65±0.74 while in control group was 11.47±1.10. There was a significant reduction in the serum bilirubin levels in the case group at 48 hours.

CONCLUSION: Administration of clofibrate before starting phototherapy was seen to be effective in reducing neonatal jaundice in term individuals.

INTRODUCTION:

In human body bilirubin is a naturally occurring antioxidant[i]. Hyperbilirubinaemiais a common problem in the neonatal period, occurring in around 60% of newborns[ii].The goal for the management of unconjugated hyperbilirubinemia is to avoidthe bilirubin toxicity[iii]. The treatment for severe jaundice is exchange transfusion and phototherapy, but the need for exchange transfusion has markedly decreased because of the availability of effective phototherapy, and however a small proportion of infants with severe hyperbilirubinemia need exchange transfusion, which leads to increased risk of infections and death[iv]. Recently the use of photo blanket have made easy outpatient treatment of neonates, still many neonates have to be hospitalized for receiving phototherapy, but this method of treatment has disadvantage of hospitalization cost, risk of nosocomial infections and loss of working hours of the parents[v].

Clofibrate increases the activity of extrahepatic lipoprotein lipase thereby increasing lipoprotein triglyceride lipolysis. This is accompanied by a slight increase in secretion of lipids into the bile and ultimately the intestine. Clofibrate also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier molecule for VLDL. Also, as a fibrate, Clofibrate is an agonist of the PPAR-α receptor[vi].

MATERIAL AND METHODS:

The present study was carried out in the Dept. of Paediatrics at Ananta Institute of Medical Sciences and Research Centre, Rajsamand. This was a

randomised control trial performed on 64 neonates admitted in the hospital during study period. Inclusion criteria in case and control groups included: Term neonate in which gestational age between 38-41 weeks, Weight ranging between 2500-4000 grams, age of the neonate between 2-7 days, Serum total bilirubin level between 17-26 mg/dl with priority of unconjugated bilirubin. Case group were treated by clofibrate and phototherapy, while control group treated only with intense phototherapy. Clofibrate was administered as a single dose of 100 mg/kg. The distance of lamps from patients was around 25cm. Phototherapy was carried out with all standard conditions and taking all the necessary precautions. Bilirubin levels in both groups were measured before and after treatment. In addition it was also measured 6, 12, 24 and 48 hours after starting phototherapy. Phototherapy was discontinued when serum bilirubin level is lower than 10mg/dl.

Patients with prematurity, neonatal sepsis, congenital anomalies, dehydration, hemolytic diseases and conjugated hyperbilirubinemia were excluded from the study. Written informed consent was obtained from the parents before registering patient for the study.

The results of two groups were compared and analysed by Chi-square and students t test. All data was entered and statistical analysis was done using SPSS software. P-value less than 0.05 were considered significant.

RESULTS

Table 1: A total of 32 cases were included in the case group while 32 were included in the control group.

Group	**Case**		**Control**	
Male	16	50%	18	56.3%
Female	16	50%	14	43.8%
Total	32	100.0%	32	100.0%

In case group (clofibrate and intense phototherapy) there were 16 (50%) male and 16(50%) female while in control group there were 18 (56.3%) male and 14 (43.8%) female.

Table 2: comparison of variables in case and control group

Variable	Case group (mean±SD)	Control group (mean±SD)	P value
Weight (grams)	2845± 282	2955±297	0.1338
Age (days)	3.1±1.0	3.4±0.8	0.1900
Total serum bilirubin (mg/dl)	19.58±3.45	19.11±2.78	0.5569
Serum conjugated bilirubin(mg/dl)	0.771±0.65	0.765±0.54	0.9681

No statistically significant difference was observed between the cases and control group in terms of mean age, weight, total serum bilirubin and serum conjugated bilirubin. In control group mean age, weight, total serum bilirubin and serum conjugated bilirubin was 2845± 282 grams , 3.1±1.0 days, 19.58±3.45 mg/dl and 0.771±0.65 respectively while in control group mean age, weight, total serum bilirubin and serum conjugated bilirubin was2955±297grams, 3.4±0.8days, 19.11±2.78mg/dl and 0.765±0.54mg/dl.

Table 3: serum bilirubin levels at 0 and 48 hours

Hours	Group	Serum bilirubin levels(mean±SD)	P value	95 % CI	t- statistics
0 hours	Case	19.58±3.45	0.5569	-2.0357 to 1.0957	-0.600
	Control	19.11±2.78			
48 hours	Case	7.65±0.74	< 0.0001	3.3515 to 4.2885	16.300
	Control	11.47±1.10			

At 48 hours Serum bilirubin levels in case group was 7.65±0.74 while in control group was 11.47±1.10. There was a significant reduction in the serum bilirubin levels in the case group at 48 hours.

DISCUSSION:

Neonatal hyperbilirubinemia is a clinical problem during the neonatal periodespecially in the first week of life. When the total serum bilirubin (TSB) rises above the 95th percentile for age during the first week of life, it will be considered as hyperbilirubinemia[vii], [viii].High bilirubin levels can be toxic for central nervous system development in neonates and may cause behavioral and neurological impairment[ix]. Several studies has been carried out to see the efficacy of clofibrate to reduce the serum bilirubin levels in the neonates[x],[xi],[xii].

Clofibrate is an antilipidemic agent similar to gemfibrozil. Clofibrate is a fibric acid derivative which is used in the treatment of hyperlipoproteinaemia Type III and severe hypertriglyceridaemia. This drug acts an activator of peroxisome proliferated activated receptors and therefore ithas effects on lipid metabolism. It is also used to lower elevated serum lipids by reducing the very low-density lipoprotein fraction (S_f 20-400) rich in triglycerides. Serum cholesterol may be decreased, particularly in those patients whose cholesterol elevation is because of the presence of low-density lipoprotein as a result of Type III hyperlipoproteinaemia[xiii].

If the serum bilirubin levels are reduced rapidly, the need of exchange transfusion, hospital stay and health care costs can be reduced. 100 mg clofibrate per kg of body weight as single dose combined with phototherapy effectively decreases the serum bilirubin levels as shown in our study. Similar results were observed by different authors in their studies[xiv],[xv]. In our study significant reduction in the serum bilirubin levels were observed after 48 hours of administration of clofibrate. In a study by Gabilan JC[xvi] et al effect was observed after12 hours while Mohammadzadeh A[11] et al showed effectiveness in 16 hours.

CONCLUSION

Administration of clofibrate before starting phototherapywas seen to be effective in reducing neonatal jaundice in term individuals.

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