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RESEARCH ARTICLE

ROLE OF FENOFIBRATE IN MANAGEMENT OF UNCONJUGATED HYPERBILIRUBINEMIA IN NEONATES.

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Abstract

Background: Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. Fibrates can increase bilirubin conjugation and excretion via induction of glucuronyltransferase activity.

Methods: Forty full term neonates admitted to the "N.I.C.U." of Benha Children Hospital suffering from neonatal indirect hyperbilirubinemia. Twenty neonates received fenofibrate (10 mg/kg) as adjuvant therapy in addition to phototherapy while the other twenty neonates received phototherapy alone.

Results: we found that neonates treated with fenofibrate and phototherapy had 5.3 mean NICU stay which is shorter than NICU stay of neonates treated with phototherapy alone whose admission duration mean was 5.8 .

Conclusion: Our study revealed that use of fenofibrate in addition to phototherapy has additional benefit regarding time of stay and rate of bilirubin reduction in comparison to treatment with phototherapy alone.

Introduction:-

Jaundice isan important problem in the first week of life. It is a cause of concern for the physician and a source of anxietyfor the parents(1).

Physiological jaundice attributable to physiological immaturity usually appears between 24-72 hours of age, peaks by 4-5 days in term and 7th day in preterm neonates and disappears by 10-14 days of life. 60 % of term newborns and 80% of preterm babies develop jaundice in the first week of life, yet only about 10% need admission(2).

Pathological jaundice is Jaundice appear in the first 24 hours , bilirubin rising faster than 5 mg/dL in 24 hours or healthy term infants with total serum bilirubin concentration > 15 mg/dL (Lower levels in preterm infants and hemolytic disease) (3).

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Pharmacological agents introduced for treatment of unconjugated neonatal jaundice include Phenobarbitone[4], metalloporph-yrinsand D–penicillamine[5], Intravenous Immunoglobulins, Intravenous albumin [6]. But, so far they have not been proved veryeffective and safe in clinical use [7].

Fenofibrate is adrug of the fibrate class. Fibrates have been used for several years as a hypolipidemic drug [8]. Fenofibrate is now the most widely used fibrate in treating hyperlipidemia and hasa comparatively much better safety profile than clofibrate[9]. Fibratesalsoincrease bilirubin conjugation and excretion via induction of glucuronyltransferase activity [10]. Its potency toinducebilirubinconjugationis manytimes more than Phenobarbitone[11].

Subjects:-
This study included forty (40) full term (FT) neonates admitted to the "N.I.C.U." of Benha Children Hospital (BENCH) suffering from neonatal indirect hyperbilirubinemia. These neonates were randomly allocated into two groups with the permission of their parents and the ethical committee of hospital. The included neonates were full or preterm and from the first to the 28th day after birth. The study didn't take the newborn's gender into consideration.

Neonates with conjugated hyperbilirubinemia, renal impairment, Infection, Liver insufficiency, congenital anomalies, respiratory distress, exchange transfusion, cephalohematoma, subgaleal bleeding, chromosomal abnormalities and surgical disorders were excluded from the study.

Ethical consideration:-
The current study was approved by the Local Ethics Committee of Faculty of Medicine, Benha University and all study participants' parents gave a written informed consent prior to enrollment in the study.

Methods:-
Blood samples were withdrawn immediately after admission and before starting any treatment for complete blood count (C.B.C), blood grouping (ABO) and Rh of neonates and their mothers, reticulocyte count, coomb's test, total bilirubin (indirect & direct), ALT, AST, Urea and creatinine, C- reactive protein.Total serum bilirubin and indirect bilirubin were measured every 12 hours till the end of phototherapy.

Both groups (A & B) received phototherapy under standard conditions. Group (A) received phototherapy plus a single oral dose of 10 mg/kg of non-micronized fenofibrate while group (B) received phototherapy alone.

Because of fenofibrate present only in tablet and capsule forms, we dissolved the content of the tablet in water to get a well-known concentration of fenofibrate suspension (e.g. 160mg tab. Dissolved in 16ml distilled water to get conc. 10mg fenofibrate in 1 ml).

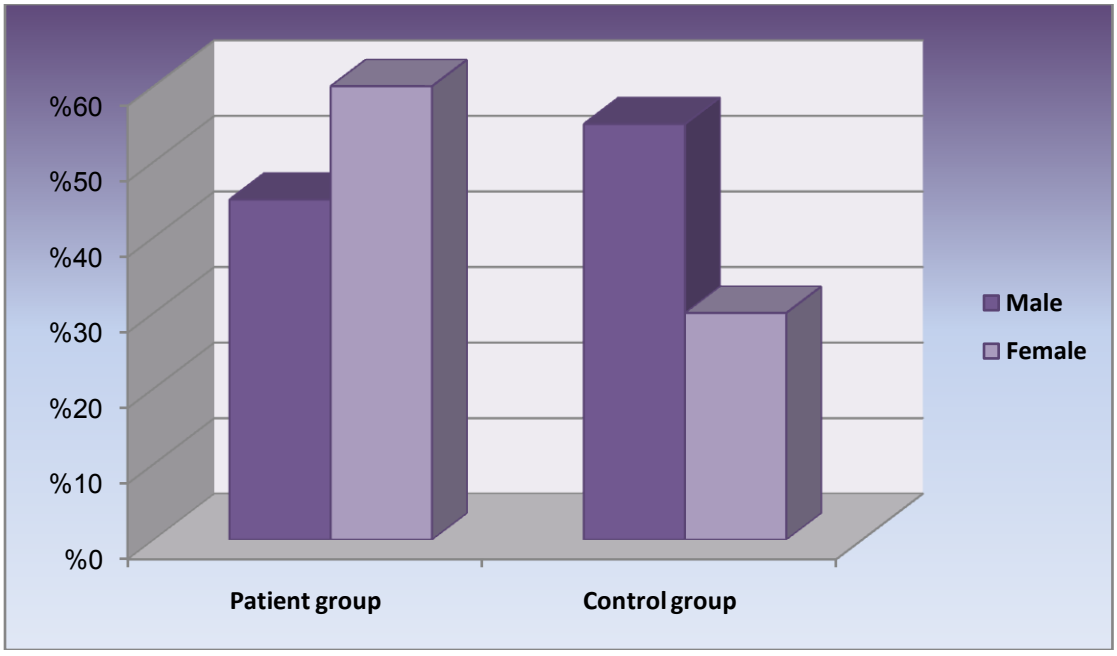
Statistical analysis:-
The collected data were organized, tabulated and statistically analyzed using SPSS (Statistical package for social science) version 13. For quantitative data, the range, mean and standard deviation were calculated. The difference between two means was statistically analyzedusing the Student t-test [Unpaired], paired t-test and Chi-square. Linearcorrelation coefficient (r) was calculated to test the association between two variables. For qualitative data, the number and percent distributionwere calculated. Z-value was used as a test of significance.

Results:-

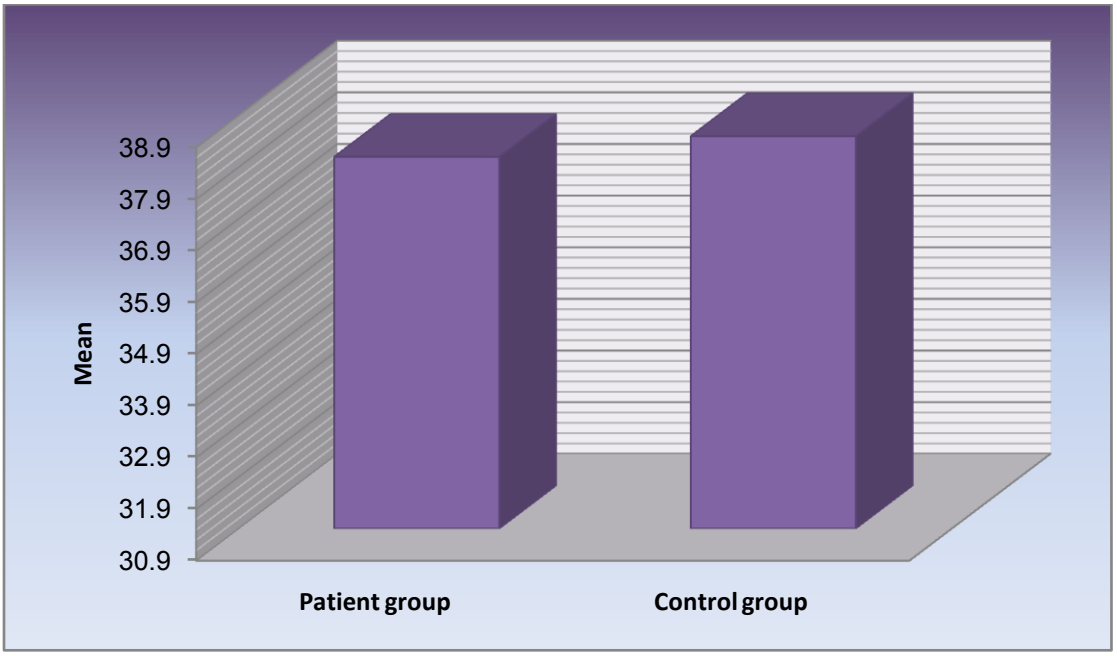
Table 1:- Comparison between the two groups regarding: sex, gestational age at presentation and weight.

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
Sex	**M**	9	11	0.34 (Chi^2)	NS
	F	11	9		
	Total	20	20		
Gestational age (weeks)	**Mean**	38.1	38.5	0.33 (t-test)	N S
	SD	1.29	0.89		
Age at presentation in days	**Mean**	4.07	5.25	0.15 (t-test)	NS
	SD	2.19	2.90		
Weight	**Mean**	2.94	3.13	0.19 (t-test)	NS
	SD	0.46	0.41		

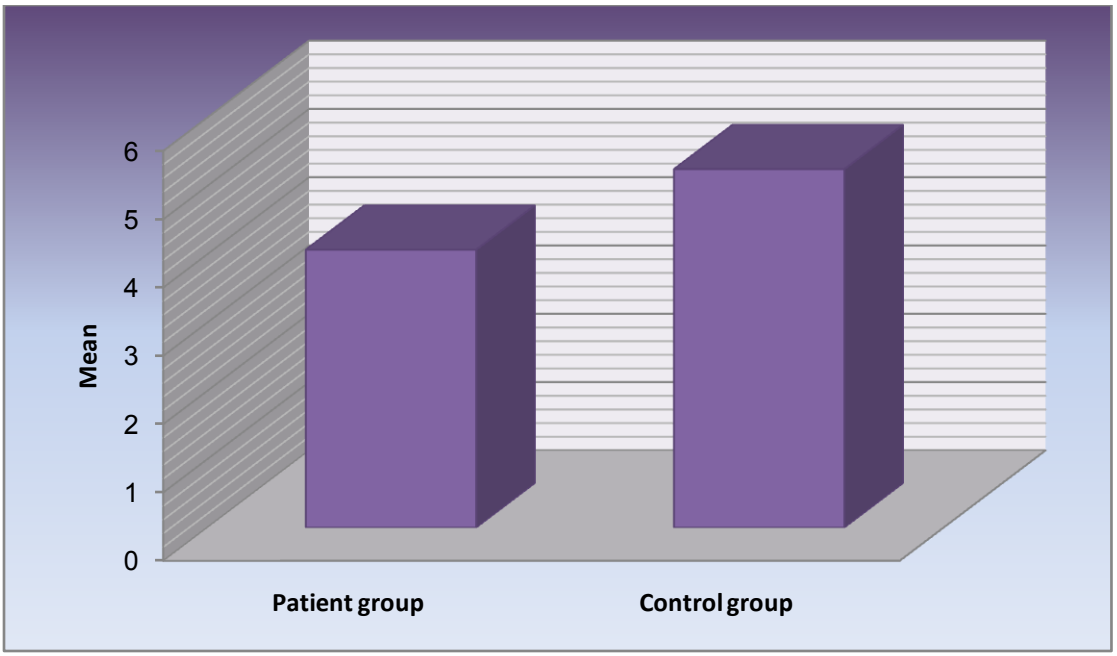
This table and the following figures show that there was no statistically significant difference between the two groups as regard sex, gestational age at presentation and weight.



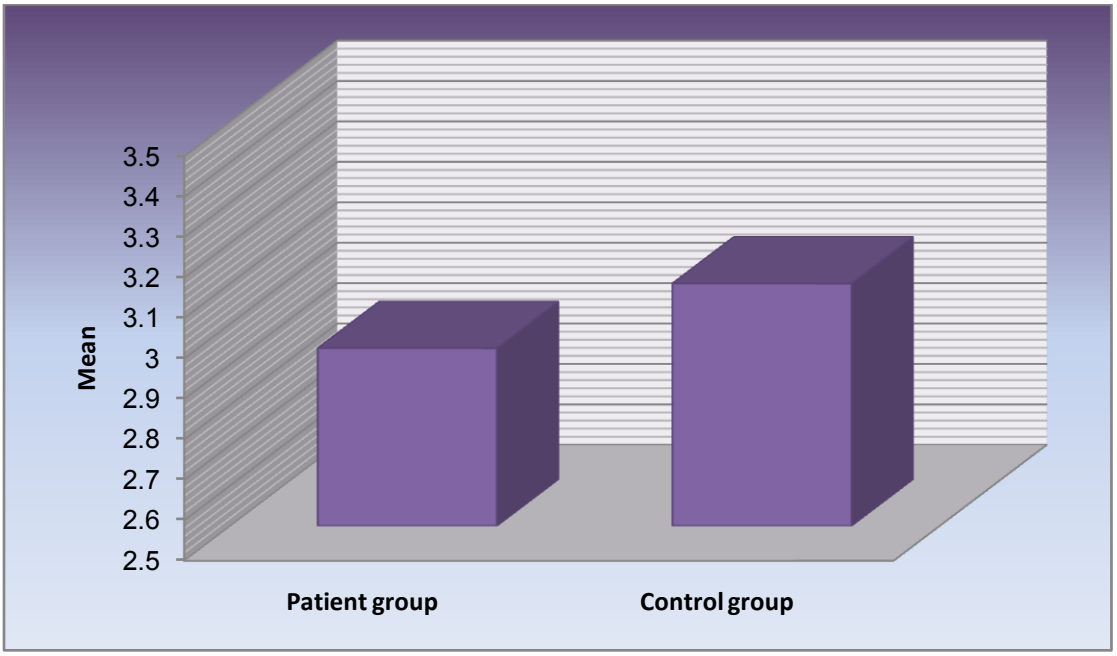
Sex of studied groups.



Gestational age of studied groups.



Age at presentation.

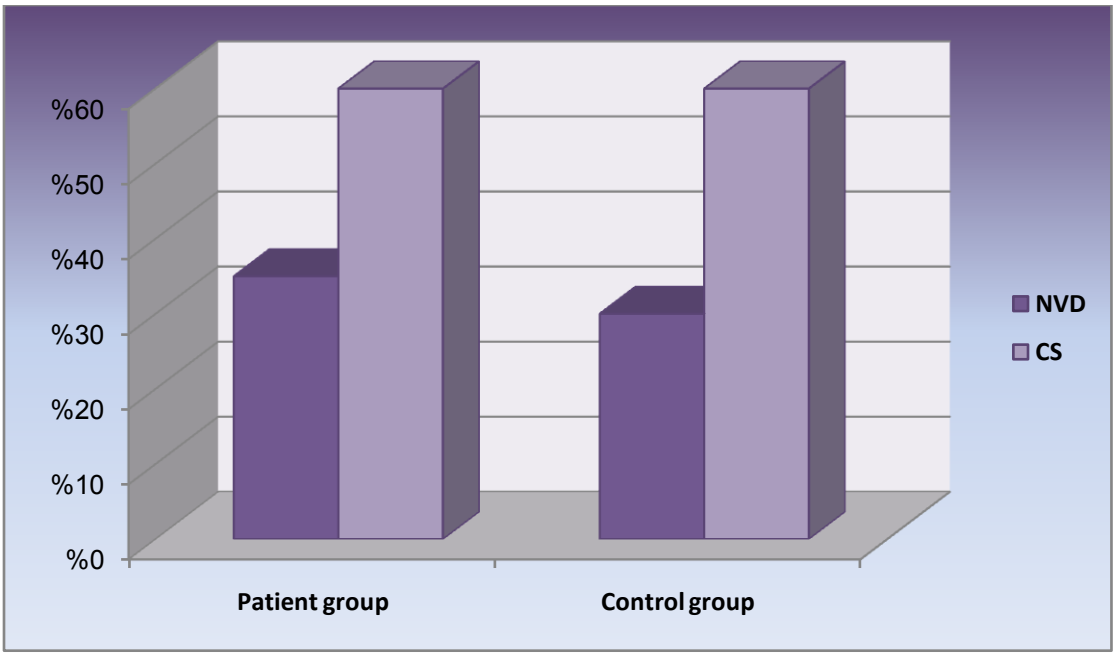


Weight of studied group.

Table 2:- Comparison between the two groups regarding: mode of delivery.

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
Mode of delivery	**NVD**	7	6	0.5 (Chi^2)	NS
	CS	13	14		

This table and the following figure show that there was no statistically significant difference between the two groups as regard mode of delivery.



Mode of delivery.

Table 3:- Comparison between the two groups regarding: feeding.

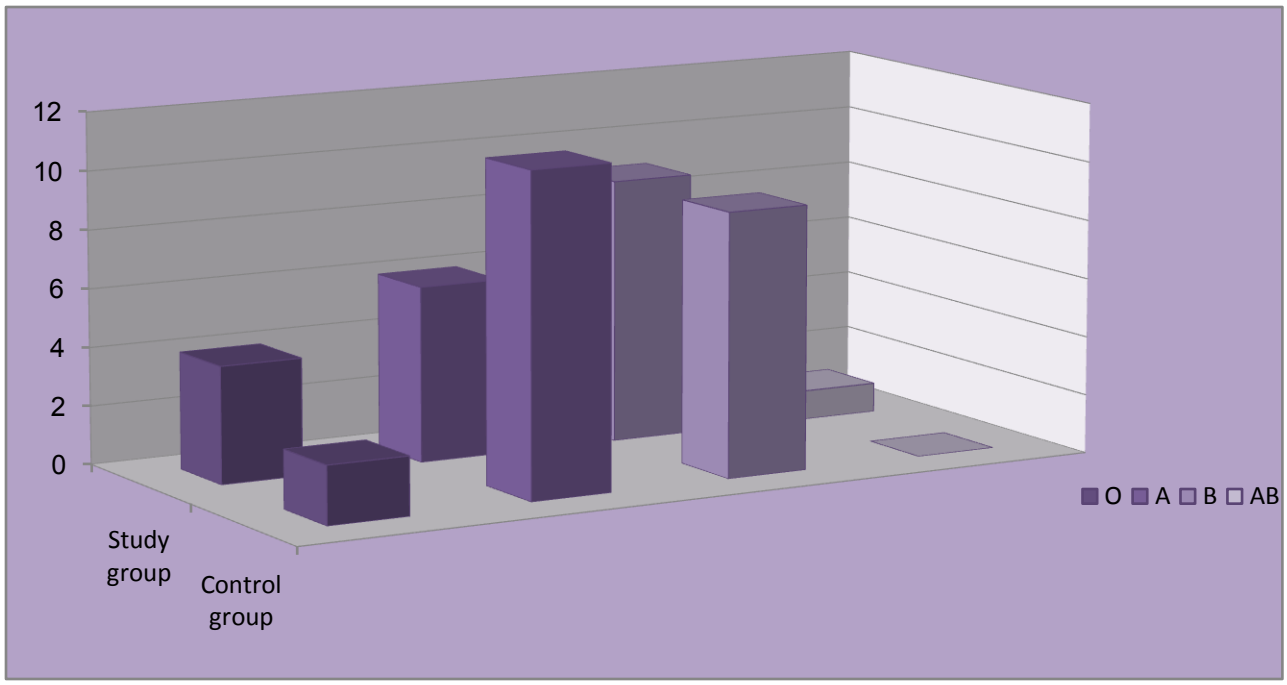
		Studygroup (20 neonates)	Control group (20 neonates)	P-value	significance
Feeding	**Breast**	20	20	0.99 (Chi^2)	NS
	Formula	0	0		

This table shows that there was no statistically significant difference between the two groups as regard feeding.

Table 4:- Comparison between the two groups regarding: ABO group.

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
ABO	**A**	6	11	0.91 (Chi^2)	NS
	B	9	9		
	AB	1	0		
	O	4	0		
Rh	**Positive**	19	20	0.5 (Chi^2)	NS
	Negative	1	0		

This table and the following figure show that there was no statistically significant difference between the two groups as regard blood group.

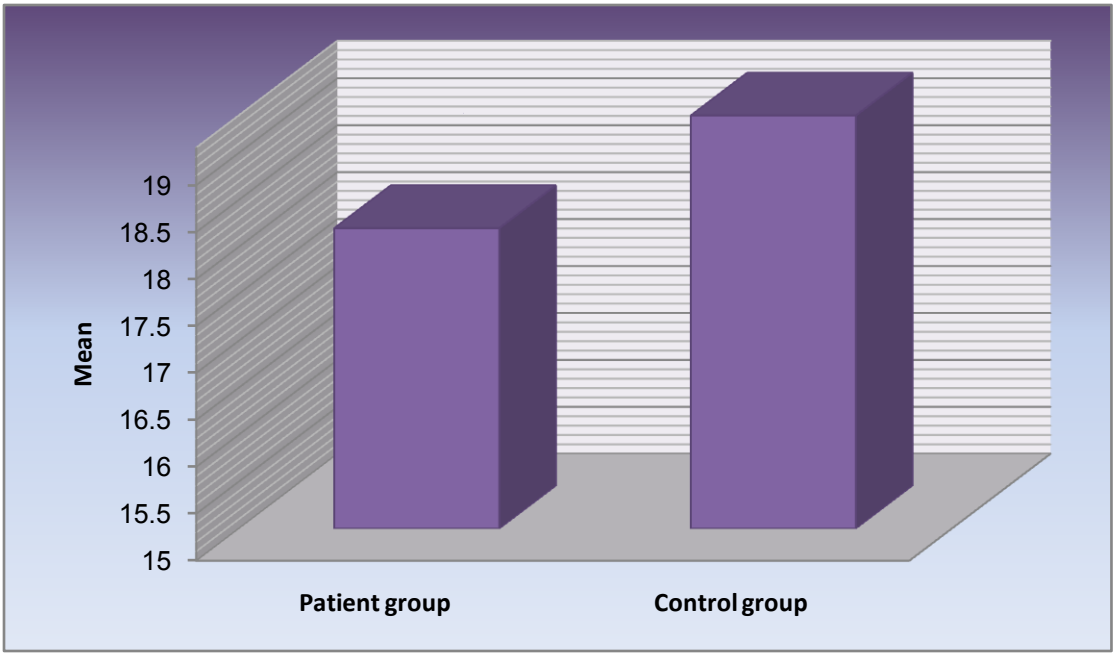


Blood group.

Table 5:- Comparison between the two groups regarding: bilirubin level at presentation.

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
Bilirubin at presentation	**Mean**	**18.2**	**19.4**	**0.39 (t-test)**	**NS**
	SD	**6.05**	**2.00**		

This table and the following figure show that there was no significant difference between the two groups as regard the level of bilirubin at presentation.

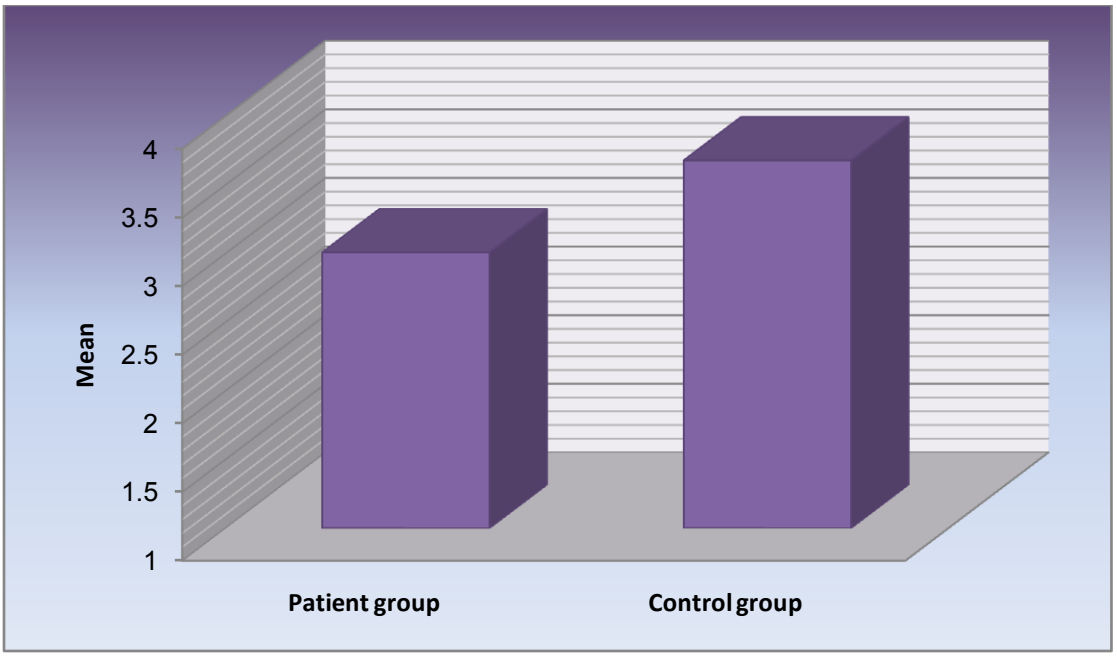


Bilirubin level at presentation.

Table 6:- comparison between the two groups regarding: the admission duration in days.

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
Admission Duration in days	**Mean**	**3.01**	**3.69**	**0.048 (t-test)**	**S**
	SD	**1.04**	**1.07**		

This table and the following figure show that there was significant difference between the two groups as regard the duration of stay in days. Regarding admission duration, neonates of the study group was admitted 3.01±1.04 days while the control group was admitted 3.69±1.07 days with significant statistical difference between the two groups (p=0.048) denoting that neonates treated with Fenofibrate and phototherapy had shorter admission duration in comparison to those treated with phototherapy alone.



Admission duration in days.

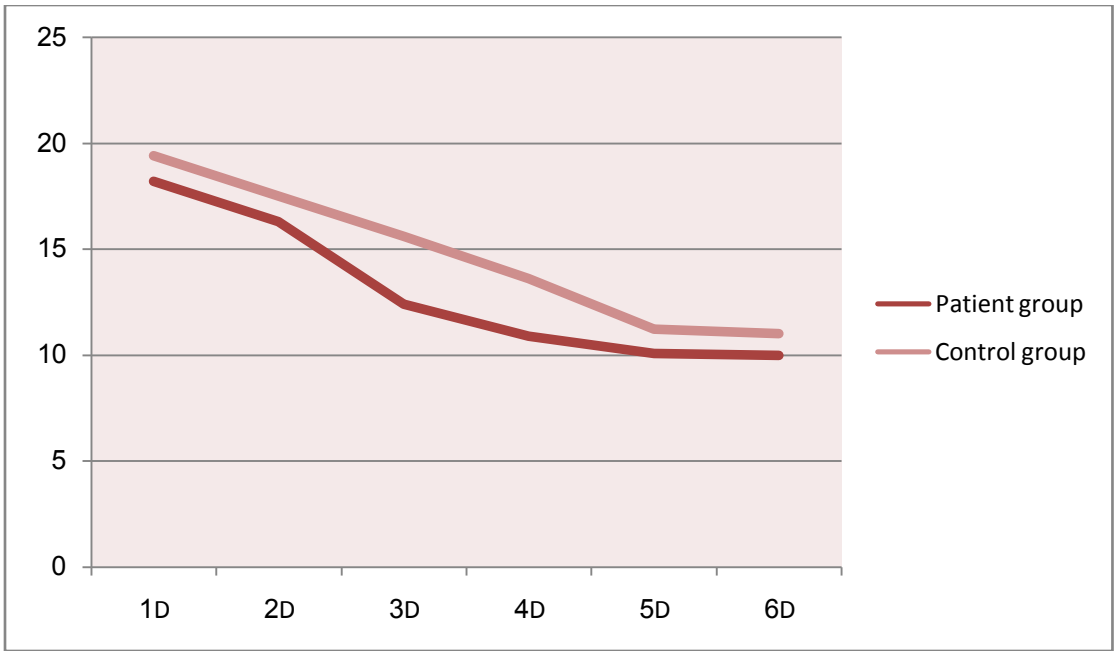
Table 7:- comparison between the two groups as regard: follow up of bilirubin level at day 2,3,4,5 and day 6 after admission.

Bilirubin level (mg/dl)		Study group (20 neonates)	Control group (20 neonates)	P-value (t-test)	Significance
At D2	Mean	16.29	17.49	0.3 (t-test)	NS
	SD	4.68	1.98		
At D3	Mean	12.36	15.59	0.004 (t-test)	HS
	SD	3.98	2.39		
At D4	Mean	10.93	13.57	0.012 (t-test)	S
	SD	3.82	3.11		
At D5	Mean	10.12	11.2	0.27 (t-test)	NS
	SD	3.12	3.04		
At D6	Mean	10.01	11.02	0.37 (t-test)	NS
	SD	3.9	3.08		

This table and the following figure show that there was significant difference between the two groups regarding the follow up levels of bilirubin at days 2,3,4,5 and 6 after admission. Regarding bilirubin level after 24 hours of admission it was 16.29±4.68 mg/dl in the study group which was lower than that of the control group which was 17.49±1.98 m/dl. Although the control group bilirubin level is higher, but there was no statistical difference between the two groups (p=0.3).

As regard to bilirubin level after48hours of therapy it was 12.36±3.98 mg/dl in study group which was markedly lower than bilirubin level of control group which was 15.59±2.39 mg/dl with highly statistical difference between the two groups (p=0.004) .As regard to bilirubin level after 72 hours of therapy it was 10.93±3.82 mg/dl in study group which was lower than that of the control group which was 13.57±3.11 mg/dl with significant statistical difference between the two groups (p=0.012).

As regard to bilirubin level after 96 hours of therapy it was 10.12±3.12 mg/dl in the study group which was lower than that of the control group which was 11.2±3.04 mg/dl with no statistical difference between the two groups (p=0.27).As regard to bilirubin level after 120 hours of therapy it was 10.01±3.9 mg/dl in the study group which was lower than that of the control group which was 11.02±3.08 mg/dl with no statistical difference between the two groups(p=0.37).

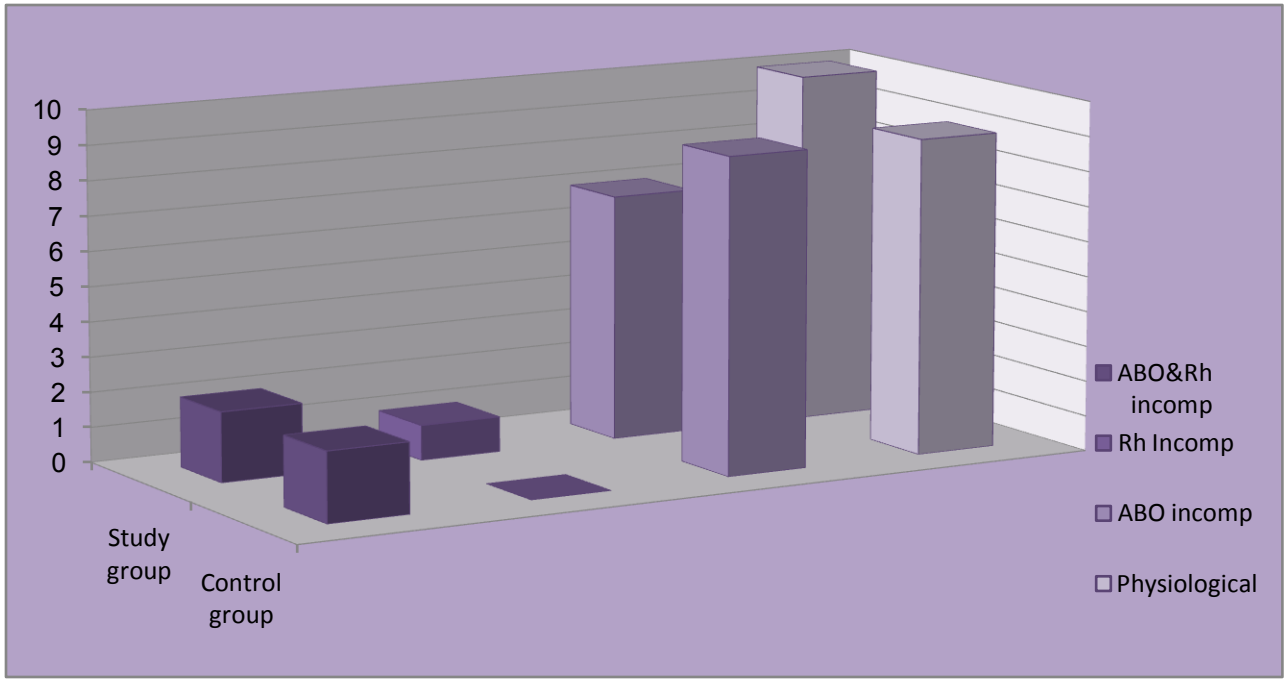


Follow-up of bilirubin level.

Table 8:- comparison of the two groups as regard: the etiology.

Etiology	**Study group (20 neonates)**	**Control group (20 neonates)**	**P-value**	**significance**
Rh incompatibility	1	0	0.73 (Chi^2)	NS
ABO incompatibility	7	9		
Physiological jaundice	10	9		
ABO and Rh incompatibility	2	2		

The following table and figure show that there was no significant difference between the two groups as regard the etiology.

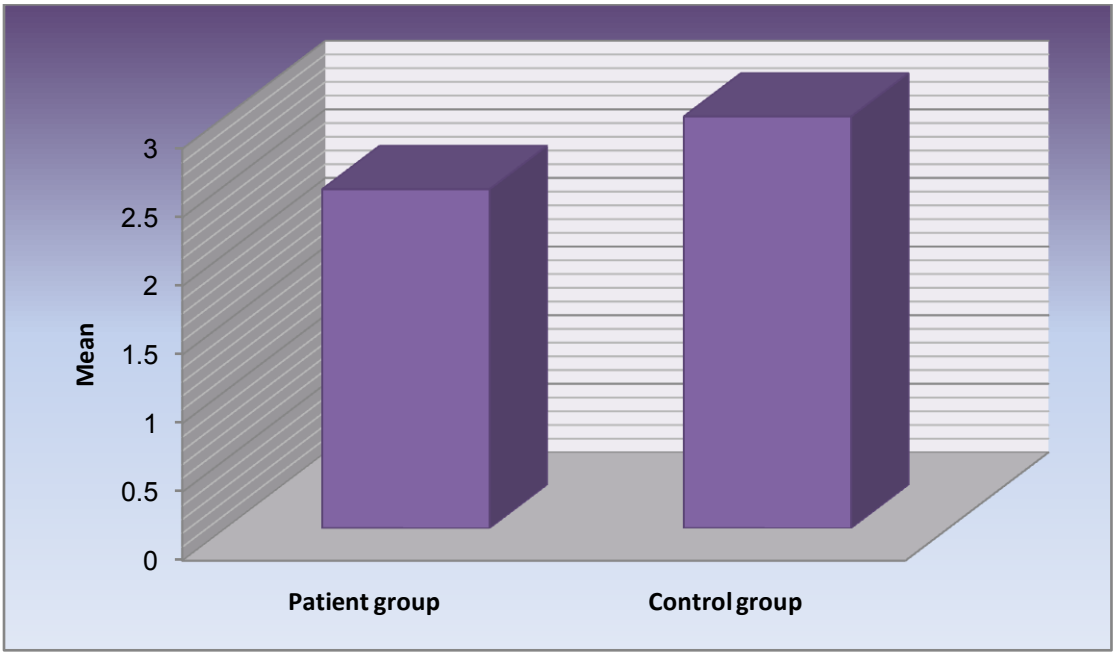


Etiology of the jaundice.

Table 9:- comparison of the two groups as regard: the age of onset

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
Age of onset	**Mean**	**2.47**	**3**	**0.12 (t-test)**	**NS**
	SD	**1.14**	**1.07**		

This table and the following figure show that there was no significant difference between the two groups as regard the age of onset.

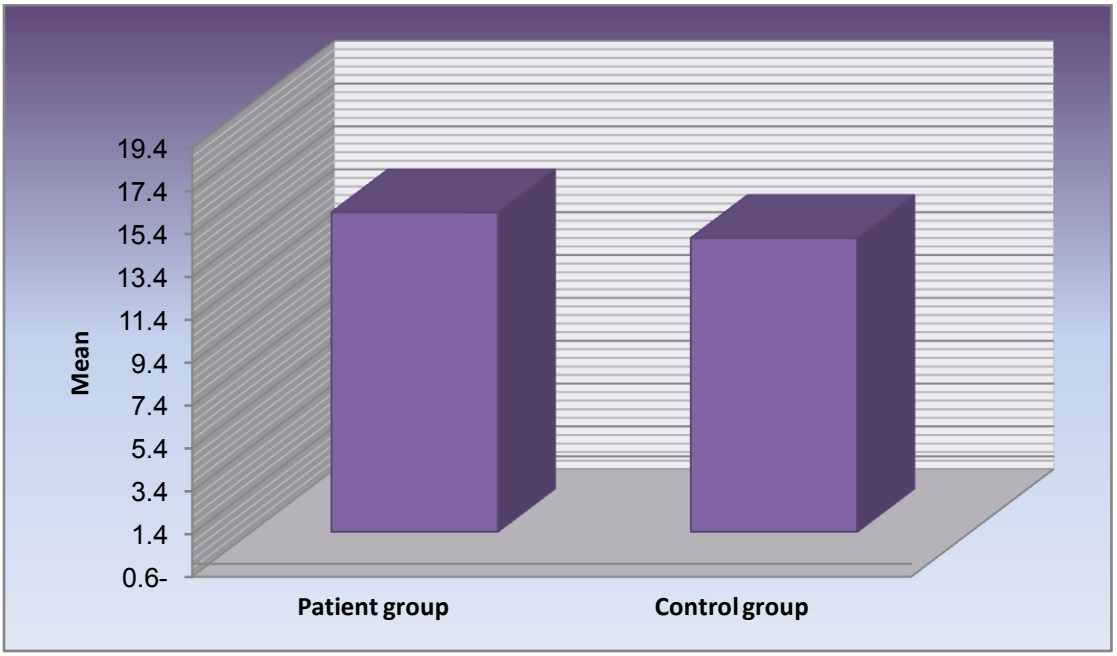


Age of onset.

Table 10:- comparison of the two groups as regard: hemoglobin level.

		Study group (20 neonates)	Control group (20 neonates)	P-value	significance
Hb	**Mean**	14.9	13.7	0.06 (t-test)	NS
	SD	2.14	2.02		

This table and the following figure show no significant difference between the two groups as regard hemoglobin level.



Hemoglobin level.

Discussion:-

Jaundice is a common sign in the neonatal period. Each year 60% of newborns become clinically jaundiced [(12)] and 80% in preterm neonates [(13)].

Fibrates have been used for several years as a hypolipidemic drug [(8)]. Its potency to induce bilirubin conjugation is many times more than phenobarbitone[(11)]. The effect of Clofibrate on uncomplicated hyperbilirubinemia was proposed in some studies [(14)].

Fenofibrate is now the most widely used fibrate in treating hyperlipidemia and has a comparatively much better safety profile than clofibrate[(9)].

The present study was designed to assess the effect of fenofibrate on uncomplicated hyperbilirubinemia of neonates during first week of life.Our study carried out on 40 neonates suffering from unconjugated hyperbilirubinemia selected from NICU of Benha children hospital (BENCH).

Study group (Group A) consisted of 9 male and 11 female neonates who will receive a single oral dose of fenofibrate (10 mg /kg) as adjuvant therapy in addition to phototherapy and control group (Group B) consisted of 11 male and 9 female neonates who will receive phototherapy alone.

When we measured bilirubin level at presentation, we found that the level of bilirubin of the study group was 18.2±6.05 mg/dl while of the control group was 19.4±2.00 mg/dl with no statistical difference between the two groups (p=0.39). These levels are not equal but close to bilirubin levels of patients in Kumar et al 2012 as this study group bilirubin mean was 19.25±0.3mg/dl while of the control group was 19.06±0.26 mg/dl (P=0.64). But our neonates bilirubin level was less than bilirubin level of neonates studied by Gowda et al 2014 as the bilirubin mean at admission was 19.8 mg/dl in the study group while 23.06 mg/dl in the control group (p=0.35).

Our results agrees with those obtained by ***Al Asy et al 2015*** who found that neonates treated with fenofibrate and phototherapy had 5.3 mean NICU stay which is shorter than NICU stay of neonates treated with phototherapy alone whose admission duration mean was 5.8 [(15)]. Also ***Kumar et al 2012*** commented that neonates treated with fenofibrate and phototherapy needed shorter period of admission than neonates treated with phototherapy alone (2days) compared to 3 days in neonates treated with phototherapy alone[(16)]. Our results do not agree with those obtained by ***Gowda et al 2014*** who found that fenofibrate had no added value in treatment of neonatal hyperbilirubinemia as regard to admission duration[(17)].

Regarding bilirubin level after 24 hours of admission it was 16.29±4.68 mg/dl in the study group which was lower than that of the control group which was 17.49±1.98 m/dl. Although the control group bilirubin level is higher, but there was no statistical difference between the two groups (p=0.3). This result is unique to our study in contrast to results obtained by ***Al Asy et al 2015 and Kumar et al 2012***. Both studies revealed that there was significant difference between the two groups regarding bilirubin after 24 hours of treatment[(15, 16)].

As regard to bilirubin level after 48 hours of therapy it was 12.36±3.98 mg/dl in study group which was markedly lower than bilirubin level of control group which was 15.59±2.39 mg/dl with highly statistical difference between the two groups (p=0.004). Our results agrees with those obtained by ***Al Asy et al 2015,Kumar et al 2012*** who found that study groups treated by fenofibrate and phototherapy had lower bilirubin level in comparison to neonates treated with phototherapy alone with significant statistical difference between the two groups[(15, 16)].

As regard to bilirubin level after 72 hours of therapy it was 10.93±3.82 mg/dl in study group which was lower than that of the control group which was 13.57±3.11 mg/dl with significant statistical difference between the two groups (p=0.012). Our results agrees with those obtained by ***Al Asy et al 2015*** who found that study group treated by fenofibrate and phototherapy had lower bilirubin level in comparison to neonates treated with phototherapy alone with significant statistical difference between the two groups[(15)].

As regard to bilirubin level after 96 hours of therapy it was 10.12±3.12 mg/dl in the study group which was lower than that of the control group which was 11.2±3.04 mg/dl with no statistical difference between the two groups (p=0.27).

As regard to bilirubin level after 120 hours of therapy it was 10.01±3.9 mg/dl in the study group which was lower than that of the control group which was 11.02±3.08 mg/dl with no statistical difference between the two groups(p=0.37).

No studies were found studying serum bilirubin after 72 hours as similar studies on effect of fenofibrate; neonates had shorter time of stay than our neonates.

Conclusion:-

In conclusion, our study revealed that use of fenofibrate in addition to phototherapy has additional benefit regarding time of stay and rate of bilirubin reduction in comparison to treatment with phototherapy alone.

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