IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access

Original Article

Phenobarbital Administration in Pregnancies Undergoing IUT Due to Rh Alloimmunization: A Single-Blinded Randomized Trial

Fatemeh Rahimi-Sharbaf[1], Sara Saeedi[1], Fatemeh Golshahi[1], Mahboobeh Shirazi[1], Behrokh Sahebdel[1], Mohamadreza Zarkesh[2], Mozhgan Sina[1], Arash Jafarieh[1,3], Sima Amini[1], Sania Saeedi[1], Parisa Najjari[1], Sare Ezzati[1], Golshan Manteghi[1]*

1. Maternal, Fetal and Neonatal Research Center, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Pediatrics, School of Medicine, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Anesthesiology, School of Medicine, Amir Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Red blood cell (RBC) alloimmunization and the ensuing hemolysis in hemolytic disease of the fetus and newborn (HDFN) result in significant prenatal and postnatal mortality and morbidity through severe fetal anemia and hyperbilirubinemia. Phenobarbital induces hepatic enzymes involved in bilirubin metabolism. This study aimed to assess the effect of maternal phenobarbital administration on reducing postnatal blood exchange transfusion and phototherapy.

Methods: This parallel-group, single-blind, randomized clinical trial with a control group was performed on 75 pregnant women undergoing intrauterine transfusion (IUT) for Rh alloimmunization. The trial is described as single-blinded (only the assessing pediatrician was blinded), and the control group received no placebo. Participants were randomly divided into intervention and control groups using the random allocation rule. The intervention group received 30 mg of phenobarbital three times daily from ten days prior to the estimated due date until actual delivery. The women were followed up until delivery to assess pregnancy outcomes, including incidence of icterus or need for postnatal phototherapy or exchange transfusion.

Results: The first total bilirubin in the intervention group was significantly ($p < 0.001$) lower than that in the control group (4.99 ± 1.39 vs. 10.52 ± 5.88). The study outcomes, including icterus ($p < 0.001$), need for phototherapy ($p < 0.001$), and exchange transfusion ($p < 0.001$), were significantly lower in the intervention group. Logistic regression analysis showed that phenobarbital prescription in the intervention group significantly ($p < 0.001$) decreased the need for exchange transfusion by 94%.

Conclusion: This trial indicates the efficacy of late-gestation maternal phenobarbital (as a safe and low-cost intervention) in reducing postnatal hyperbilirubinemia and the need for phototherapy and exchange transfusion in neonates with severe Rh alloimmunization treated by IUT.

Keywords: Exchange transfusion, Hemolytic disease of the fetus and newborn (HDFN), Hyperbilirubinemia, Phenobarbital, Phototherapy

Introduction

Hemolytic disease of the fetus and neonate following maternal alloimmunization to

* *Corresponding author*: Golshan Manteghi, Maternal, Fetal and Neonatal Research Center, Yas Complex Hospital, Tehran University of Medical Sciences, Tehran, Iran. Email: golshanmanteghi.zums@gmail.com

Please cite this paper as:
Rahimi-Sharbaf F, Saeedi S, Golshahi F, Shirazi M, Sahebdel B, Zarkesh M, Sina M, Jafarieh A, Sima Amini A, Saeedi S, Najjari P, Ezzati S, Manteghi G. Phenobarbital Administration in Pregnancies Undergoing IUT Due to Rh Alloimmunization: A Single-Blinded Randomized Trial. Iranian Journal of Neonatology. 2026 Oct: 17(4). DOI: 10.22038/ijn.2026.91234.2776

incompatible red blood cell (RBC) antigens is associated with severe fetal anemia, a rapid rise in serum bilirubin levels after birth, and subsequent bilirubin-induced neurotoxicity (1). The crossing of maternal immunoglobulins results in the destruction of fetal RBCs. If left unchecked, the condition may progress to fetal hydrops and perinatal death, as well as significant neurodevelopmental impairment in surviving fetuses (2, 3).

Although the advent of the therapeutic use of anti-D immunoglobulin to prevent RhD immunization has significantly reduced the incidence and severity of the disease since the 1970s, hemolytic disease of the fetus and neonate remains one of the major causes of fetal morbidity and mortality in developing countries (4). Despite the widespread availability of anti-D immunoglobulin, its suboptimal usage in developing countries may be related to a lack of awareness, restricted distribution in distant areas, and development costs. Previous studies have estimated a 2.5 million dose gap between the minimum threshold for doses of RhD immunization recommended by the World Health Organization, suggesting that 50% of women globally are not receiving proper immunization and are at increased risk of fetal and neonatal loss secondary to Rh disease.

Along with the use of RhD immunization, a number of other therapeutic interventions directed against the manifestations of the disease have also been utilized, which have resulted in a significant reduction in the continuing burden of the disease. Intrauterine blood transfusions (IUT) have been used since 1963 to treat moderate to severe fetal anemia by fetal placental blood administration, with indications for its use spanning several diseases and conditions (5). Survival rates of IUT for red cell alloimmunization in general have been reported to exceed 80% in specialized centers (6).

The use of exchange transfusion to treat severe hyperbilirubinemia caused by sustained hemolysis in the fetus is associated with mortality rates of less than 0.3% in term neonates and 10% in preterm infants (7, 8). Serious side effects include portal vein thrombosis, thrombocytopenia, necrotizing enterocolitis, and cardiac arrest, among others. As such, seeking alternative measures to reduce the need for further, potentially avoidable outcomes of transfusion may result in improved pregnancy outcomes (9).

Phenobarbital, the most widely prescribed antiepileptic drug worldwide for drug-resistant epilepsy, is also a potent inducer of several hepatic enzymes involved in bilirubin metabolism, including UDP-glucuronyl transferase (10). Accordingly, phenobarbital has been used antenatally and postnatally to prevent and treat neonatal jaundice through the upregulation of hepatic bilirubin metabolism in the recipients (11-14).

Although the effect of phenobarbital in hemolytic disease of the fetus has been assessed, its role in reducing the need for postnatal phototherapy and exchange transfusions in Rh disease specifically has not yet been evaluated. On the other hand, despite the existence of anti-D immunoglobulin, we have fetuses with anemia secondary to RBC alloimmunization in our country, and our expert perinatologists try to save them with IUT procedures and supportive treatment. Hence, this study aims to evaluate the effect of antenatal phenobarbital administration in pregnancies undergoing IUT for fetal anemia secondary to RBC alloimmunization.

Methods

This randomized clinical trial was conducted on 75 pregnant women with an indication for intrauterine transfusion (IUT) who were referred to our perinatology unit at Yas Hospital, affiliated with Tehran University of Medical Sciences, between May 2021 and December 2022.

This study was conducted in compliance with the Helsinki Declaration and approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.850) and the Iranian Registry of Clinical Trials (IRCT20201028049169N2). All participants signed informed consent forms and were aware of their anonymous, confidential study results and voluntary participation.

Inclusion criteria were pregnant women with a gestational age of 17 to 35 weeks, a positive antibody screen test, and diagnosed anemia due to RBC alloimmunization. The exclusion criteria were an anomaly in the fetal scan ultrasound and withdrawal from participation.

When the middle cerebral artery peak systolic velocity (MCA-PSV) value in the fetal Doppler ultrasound was ≥ 1.5 multiples of the median, or hydrops as a characteristic sign of fetal anemia was detected by ultrasonography, a blood sample was collected from the fetus to assess hemoglobin (Hb) concentration. Anemia was diagnosed if Hb was less than two standard deviations from the mean of Hb for the respective gestational age.

The IUT was conducted by an expert

Packed cell volume= (FPV (hematocrit target-fetal hematocrit))/(hematocrit donor blood)

Fetoplacental blood volume (FPV)=1.046 + (0.14x ultrasound estimated fetal weight (g))

Figure 1. The formula of calculating packed cell volume

perinatologist. Before IUT, the mother was prescribed amoxicillin 1000 mg and nifedipine 10 mg orally, and pethidine 50 mg and promethazine 25 mg intramuscularly. The injected blood was packed cells, blood group O, negative for Rh antigen and CMV, irradiated, and leukocyte-free with a hematocrit between 75% and 80%, which was exposed to gamma rays less than 6 hours before injection. The volume of packed cells was calculated based on the formula (Figure 1).

IUT was performed through the umbilical vein at the root of the placenta or in a free loop of the placenta. A spinal needle (20 G) was used to perform IUT. The target hematocrit proportion was 45–50%. Although in this study we only reported the data of the first IUT (the most reliable ones), further IUT procedures were performed if needed. The last IUT procedure was performed at 34–35 gestational weeks.

The random allocation rule was applied in the randomization process. First, 19 letters A and 19 letters B were written on special papers that were not marked inside. Then all of them were placed in a bag, and for each patient, after obtaining informed consent, a paper was removed randomly and without replacement, and based on the letter written on it, the desired intervention was performed for the patient. In addition, interventions A or B were determined by lot. This study was performed single-blind; only the pediatrician who assessed neonatal icterus and phototherapy indication was unaware of the treatment allocation.

In the intervention group, two 15-milligram tablets of phenobarbital (Marham Daru Pharmaceutical Co., Tehran, Iran) were prescribed every 8 hours for ten days (until delivery according to the forecasted delivery time by the perinatologist). No mothers received less or more than 10 days of phenobarbital, even if delivery did not occur after 10 days of phenobarbital initiation. In the control group, no additional measures were taken, and a placebo was not administered.

The women's age, body mass index (BMI), obstetric history, past medical history, blood group, antibody titer, and IUT information, as well as neonatal total, indirect, and maximum bilirubin levels, Hb, and reticulocyte count, were recorded. Bilirubin level was measured when blood sampling was performed for cell blood count checking in the delivery room. In the follow-up visits, as a routine, if there was any possibility of icterus, bilirubin levels were measured with blood sampling.

Indications for exchange transfusion and phototherapy in the study were adapted from the consensus guidelines for neonatal hyperbilirubinemia by Horn et al. (15). The primary outcomes of this study were icterus, need for phototherapy, and blood exchange in newborns. The other outcomes were Apgar at 1 minute, Apgar at 5 minutes, neonatal intubation, hospitalization, hearing deficiency, and newborn death in the first 24 hours after birth. Otoacoustic emission (OAE) and automatic auditory brainstem response (ABR) were applied as audiological screening tests for any hearing deficiencies.

Using the value reported in Thomas et al.'s study (11), study power of 80%, confidence interval of 95%, and formula for proportion comparison studies, the sample size in each group was estimated at 40 and totally was 80.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM, New York, USA). A p-value < 0.05 was considered statistically significant. First, the normality of data distribution was checked with the One-Sample Kolmogorov–Smirnov test. Since all had normal distribution, the Independent t-test was used to test mean differences in quantitative variables. The Chi-square test and Fisher's exact test were used to test differences in proportions. Logistic regression analysis was performed for multiple comparisons.

Ethical approval

This manuscript was performed in accordance with the Helsinki Declaration. All patient data were kept confidential. This study was approved by the Ethics Committee of Tehran University of Medical Sciences.

Results

In this study, 93 pregnant women were assessed for eligibility; of them, seven women were excluded due to fetal anomalies on ultrasound, and six women declined to participate. In total, 80 women were randomized to the intervention and control groups. During the study, 5 participants (4 in the phenobarbital group and 1

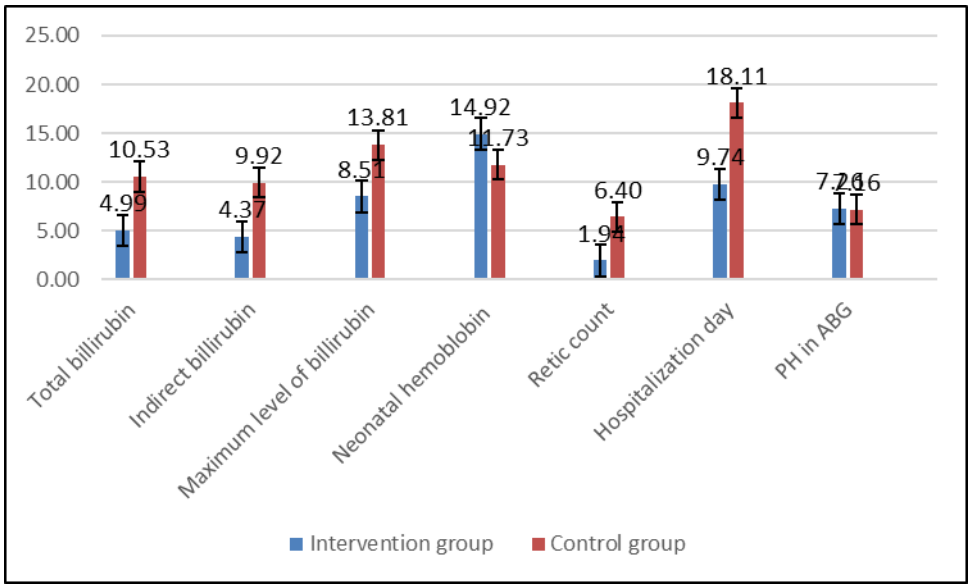

Figure 2 The offspring hemolysis indexes at time of delivery

in the control group) were lost to follow-up due to failure to return for delivery at our hospital. Finally, 75 women were analyzed on a per-protocol basis according to the intention-to-treat principle (Figure 2).

The mean age of pregnant women was 31.83 ± 5.41 years, ranging from 22 to 45 years. There were no significant differences regarding baseline characteristics, including maternal age, BMI, number of gravidity/live birth/IUFD/death, IUT in the previous child, maternal blood group, and antibody titer between the two study groups (Table 1).

The mean number of IUTs was 3.53 ± 1.69 in the intervention group, with no significant difference (p = 0.240) compared to the control group (4.08 ± 2.25). Maternal and fetal characteristics at the first IUT, such as number of needlings, placenta location, and signs of fetal anemia, did not differ significantly (p > 0.05) between the two groups and are illustrated in Table 2.

The type of delivery in 80% of cases was cesarean section, with a mean gestational age at termination of 36.49 ± 0.68 weeks, with no significant (p = 0.404) differences between the

Table 1 Baseline Characteristics of participants

Characteristics	Intervention group N=36	Control group N=39	P-value
Maternal history			
Age	31.00±4.54	32.59±6.06	0.201
Body mass index	27.72±3.68	28.53±4.44	0.399
Obstetrics history			
Gravidity	3.36±1.75	3.9±1.98	0.221
Live birth	1.26±1.03	1±0.77	0.231
IUFD	0.37±0.61	0.96±1.34	0.058
Death	0.62±1.04	0.76±1.1	0.612
IUT in previous pregnancy	4 (11.1)	7 (17.9)	0.351
Maternal blood group			
A-	13 (36.1)	11 (28.2)	0.191
B-	11 (30.5)	11 (28.2)	
AB-	4 (11.1)	12 (30.7)	
O-	8 (22.2)	5 (12.8)	
Antibody titer*			
1/32	2 (5.6)	2 (5.1)	0.107
1/64	3 (8.3)	3 (7.7)	
1/128	8 (22.2)	4 (10.3)	
1/256	1 (2.8)	11 (28.2)	
1/512	8 (16.6)	5 (12.8)	
1/1024	4 (11.1)	3 (7.7)	

*Missing data: 10 in intervention group and 11 in control group.

Table 2. Maternal and fetal characteristics at the first intrauterine transfusion

Characteristics		Intervention group N=36	Control group N=39	P-value
Number of needling		1.13±0.35	1.15±0.43	0.870
Placenta location	Anterior	14 (38.8)	24 (61.5)	0.083
	Posterior	21 (58.3)	14 (35.8)	
	Anterolateral	1 (2.7)	0	
Fetus anemia signs at first ultrasound examination	No sign	25 (69.4)	22 (56.4)	0.201
	Polyhydramnios	3 (8.3)	1 (2.5)	
	Ascites	7 (19.4)	11 (28.2)	
	Hydrops	1 (2.7)	5 (12.8)	

Table 3. The study outcomes of newborns

Characteristics	Intervention group N=36	Control group N=39	P-value
Apgar 1 min	8.63±1.19	7.71±1.97	0.018
Apgar 5 min	9.66±0.99	9.28±1.21	0.155
Hemoglobin	14.91±2.41	11.73±2.33	<0.001
Icterus	14 (38.8)	33 (84.6)	<0.001
Need to phototherapy	23 (63.8)	38 (97.4)	<0.001
Blood exchange	11 (30.5)	32 (82.0)	<0.001
Hearing deficiencies	0	2 (5.1) *	0.169

*One of them had positive family history of deafness.

two study groups in this regard. The most common cause of cesarean section was a previous cesarean section in both groups, with no significant differences (p = 0.105).

Most (64%) newborns were boys. The mean baby weight in the intervention group was 3149.71 ± 356.88 g, and this was 3015.00 ± 421.95 g in the control group, with no significant difference (p = 0.151).

The analysis of newborn hemolysis indexes at the time of delivery showed that the first total bilirubin in the intervention group was significantly (p < 0.001) lower than that in the control group (4.99 ± 1.39 vs. 10.52 ± 5.88). In the two study groups, the mean difference between the first total bilirubin and the maximum level was statistically (p = 0.770) similar; however, because of higher first total bilirubin levels in the control group, the maximum level was significantly (p < 0.001) higher in the control group (13.80 ± 5.29) than in the phenobarbital group (8.50 ± 2.56). Hemolysis indexes were significantly better in the offspring of the intervention group.

The study outcomes, including icterus (p < 0.001), need for phototherapy (p < 0.001), and exchange transfusion (p < 0.001), were significantly lower in the intervention group. Furthermore, hearing deficiencies were reported in 1 newborn of the control group (Table 3).

Logistic regression analysis showed that phenobarbital prescription in the intervention group significantly (p < 0.001) decreased the need for exchange transfusion by 94% (Table 4). No maternal side effects such as sedation, dizziness, etc. were reported during the study.

Table 4. Logistic regression for need to blood exchange in the newborns

Characteristics		Adjusted Odds Ratio	95% Confidence Interval	P-value
Maternal blood group	O	Ref.		
	A	7.275	1.196-44.249	0.031
	B	1.945	0.342-11.074	0.454
	AB	3.570	0.477-26.712	0.215
Phenobarbital prescription		0.061	0.016-0.238	<0.001
IUT number		1.080	0.797-1.462	0.620
Gestational week at delivery		1.904	0.784-4.628	0.155

Discussion

Despite normal neurodevelopmental outcomes in the majority of pregnancies (over 95%) with IUT, an increasing number of IUTs performed in each pregnancy is associated with long-term neurodevelopmental impairment, hydrops fetalis, and perinatal morbidity and mortality (16), which may be related to the hyperbilirubinemia caused by continued hemolysis. The incentive to seek additional treatment strategies for neonatal

hyperbilirubinemia in HDFN is partially fueled by the adverse effects of currently available treatment modalities. Whereas phototherapy is generally considered a safe procedure with only a minor increase in the risk of developing cancer, exchange transfusions, reserved for refractory cases, are accompanied by significant morbidity and mortality (8). The heterogenic mechanisms of hemolysis in HDFN caused by various antigens and different settings such as ABO incompatibility, Rh alloimmunization, and Kelly and Duffy system mismatched RBCs (17, 18) manifest as fetal hemolytic anemia that may progress to hyperbilirubinemia and kernicterus; as such, therapeutic agents modifying the pathways in bilirubin metabolism may be useful in the prevention of disease-related or iatrogenic insults in the newborn.

The cost-effectiveness and availability of phenobarbital have not only made it an enticing choice for the treatment of neonatal and childhood refractory seizures but also for its other potential uses, despite its significant tolerability issues in users (10). Phenobarbital can reduce adverse fetal effects by upregulating hepatic metabolism and enzyme maturation in the perinatal period, leading to increased hepatic uptake of bilirubin, enhanced glucuronide formation, and subsequent bilirubin excretion (14, 15, 19, 20). The results of this study demonstrated that antenatal use of phenobarbital results in a reduction in the number of fetal hydrops cases, neonatal jaundice, and the need for exchange transfusions and phototherapy. Furthermore, the results did not show a significant difference in the incidence of intubation, neonatal mortality, and hearing loss in the evaluated pregnancies.

A number of studies have investigated the effects of phenobarbital use in both mothers in the perinatal period and the newborn following delivery. For instance, phenobarbital administration in 100 mg daily doses in the weeks prior to delivery reduced the incidence of marked hyperbilirubinemia in cases with cumulative doses of greater than 1 gram in a study by Valaes et al. (21). Follow-up examination in a small subset of the children in the same study demonstrated better results in the Draw-A-Woman and Verbal Intelligence Tests in those with maternal administration of phenobarbital. Furthermore, there were no differences in those with maternal phenobarbital administration versus controls in terms of morbidity and mortality (21).

In another study on HDFN cases with serial IUTs, phenobarbital administration in doses similar to this study after the last IUT significantly lowered the incidence of exchange transfusion (22). Moreover, infants receiving 2.5 mg/kg phenobarbital every 12 hours for 3 days to treat hemolytic disease caused by ABO and/or Rh incompatibility had lower bilirubin levels and a reduced number of exchange transfusions (23).

However, in another study, postnatal administration of phenobarbital in doses of 10 mg/kg followed by 5 mg/kg in the newborn did not reduce the duration of phototherapy, incidence of rebound hyperbilirubinemia, or the need for exchange transfusion in a double-blind randomized setting (24).

The present study has several limitations, including the lack of using a placebo in the control group, being single-blinded, small sample size, and lack of long-term neurodevelopmental follow-up to assess the safety of antenatal phenobarbital exposure. Despite these limitations, our results are consistent with previous findings and suggest a clinical benefit. However, larger trials are needed to provide stronger evidence.

Conclusion

The results of this study suggest that the use of phenobarbital is associated with reduced morbidity in HDFN pregnancies caused by Rh alloimmunization. Our results compare favorably with other studies demonstrating the potent efficacy of phenobarbital in inducing bilirubin clearance in the newborn.

Acknowledgments

None.

Conflicts of interest

The identity of the participants has not been disclosed.

References

1. Tate DL, Samson JE, Mari G. Hemolytic disease of the fetus/neonate. InMaternal-Fetal Evidence Based Guidelines 2017 (491-500). CRC Press.
2. Basu S, Kaur R, Kaur G. Hemolytic disease of the fetus and newborn: Current trends and perspectives. Asian J Transfus Sci. 2011;5(1):3-7.
3. Hendrickson JE, Delaney M. Hemolytic disease of the fetus and newborn: Modern practice and future investigations. Transfus Med Rev. 2016;30(4):159-164.
4. Pegoraro V, Urbinati D, Visser GHA, Di Renzo GC, Zipursky A, Stotler BA, et al. Hemolytic disease of the fetus and newborn due to Rh(D) incompatibility: A preventable disease that still produces significant

morbidity and mortality in children. PLoS One. 2020;15(7):e0235807.
5. Oepkes D, Adama van Scheltema P. Intrauterine fetal transfusions in the management of fetal anemia and fetal thrombocytopenia. Semin Fetal Neonatal Med. 2007;12(6):432-438.
6. Deka D, Dadhwal V, Sharma AK, Shende U, Agarwal S, Agarwal R, et al. Perinatal survival and procedure-related complications after intrauterine transfusion for red cell alloimmunization. Arch Gynecol Obstet. 2016;293(5):967-973.
7. Chitty HE, Ziegler N, Savoia H, Doyle LW, Fox LM. Neonatal exchange transfusions in the 21st century: a single hospital study. J Paediatr Child Health. 2013;49(10):825-832.
8. Steiner LA, Bizzarro MJ, Ehrenkranz RA, Gallagher PG. A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. Pediatrics. 2007; 120(1):27-32.
9. Ree IMC, Smits-Wintjens VEHJ, van der Bom JG, van Klink JMM, Oepkes D, Lopriore E. Neonatal management and outcome in alloimmune hemolytic disease. Expert Rev Hematol. 2017;10(7):607-616.
10. Brodie MJ, Kwan P. Current position of phenobarbital in epilepsy and its future. Epilepsia. 2012;53 Suppl 8:40-46.
11. Trevett TN Jr, Dorman K, Lamvu G, Moise KJ Jr. Antenatal maternal administration of phenobarbital for the prevention of exchange transfusion in neonates with hemolytic disease of the fetus and newborn. Am J Obstet Gynecol. 2005;192(2):478-482.
12. Trolle D. Decrease of total serum-bilirubin concentration in newborn infants after phenobarbitone treatment. Lancet. 1968; 2(7570):705-708.
13. Levin GE, McMullin GP, Mobarak AN. Controlled trial of phenobarbitone in neonatal jaundice. Arch Dis Child. 1970;45(239):93-96.
14. Stern L, Khanna NN, Levy G, Yaffe SJ. Effect of phenobarbital on hyperbilirubinemia and glucuronide formation in newborns. Am J Dis Child. 1970;120(1):26-31.
15. Horn AR, Kirsten GF, Kroon SM, Henning PA, Möller G, Pieper C, et al. Phototherapy and exchange transfusion for neonatal hyperbilirubinaemia: neonatal academic hospitals' consensus guidelines for South African hospitals and primary care facilities. S Afr Med J. 2006;96(9):819-824.
16. Hudon L, Moise KJ Jr, Hegemier SE, Hill RM, Moise AA, Smith EO, Carpenter RJ. Long-term neurodevelopmental outcome after intrauterine transfusion for the treatment of fetal hemolytic disease. Am J Obstet Gynecol. 1998;179(4):858-863.
17. Kornstad, L. New cases of irregular blood group antibodies other than anti-D in pregnancy. Frequency and clinical significance. Acta Obstet Gynecol Scand, 1983;62(5):431-436.
18. Koelewijn JM, Vrijkotte TG, de Haas M, van der Schoot CE, Bonsel GJ. Risk factors for the presence of non-rhesus D red blood cell antibodies in pregnancy. BJOG. 2009;116(5):655-664. .
19. Kreek, M, Sleisenger M. Reduction of serum-unconjugated-bilirubin with phenobarbitone in adult congenital non-haemolytic unconjugated hyperbilirubinaemia. Lancet. 1968;292(7559): 73-78.
20. Rayburn W, Donn S, Piehl E, Compton A. Antenatal phenobarbital and bilirubin metabolism in the very low birth weight infant. Am J Obstet Gynecol. 1988;159(6):1491-1493.
21. Valaes T, Kipouros K, Petmezaki S, Solman M, Doxiadis SA. Effectiveness and safety of prenatal phenobarbital for the prevention of neonatal jaundice. Pediatr Res. 1980;14(8):947-952.
22. Trevett TN Jr, Dorman K, Lamvu G, Moise KJ Jr. Antenatal maternal administration of phenobarbital for the prevention of exchange transfusion in neonates with hemolytic disease of the fetus and newborn. Am J Obstet Gynecol. 2005;192(2):478-482.
23. Kaabneh MA, Salama GS, Shakkoury AG, Al-Abdallah IM, Alshamari A, Halaseh RA. Phenobarbital and phototherapy combination enhances decline of total serum bilirubin and may decrease the need for blood exchange transfusion in newborns with isoimmune hemolytic disease. Clin Med Insights Pediatr. 2015;9:67-72.
24. Venkatnarayan K, Sankar MJ, Agarwal R, Paul VK, Deorari AK. Phenobarbitone in Rh hemolytic disease of the newborn: a randomized double-blinded placebo-controlled trial. J Trop Pediatr. 2013;59(5):380-386.