Week 4: Neonatology

Neonatal Hematology & Bilirubin Metabolism

Friday, July 24 4:30-6:00 pm EDT

Moderators
Ronald Wong
Sripriya Sundararajan

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Note: Schedule subject to change based on presenter availability.
TITLE: Effect of Phlebotomy-Induced Anemia and Erythropoietin Treatment on Neonatal Mouse Microglial Activation

PRESENTER: Garima Singh

AUTHORS (LAST NAME, FIRST NAME): Singh, Garima; Georgieff, Michael K.; Gisslen, Tate

AUTHORS/INSTITUTIONS: T. Gisslen, University of Minnesota, Minneapolis, Minnesota, UNITED STATES; G. Singh, University Of Minnesota, Minneapolis, Minnesota, UNITED STATES; M.K. Georgieff, Pediatrics, University of Minnesota, Saint Paul, Minnesota, UNITED STATES;

CURRENT CATEGORY: Neonatology

SESSION TITLE: Neonatal Hematology & Bilirubin Metabolism | Neonatal Hematology & Bilirubin Metabolism

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:
Background: Premature infants are at risk for severe anemia particularly due to illness requiring frequent blood collection. Optimal treatment for phlebotomy-induced anemia (PIA) is unresolved, however recent evidence suggests that more severe anemia results in poorer neurodevelopmental outcomes. In our mouse model of severe PIA, we found significant neurodevelopmental deficits at young and adult ages and hippocampal upregulation of pro-inflammatory pathways at postnatal (P) day 14. Erythropoietin (EPO) treatment for PIA has shown improved neurodevelopmental outcomes in neonates and attenuated the inflammatory effects found in our PIA model. Microglia, the immune cells of the brain, likely have a role in modulating inflammation caused by PIA and attenuated by EPO.

Objective: To determine the effects of severe PIA and EPO treatment on microglia activation.

Design/Methods: Neonatal mice were phlebotomized from P3 to P13 via facial venipuncture. Blood was drawn twice daily at 5.25 uL/g until goal hematocrit (htc) of 18% was reached and once thereafter (3.5 µL/g) to maintain hct levels. A subset of these pups were treated with 5000 U/kg i.p. huEPO twice a day once goal hct was reached. In this pilot study, single cell suspension of brain tissue was obtained from non-bled control, 18% PIA, and 18%+EPO treated pups (n=2/group) at P14, and then microglia were analyzed by flow cytometry for markers of activation associated with pro-(TNFα, iNOS, MHCII) and anti-inflammatory (CD206) activity.

Results: PIA to hct of 18% caused an increased number of microglial cells compared to controls and was further increased by EPO treatment. TNFα and iNOS positive microglia were both increased in the 18% hct group compared to non-bled controls, but the effect attenuated when treated with EPO. CD206 positive microglia were decreased in the 18% hct group compared to non-bled controls, but the effect did not change after treatment with EPO. MHCII+ microglia were decreased by severe anemia, but further decreased by EPO treatment.

Conclusion(s): Severe anemia results in increased pro-inflammatory and decreased anti-inflammatory markers in activated microglia. Treatment with EPO attenuated the pro-inflammatory effect without affecting anti-inflammatory effect. Poor neurodevelopmental outcomes associated with PIA may be related to pro-inflammatory microglial activation; improved outcomes following EPO treatment may be due to its affect in attenuating inflammation.

(No Image Selected)
AUTHORS (LAST NAME, FIRST NAME): Brown, Nicole2; Rustogi, Deepika3; Yusuf, Kamran1

AUTHORS/INSTITUTIONS: K. Yusuf, Pediatrics, University of Calgary, Calgary, Alberta, CANADA; N. Brown, Memorial University of Newfoundland, St. John’s, Newfoundland, CANADA; D. Rustogi, Neonatal perinatal medicine, Cumming school of medicine, Calgary, Alberta, CANADA;

CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal Hematology & Bilirubin Metabolism

KEYWORDS: Small for gestation, Blood transfusion, Oxidative Stress.

SESSION TITLE: Neonatal Hematology & Bilirubin Metabolism | Neonatal Hematology & Bilirubin Metabolism

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Compared to appropriate for gestation (AGA) infants, small for gestation (SGA, defined as < 10 percentile birthweight for gestation and sex) infants are at higher risk of bronchopulmonary dysplasia and retinopathy of prematurity, diseases associated with oxidative stress. Although blood transfusions are associated with oxidative stress, it is unknown how SGA and AGA infants react to blood transfusion.

Objective: To determine oxidative stress in SGA and AGA infants after blood transfusion.

Design/Methods: A prospective observational study of infants <30 weeks gestation at birth who received blood transfusion. Exclusion criteria included any blood product administered within 3 weeks, sepsis, renal and liver disorders. Urine was collected pre-transfusion, and at 24-48 and 49-72-hours post-transfusion. ELISAs were used to measure thiobarbituric acid reactive substances (TBARS), 8-isoprostane and 8-hydroxy-2-deoxyguanosine (8-OHdG) as markers of lipid peroxidation and DNA oxidative injury. Levels were normalized to the urinary creatinine levels. Statistical analysis was performed using a two-way non-paired Student t test or Mann-Whitney test for continuous variables as appropriate and χ2 or Fisher's exact test for categorical variables. Linear regression was performed to adjust for confounders.

Results: Table 1 shows the demographic variables of the AGA (n=58) and SGA (n=14) groups. There were significantly higher levels of urinary 8-OHdG in SGA infants compared to AGA infants at the two post-transfusion time points. (Table 2). Oxidative stress was further increased in SGA infants at 49-72 hours whereas levels were declining in AGA infants (Table 2). Using a general linear model adjusted for gestational age, birthweight, post-natal age in days, sex, antenatal steroids and mode of delivery the differences in 8-OHdG remained significant, P=.009 at 24-48 and P=.04 at 49-72 hours.

Conclusion(s): SGA infants have increased oxidative stress after blood transfusions which may contribute to the higher incidence of BPD and ROP in this population. Our data suggests that transfusing blood to SGA infants should be done judiciously.

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<th>Table 1: Demographic characteristics of study participants</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>Birth age (weeks)</td>
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<td>Gestational age (weeks)</td>
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<td>Birthweight (kg)</td>
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<td>Neonatal pneumonia</td>
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<td>Maternal history of diabetes</td>
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<td>History of blood transfusion</td>
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<td>Antenatal steroids</td>
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<th>Table 2: Oxidative stress markers in urine normalized to creatinine. Values are expressed in mol/L/gCr and compared to parameters to prevent preterm complications.</th>
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<td>Time (pre-transfusion and post-transfusion)</td>
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<td>Pre-transfusion</td>
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<td>First day post-transfusion</td>
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<td>Second day post-transfusion</td>
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IMAGE CAPTION:
CONTROL ID: 3374904

TITLE: PRETERM NEONATES BENEFIT FROM LOW PROPHYLACTIC PLATELET TRANSFUSION THRESHOLD DESPITE VARYING RISK OF BLEEDING OR DEATH

PRESENTER: Susanna Frederika Fustolo-Gunnink

AUTHORS (LAST NAME, FIRST NAME): Fustolo-Gunnink, Susanna F.¹

AUTHORS/INSTITUTIONS: S.F. Fustolo-Gunnink, Clinical Transfusion Research, Sanquin Blood Supply Foundation, Amsterdam, Noord Holland, NETHERLANDS;

CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal Hematology & Bilirubin Metabolism

KEYWORDS: platelet transfusions, major bleeding, PlaNeT-2 trial.

SESSION TITLE: Neonatal Hematology & Bilirubin Metabolism | Neonatal Hematology & Bilirubin Metabolism

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: The Platelets for Neonatal Thrombocytopenia (PlaNeT-2) trial reported an overall unexpected benefit of a prophylactic platelet transfusion threshold of 25x10^9/L compared to 50x10^9/L for major bleeding and/or mortality in preterm neonates (7% absolute risk reduction). However, some neonates in the trial may have experienced little benefit or even harm from the 25x10^9/L threshold.

Objective: We aimed to assess this heterogeneity of treatment effect in the PlaNet-2 trial, in order to investigate whether all preterm neonates benefit from the low threshold.

Design/Methods: We developed a multivariable logistic regression model in the PlaNet-2 data to predict baseline risk of major bleeding and/or mortality for all 653 neonates. We then ranked the neonates based on their predicted baseline risk and categorized them into four risk quartiles. Within these quartiles we assessed the absolute risk difference between the 50x10^9/L and 25x10^9/L threshold group.

Results: A total of 146 neonates died or developed major bleeding. The internally validated C-statistic was 0.63 (95% confidence interval 0.58–0.68). The 25x10^9/L threshold was associated with absolute risk reduction in all risk groups, varying from 4.9% in the lowest to 12.3% in the highest risk group.

Conclusion(s): These results suggest that a 25x10^9/L prophylactic platelet count threshold can be adopted in all preterm neonates, irrespective of predicted baseline outcome risk. Future studies are needed to improve the predictive accuracy of the baseline risk model.
Absolute risk difference (ARD) between a high (50x10^9/L) and low (25x10^9/L) threshold for prophylactic platelet transfusion thresholds in preterm neonates with respect to major bleeding and/or mortality within 28 days after randomization. Event rates (panel A), odds ratios (panel B) and absolute risk differences (panel C) are presented for all four risk categories, vertical lines represent 95% confidence intervals, horizontal lines represent overall trial results. A negative absolute risk reduction represents the risk decrease for a low prophylactic platelet transfusion threshold as compared to a high threshold.

**IMAGE CAPTION:**
Absolute risk difference (ARD) between a high (50x10^9/L) and low (25x10^9/L) threshold for prophylactic platelet transfusion thresholds in preterm neonates with respect to major bleeding and/or mortality within 28 days after randomization. Event rates (panel A), odds ratios (panel B) and absolute risk differences (panel C) are presented for all four risk categories, vertical lines represent 95% confidence intervals, horizontal lines represent overall trial results. A negative absolute risk reduction represents the risk decrease for a low prophylactic platelet transfusion threshold as compared to a high threshold.

**CONTROL ID:** 3381796

**TITLE:** Ex vivo effect of bilirubin on signaling and trafficking of L1 cell adhesion molecule in cerebellum of Gunn rat pups.

**PRESENTER:** Spencer T. Kitchen

**AUTHORS (LAST NAME, FIRST NAME):** Kitchen, Spencer T.; Tang, Ningfeng; Tang, Ningfeng; Waddell, Jaylyn; Bearer, Cynthia F.

**AUTHORS/INSTITUTIONS:** S.T. Kitchen, C.F. Bearer, Pediatrics, Case Western Reserve University, Cleveland, Ohio, UNITED STATES; N. Tang, J. Waddell, University of Maryland School of Medicine, Baltimore, Maryland, UNITED STATES; N. Tang, Johns Hopkins University, Baltimore, Maryland, UNITED STATES; Neonatology
Background: Hyperbilirubinemia in preterm babies occurs with alarming frequency, yet the mechanism of cerebellar neurotoxicity is still unclear. Lipid rafts (LR) are microdomains of the plasma membrane critical for cell signaling and hence the development of the cerebellum. Our hypothesis is that free bilirubin (Bf) disrupts LR leading to cerebellar injury. The L1 cell adhesion molecule (L1) is a LR-dependent protein critically important for development of the cerebellum and serves as a reporter for LR function. We previously discovered that elevated Bf disrupts LR function in vitro, and choline, a precursor to LR, ameliorates these effects. L1 is tyrosine phosphorylated (PY-L1), traffics through LR and is dephosphorylated on a specific tyrosine (Y1176-L1) in an endocytic recycling pathway. Disruption of LR blocks this pathway and can be determined by the phosphorylation state and LR distribution of L1. We predict that Bf will alter the phosphorylation state and distribution of L1 in LR of the cerebellum, and that choline will reduce these effects. We will use the Gunn rat which lacks glucuronyl transferase, to model preterm hyperbilirubinemia to test these predictions.

Objective: Determine if hyperbilirubinemia in a preterm model alters the phosphorylation state and lipid raft distribution of L1 and to determine if choline ameliorates these effects.

Design/Methods: Gunn rat dams were placed on choline deficient diets on gestational day 2 to mimic choline status of pregnant women. On postnatal day (P) 2, heterozygous (Nj) and homozygous (jj) pups were randomized to 4 treatment groups: saline (S) or choline (C) from P2 - 5 subcutaneous injections and S or sulfamethoxadine (SD) intraperitoneal (ip) injection on P5: SS, CS, SSD, CSD. SD displaces Bf from albumin and allows Bf to enter the brain. We have shown behavioral abnormalities at P30 of jj pups treated with SD on P5. Pups were sacrificed 4 h after ip injections and cerebella analyzed for L1 phosphorylation state and LR distribution. Due to constraint of the ultracentrifuge, 6 of the possible 8 groups are shown (Fig. 1-4). Results were analyzed by ANOVA with Tukey pairwise comparison.

Results: Using Nj SS as the control, only jj SSD had significantly altered phosphorylation state and LR distribution of L1.

Conclusion(s): L1 was not affected by any treatment in Nj rats. jj pups treated with SD had significantly altered L1 phosphorylation and LR distribution indicating a disruption of LR. Choline pretreatment appeared to prevent the effects of SD.
Fig. 2. Hyperbilirubinemia alters L1 phosphorylation state and choline ameliorates the changes. Mean +/- SEM of relative densitometric units showing for 1) PY-L1 significant differences in tyrosine phosphorylation of L1 between jj SSD and both Nj CSD and jj CS (ANOVA, p=0.0068, Tukey, p<0.05 and p<0.01 respectively) (light gray bars); 2) Y1176-L1 significant differences between jj SSD and all other conditions (ANOVA, p=0.0007; Tukey, p<0.01)(dark gray bars)(n=3)

Fig. 3. Hyperbilirubinemia increase the percent of L1 in lipid rafts (LR). Lipid rafts (LR) and non-lipid rafts (N) isolated and pooled, then equivolume immunoblotted for L1. Representative blot shown.

Fig. 4. Hyperbilirubinemia increases L1 in lipid rafts and choline ameliorates this effect. Immunoblots scanned and plotted as relative densitometric units, shown as mean +/- SEM. jj SSD significantly increases the percent of L1 in lipid rafts (%L1 in LR) compared to all other treatments (ANOVA p=0.0087, Tukey p<0.05 jj SSD versus any other treatment)(n=3)

**IMAGE CAPTION:**
Fig. 1 Effects of hyperbilirubinemia on L1 phosphorylation state. Nj - heterozygote; jj - homozygote. S-saline P2-5; C-choline P2-5; S- saline P5; SSD-sulfadimethoxine P5. (A) Representative blot for PY-L1. (B) Representative blot for Y1176-L1

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CONTROL ID: 3383286

TITLE: Evaluation of a near-patient diagnostic platform for G6PD
PRESENTER: Charles Micheal Cotten

AUTHORS (LAST NAME, FIRST NAME): Cotten, Charles M 1; Kicklighter, Stephen D 2; Nock, Mary 3; Fisher, Kimberly A. 1; Sista, Ramakrishna 4; Roberts, Christopher 4; Pamula, Vamsee 4

AUTHORS/INSTITUTIONS: C.M. Cotten, K.A. Fisher, Pediatrics, Duke University, Durham, North Carolina, UNITED STATES; S.D. Kicklighter, WakeMed Medical Center, Raleigh, North Carolina, UNITED STATES; M. Nock, Pediatrics, Neonatology, Rainbow Babies and Children's Hospital, Cleveland, Ohio, UNITED STATES; R. Sista, C. Roberts, V. Pamula, Baebies, Durham, North Carolina, UNITED STATES;

CURRENT CATEGORY: Neonatology
CURRENT SUBCATEGORY: Neonatal Hematology & Bilirubin Metabolism
KEYWORDS: G6PD deficiency, screening, hyperbilirubinemia.
SESSION TITLE: Neonatal Hematology & Bilirubin Metabolism | Neonatal Hematology & Bilirubin Metabolism
SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited enzymopathy which can cause antenatal, perinatal and later disease. Neonates with undetected G6PD deficiency are at risk for extreme hyperbilirubinemia. The American Academy of Pediatrics recommends G6PD testing for jaundiced newborns under phototherapy whose family history or ethnic or geographic origin suggest likelihood of G6PD deficiency, or whose response to phototherapy is poor. Turn-around time (TAT) for send-out G6PD testing is 2-3 days and requires ≥ 1mL whole blood. Manual, qualitative assays are used for neonatal testing in some centers. An automated, quantitative, low blood volume platform for G6PD testing could facilitate G6PD deficiency detection.

Objective: Evaluate a G6PD testing platform that uses 50 µL whole blood samples with TAT of 15 minutes.

Design/Methods: Three evaluations were done: #1) new platform compared with current standard; #2) finger stick compared with venipuncture samples on the new platform, and #3) precision tests of samples across 3 clinical sites on the new platform. For #1 and #2, 50 adults provided venipuncture (Li Heparin 2mL BD Vacutainer®) and finger stick capillary (Li Heparin Sarstedt 100μL Microvette®) whole blood samples. To cover the testing range in #1, 1 affected venous sample (~3 U/gHb) from BioIVT (Westbury, NY) was used to make 10 contrived samples. In #1, duplicate samples were run on the gold standard Pointe Scientific (PS, Canton, MI) G6PD assay with hemoglobin concentration normalization on the Roche Cobas Mira Plus (Roche Diagnostics, Switzerland) and 50 µL samples were run on the Baebies FINDER G6PD assay (R44HD072853). For #2, 50 µL venipuncture and capillary samples were compared on FINDER. For #3, precision was assessed using venipuncture blood procured from BioIVT, sent to 3 sites every day for 3 days, and tested on FINDER (n=5 per day) by multiple users.

Results: Time to result on FINDER was ~15 minutes and ~1h on standard. For evaluation #1, R-value = 0.841 between FINDER and standard (Fig 1). For #2, venipuncture and capillary samples' FINDER values had a mean difference of 5.6% (Fig 2), which is within the reproducibility range of 6.2% between-sites variation observed in evaluation #3.

Conclusion(s): Using 50 µL samples, FINDER G6PD results were available within 15 minutes, correlated well with current methodology, had similar results for capillary and venous samples, and between-site and user results were similar. These capabilities open the possibility for pre-discharge G6PD testing.
Background: The Bhutani Total Serum Bilirubin (TSB) nomogram has, since 1999, served as a valuable guide for managing neonatal hyperbilirubinemia. However, based on only 2,840 neonates, it was not large enough for subgroup risk-analysis for gestational age, gender, race and other risk factors.

Objective: To gather multi-hospital data on enough neonates to create a new bilirubin nomogram and conduct rigorous subgroup analyses to evaluate risk-factor associations with gestational age, gender, and race.

Design/Methods: We created a new total serum bilirubin (TSB) nomogram based on 15 years of data from the Intermountain Healthcare hospitals universal bilirubin screening program (54.3% of Utah livebirths). Using these data we performed various subgroup risk-analyses.
Results: We collected the initial TSB value drawn on 421,267 neonates, of which 397, 395 qualified for inclusion in the dataset from which an hour-specific bilirubin nomogram was constructed. New information included; 1) robust data in the first 12 hours after birth (which was not included in the 1999 nomogram), 2) general agreement with the 1999 nomogram for values in the first 60 hours, but higher 75th and 95th percentile TSB values thereafter in the new nomogram, 3) no difference in TSB between male and female neonates, 4) higher TSB values, after the first 36 hours, among earlier gestation neonates (35 0/7 - 36 6/7 weeks vs. ≥37 weeks, p<0.0001), 5) lower TSB values in neonates of Black race (p<0.0001).

Conclusion(s): We constructed a new neonatal hour-specific bilirubin nomogram using the methodology of the Bhutani nomogram but including about 140 times the number of subjects in the 1999 version. We found higher TSB values in younger gestation neonates, no difference by sex, and lower values among neonates of Black race.

The 2020 Utah Bilirubin Nomogram.

IMAGE CAPTION:
The 2020 Utah Bilirubin Nomogram.

CONTROL ID: 3380892
TITLE: Fenofibrate as an adjuvant to phototherapy in pathological unconjugated hyperbilirubinemia in neonates: a randomized control trial.
PRESENTER: Islam Nour
AUTHORS (LAST NAME, FIRST NAME): Shabaan, Abd Elaziz A.1; Amer, Sahar2; Nour, Islam1; Hafez, Mona1; Awad, Mohammad H.1
AUTHORS/INSTITUTIONS: A.A. Shabaan, I. Nour, M. Hafez, M.H. Awad, Pediatrics, Mansoura University, Toronto, north York, Ontario, CANADA; S. Amer, insurance hospital, Dakahlyia, EGYPT
CURRENT CATEGORY: Neonatology
CURRENT SUBCATEGORY: Neonatal Hematology & Bilirubin Metabolism
KEYWORDS:
SESSION TITLE: Neonatal Hematology & Bilirubin Metabolism | Neonatal Hematology & Bilirubin Metabolism
SESSION TYPE: Webinar|Platform
ABSTRACT BODY:
Background: Despite phototherapy use, many newborn infants remain in need of other lines of therapy such as intravenous immunoglobulins and exchange transfusions.

Objective: To assess the efficacy and the safety of adding fenofibrate to phototherapy for treatment of pathological jaundice in neonates.

Design/Methods: Study design: We conducted a double blinded randomized control pilot study in the neonatal intensive care unit of Mansoura University children hospital from June 2016 to December 2018.
Methodology: full-term infants with pathological unconjugated hyperbilirubinemia who were candidate for phototherapy
according to American academy of pediatrics guidelines were included. Preterm infants and full-term infants with (congenital malformations, small for gestational age; candidate for exchange transfusion) were excluded. Fenofibrate was given in dose of 10 mg /kg /day orally once daily for one day or once daily for two days in addition to phototherapy versus, placebo with phototherapy. **Primary outcome:** Decline in total serum bilirubin values after 12, 24, 36, 48 hours from intervention. **Secondary outcomes:** Total duration of treatment, number of exchange transfusions, need for intravenous immunoglobulin, exclusive breast-feeding on discharge, mortality on discharge, assessment of serum triglycerides level.

**Results:** 180 full-term infants were randomly assigned either to Group I, 60 infants received phototherapy with single oral dose of fenofibrate or Group II, 60 infants received phototherapy with two oral doses of fenofibrate, and Group III, 60 infants received phototherapy alone. All groups were matched regarding baseline and laboratory characteristics. Fenofibrate administration results in significant reduction of bilirubin levels at 36 ,48 hours and on discharge (p: 0.002, 0.002, 0.003) respectively. Infants in group 2 showed significant reduction of bilirubin levels at 36 ,48 hours and on discharge compared to group 3 (p: 0.006, 0.01, 0.003) respectively. Fenofibrate administration was associated with significant shorter duration of phototherapy (p 0.0001), shorter hospital stay(p: 0.0001), higher frequency of exclusive breast feeding (p: 0.001) compared to phototherapy alone.

**Conclusion(s):** Fenofibrate as an adjuvant to phototherapy is well tolerated and associated with significant reduction of serum bilirubin level especially with double dosage, shorter duration of phototherapy, shorter hospital stay and higher frequency of exclusive breast feeding, without significant adverse effects.