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The Effect Of Packed RBCs Transfusion On Development Of Parentral Nutrition Associated Liver Disease In Neonates At Zagzig University.

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ABSTRACT

Anemia is a common problem in neonates specially preterm ones which is multifactorial so when they are admitted to NICU they will receive packed RBCs. Parenteral nutrition associated liver disease(PNALD) defined as direct bilirubin >2mg/dl is a common problem of prolonged administration of total parenteral nutrition more than 2 weeks. This study detects the rule of packed RBCs transfusion on the development of (PNALD) in neonates. This cohort study was conducted on 54 neonates who received TPN more than 2 weeks divided into 3 groups: 12 in non-transfusion group (received no packed RBCs), 23 in low transfusion group (received less than 70 ml of packed RBCs), 19 in high transfusion group (received more than 70 ml of packed RBCs) and we assessed the development of PNALD (direct bilirubin >2mg/dl) in each group.The results of our study showed that direct bilirubin level was statistically significantly higher in neonates received more than 70 ml packed RBCs compared with those received no packed RBCs. Similarly, direct bilirubin was statistically significantly higher in neonates received more than 70ml packed RBCs compared with those received less than 70 ml packed RBCs. So we conclude that packed RBCs transfusion increase the incidence of PNALD in neonates

Keywords: PNALD, packed RBCs, Total parenteral nutrition , neonates .

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INTRODUCTION

Numerous sick neonates can't get satisfactory nutrition by means of the GI tract and in this way,they require parenteral nourishment particularly preterms.[1] In some neonates , GIT action is satisfactory to permit few feedings. In others, the GI tract may not work for a considerable length of time up to months (e.g., necrotizing enterocolitis, entrail inconsistencies), so the neonate gets all his nutritional requirements parenterally (Total Parenteral Nutrition, TPN) to keep up their caloric needs[2].

PNALD is a common complication in neonates getting TPN and means increase in serum conjugated bilirubin >2 mg/dl (34.2 micromole/L) ,elevated alkaline phosphatase, aminotransferases ,and gamma glutamyl transferase after receiving parenteral nutrition for 2 weeks to 2 months or more and after exclusion of different reasons for liver illnesses, as cystic fibrosis, infectious hepatitis and inborn errors of metabolism.

PNALD includes:

- cholestasis
- steatosis
- steatohepatitis
- fibrosis
- cirrhosis
- biliary sludge , gall stones
- cholecystitis [3]

Anemia is a common issue in neonates and the main reasons for it in them are:

- nutritional deficiencies and lack of stores .
- iatrogenic blood loss
- immaturity of the hematopoietic system, shorter RBC life span and that the preterm neonates produce less erythropoietin .
- blood loss because of medical conditions such as sepsis, hemolysis, bleeding disorders and surgery .[4]

And according to these reasons most of neonates admitted to NICU require packed RBCs transfusion in different amounts .We aimed to evaluate packed RBCs transfusion as a risk factor for PNALD.

SUBJECTS AND METHODS

This study was a cohort study that was carried out at neonatal intensive care unit of Zagazig University Hospitals and was conducted on 54 preterm and full term neonates receiving total parenteral nutrition more than 2 weeks.

Inclusion criteria:-This study included neonates who received TPN more than 2weeks and we assessed the development of PNALD defined as direct bilirubin> 2 mg /dl and amount of packed RBCs they received and according to this they were divided into 3 groups:

1. Non –transfusion group: including neonates received TPN more than two weeks without packed RBCs transfusion.
2. Low transfusion group:-including neonates received packed RBCs < 70 ml and TPN more than 2weeks.
3. High transfusion group:-including neonates received packed RBCs >70 ml and TPN more than two weeks.

The cut point 70 ml was defined by the median volume of packed RBCs transfused in this cohort study neonates. Then we assessed the relation between the amount of packed RBCs transfused and the development of PNALD defined as direct bilirubin >2 mg/dl

Exclusion criteria: neonates with cholestasis due to other causes as cystic fibrosis , inborn errors of metabolism (galactosemia , tyrosinemia) , alpha 1 anti-Trypsin deficiency , biliary artesian , choledochal cyst, congenital infections and viral hepatitis.

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Methods:
All patients will be subjected to the following:

A- Full history taking including: gestational age, birth weight, sex, maternal risk factors, mode of delivery and need for resuscitation.
B- General examination including: Apgar score, vital signs (HR, BL.pressure, Respiratory rate).
C- Mode of respiratory support and oxygen delivery.
D- Calculation the amount of packed RBCs transfusion.
E- Duration of receiving parenterals nutrition.
F- Investigations:

Complete blood picture, Total and direct bilirubin level, Alanine aminotransferase (ALT). Aspartate aminotransferase (AST), C – reactive protein, Blood culture. PT, PTT, INR.

RESULTS

Our study was cohort study included 54 neonates at ZAGZIG University NICU who received TPN more than 2 weeks and we assessed the occurrence of PNALD and the volume of packed RBCs they received and the results are discussed below.

Baseline characteristics of our studied neonates in **table 1** showed that: mean age is 34.4 weeks, mean birth weight is 1.9 kg , 30 neonates (55.6 %) were males and 24 neonates (44.4%) were females . 17 neonates (31.5%) come by vaginal delivery while 37 neonates (68.5%) come by caesarian section . 38 neonates (70.4%) received usual resuscitation including warming , drying , suction while 16 neonates (29.6%) required advanced resuscitation as intubation ,ambou bagging , iv fluids .

Table 1: Baseline characteristics of the studied neonates

Variables	
Gestational age (weeks)	
○ Means	34.4±3.6
○ Median(Range)	34(27-40)
Birth weight (kg)	
○ Means	1.9±0.66
○ Median(Range)	1.7(0.9-3.5)
Sex, *n*, (%)	
○ Male	30(55.6%)
○ Female	24(44.4%)
Mode of delivery, *n,* (%)	
○ Vaginal delivery	17(31.5%)
○ Cesarean section	37(68.5%)
Need for resuscitation, *n,* (%)	
○ Usual	38(70.4%)

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○ Advanced	16(29.6%)

In our studied neonates, 14 (25.9%) developed PNALD defined as direct bilirubin > 2mg / dl and 40 (74%) did not develop PNALD as in **table 2**. According to the amount of packed RBCs they received we divided them into three groups where 12 neonates (22.2%) did not receive packed RBCs , 23 neonates (42.6%) received less than 70 ml of packed RBCs and 19 neonates (35.2%) received more than 70 ml of packed RBCs. Correlating baseline characteristics of studied neonates to the amount of packed RBCs transfused detected the following:-

Table 2: classification of studied neonates into PNALD (direct bilirubin > 2) or not

Variable	
PNALD (direct bilirubin >2mg/dl)	14 (25.9 %)
Non PNALD	40 (74 %)

Gestational age , our study showed that neonates received less than 70 ml blood have statistically significant lower gestational age than those who did not receive packed RBCs who have higher gestational ages as shown in **table 3** . No statistically significant difference between the three groups of our study regarding birth weight, sex, mode of delivery and need for resuscitation as shown in **table 3.**

Table 3: Baseline characteristics of the studied neonates grouped according amount of packed RBCs transfusion

Variables	Non transfusion *n=12*	Less than 70 ml *n=23*	More than 70 ml *n=19*	Test of significance	*P*-value
Gestational age (weeks) Means	36.5±3.0	33.3±2.6	34.5±4.5	ANOVA [a] *F*=4.9	**0.016***
		P1=**0.014***	*P2*= 0.32		
			P3= 0.53		
Birth weight (kg) Median(Range)	1.9(1.3-3.0)	1.5(1.2-3.0)	1.8(0.9-3.5)	Kreskas Wallis test H =2.5	0.29
Sex, *n,* (%)					
Male	8(66.7%)	14(60.9%)	8(42.1%)	Chi-squared test (χ^2)= 2.26	0.32
Female	4(33.3%)	9(39.1%)	11(57.9%)		
Mode of delivery, *n*, (%)					
Vaginal delivery	3(25.0%)	7(30.4%)	7(36.8%)	Chi-squared test (χ^2)=0.50	0.78
Cesarean section	9(75.0%)	16(69.6%)	12(63.2%)		
Need for resuscitation, *n,* (%)					
Usual	10(83.3%)	14(60.9%)	14(73.7%)	Chi-squared test (χ^2)=2.06	0.36
Advanced	2(16.7%)	9(39.1%)	5(26.3%)		

P1: No transfusion *vs.* Less than 70 ml , *P2:* No transfusion *vs.* More than 70 ml ,*P3:* Less than 75 ml *vs.* More than 70 ml [a] Welch's ANOVA, *significant(*P*<0.05)

Correlating Liver function tests of the studied neonates to the amount of packed RBCs transfused as in **table 4** showed the following results : direct bilirubin level was statistically significantly higher in neonates received more than 70 ml packed RBCs compared with those received no packed RBCs *(P* =0.028) and those received less than 70 ml packed RBCs *(P*=0.006). neonates received no packed RBCs had a statistically significantly increase in AST level compared with neonates received less than 70 ml packed RBCs (*P*=0.021). No

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statistically significant differences existed in AST level between neonates received no packed RBCs and those received less than 70 ml compared with neonates received more than 70 ml (*P*>0.05). Parenterals nutritional associated liver disease (PNALD**)**, Post hoc analysis showed that percent of neonates with direct bilirubin≥2 (52.6%) was statistically significantly higher in neonates received more than 70 ml packed RBCs compared with neonates received no packed RBCs (8.3%) and those received less than 70 ml(13%) (*P*<0.05).as in **figure 1**.

Table 4: Liver function test of the studied neonates grouped according amount of packed RBCs transfusion.

Variables	No transfusion *n=12*	Less than 70 ml *n=23*	More than 70 ml *n=19*	Test of significance	*P*-value
Total bilirubin(mg/dL) Median (Range)	2.75(0.8-17)	5(0.26-12.4)	8(0.6-16)	Kruskal wallis test H =2.9	0.24
Direct bilirubin(mg/dL) Median (Range)	0.8(0.2-2.2)	0.7(0.1-5.8)	2(0.3-13.5)	Kruskal wallis test H =11.22	**0.004****
		P1>0.99	*P2*=**0.028***		
			P3=**0.006****		
Parenterals nutritional associated liver disease (PNALD) Direct bilirubin<2 (mg/dL) Direct bilirubin≥2 (mg/dL)	11(91.7%)[a] 1(8.3%)[a]	20 (87%)[a] 3(13%)[a]	9 (47.4%)[b] 10(52.6%)[b]	Fisher's Exact Test=9.87	**0.006****
ALT (U/L) Median (Range)	10.5(6- 47)	11(3- 77)	77(15-139)	Kruskal wallis test H =3.1	0.21
AST(U/L) Median (Range)	34.5(19-131)	20(4-271)	27(13-304)	Kruskal wallis test H=8.1	**0.018***
		P1=**0.021**	*P2*=0.93		
			P3=0.18		

P1: No transfusion *vs.* Less than 70 ml ,*P2:* No transfusion *vs.* More than 70 ml ,*P3:* Less than 75 ml *vs.* More than 70 ml *significant(*P*<0.05), ** highly significant (*P*<0.01)Values in a row without a common superscript letter statistically significantly differ (*P*<0.05)

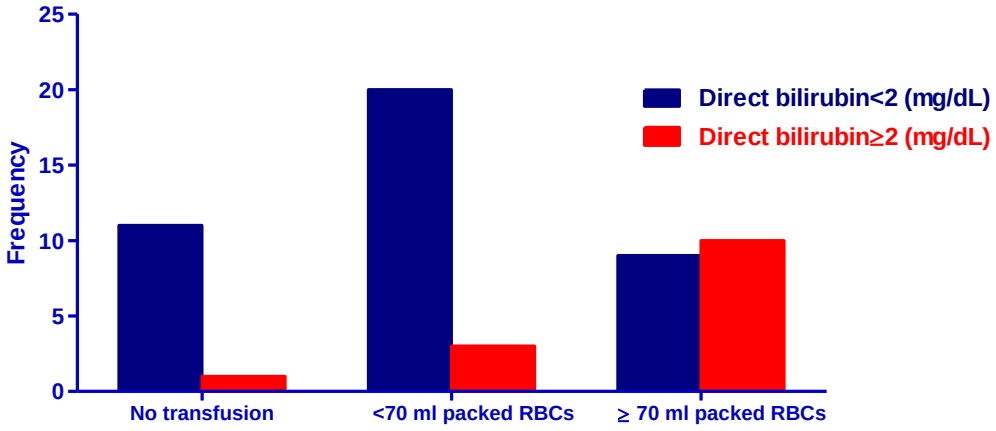

Figure 1: Bar chart representing frequency distribution of parenteral nutritional associated liver disease (PNALD)of the studied neonate.

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In this cohort study, among the 19 high transfusion neonates 10 (52.6%) developed PNALD. Further , among 14 neonates who developed PNALD in our cohort group , 10 neonates (71.4%) received packed RBCs > 70 ml while only 3 neonates (21.4%) received packed RBCs less than 70 ml and only one neonate (7%) did not receive packed RBCs ($p < 0.01$) . Further, among all 21infants who developed PNALD, 17/21 (81%) received PRBC ≥ 70 mL while only 10/28 (36%) received < 70 mL PRBC volumes. Our results showed no statistically significant differences neither in total bilirubin nor ALT levels in the studied neonates ($P>0.05$) .

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Logistic regression predicting likehood of parenteral nutritional associated liver disease (PNALD) based on amount of packed RBCs transfusion in the studied neonates showed that neonates received more than 70 mL packed RBCs had 12.22 times higher odds to develop parenteral nutritional associated liver disease (PNALD) than those received no transfusion (P=0.028) as showen in **table 5.**

Table 5: Logistic regression predicting likelihood of parenteral nutritional associated liver disease (PNALD) based on amount of packed RBCs transfusion in the studied neonates.

Packed RBCs transfusion	β	S.E	Wald	Odds ratio (95% CI)	*P*-value
No transfusion				1 (reference)	
Less than 70mL packed RBCs	0.501	1.21	0.170	1.65(0.153 to 17.82)	0.68
More than 70 mL packed RBCs	2.503	1.14	4.81	12.22 (1.31 to 114.4)	**0.028***
Constant	-2.398	1.04			

***significant (P<0.05), β, Regression coefficients, S.E, standard error**

DISCUSSION

In our studied neonates, 14 (25.9%) developed PNALD defined as direct bilirubin > 2mg / dl G. Lauriti *et al*. [5] and 40 (74%) did not develop PNALD as shown in **table 2** nearly like A. D'Souza et al. [6] where 21 (43%) of his studied 49 neonates developed PNALD and 28 (57 %) did not develop PNALD also quite similar to P. Koseesirikul et al. [7] and A. Kubota *et al.* [8]where 8 neonates(33.3%) developed PNALD and 16 (66.6%) did not develop PNALD. This difference is due to different number of cases included in each study.

According to the amount of packed RBCs they received, we divided the neonates into three groups: non-transfusion group : who received no packed RBCs , low transfusion group: who received packed RBCs less than 70 ml , high transfusion group:who received packed RBCs more than 70 ml . This is different from A. D'Souza et al. [6]who divided neonates into two groups only : low transfusion and high transfusion .

Adding of non-transfusion group in our analysis was useful in focusing on that there are other precipitating factors for PNALD as preterms , sepsis , low birth weight and intolerance of enteral feeding . [9] [10]**.** Our study showed that neonates received less than 70 ml blood have statistically significant lower gestational age than those who did not receive packed RBCs who have higher gestational ages as shown in **table 3** . This is similar to O. A. Valieva et al. [11] and R. O. Ugwu et al. [12] whose results showed that Preterm neonates are more likely to be transfused and are also more likely to receive multiple blood transfusions, and this is explained by that prematurity is associated with increased packed RBCs transfusion due to high risk of anemia . Our study showed no statistically significant difference between the three groups of study according to birth weight which is different from the study of O. A. Valieva et al. [11] , K. J. Collard et al [13] and K J .collard , S.Godeck et al. [14] whose results showed increased packed RBCs transfusion with decrease birth weight . This can be explained by that the mean weight for our neonates is low (1.9 ± 0.66) .

Correlating Liver function tests of the studied neonates to the amount of packed RBCs transfused as in **table 4** showed that percent of neonates with direct bilirubin≥2 (52.6%) was statistically significantly higher in neonates received more than 70 ml packed RBCs compared with neonates received no packed RBCs (8.3%) and those received less than 70 ml(13%) (P<0.05) and this agrees with A. D'Souza et al. [6].

In this cohort study , among the 19 high transfusion neonates 10 (52.6%) developed PNALD. Further , among 14 neonates who developed PNALD in our cohort group , 10 neonates (71.4%) received packed RBCs > 70 ml while only 3 neonates (21.4%) received packed RBCs less than 70 ml and only one neonate (7%) did not receive packed RBCs ($p < 0.01$) These results agree with A. D'Souza et al. [6]whose results showed that among the 27 high transfusion neonates, 17 (64%) developed PNALD, while PNALD was seen in only 4/22 neonates (18%) in the low transfusion group. Further, among all 21 neonates who developed PNALD, 17/21 (81%) received PRBC ≥ 70 mL while only 10/28 (36%) received < 70 mL PRBC volumes.

Our study revealed that neonates received no packed RBCs had a statistically significantly increased AST level compared with neonates received less than 70 ml packed RBCs (P=0.021). No statistically significant differences existed in AST level between neonates received no packed RBCs and those received less than 70 ml compared with neonates received more than 70 ml (P>0.05) . This differs from A. D'Souza et al. [6]whose results showed statistically significant elevated AST level in high transfusion group more than low transfusion . This can be explained by short duration of our study and that changes in liver enzymes due to PNALD require weeks to months to occur as seen in P. Koseesirikul et al. [7]where transaminases increases aroud fourth week of TPN adminstriation .

Our results showed no statistically significant differences neither in total bilirubin nor ALT levels in the studied neonates ($P > 0.05$) and this is quite similar to M. B. Badia-Tahull *et al.* [15] whose results showed no statistically significant difference in ALT results ($P = 0.057$) but showed statistically significant difference in total bilirubin ($P < 0.05$).

Logistic regression predicting probability of parenteral nutritional associated liver disease (PNALD) based on amount of packed RBCs transfusion in the included neonates, showed that neonates received more than 70 mL packed RBCs had 12.22 times higher risks to develop parenteral nutritional associated liver disease (PNALD) than those received no transfusion (P=0.028) . These results are quite similar or even higher than A. D'Souza et al. [6]whose results showed that the calculated odds ratio for developing PNALD, based on being in the high versus low transfusion group, was 7.6 .

CONCLUSION

The high incidence of PNALD among high transfusion group suggests that repeated packed RBCs transfusion is a risk factor for parenteral nutrition associated liver disease.This directs us to be cautious during making the decision of blood transfusion in neonates and that we should use alternatives to packed RBCs like erythropoietin and taking measures to decrease occurrence of PNALD.

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REFERENCES

[1] Baudouin A. *et al.*, "[Advantages and special features of hospital preparations of parenteral nutrition in neonatalogy].," *Ann. Pharm. Fr.*Mar.2015 vol. 73, no. 2, pp. 150–159 .

[2] Blackmer A.B and Partipilo M.L, "Three-in-one parenteral nutrition in neonates and pediatric patients: risks and benefits," *Nutr. Clin. Pract. Off. Publ. Am. Soc. Parenter. Enter. Nutr.*,Jun 2015 vol. 30, no. 3, pp. 337–343.

[3] Cavicchi M, Beau P, Crenn P , Degott C , and Messing B , "Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure," *Ann. Intern. Med.*, Apr.2000 vol. 132, no. 7, pp. 525–532.

[4] "Handbook of. Transfusion. Medicine. United Kingdom Blood Services. 5th edition.published 2013 Editor: Dr Derek Norfolk - PDF." [Online]. Available: https://docplayer.net/23290132-Handbook-of-transfusion-medicine-united-kingdom-blood-services-5th-edition-editor-dr-derek-norfolk.html. [Accessed: 11-Jul-2018].

[5] Lauriti G *et al.*, "Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review," *JPEN J. Parenter. Enteral Nutr.*, Jan 2014 vol. 38, no. 1, pp. 70–85.

[6] D'Souza A. and Anushree Algotar, "Packed red blood cell transfusions as a risk factor for parenteral nutrition associated liver disease in premature infants." world J clin pediatr ., Nov 2016, vol .5 , no.4 ,pp.365-369. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5099588/. [Accessed: 11-Jul-2018].

[7] Koseesirikul P, Chotinaruemol S, and Ukarapol N, "Incidence and risk factors of parenteral nutrition-associated liver disease in newborn infants," *Pediatr. Int.*, 2012, vol. 54, no. 3, pp. 434–436 .

[8] Kubota A *et al.*, "Total parenteral nutrition—associated intrahepatic cholestasis in infants: 25 years' experience," *J. Pediatr. Surg.*Jul.2000 . vol. 35, no. 7, pp. 1049–1051.

[9] Btaiche IF, Khalidi N. "Parenterals nutrition-associated liver complications in children". Pharmacotherapy. Feb.2002. vol.22, n.2, pp.188-211 .

[10] cole CR , Ferm JC , Schmotzer B , Gewirtz AT, Meddings JB , Gold BD, Ziegler TR. "The rate of bloodstream infection is high in infants with short bowel syndrome : relationship with small bowel bacterial overgrowth ,entral feeding ,inflammatory and immune responses" j pediatr. 2010. vol.156 , no .6 , pp . 941-947 .

[11] Valieva O .A , Strandjord T . P, Mayock D.E , and Juul S.E , "Effects of Transfusions in Extremely Low Birth Weight Infants: A Retrospective Study," *J. Pediatr.*, Sep. 2009 . vol. 155, no. 3, p. 331–337.e1.

[12] Ugwu R.O , Eneh A.U , and Oruamabo R.S , "Blood transfusion therapy in neonates admitted into the Special Care Baby Unit (SCBU) of University of Port Harcourt Teaching Hospital, Port Harcourt.," *Niger. J. Med. J. Natl. Assoc. Resid. Dr. Niger.*, Oct .2006 .vol. 15, no. 4, pp. 401–405.

[13] Collard K.J ."Transfusion related morbidity in premature babies: Possible mechanisms and implications for practice," *World J. Clin. Pediatr.*, Aug.2014. vol. 3, no. 3, pp. 19–29.

[14] Collard K.J , Godeck S , Holley JE." Blood transfusion and pulmonary lipid peroxidation in ventilated premature babies . Pediatr . Pulmonal .Mar 2005. vol .39 , no.3 , pp .257-261 .

[15] Badia-Tahull M.B *et al.*, "Liver function test alterations associated with parenteral nutrition in hospitalized adult patients: incidence and risk factors," *Nutr. Hosp.*, Aug 2012 vol. 27, no. 4, pp. 1279–1285.