COMPARISON OF FREQUENCY OF ADVERSE EVENTS OF EXCHANGE TRANSFUSION BETWEEN TWO GROUPS OF NEWBORN INFANTS

Farid Ullah[1], Hazrat Bilal[2], Farman Ali[3], Sami U Khan[4], Hamid Iqbal[3]

ABSTRACT

Objective: The objective of this study was to compare the frequency of adverse events (hypoglycemia and hypocalcaemia) in Jaundiced Neonates (having bilirubin level of >20mg/dL) with and without co-morbid conditions (anemia (Hb<10mg/dl) and sepsis (culture proven)

Material and Methods: This study was conducted at Special Care Baby Unit Khyber Teaching Hospital, Peshawar. Duration of study was one year and study design was prospective observational study. Patients without co-morbid conditions were included in group "A" and those with co-morbidity were in group "B". 62 patients in each group were enrolled. Inclusion criteria of the study was Jaundiced neonates having total serum bilirubin >20mg/dl and Jaundiced neonates with and without comorbid condition while exclusion criteria was exchange transfusion for polycythemia and birth asphyxia grade III.

Results: Hypocalcaemia was analyzed showing that in Group "A" out of n=38(61.29%) male neonates, only n=13(34%) had Hypocalcaemia which ranged from 6.5-8.9 mg/dl with a mean Hypocalcaemia level of 7mg/dl with SD±0.81mg/dl while out of n=24(38.71%) female neonates only 5(20%) had Hypocalcaemia ranging from 6.2-8.8 mg/dl with a mean Hypocalcaemia level of 7mg/dl with a SD ±0.76 mg/dl. Where as in Group "B" out of 30(48.38%) male neonates only 3(10%) had Hypocalcaemia ranging from 6.6-8.8 mg/dl with a mean hypocalcaemia level of 7mg/dl with a SD ±0.68 mg/dl while n=32(51.61%) female neonates only 3(9%) had hypocalcaemia which ranged from 6.1-8.9 mg/dl with a mean hypocalcaemia level of 7mg/dl with a SD ±0.69 mg/dl.

Hypoglycemia among two groups was analysis as in Group "A" n=38(61.29%) male neonates only 13 had Hypoglycemia which ranged from 18-45 mg/dl with a mean Hypoglycemia level of 33mg/dl with a SD±5.23 mg/dl while n=24(38.71%) female neonates only 10 had hypoglycemia which ranged from 16.2-44.5 mg/dl with a mean Hypoglycemia level of 31mg/dl with a SD ±6.01 mg/dl. Where as in Group "B" n=30(48.38%) male neonates only 5 had Hypoglycemia which ranged from 20-44.6 mg/dl with a mean hypoglycemia level of 33mg/dl with a SD ±6.22 mg/dl while 32(51.61%) female neonates only 4 had Hypoglycemia which ranged from 19-45 mg/dl with a mean Hypoglycemia level of 30mg/dl with a SD ±6.39 mg/dl.

Conclusion: It was concluded from the study that adverse events of hypocalcemia and hypoglycemia are significantly higher in neonates with comorbid conditions relative to ones without comorbid conditions. Moreover number of female neonates suffering from these conditions is higher than male neonates, in our study which is irrespective of the comorbid conditions.

Key Words: Exchange transfusion, Neonatal jaundice, hypocalcemia, hypoglycemia

INTRODUCTION

Neonatal jaundice is a common disorder worldwide affecting 30-70% of newborn infants. Mostly jaundice is benign, transitional phenomenon of no clinical significance and subsides itself but in minority of cases, it is pathological and needs treatment. The treatment options are phototherapy, exchange transfusion and pharmacological therapy[1]. Exchange transfusion is indicated for avoiding bilirubin neurotoxicity when other therapeutic modalities have failed[2].

There is controversy in defining the level of danger hyperbilirubinemic level that will need treatment in term and pre-term babies. Recommended threshold levels of serum bilirubin differ among studies, though a level of 20-25mg/dL is considered as standard threshold with modifications for maturity and general condition of the infant[3].

[1] Senior Medical Officer Women & Children Hospital Charsada -Pakistan
[2] Department of Paediatric Gajju Khan Medical College Sawabi-Pakistan
[3] Department of Paediatric Khyber Teaching Hospital Peshawar- Pakistan
4 Oncology Department, Atomic Energy Cancer Hospital (DINAR), D.I.Khan- Pakistan

Address for correspondence:
Dr. Farid Ullah
Senior Medical Officer Women & Children Hospital Charsada -Pakistan
Contact No:+923339953661
E-mail: drfaridullah@gmail.com

Many researchers had retrospectively observed the adverse events of exchange transfusion in the past. The adverse events are thrombocytopenia, hypocalcaemia, metabolic acidosis, sepsis, necrotizing enterocolitis, anemia, reactive hypoglycemia, hypothermia, hyperkalemia, apnea, cardiac arrest and death. These complications occur in 5-10% of infants. Exchange transfusion should be delayed until the risk of bilirubin encephalopathy is as high as the risk of severe complications from the procedure itself. [4]

In all the previous studies, these adverse events were not quantified for jaundiced neonates with and without comorbid conditions[5]. It was hypothysed that newborn babies with co-morbid conditions are more likely to develop metabolic complications like hypoglycemia, hypocalcaemia than newborn babies who are otherwise well and undergo exchange transfusions just for pathological hyperbilirubinemia. This study is expected in reviewing protocol for exchange transfusion for jaundiced patients in light of co-morbid conditions.

MATERIAL AND METHODS

Setting: Specialized nursery of tertiary care public hospital

Duration of study: One year

Sample size: Sixty two number of subjects (n=62) were included in each group

Study design: Prospective observational study.

Inclusion criteria:

Jaundiced neonates having total serum bilirubin >20mg/dl

Parents who gave informed written consent

Exclusion criteria:

Exchange transfusion for polycythemia.

Birth Asphyxia Grade III.

Method

All the patients in the study were investigated for routine lab tests. The standard case management for hyperbilirubinemia was exactly similar for the two groups. Diagnostic criteria were serum bilirubin level for jaundice[8], hemoglobin level for anemia, and blood culture was used for sepsis. Subsequently neonates were observed for the adverse events of exchange transfusion at 0, and 12 hours after exchange transfusion between the two groups of newborn infants and recorded.

Primary outcome measure was to determine the proportion of patients with adverse events in the two groups. Data was analyzed in SPSS10. Frequency and percentages were calculated for categorical variables. Chi-square test was applied to compare hypoglycemia and hypocalcaemia between two groups of newborn infants. The p value of ≤ 0.05 was considered significant.

RESULTS

Age distribution analysis among two groups showed that all the patients were between age rang of 0-22 days. The mean age was 18 days.

Table 1: Sex Distribution of Neonates in Group A & B (N=124)

	Neonates	
	Group A	Group B
Male	38(61.29%)	30(48.38%)
Female	24(38.71%)	32(51.62%)
Total	62(100%)	62(100%)

Table No 2: Duration of Hospital Stay in Group A & B (N=124)

	Duration of Hospital Stay	
	Group A (Mean and SD)	Group B (Mean and SD)
Male	3-18 (7±3.2)	2-10 (4±2.2)
Female	3-20 (9±4.3)	3-11 (10±4)
Total	62(100%)	62(100%)

Table No: 3: Bilirubin Levels in Group A & B (N=124)

	Bilirubin Levels	
	Group A (Mean and SD)	Group B (Mean and SD)
Male	20-48 (33±1.23)	20-44 (32±1.34)
Female	20-45 (33±1.51)	20-45 (33±1.43)
Total	62(100%)	62(100%)

Table No 4: Distribution of Blood Culture Positive Cases in Group A & B (N=124)

	Distribution of Blood Culture Positive Cases	
	Group A	Group B
Male	25(66%)	00(00%)
Female	23(96%)	00(00%)
Total	48(77%)	00(100%)

Table No 5: Distribution of Anemia in Group A & B (N=124)

	Anemia	
	Group A	Group B
Male	18(47%)	00(00%)
Female	16(67%)	00(00%)
Total	34(55%)	00(100%)

Table No 6: Distribution of Hypocalcaemia in Group A & B (N=124)

	No of Patients	No of neonates with Hypocalcemia	Range (mg-dL)	Mean mg/dL	St. Dev.
Group A					
Male	38	13 (34.21%)	6.5-8.9	7.23	+-0.81
Female	24	5 (20.83%)	6.2-8.8	7.28	+-0.76
Total	62	18 (29.03%)	6.2-8.9	7.25	+-0.78
Group B					
Male	30	3 (10%)	6.6-8.8	7.33	+-0.68
Female	32	3 (9.37%)	6.1-8.9	7.42	+-0.69
Total	62	6 (9.67%)	6.1-8.9	7.37	+-0.68

Table No 7: Distribution of Hypoglycemia in Group A & B (N=124)

	No of Patients	No of neonates with Hypoglycemia	Range mg-dL	Mean mg/dL	St. Dev.
Group A					
Male	38	13	18-45	33.25	+-5.23
Female	24	10	16.2-44.5	31.56	+-6.01
Total	62	23	16.2-45	32.33	+-5.71
Group B					
Male	30	5	20-44.6	33.88	+-6.22
Female	32	4	19-45	30.65	+-6.39
Total	62	9	19-44.6	32.05	+-6.30

Gender distribution analysis of neonates among two groups showed that in Group A n=38(61.29%) neonates were male and n=24(38.71 %) neonates were female while in Group B n=33(48.38%) neonates were male and n=32(51.62%) neonates were female. (Table No 1)

Duration of Hospital Stay among two groups showed that in Group A n=38(61.29%) male neonates had stayed from 3-18 days with a mean hospital stay of 7 days and a standard deviation of ±3.2 days, while n=24(38.71 %) female neonates had stayed from 3-20 days with a mean hospital: stay of 9 days and standard deviation of ±4.3 days. Where as in Group B n=30(48.38%) male neonates had stayed from 2-10 days with a mean hospital stay of 4 days and standard deviation of ±2.2 days while n=32(51.61%) female neonates had stayed from 3-11 days with mean a hospital stay of 10 days and standard deviation of:± 4 days (Table No 2).

Bilirubin Level analysis in Group A showed that n=38(61.29%) male neonates had serum bilirubin level ranging from 20-48 mg/dl with a mean serum billirum level of 33mg/dl with SD ±1.23 mg/dl. while n=24(38.71 %) female neonates had serum billirubin level ranging from 20-45 mg/dl with a mean serum bilirubin level of 33mg/dl with SD ±1.51 mg/dl. Where as in Group B n=30(48.38%) male neonates had serum bilirubin level ranging from 20-44mg/dl with a mean serum bilirubin level of 32mg/dl with SD ±1.34 mg/dl while n=32(51.61%) female neonates had serum bilirubin level ranging from 20-45 mg/dl with a mean serum bilirubin level of 33mg/dl and SD ±1.43 mg/dl. (Table No 3).

Analysis of blood culture test among two groups showed that in Group A out of 38 male neonates of n=25(66%) neonates had positive blood culture while out of 24 female neonates only n=23(96%) had positive blood culture. In Group B none of the patients were positive blood culture. (As shown in Table No 4)

Analysis of anemia among two groups showed that in Group A out of 38 male neonates had only n=18(47%) were anemic and out of 24 female neonates only n=16(67%) were anemic. In Group B none of the patients were anemic. (As shown in Table No 5)

Hypocalcaemia among two groups was analyzed which showed that in Group A out of 38 male neonates only n=13(34%) had Hypocalcaemia which ranged from 6.5-8.9 mg/dl with a mean Hypocalcemia level of 7mg/dl with SD±0.81mg/dl while out of 24 female neonates only n=5(20%) had Hypocalcemia ranging from 6.2-8.8 mg/dl with a mean Hypocalcemia level of 7mg/dl with a

SD ±0.76 mg/dl. Where as in Group B out of 30 male neonates only n=3(10%) had Hypocalcaemia ranging from 6.6-8.8 mg/dl with a mean Hypocalcemia level of 7mg/dl with a SD ±0.68 mg/dl while out of 32 female neonates only n=3(9%) had Hypocalcaemia which ranged trom 6.1-8.9 mg/dl with a mean Hypocalcaemia level of 7mg/dl with a SD ±0.69 mg/dl. (As shown in Table No 6)

Hypoglycemia analysis showed that in Group A out of 38 male neonates only n=13 had Hypoglycemia which ranged from 18-45 mg/dl with a mean Hypoglycemia level of 33mg/dl with a SD±5.23 mg/dl. While out of 24 female neonates only n=10 had Hypoglycemia which ranged from 16.2 44.5 mg/dl with a mean Hypoglycemia level of 31mg/dl with a SD ±6.01 mg/dl. Where as in Group B out of 30 male neonates only n=5 had Hypoglycemia which ranged from 20-44.6 mg/dl with a mean Hypoglycemia level of 33mg/dl with a SD ±6.22 mg/dl while out of 32 female neonates only n=4 had Hypoglycemia which ranged from 19-45 mg/dl with a mean Hypoglycemia level of 30mg/dl with a SD ±6.39 mg/dl. (As shown in Table No 7)

DISCUSSION

The study reveal that the frequency of most of the adverse events is consistently higher in the neonatal group with comorbidities as compared to the neonatal group without them.

The duration of hospital stay was more for male neonates in comorbid group as compared to normal group (Mean stay in days 7.1 vs 4.2) but was comparable for females in both groups (Mean stay in days 9.3 vs 9.5) which is consistent with another study which also found that female neonatal stay was statistically insignificant in two groups of Neonates (with and without comorbid conditions) in India.[7] This most probably can be best explained because of gender disparities in this part of the world where male children are given more importance as compared to female children and this may be one of the reason that female children with problems are brought late to the hospital as compared to male children which explains female babies longer stay irrespective of the associated problems.

The Bilirubin levels in both groups of neonates were almost similar with non-significant differences which apparently were because of the severity of some conditions even in the normal group like Rh Incompatibility, G6PD Deficiency and ABO Incompatibility. A few earlier studies conducted in Bangladesh[7,8] and India[9,8] also found out similar findings in two small independent hospital based studies. However another large sized trial conducted in United States has reported significantly higher levels of bilirubin in neonates with associated comorbid conditions as compared to normal infants.[79] This could be due to the fact that most of the infants present earlier in developed countries because of a robust health care system while in developing countries like ours, most of the children are either treated at home or by quacks in periphery before being brought to a tertiary care hospital. Moreover incidence of Rh Incompatibility, which is a major cause of neonatal jaundice requiring exchange transfusion in developing countries, has been decreased in developed countries because of better level of ante natal care services and available of Anti-Rh antibodies based vaccination.[8]

The frequency of Blood Culture positivity rate in comorbid group was 45.61. Higher number of cases were expected to have positive blood culture but because of the poor laboratory quality control systems, blood cultures don't carry high sensitivity and false negative rates are usually high due to laboratory factors. Three studies conducted in Norway, Denmark and Germany have shown high rates of culture proven sepsis in a small number of neonates mostly Asian immigrants.[8] These studies have shown a few number of sepsis cases in their sample but because of better lab measures, the rate of culture proven sepsis was high even in small number of infants.

The number of anemic children in comorbid group comprised of 54% of the total sample of this group, and a further stratification according to sex showed that the frequency of female was higher as compared to males in this group (66.66% vs 47.36%). This higher proportion of anemia in female infants once again speaks volumes about the poor attention given to female children in our society. Partly this is also explained by a higher number of maternal malnutrition and micronutrient deficiencies in our country because of gender disparities and poor health infrastructure and poor quality of Maternal and Child Health services. Our findings do not correlate with similar studies done in west. Two large multicenter trials have failed to demonstrate any significant differences between prevalence of Anemia in jaundiced neonates in male and female infants (13.54% vs 14.73%) and (18.91% vs 20.12%) respectively.,[8,11] In another study conducted in Saudi Arabian Royal Military Hospital, the researchers found a relatively higher proportion of female jaundiced neonates suffering from anemia but the results were statistically insignificant.[812] Similarly the degree of severity of Anemia was also higher in female neonates in our study which might be explained by the same factors as described above. A south Indian community based Study in Indian State of Kerala has also found higher severity of anemia in female neonates even when the sex stratification was controlled for other confounding factors.[14] This probably forms a part of the larger picture seen particularly in South Asia where cultural factors also play their significant role in health and disease and hence consistently disease burden and severity is found more pronounced in females irrespective of the age groups.[15]

As far as adverse events of exchange transfusion in both groups were concerned, based on our observations we found out that more neonates suffered from

Hypocalcaemia in comorbid group as compared to control group (29.03% vs 9.67%) which were statistically significant ($p<0.00637$). This conforms to many studies in literature which have consistently found higher proportions of neonates suffering from hypocalcemia.[8,9,16] This is readily explained by different pathophysiological mechanisms which lead to deranged metabolic functions in neonates suffering from comorbid conditions like Sepsis, severe anemia, Pneumonia, and as a consequence blood calcium level drops more readily in such babies.[9,17] However sex stratification in both comorbid and control group lead to the observation that male neonates suffering from hypocalcaemia were relatively higher than female neonates (34.21% vs 20.83%) and (10% vs 9.37%). This is in contrast to what we found from some other studies in the literature where it has been reported that more female neonates suffered from Hypocalcaemia as compared to male neonates.[18] We don't think that this finding has a value for generalization because the non probability convenient sampling method has a potential for introducing bias in the study, and this finding could probably be attributed to random errors because of the study design. However much larger multicentre trials are required to see if such patterns emerge in future or is it just a coincidence.

Hypoglycemia is another recognized adverse effect of exchange transfusion in neonates. Defined as a blood glucose level of less than 9 mg/dL, we found out that the frequency of Hypoglycemia was far higher in the comorbid group as compared to the control group. Again this is explained by metabolic over activity and derangement in comorbid conditions which increases the probability for hypoglycemia in such neonates. The study reveled that 37.09% of the neonates in the comorbid group suffered from hypoglycemia as compared to control group (14.51%) and the results were statistically very significant ($p< 0.004$). This has been consistently demonstrated in three other large trials conducted in the west, which also have demonstrated significantly higher proportion of neonates suffering from comorbid conditions, who developed hypoglycemia after exchange transfusion.[9] However in between the groups the results according to sex stratification were insignificant.

CONCLUSION AND RECOMMENDATIONS

This study showed that the frequency of adverse effects namely Hypocalcaemia and Hypoglycemia which we thoroughly studied, is significantly higher in neonates with comorbid conditions as compared to neonates without comorbid conditions. Moreover frequency of female neonates suffering from these conditions is higher than male neonates, in our study which is irrespective of the comorbid conditions.

It is recommended that health care services be made more responsive to comprehensive child care at the primary level so the conditions can be recognized at an earlier stage, which can go a long way in reduction the frequency of such adverse events. This should be coupled with stringent maternal care services at the same level so that the predisposing factors leading to these conditions can be deceased.

Neonatal care services also need to be strengthened so that these adverse events can be quickly recognized and treated.

A larger framework of gender equity needs to be practiced through integrated health education services and uplift of the social sector which will help in the long term to decrease the gender based differences in such adverse events in neonates.[20]

REFERENCES

1. Juretschke LJ. Kernicterus: still a concern. Neonatal Netw 2005; 17(2): 167-9.
2. Mohammadzadeh A, Farhat AS, Iranpour R. Effect of clofibrate in jaundiced term newborns. Indian J Paediatr 2005:72:123-6.
3. Janjidamai W, Tansantiwong T. Accuracy of transcutaneous bilirubinometer estimates using Bilicheck in Thai neonates. J Med Assic Thai 2005; 88(2):187-90.
4. Stoll BJ, Piazza JA. Digestive system disorder. In: RE Behrman, RM Kliegman, HB Jenson, Stanton. Nelson textbook of Pediatrics. 18th ed. Philadelphia: WB. Saunders Company. 2007; 753-66.
5. Khan PA. Neonatology. In: Khan PA. Basis of Pediatrics. 7th ed. Multan: Nishtar books; 2007. 123-97.
6. Stoll BJ. The fetus and the neonatal infant. In: RE Behrman, RM Kliegman, HB Jenson, Stanton. Nelson textbook of Pediatrics. 18th ed. Philadelphia: WB. Saunders Company. 2007; 671-812.
7. Lawrence M. Gartner, CarlaT. Herrarias and Robert H. Sebring. Practice Patterns in Neonatal Hyperbilirubinemia. PEDIATRICS. 101 (1);1998:25-31.
8. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004. 114(1): 297-316.
9. Badiee Z. Exchange transfusion in neonatal hyperbilirubinemia: experience in Isfahan, Iran. Singapore Med J. 2007; 48 (5): 421-3.
10. Patra K, Storfer-Isser A, Siner B, Moore J, Hack M. Adverse events associated with neonatal exchange transfusion in the 1990s. J Pediatr. 2004; (5): 626-31.
11. Haneef SM, Maqbool S, Arif MA.ed's. Textbook of Paediatrics. 1st ed. Lahore: International book bank; 2006. p.165-48.
12. Sanpavat S. Exchange transfusion and its morbidity in ten-year period at King Chulangkorn Hospital. J Med Assoc Thai. 2005; 88 (5): 588-92.
13. Stoll BJ, Piazza JA, . Blood disorder. In: RE Behrman, RM Kliegman, HB Jenson, Stanton. Nelson textbook of Pediatrics. 18th ed. Philadelphia: WB. Saunders Company. 2007; 766-75.

14. Maisels MJ, Gifford K. Normal serum bilirubin levels in the newborn and the effect of breast- feeding. Pediatrics. Nov 1986;78(5):837-43.

15. [Guideline] Atkinson LR, Escobar GJ, Takyama JI, Newman TB. Phototherapy use in jaundiced newborns in a large managed care organization: do clinicians adhere to the guideline?. Pediatrics. 2003;111:e555.

16. Moore LG, Newberry MA, Freeby GM, Crnic LS. Increased incidence of neonatal hyperbilirubinemia at 3,100 m in Colorado. Am J Dis Child. Feb 1984;138(2):157-61.

17. Sarici SU, Serdar MA, Korkmaz A, et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. Pediatrics. 2004;113:775-780

18. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. Pediatr Res. Nov 2004;56(5):682-9.

19. Yusoff S, Van Rostenberghe H, Yusoff NM, Talib NA, Ramli N, Ismail NZ. Frequencies of A(TA)7TAA, G71R, and G493R mutations of the UGT1A1 gene in the Malaysian population. Biol Neonate. 2006;89(3):171-6.

20. Slusher TM, Vreman HJ, McLaren DW, Lewison LJ, Brown AK, Stevenson DK. Glucose-6-phosphate dehydrogenase deficiency and carboxyhemoglobin concentrations associated with bilirubin-related morbidity and death in Nigerian infants. J Pediatr. Jan 1995;126(1):102-8.