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Evaluation the efficacy of IVIgG in treatment of Hemolytic Disease of Newborn

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Abstract:

Background*: Hemolytic disease of newborn (HDN) is an important cause of hyperbilirubinemia in the neonatal period,and delayed diagnosis and treatment may lead to permanent brain damage. Traditional neonatal treatment of HDN is intensive phototherapy and exchange transfusion.Intravenous immunoglobulin(IVIgG) has been introduced as an alternative therapy to exchange transfusion. This study was conducted to assess the effect of IVIG in HDN .*

Material and method*: we performed a cohort study in 2011,in 56 healthy newborn with jaundice and hemolysis due to ABO and RH incompatibility that admitted in neonatal ward of Mahdieh hospital with gestational age of 35 weeks and more . Infants with jaundice due to other causes ,sick and preterm infants with gestational age less than 35 weeks were excluded.*

In our study we use 500mg/kg IVIgG for treatments of HDN in addition of phototherapy, and in cases with continued hemolysis , second or third same dose of drug was used .In cases with high bilirubin levels in accordance with AAP guideline for treatment of hyperbilirubinemia, without appropriate response to those modalities of treatment exchange transfusion was done. To evaluate the effect of treatment with IVIgG ,we compared results of therapy with results of traditional therapy (exchange& phototherapy) in newborns with the same condition without use of IVIgG . Total duration of phototherapy and hospital stay,need for exchange transfusion and simple transfusion of packed red blood cell was compared in two groups ,and probable side effect of was evaluated .

Results *:27 neonates in IVIG group with mean birth weight of 2873±538.9 gm and 29 neonates in the control group with mean birth weight of 3086±497 gm were included and compared (p=0.13).Mean age of admission in IVIG group was 47.5±52 hour and in control group was 83.9±54.3.(p=0.007) ,Mean level of bilirubin in admission time was 14.7±4.5mg/dl in IVIG group and 15.5±4.7 mg/dl in control group(p=0.5) .Mean age of neonates at the time of drug administration was 64.5±45.6hr, mean frequency of IVIG use was 1.6±0.69,average days of phototherapy in IVIG group was 4.8±4.6 days and in control group was 2.4±1.05 days(p=0.009).37% in IVIG group needed packed cell transfusion due to anemia but none of control group needed packed cell transfusion.(p=0.0001).Mean hemoglobin level in IVIG group was 12.4±2.7mg/dl and in control group was 16.7±7.1 mg/dl (p=0.004). 3 patients (10.7%) in IVIG group had positive coombs test. There was no side effects attributed to IVIgG use .*

Conclusion*: In this study we found that IVIG doesn't have any significant effect on duration of phototherapy and hospital stay and need for Packed red blood cell transfusion in neonates with hemolytic disease of newborn, according to unavailability and high cost of this drug routine use of IVIgG in mild cases of HDN is not recommended..*

Key words*: IVIgG, hyperbilirubinemia ,neonates ,Hemolytic Disease of Newborn*

I. Introduction

Hemolytic disease of newborn (HDN) is one of the most important causes of jaundice and anemia in neonatal periods which is the results of Rh ,ABO or minor group incompatibility between mother and her neonate. (1)
In past decades Rh hemolytic disease was the most common cause of sever hemolytic hyperbilirubinemia and frequent cause of kernicterus but in recent years, preventive use of anti- D immunoglobulin G (RhoGAm) in Rh negative mothers combined with aggressive fetal surveillance and intrauterine blood transfusions has greatly reduced the incidence and severity of disease,and ABO incompatibility is the main reason of HDN with milder clinical picture of hemolysis .(2)

Although infrequently sever hemolysis may occur and despite the traditional treatment of jaundice such as phototherapy and exchange transfusion (ET), kernicterus can still be seen(3) .
Although exchange transfusion is very effective in reducing the hyperbilirubinemia and its side effects but because it is an invasive procedure and has its own side effects ,measures to reduce the frequency of this should be encourage .These measures include early determination of jaundice, intensive phototherapy and use of IVIgG.,for this reason in recent years IVIG combined with phototherapy in infants with HDN in some studies had been found to be effective in prevention or reduction the number of exchange transfusion . (4)
Although the exact mechanism of action of IVIG remained elusive, many theories has been postulated .It is thought that IVIG can block FC receptors on macrophages thus competing with the anti D sensitized neonatal erythrocytes and preventing further hemolysis(5)-shorter half-life of antibodies(anti –Rh antibodies) in circulation,a third hypothesis is the presence of anti-idiotypic antibodies as a result of IVIg treatment neutralizing anti-Rh antibodies.(6)
Due to these points ,since 2004 AAP (American Academy of Pediatrics) recommended IVIG in (HDN) 500-1000 mg/kg (7),but recently this recommendation has been questioned,because recent studies have proven otherwise(8)on the other hand due to unavailability and high cost of IVIgG ,despite recommendations this drug should not be used routinely .
This study was designed to evaluate the effectiveness of IVIG in hemolytic disease of neonates with HDN inMahdiyeh hospital. Our primary outcome was determine the efficacy of IVIg in reduction of exchange transfusion and duration of phototherapy in neonates with HDN and secondary outcomes were assess effect of IVIg in anemia and need for packed cell transfusion and side effects of drug .

II. Material &Methods:

This is a cohort study performed in 2011,in healthy newborns with 35 weeks < of gestational age just admitted because of jaundice in Mahdiyehhospital.
Inclusion criteria was indirect hyperbilirubinemia in term and late preterm neonates that require to phototherapy due to blood group and Rh or minor group incompatibility between mother and her baby (mother with blood group O infant with blood group A or B , mother Rh negative and baby Rh positive ,respectively)and one or more of other signs of hemolytic disease of newborn: anemia(hemoglobin concentration equal or less than 12 mg/dl), positive coombs test ,high reticulocytes count more than 5%.
Exclusion criteria's were: jaundice in sick newborns,or due to other causes such as G6PD deficiency ,… and jaundice in premature infants. (gestational age <35 week),direct hyperbilirubinemia
In our study we used 500mg/kg IVIgG with the infusion rate of 2-3 hours for treatments of HDN in addition of phototherapy, and in cases with continued hemolysis means increasing levels of bilirubin or decreasing levels of hemoglobin despite phototherapy and first dose of IVIgG , second or third same dose of drug was used .In cases with higher bilirubin in levels of exchange transfusion in accordance with AAP guideline for treatment of hyperbilirubinemia, exchange transfusion was done. By study the medical records of newborns with the same condition without use of IVIgG that were treated by exchange& phototherapy, we had a cohort study for evaluate the effect of treatment with IVIgG ,we compared results of therapy with results of traditional therapy .Due to lack of use in second group of study was unavailability of medication.. Total duration of phototherapy and hospital stay,need for exchange transfusion and simple transfusion of packed red blood cell was compared in two groups ,and probable side effect of was evaluated
During study periods ,bilirubin level , hemoglobin , hematocrite and reticulocyte count were checked serially.In patients with persistant evidence of hemolysis such as continued anemia and reticulocytosis with hyperbilirubinemia a second or third dose of IVIG with same dose was administered .In patients that needed to exchange transfusion we didn't use IVIgG .In cases with severe and progressive anemia (hemoglobin concentration < 8 mg/dl)packed RBC cross matched with mother and neonates was transfused.
We compare data's such as gestational age ,birth weight,gender ,maternal and neonatal blood group Rh, hemoglobin and bilirubin level , reticulocyte count, coombs test, ,times of packed RBC transfusion and IVIG administration and exchange transfusions. duration of phototherapy . between two groups.If there was any complication of IVIgG administration , it have been recorded.
Data analyzed by SPSS No18.

III. Result:

In this study ,a total 56 neonates were evaluated. 27(48.2%) were in the IVIG group, 29 (51.7%) were in control group. In IVIG group 12 neonate (44.4 %) were male and 15 (55.6) were female, mean birth weight was 2873.3 ± 538.9 kg and in control group 13 neonate were male and 16 female and mean birth weight was 3086.09 ± 497 kg (PValue=0.13) without any significant difference between them. Mean age of patients in the IVIG group was 47.57 ± 52 hours and in the control group's was 83.09± 54.3 hours (Pvalue= 0.007) which was significantly higher in the control group.

In IVIG group 21 (70%) neonate had ABO incompatibility, 9 (30%) cases had Rh incompatibility while in the control group 15 (53.6 %) neonates had ABO incompatibility, 10 (35.7) cases had Rh incompatibility (Pvalue 0.14) .In 3 (10.7%) cases ABO and Rh incompatibilities existed simultaneously. There weren't any cases of minor blood group incompatibility in our research period.

Mean bilirubin levels during admission in the IVIG and control group were 14.7 ± 4.5 $^{mg}/_{dl}$ and 15.5 ± 0.4 $^{mg}/_{dl}$ respectively. There were no statistically significant between two groups. (Pvalue=0.5)

Mean hemoglobin levels during admission in the IVIG group 12.48 ± 2.7 $^{mg}/_{dl}$ and in the control group 16.47 ± 7.1 $^{mg}/_{dl}$ that was statistically significantly higher in second group (Pvalue=0.04).

Mean reticulocyte counts in IVIG group was 7.3±3.6 and in control group was 2.7 ± 3.1 that significantly higher in first group (Pvalue = 0.01). Direct coombs test in 3 (10.7) cases in the IVIG group were positive while in the control group there was no positive coombs test.

The average of neonatal age that received IVIG were 64.5 ± 45.6 hr and the average number of the IVIG infusions 1.6 ± 0.69 (between 1-3 times). A single dose of IVIG was infused in 14 (50%) neonates.

In 11 (29.3) cases were received two times of IVIG with duration of 14-24hr intervals. Any side effects such as hypotension, tachycardia and allergic reactions had not been reported. The mean duration of hospitalization and phototherapy were 4.8 ± 4.6 days in IVIG group and 2.4 ± 1.05 days in control group which was statistically significantly higher in first group. (Pvalue = 0.009)

In IVIG group 10 neonates (37%) need to packed RBC transfusion due to severe anemia, but in control group none of neonate didn't need to packed RBC transfusion (Pvalue=0.0001). that statistically significantly higher in second group.

	Ivig +	Ivig-
male	12(44.4%)	13(44.8%)
Birth weight(gm)	2873±538.9	3086±497
Age (admission)hr	47.5±52	83.9±54.3®
ABO	21(70%)	15(53.6%)
RH	9(30%)	10(35.7%)
ABO/RH	-	3(10.7%)
Bil(admission)mg/dl	14.7±4.5	15.5±4.7
Hgb (admission)mg/dl	12.48±2.7	16.47±7.1®
Positive coombs	3(10.7%)	-®
Duration of admission(day)	4.8±4.6	2.4±1.05®
Packed cell transfusion	10(37%)	-®
Ex change -	-	-
IUT	-	-
IVIG doses	14(50%:)1 11(29.3%):2 3(10.7%):3	-

Table No.1: Baseline characteristics of the patients

In both groups any patients need to exchange transfusions. No signs of acute bilirubin encephalopathy were seen in neonate under this study.

IV. Discussion:

In this cohort study we found that, use of IVIG in neonates with HDN did not reduce duration of hospitalization and phototherapy and need to packed cell transfusion and rate of hemolysis.

Age of infants in IVIG group was significantly lower than control group because of more severe jaundice and hemolysis.In our study the main reasons of hemolysis were ABO incompatibility .
In a study was conducted by the Nasseri and colleagues(9)IVIG markedly reduces the need for the exchange transfusion in severe hemolysis due to Rh incompatibility, but in ABO incompatibility did not have significantly effects same as our study. It should be noted that in Nasseri's study all cases had direct coombs positive test but we found only 3 cases with positive coombs test.because of small number of coombs positive cases neither comparison nor conclusion could be drawn.
In study was done by Migdad AM and colleagues (10) they identified that 30% of infants with ABO incompatibility need to exchange transfusion andAdministration of IVIG to newborns with significant hyperbilirubinemia due to ABO hemolytic disease with positive direct Coomb's test reduces the need for exchange transfusion without producing immediate adverse effects. In other study by Monopux (11) they found that IVIG can cause reduce duration of hospitalization and phototherapy. But this result is contrary to our study , may be the result of repeated dose of drug.
Hemoglobin levels in IVIG groups were significantly lower than control group that can be proven with severe hemolysis and this is an explanation for admission in lower ages of patients. And also more needs to packed cell transfusion and these results confirmed that IVIG could not prevent from anemia and need to transfusion in HDN.
None of the patients in the control group had positive coombs test, because of ABO in compatibility can cause weakly positive or falsely negative of test , however in many cases of Jaundice, there is no ABO incompatibility and just mother and neonate have different blood groups without any significant hemolysis.
Length of stay in infants in IVIG groups was significantly more than control group due to earlier onset of jaundice and more severe hemolysis but it was confirmed that administration of IVIG couldn't have reduction in duration of hospital stay and periods of phototherapy.
In both study groups any infant required exchange transfusion,and photo therapy and IVIgG decrease need to exchange transfusion maybe because of our study was done in a nursery ward that we had close follow up of our patients , and more earlier initiation of phototherapy could treat the patients.
Elalfy(12)compered early two- dose regimen of IVIgG and conventional therapy in severe Rh hemolytic disease of newborn and conclude that IVIgG at 12 h was effective ,the low dose IVIgG (0.5 g/kg)was as effective as high dose(1g/kg) in reducing of phototherapy and hospital stay ,but less effective in avoiding exchange transfusion.in our study in 50% of patients we use only 1 dose of IVIgG and as needed in cases with continued hemolysis second or third dose was used.
Smiths- Wintjens et al(13)included eighty infants in a randomized,double-blind,placebo- controlled trial in neonates with rhesus hemolytic disease and they used IVIg as a prophylaxis in neonates with history of intrauterine transfusion ,in their study there wasn't any difference in the rate of exchange transfusion and duration of phototherapy between the IVIg and placebo groups and they concluded that prophylactic IVIg does not reduce the need for exchange transfusion or the rate of other adverse neonatal outcomes although in our study we didn't use IVIg as prophylaxis but we use the drug as a rescue therapy in cases with identified HDN.
Although infants treated with IVIG in this study, had any side effects of medication during hospitalization but some other studies have shown some complication such as higher incidence of NEC in a study was conducted by Josep Figueras-Aloy (14)innear – term infants with rhesus hemolytic disease treated with IVIg without any other risk factors of NEC.
Limitations of our study were that because of unavailability of drug we couldnt design a double blind randomize control trial as the best method of study and small sample size also.

V. Conclusion:

We conclude that IVIG could not prevent and treat HDN and decrease duration of phototherapy and hospital stay, need for blood transfusion due to anemia. However, because of the low number of infants in this research, planned studies with larger sample size and RCT (randomized controlled study) for demonstration the efficiency of the drug required and because of IVIG is a high-cost and low availability medication with no significant impact on HDN and concerns about its possible complications,so it's not logical to use IVIG expect for sever progressive hemolysis, as a routine treatment ..

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