

Original Research Article

Clinical usage of intravenous immunoglobulin in neonates in a tertiary care centre: a retrospective observational study

Sharath S. Ghalige, Vaideeswaran M.*, Mangalabharathi S.

Department of Neonatology, Madras Medical College, Chennai, Tamil Nadu, India

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***Correspondence:**

Dr. Vaideeswaran M,

E-mail: vdswaran@gmail.com

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ABSTRACT

Background: Intravenous Immunoglobulin (IVIG) is a blood product manufactured from pooled plasma. With increasing availability, an increased usage in neonates is being noted, though its utilisation has not been audited thoroughly. The objectives of this study are to describe the usage pattern and indications of IVIG and its outcome in a state-run tertiary care NICU.

Methods: This retrospective observational study was carried out at the inborn unit of Department of Neonatology, Madras Medical College, Chennai on a cohort of neonates who received IVIG over 3.5 years from January 2016 to June 2019. Data was collected from drug register, neonatal case records, exchange transfusion register and death register.

Results: Our study cohort had 55 neonates who received IVIG over 3.5 years. Indications for IVIG usage were Rh-alloimmunisation (23), ABO-alloimmunisation (7), prophylaxis of perinatal varicella (20), and other immune thrombocytopenia (5). Among 30 neonates with ABO/Rh-incompatibility, 11 required exchange transfusion (ET). ET rates have shown a decreasing trend during this period. 2 babies with Rh-immunisation and Hydrops expired. None of the babies given prophylaxis for perinatal varicella manifested the disease. Neonates treated for immune thrombocytopenia were successfully discharged.

Conclusions: This study shows the IVIG usage pattern in a tertiary care neonatal unit. In neonates with Hemolytic disease due to Rh-/ABO-alloimmunisation treated with IVIG, a reduction in rates of exchange transfusion has been noted. IVIG is being used increasingly for prophylaxis of perinatal varicella and immune related thrombocytopenia with promising benefits. It is prudent to have SOPs for IVIG administration with standardised issue and transfusion forms for documentation to regulate its judicious use.

Keywords: Alloimmunisation, Intravenous Immunoglobulin, Neonates, Thrombocytopenia, Varicella

INTRODUCTION

Intravenous Immunoglobulin (IVIG) is a blood product manufactured from plasma pooled from more than 1,000 healthy blood donors and includes mostly IgG, although traces of IgA may also be present.¹ Across all age groups the usage of IVIG is increasing with better understanding of many disease processes having immunological basis.

Indications for IVIG usage in neonates include but are not limited to.²

- Neonatal alloimmune thrombocytopenia (NAIT)
- Haemolytic disease of the newborn (HDN) (alloimmunisation)
- Immune thrombocytopenic purpura
- Primary immunodeficiency diseases
- Secondary hypogammaglobulinaemia

- Neonatal haemochromatosis - gestational alloimmune liver disease (GALD)
- Neonatal myasthenia gravis
- Severe neonatal enterovirus infection including myocarditis or hepatitis.

There are a very few well defined indications for usage of IVIG in neonates due to limited number of research trials. Earlier sepsis was also considered as an indication for its usage globally but showed no benefit as supported by the INIS study.³ It was also reiterated by the Cochrane review in 2015 by Ohlsson A et al, In coherence with increased availability of IVIG world-over, an increased usage in neonates is being noted, though its utilisation has not been investigated or audited thoroughly.^{4,5}

This study was planned to put light of IVIG usage in our hospital in the intramural neonatal unit. The objective of this study was to describe the usage pattern and indications for IVIG and its outcome in a state-run tertiary care NICU.

METHODS

This Retrospective study was carried out at the intramural unit of Department of Neonatology, Madras Medical College, Chennai. It is a descriptive observational study. The study was done on a cohort of neonates who received IVIG during a period of 3.5 years from January 2016 to June 2019. The intramural unit has a high delivery rate with around 15,000 deliveries per year on an average. Data was collected from the drug register, neonatal case records, Exchange transfusion register and death register. Data retrieved included information of patient demographic features, antenatal maternal details, neonatal laboratory results, treatment details, adverse events, and patient outcomes.

Data were entered into worksheet and standard methods were used for statistical analysis. In general, categorical data were reported as frequencies, proportions or percentages, and continuous variables were reported as means with standard deviations (SDs) or medians with inter-quartile ranges (IQRs) or range when data were noted to be skewed.

RESULTS

These study cohort consisted of 55 neonates who received IVIG for 3.5 year period. During the same period, an average 15,500 newborns were delivered per year. This comes to an average usage of 0.12% (i.e. 12 per 10,000 deliveries). Baseline demographic features are shown in Table 1. In the study, 34 neonates were males and 21 were females. The median gestational age of neonates was 37 weeks (range of 31 weeks - 40 weeks).

Out of 55 neonates, 30 neonates received IVIG for Hemolytic disease of Newborn (HDN), 20 for prophylaxis of perinatal varicella and the rest 5 for thrombocytopenia

of immune origin. Of the 30 neonates with HDN, 23 had Rh-incompatibility and 7 had ABO-incompatibility.

Table 1: Demographic patterns of newborns (n=55).

Characteristics	No. (n=55)	Percentage
Gender		
Male	34	62
Female	21	38
Gestational age		
<32 weeks	1	2
32-36 weeks	13	24
≥ 37 weeks	41	74
Birth weight		
< 2 kg	1	2
2-2.5 kg	14	25
>2.5 kg	40	73
Mode of delivery		
LSCS	35	64
LN	20	36
Maternal blood group		
Rh Negative	24	44
Rh Positive	31	56
O group	19	35
Other than O (A, B or AB)	36	65
Baby direct coomb test		
Positive	30	55
Negative	25	45
Indication for IVIG		
Hemolytic disease	30	55
Non hemolytic		
Varicella	20	36
Immune thrombocytopenia	5	9
Median dose of IVIG received	0.5 g/kg	0.4-1.0 g/kg*
Median duration of IVIG infusion	4 hours	0.5-4 hours*
Median age of IVIG receipt	3 days	1-18 days*
Outcome of babies who received IVIG		
Hemolytic disease (n=30)		
Discharge	28	93
Death	2#	7
Non haemolytic disease (n=25)		
Discharge	25	100
Death	0	0

*Represent values in range; # Both babies were Rh-alloimmunisation with hydrops.

Out of these 30 neonates with either ABO-/Rh-incompatibility, 11 underwent exchange transfusion apart from receiving intensive phototherapy and IVIG. Two neonates with Rh all immunisation had Hydrops at birth and both these babies received Double volume Exchange Transfusion (DVET) followed by IVIG administration

but died despite best efforts. Mean duration of Phototherapy for babies who received IVIG for HDN was 3.5 (± 1.5) days. Exchange transfusion was done at an average mean age of 64.5(± 42) hours. Exchange transfusion rates have shown a decreasing trend with an increase in IVIG usage during these 3.5 years as shown in Figure 1.

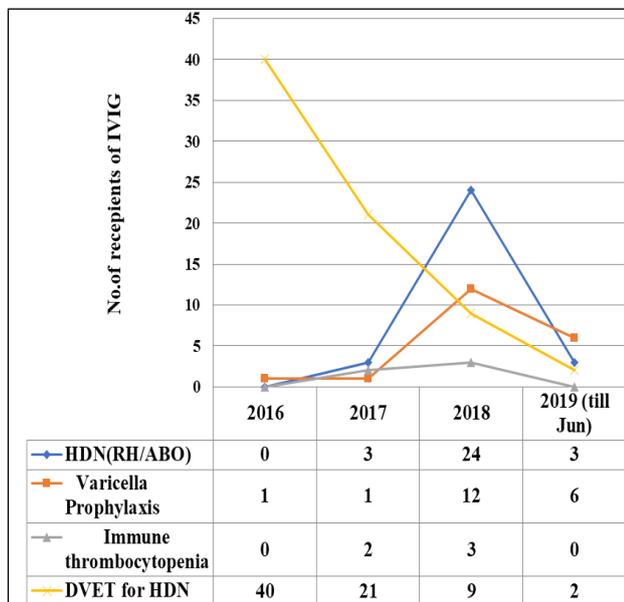


Figure 1: Trends in IVIG usage in the study.

For prophylaxis of perinatal varicella, babies were considered as at-risk if mother developed onset of clinical varicella rash from 5 days prior to date of delivery to 2 days after delivery. Twenty such at-risk babies received IVIG for prophylaxis for perinatal varicella in our study. None of the neonates who received IVIG for prophylaxis were found to have developed Varicella infection till discharge. In the study, 5 babies received IVIG for thrombocytopenia due to immunologic origin. Among these, 4 babies had mothers who had Idiopathic Thrombocytopenic Purpura. One baby was treated as Neonatal Alloimmune Thrombocytopenia (NAIT). All babies had thrombocytopenia resolution with IVIG administration along with supportive care. The usage pattern of IVIG was also variable in the 55 neonates in the study. The median dose of IVIG given was 0.5 g/kg with a range of 0.4 - 1 g/kg. The median duration of IVIG infusion was 4 hours with a range of 0.5 - 4 hours. The average age at receiving IVIG was an average of 2 days with a range of 1 to 18 days. No chart-documented acute or long term adverse events attributed to the IVIG were noted.

DISCUSSION

This study throws light on the patient demographics, treating physician ordering patterns, laboratory results, treatment details, and adverse events in those neonates who received treatment with IVIG. IVIG has been mostly

ordered for Hemolytic Disease of the newborn (more frequently for Rh-alloimmunisation in 23 cases than ABO-alloimmunisation in 7 cases) which accounts for 55% of usage in the study cohort. This is followed by prophylaxis for perinatal varicella in 36% of study neonates. Neonates with thrombocytopenia of immunologic basis, proven or suspected received IVIG in 9% of cases. IVIG usage has increased over the years with its increased availability in global market. Usage in neonates is also following the same trend. However, because of the scarcity of research in neonates, off-label usage is more likely. Usage rate in our unit was 0.12%. In a study done by Liberman et al, 37 neonates received IVIG over a 11-year period from 2003 to 2013 in a Canadian Tertiary care hospital which has on an average 4200 deliveries per year giving it a usage rate of around 0.08%.⁵ The non-availability during yester years, the relatively high cost and the timely availability in current period, treating team decision are factors that would have influenced IVIG use.

In this study, only 11 out of 30 babies with HDN who received IVIG underwent exchange transfusion (ET) thus averting Exchange transfusion in 19 neonates. In a study by Santos et al, involving 92 neonates, IVIG was not effective in preventing the need for exchange transfusion in newborns with rhesus hemolytic disease.⁶ However, American Academy of Pediatrics 2004 recommendation suggests using IVIG at a dose from 0.5 to 1.0 g/kg to treat HDN when phototherapy is failing to avoid ET.⁷ More recently, based on all included studies a Cochrane review by Zwiers C et al, in 2018 could make no conclusions on the benefit of IVIG in preventing ET or top-up transfusion and therefore routine use in alloimmune HDN is not recommended.⁸ In this study Exchange transfusion rates have shown a decreasing trend with an increase in IVIG usage during these 3.5 years as shown in Fig 1. The reason for apparent reduction in ET rates may not necessarily be IVIG alone but earlier recognition and better management, including effective intensive phototherapy and supportive care. When authors tried to check for a possible comparative group, we found that during this study period there were 91 neonates with hemolytic disease with Serum Bilirubin (SBR) in near-exchange range as shown in Table 2.

Table 2: Neonates with hemolytic disease with SBR in near DVET range (n=91).

IVIG reception status	Total no. of neonates (n)	No. of neonates who required DVET	%
IVIG received	30	11	37
IVIG not received	61	61	100

In 61 of these neonates, due to non-availability of IVIG all babies ended up having DVET. In the group of remaining 30 babies who received IVIG, only 11 needed

DVET, which showed an apparent decrease by 63%. However, more studies with a better design with controls are necessary to show any such real benefit. Recent drop in need for IVIG usage in HDN might be due to better understanding of the appropriate use as well as earlier detection and increasing usage of Anti-D in mothers to prevent sensitization. In these studies, out of 20 babies who received prophylaxis for perinatal varicella, none had evidence of varicella until discharge. In a study by Huang et al, with 15 at-risk neonates, 2 out of 4 neonates who received IVIG alone developed symptoms of varicella, but none of the 10 babies receiving both IVIG and acyclovir developed varicella.⁹ Due to the non-availability of VZIG in India, IVIG can be used with the scenario with good results.

In cases where thrombocytopenia of immune origin was the cause for administration of IVIG, resolution of thrombocytopenia was noted in all cases. However, 2 babies received repeat dose of IVIG. Thrombocytopenic newborns with Maternal Immune thrombocytopenia as well as Immune thrombocytopenia in neonates is a standard accepted indication for IVIG with good benefits. In a study by Bahyan et al, 12 of the 20 neonates with thrombocytopenia (60.0%) required treatment to increase the platelet counts.¹⁰ In a study by van der Lugt NM et al, with 18 babies needing treatment, 3 received only platelet transfusions, 2 only prednisone, 1 only intravenous immunoglobulin (IVIG), 11 received platelet transfusions and IVIG, and 1 both platelet transfusion and prednisone.¹¹ In these study, 1 baby with Neonatal alloimmune thrombocytopenia, platelet count improved after IVIG administration and platelet transfusion.

The usage pattern of IVIG has been varied in our study group over last 3.5 years with regard to initial dose, need for repeat dose, duration of infusion and laboratory threshold to start therapy. This is possibly due to the varying guidelines and inter-physician variability. Absence of Standard operating procedures (SOPs) for IVIG administration might also have contributed for the same. Though IVIG actually is a blood product, blood bank in our hospital (as most others outside) is not involved anywhere in the loop of acquisition and dispensing of IVIG.

This study gives these unit an opportunity for auditing our IVIG usage. However, the study, being retrospective in design has limitations. Chances of some data being missed from the registers and inadequate documentation are very likely. More so, the absence of matched controls makes any comparative analysis inappropriate. However, it opens our vision to have SOPs and design better studies with controls for further research in the area.

CONCLUSION

This study shows the IVIG usage pattern in a tertiary care neonatal unit. In neonates with Hemolytic disease due to Rh-/ABO-alloimmunisation treated with IVIG, a

reduction in rates of exchange transfusion has been noted. IVIG is being used increasingly for prophylaxis of perinatal varicella and immune related thrombocytopenia with promising benefits. It is prudent to have SOPs for IVIG administration with standardised issue and transfusion forms for documentation to regulate its judicious use.

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