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A Retrospective Study of the Use of Intravenous Immunoglobulin in the Neonatal Intensive Care Unit

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by

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ABSTRACT OF THE THESIS

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Master of Science in Clinical Research

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Professor Elliot Landaw, Chair

The medical indications for intravenous immunoglobulin (IVIG) use in neonates include hemolytic disease of the newborn, some congenital immunodeficiencies, and severe sepsis, particularly those with neutropenia. However, IVIG has been used for other conditions in the neonatal period. The UCLA NICU has extensive experience in the management of critically-ill neonates, and IVIG is given to newborns with varied diagnoses, from sepsis to congenital heart defects. The objective of this study is to characterize the indications, frequency, and results of polyclonal IVIG use in a level IV neonatal intensive care unit over a 56 month period (January 2004 through June 2008). A subgroup analysis of those treated for suspected or culture-proven sepsis was also performed. Overall, mortality was high in IVIG-treated patients. Therefore, IVIG is unlikely to improve mortality in critically-ill infants.

The thesis of Kellie Jane Lim is approved.

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Introduction

Infants are at particular risk of immunodeficiency based on lack of maturity, both in the innate and the adaptive immune systems. Nearly 1 out of 6 premature infants born in North America develops a serious infection that may lead to mortality or long-lasting organ damage. Premature infants respond to a harmful insult with an attenuated innate immune response. This may be a protective response to prevent organ damage if it occurred in utero; however, this protective mechanism becomes a major clinical disadvantage after premature birth.[1]

The adaptive immune system does not fully develop until several months after birth. Maternal-to-fetal transfer of immunoglobulins, specifically immunoglobulin G (IgG), occur in the mid-to-late third trimester, beginning at 32 weeks of gestation.[2] Infants born in prematurity may have profoundly low IgG, which places them at high risk for overwhelming infections. Fortunately, for these premature and/or immunologically immature infants, medical innovations have been able to support life until human physiology matures.

Near the end of pregnancy, IgG is actively transported to the fetus, such that they have adequate amounts for protection at birth. These antibodies metabolize over several months, during which the infant's own production of antibodies matures. The immune system matures over the course of one's first few years. However, the toll of pathophysiologic stressors may impede this development, and actually

cause an immunodeficient state, which predisposes the infant to a myriad of bacterial, viral, and fungal infections.

Intravenous immunoglobulin (IVIG) is a polyclonal immunoglobulin G (IgG) product that is pooled from several thousands of individuals. IVIG has been used to replace loss of immunoglobulins and to prevent and treat infection. IVIG modulates cytokine production and expression, inhibits complement activation, and reduces neutrophil-mediated inflammation.[2,3] Therefore, IVIG has great potential in the management of physiologically stressed infants with immature immune responses.

Some indications for IVIG use in neonates include hemolytic disease of the newborn, some congenital immunodeficiencies, and severe sepsis, particularly those with neutropenia. However, IVIG has been used for several other disorders in the newborn period. The UCLA neonatal intensive care unit (NICU) has extensive experience in the management of critically-ill neonates, and IVIG is given to newborns with varied diagnoses, ranging from sepsis to congenital heart defects. In this retrospective study, the objectives are to review which clinical conditions have been managed with IVIG and to describe if its administration improved length of hospitalization and mortality. A subgroup analysis of patients who developed sepsis was also performed.

Methods

IRB approval was obtained prior to any investigation. This retrospective descriptive study evaluated use of IVIG in a cohort of 1973 infants younger than 7 months of age admitted to the UCLA NICU between January 2004 and June 2008. This was confirmed by cross-linking pharmacy records, the NICU clinical database, and electronic medical records. Exclusion criteria included age >7 months of age and those who did not receive IVIG before 7 months of age.

Laboratory tests (e.g. complete blood counts, quantitative immunoglobulins, albumin, CRP, ESR), were obtained before and after IVIG administration for analysis; these tests must have been obtained within one week prior or after IVIG administration.

Descriptive statistics regarding clinical condition necessitating IVIG use, length of hospitalization, and mortality were completed. Because neonatal sepsis is a primary cause of mortality and morbidity, a subset analysis was performed in patients with suspected or culture-proven sepsis. They were matched to controls who did not receive IVIG and who were admitted to the NICU within the same period. Subjects and controls were matched 1:1 based on the hierarchy of gender, gestational age, and birth weight, respectively. Main outcomes were length of hospitalization and mortality rate. A Kaplan-Meier curve (with censoring at hospital discharge or transfer to an outside hospital) was developed based on

mortality rate. An ROC curve and a logistic regression model with forward progression (probability set to enter at 0.25 and to leave at 0.1) based on gender, gestational age, and birth weight were done to assess predictability of mortality. Cox proportional hazards and chi-squared tests for the variables of gender, gestational age, and birth weight, along with the interactions between the variables were also performed.

Results

Figure 1 describes the frequency of IVIG administration in the NICU on an annual basis from 2004 through 2008. Ninety-nine patients (5%) out of 1973 infants admitted received at least one dose of IVIG. The five most common indications for IVIG were: hypogammaglobulinemia (45%), suspected or culture-proven sepsis (21%), hemolytic anemia (16%), neutropenia (12%), and other causes (Figure 2). Table 1 provides further details of each clinical indication, including number of IVIG doses administered, pertinent laboratory testing, and mortality rate. Laboratory tests were not consistently drawn before or after IVIG administration; thus trends in values could not be defined. Overall mortality of those who received IVIG was 26% (Figure 3). The majority of the patients received only one dose of immunoglobulin (57%), and most were of male gender (57%).

Table 2 shows the 1:1 matching with controls to the 21 subjects who received IVIG for suspected or culture-proven sepsis. A logistic regression model, ROC curve, and Cox proportional hazards showed general trends of increased length of hospitalization and increased mortality for those who received IVIG. On average, the length of hospitalization was shorter in the control group versus the treatment group (38.7 vs. 54.7 days). Eight of the 21 patients who received IVIG died, whereas 3 of the 21 controls died. Thus, for subjects receiving IVIG, there was an odds ratio of mortality at 3.58 (95% confidence interval 0.6869, 25.0249,

p=0.16). A logistic regression model showed a trend for older gestational age and improved survival (p=0.14), but did not show a trend for the variables of birth weight and gender.

A Kaplan-Meier curve of mortality showed increased mortality for the IVIG group. However, considering length of hospitalization at 75 days, the IVIG group has a mortality rate of 50% compared to approximately 10-15% in the control group.

Cox proportional hazards performed on gender, gestational age, and birth weight also showed increased mortality in the treatment group. Moreover, female gender, older gestational age, and higher birth weight were less likely to die. The control group and older gestational age showed p-values <0.2 (see statistical appendix). This subanalysis did not differentiate between early-onset or late-onset sepsis. Therefore, data derived may not be applicable to studies with specific inclusion and exclusion criteria for neonatal sepsis.

Discussion

IVIG appears to be a supportive measure that has an undefined impact on mortality when administered in the neonatal intensive care unit. This treatment modality was administered to a wide variety of medical conditions, and it likely does not have an influence in survivability in non-approved conditions.

Because IVIG is a human-derived product, it has a limited supply. This retrospective study did not show excessive or unnecessary use. Over the course of 4.5 years, its rate of administration on an annual basis did not show a consistent upward trend. Particularly in the case of sepsis, about 10% received intravenous immunoglobulin. A 2010 Cochrane review did not declare a firm conclusion whether intravenous immunoglobulin decreased mortality rate in neonates <28 days old. The authors stated that the studies were of variable quality.[4] In 2011, the International Neonatal Immunotherapy Study (INIS) Collaborative Group published results from a double-blind, randomized, placebo-controlled trial in 3493 infants diagnosed with suspected or culture-proven sepsis. It found that intravenous immunoglobulin did not change the primary outcome of mortality or major disability at 2 years of age.[5]

Our study design was retrospective and cannot clearly conclude whether there is a beneficial outcome with use of IVIG. The mortality rate was much higher in the IVIG-treated infants. One may question if administering IVIG in this population

can be actually detrimental. Though polyclonal immunoglobulin G is naturally occurring and hypothetically should not cause undue physiologic stress, this study's results are contrary to what is expected. IVIG is no longer a natural product, and it is possible that the manufacturing process or the act of giving this exogenous proteinaceous fluid causes an unintended harmful outcome. However, these data suggest that IVIG was administered as salvage therapy for the severely ill patients. Further prospective studies would help define the exact reasons why clinicians prescribe IVIG and whether is has a positive or detrimental effect on morbidity and mortality.

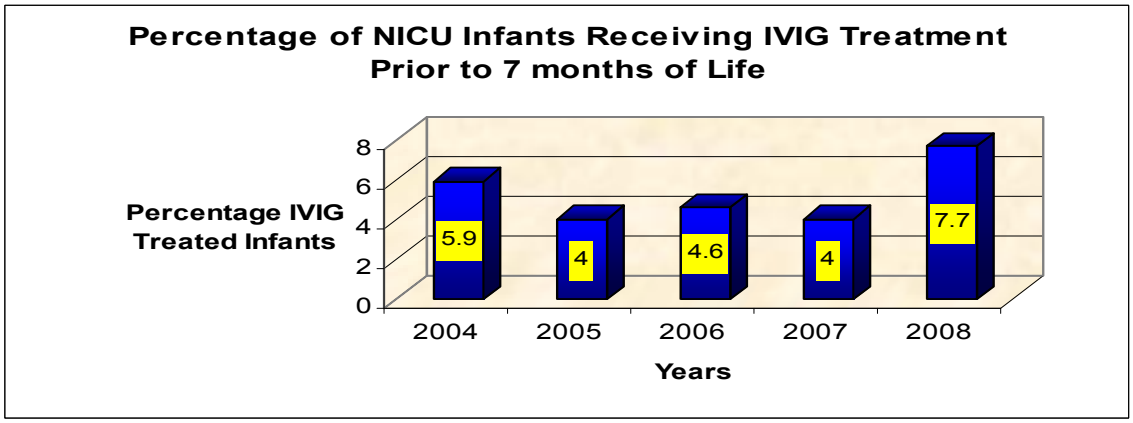


Figure 1: IVIG use in the NICU on an annual basis from 2004 through 2008.

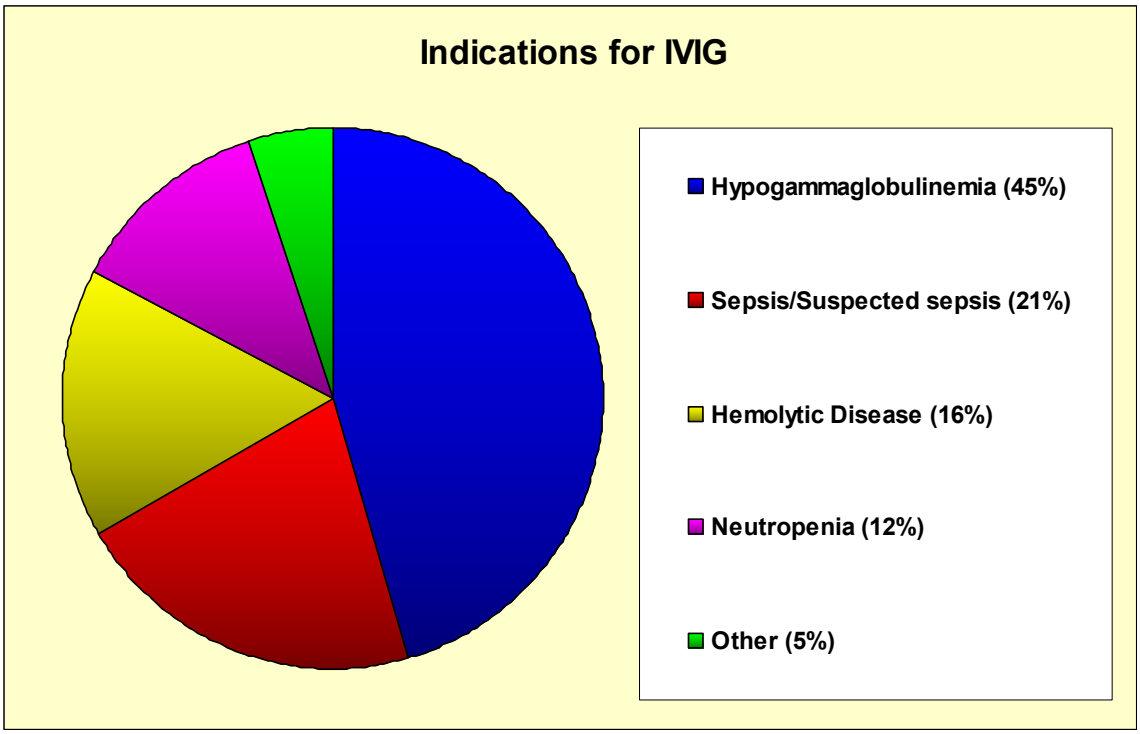


Figure 2: Major clinical indications for IVIG use in the neonatal population.

Hypogammaglobulinemia (n = 45)

- Identified Diagnoses:
  - Low IgG levels following post-cardiac surgery (60%)
  - Renal Failure dependent on peritoneal dialysis (PD) (18%)
  - Others Etiology Unknown (12%)
- IVIG Dose Ranges (1-15) with 18% receiving = 8 doses
  - PD Dependent (3)
  - CMV Viremia with Primary Immunodeficiency (1)
  - Post-cardiac Surgical Chylothorax (1)
- IgG level pre-IVIG mean 205 (range 13 to 537)
- Mortality 29% before 6 months of life

Sepsis (n = 22)

- Identified Diagnoses:
  - Suspected Sepsis (55%)
  - Culture Proven Sepsis (45%)
- Mortality 45% before 6 months of life (8 during IVIG treated illness)

Hemolytic Disease (n = 16)

- Identified Diagnoses:
  - ABO incompatibility
  - Rh-alloimmune Hemolytic Disease
  - Minor Blood Group Antigen Incompatibility
    - anti- D, anti-JK, anti -C, anti -E
- Total Bilirubin (TB) level pre-IVIG averaged 14.3 mg/dl
  - 3 Exchange Transfusions (TB range 11.5 to 32.6 mg/dl)
- IVIG Doses 1 to 3 (average 0.5 to 1 gram/kilogram/dose)

Neutropenia (n = 12)

- Identified Diagnoses:
  - Necrotizing Enterocolitis
  - Chemotherapy (1)
  - Neonatal Alloimmune Neutropenia (1)
- Absolute Neutrophil Count (ANC)
  - Pre-IVIG ANC averaged 1700 x10E3/uL (Range 0 to 7600)
  - Post-IVIG ANC averaged 1400 x10E3/uL (Range 0 to 5300)
- Mortality 8% – 1 death related to liver failure at 5 months of life

Other (n = 5)

- Identified Diagnoses:
  - Post-surgical Duodenal Atresia; Conjoined Twin Separation
  - Hyperbilirubinemia of Unknown Etiology
  - Congenital Thrombocytopenia
  - CHARGE Syndrome

Table 1: Detailed data regarding the most common clinical indications for IVIG administration.

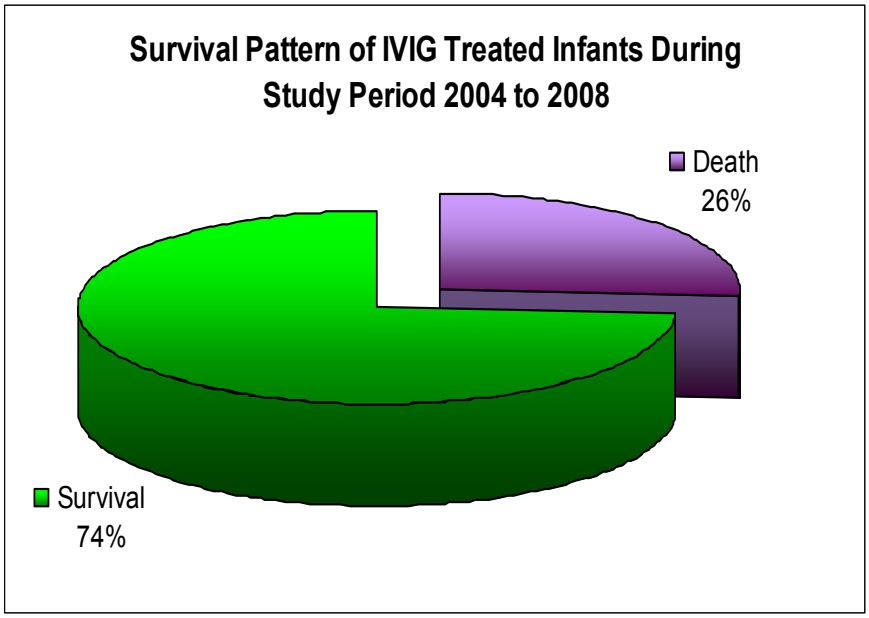


Figure 3: Mortality and survival among those who received IVIG.

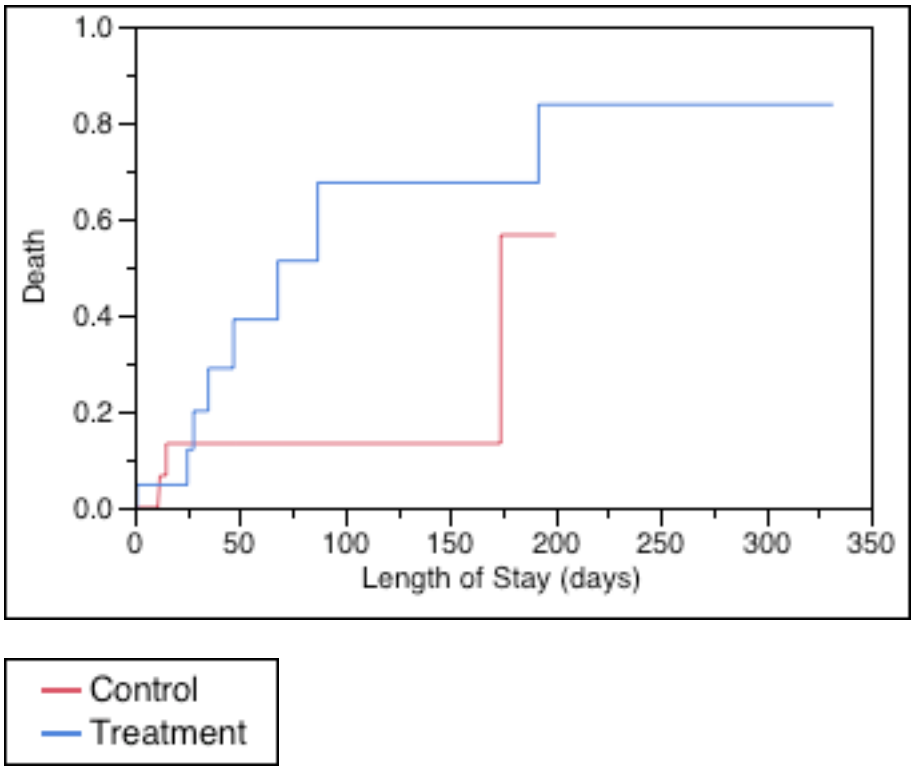


Figure 4: Kaplan-Meier curve for mortality for subjects with suspected or culture-proven sepsis with and without IVIG treatment.

	Gender	Gestational age (weeks)	Birth weight (g)	Length of Stay (days)	Death
Subject 1	M	29.1	1665	87	Yes
Control 1	M	29.4	1692	15	Yes
Subject 2	F	39.3	3045	20	No
Control 2	F	39	3019	7	No
Subject 3	M	30	1047	1	Yes
Control 3	M	30	1040	15	No
Subject 4	F	29	980	12	No
Control 4	F	28.3	1010	43	No
Subject 5	M	27.4	420	192	Yes
Control 5	F	27.5	653	3	No
Subject 6	M	38	3200	56	No
Control 6	M	38	3260	15	No
Subject 7	F	27.4	1085	332	No
Control 7	F	27.7	971	35	No
Subject 8	M	32	1424	68	No
Control 8	M	32	1321	48	No
Subject 9	F	39	3573	35	Yes
Control 9	F	38.6	3867	15	No
Subject 10	F	36.3	2520	20	No
Control 10	F	36	2393	70	No
Subject 11	F	25.4	752	25	No
Control 11	F	25.4	755	47	No
Subject 12	M	22.7	569	23	No
Control 12	M	22.7	468	200	No
Subject 13	F	41	3553	6	No
Control 13	F	40.6	3330	23	No
Subject 14	M	27	1326	34	Yes
Control 14	M	27	1035	11	No
Subject 15	F	27	1000	27	No
Control 15	F	26.6	970	12	Yes
Subject 16	F	37.4	3400	28	Yes
Control 16	F	37	3459	5	No
Subject 17	F	36	2369	18	No
Control 17	F	36.3	2124	6	No
Subject 18	F	25.4	870	47	Yes
Control 18	F	25	830	174	Yes
Subject 19	M	38	3945	41	No
Control 19	M	38	3743	49	No
Subject 20	M	40	3082	10	No
Control 20	M	40	3144	2	No
Subject 21	F	39	2845	68	Yes
Control 21	F	39	2802	17	No

Table 2: Characteristics of subjects and matched controls treated for suspected or culture-proven sepsis.

Statistical Appendix

1. Excel was used to generate descriptive statistics and pertinent tables and graphs.

2. JMP was used to generate the logistic regression model, Cox proportional hazards, Kaplan-Meier curve (based on mortality), and a contingency table (chi-square test).

A logistic regression model of mortality as the outcome was created based on the factors of gender, birth weight, gestational age, and their interactions. The only significant finding was older gestational age as a positive influence on survival (p-value 0.135). This was a stepwise forward progression model with the probability to enter at 0.25 and the probability to leave at 0.1.

Lock	Entered	Parameter	Estimate	Wald/Score ChiSq	"Sig Prob"
X	X	Intercept[1]	-2.0249181	0	1
		Gender{0-1}	0	0.597616	0.43949
		Birth Weight (grams)	0	0.338301	0.56081
	X	Gestational Age	0.09588639	2.231574	0.13522
		Birth Weight (grams)*Gestational Age	0	0.165569	0.68408
		Gender{0-1}*Birth Weight (grams)	0	1.05306	0.3048
		Gender{0-1}*Gestational Age	0	0.623519	0.42974

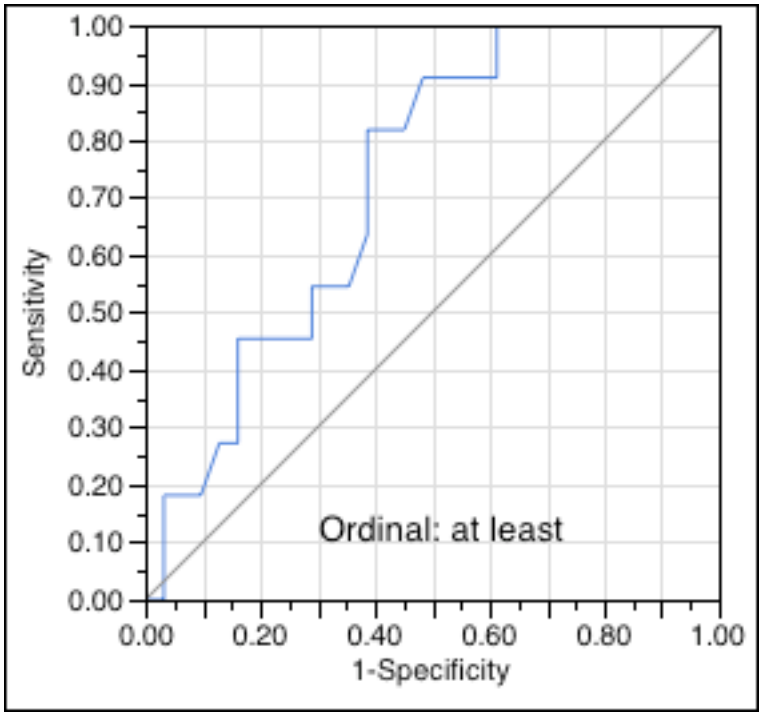
Cox proportional hazards

Cox proportional hazards looked at mortality of the individual variables of group, gender, gestational age, birth weight, and their interactions. This analysis agreed with the trends of other statistical methods: IVIG group (p=0.0751) and older gestational age (p=0.1228) had higher rate of mortality.

Term	ChiSquare	Prob>ChiSq	P-value
Group[Control]	2.89	0.0892	0.0751
Gender[0=female]	0.26	0.6134	0.6106
Gestational Age	2.23	0.1352	0.1228
Birth weight (grams)	1.51	0.2195	0.204
Group[Control]* Gender[0]		0.9436	
Group[Control]*(Birth Weight (grams)- 2013.24)		0.4319	
Group[Control]*(Gestational Age- 32.6857)		0.2885	
Gender[0]*(Birth Weight (grams)- 2013.24)		0.5646	
Gender[0]*(Gestational Age- 32.6857)		0.8467	
(Birth Weight (grams)- 2013.24)*(Gestational Age- 32.6857)		0.5005	

Receiver Operating Characteristic

The ROC curve included the variables of treatment group, gender, birth weight, and gestational age and their effects on mortality. The area under the curve was 0.73, which indicated that these factors in combination had decent probability of predicting mortality.



Contingency table (chi-square test)

A contingency table of mortality between the treatment group and the controls is below, along with the Fisher's exact test. The p-value is 0.0751. The IVIG group has a more significant probability of death compared to controls.

	Survived	Died	Total
Treatment	13	8	21
Control	18	3	21
Total	31	11	42

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	0.9838	Prob(Death=1) is greater for Group=Control than Treatment
Right	0.0795	Prob(Death=1) is greater for Group=Treatment than Control
2-Tail	0.1589	Prob(Death=1) is different across Group

Limitations

The statistical methods in this study have limitations. Pairing of the group with discordance would strengthen the statistical findings of this study. There were overall 6 discordant outcomes, with only one in which the control died and the treated subject survived. Additionally, a propensity score analysis may be used an alternative approach.

The database can only provide retrospective data. A prospective study would provide more ideal data. One approach could be to develop a questionnaire that would ask the clinician about their decision on ordering IVIG prior to any IVIG administration. This study reviewed usage from 2004-2008; a comparative study of the period between 2008 and 2013 can be performed to determine if IVIG use has changed.

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