THE RESULTS OF PROPHYLACTIC IVIG ADMINISTRATION IN PREMATURE INFANTS

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SUMMARY

In this study, we tried to evaluate the effect of intravenously administered IgG on serum immunoglobulin levels of preterm babies and its efficacy on preventing nosocomial infection and sepsis.

Serum IgG, IgM, IgA levels were evaluated in cord blood of 50 preterm and 25 term newborns who were born in Gülhane Military Medical Academy Haydarpaşa Training Hospital between March 1992 and April 1993. The correlation of babies' immunoglobulin levels to their mothers' levels and gestational age was evaluated. The immunoglobulin levels of the preterm newborns were found to be significantly lower when compared to term newborns. ($p<0.001$).

The premature group was divided into two comparable groups according to the gestational age, birth weight and sex. Intravenous immunoglobulin G (IVIG) was administered to the first group (treatment group) on days 0, 10, 20 and 30 with a dose of 0.5 g/kg. No therapy was given to the second group (control group). The serum immunoglobulin levels were compared on the 2nd and 30th days. A significant increase in immunoglobulin G levels was observed in the treatment group ($p<0.001$). No suppression of endogenous immunoglobulin synthesis was observed in the treatment group. On the 30th day, as the immunoglobulin levels decreased, the IgG levels were still significantly high in the treatment group as compared to the controls ($p<0.001$).

The administration of IVIG did result in a significant increase in IgG levels in the treatment group but did not effect the nosocomial infection rate (20% versus 24%), sepsis and mortality rates (12% versus 12%).

Key Words : IVIG, premature infant, sepsis

INTRODUCTION

Maternal IgG crosses placenta by active transport and this phenomenon accelerates during the second part of the third trimester. Fetal IgG levels correlate directly with gestational age. Preterm babies lack this opportunity of passive immune protection. Although improved intensive care options increase the rate of survival of preterm neonates, the longer the inpatient period, the greater is the risk of nosocomial infections and neonatal sepsis due to hospital pathogens. Nosocomial infection rate is still as high as 20 per cent among preterm babies (1, 2).

The immunologic immaturity of these babies makes them more susceptible to infections. The high risk period of preterm babies lasts approximately 30 - 45 days (3). In this period, supporting the humoral immunity of these babies by infusion of intravenous immunoglobulin G (IVIG), thus keeping the immunoglobulin levels above 7 gr/L. may result in a better outcome for these babies (4).

Conflicting data have been reported in this field. In some studies encouraging results are reported, while no significant difference was observed in morbidity and mortality in other studies.

To achieve theoretical protective levels of immunoglobulins, higher doses are required as the immaturity of the preterm increases. At this point, complications may arise due to volume overload and a detrimental effect may be encountered on immunity due to RES blockade when higher doses are given.

The causative organisms of nosocomial sepsis vary regionally. The assessment of regional microbial flora and the immunologic properties of IVIG preparations are thought to be very important factors.

Our aim in this study is primarily to determine the distribution of colonisation and infection of the preterm neonates in our neonatal intensive care unit

and measure the influence of prophylactic administration of intravenous immunoglobulin on the infection, sepsis and mortality rates of these babies.

MATERIALS AND METHOD

We enrolled 50 preterm babies according to the following criteria: All preterm newborns were from uncomplicated pregnancies and uneventful deliveries. All babies were found to be normal on systemic examination. No gross anomalies were observed. We did not include babies whose gestational ages were more than 34 weeks. Gestational age was computed according to the history, ultrasonographic examination and Tunçer method. A detailed prenatal history was taken from all mothers and their obstetricians, including maternal debilitating disease, immune deficiency disorders, immunomodulatory drug therapy and other diseases that may effect the maternal and fetal immune status. All drug and instrumentation used in delivery were registered which may effect the outcome of the babies in terms of morbidity and mortality.

At the beginning of the study healthy term babies and their mothers were selected in order to compare their intial serum immunoglobulin levels with preterm babies. No further observation and assessment were done on this group of babies.

The blood samples of the babies were obtained from cord at delivery simultaneously with mothers' samples that were taken by venous access. Then the babies were randomly assigned to the control or treatment groups by their sex, birth weight and gestational age. Their throat, umbilicus and conjunctiva cultures were obtained within 24 hours.

The randomly selected treatment group was given intravenous immunoglobulin within 24 hours following delivery in a dose of 0.5 g/kg by slow infusion rate at 0.01ml/min or at a slower rate according to their gestational age and birth weight. The preterm control group babies did not receive any treatment.

The diagnoses of infection and sepsis were made according to clinical (hypo- and hypertermia, apnea, hypotonia, feeding difficulties, convulsions, etc.) and laboratory criteriae (complete blood counts, band/granulocyte rate, toxic granulation; blood, CSF and other cultures, CRP).

On days 2 and 30, immunoglobulin levels were measured in both groups and the treatment group was given IVIG in the same doses disregarding their immunoglobulin levels. All cultures were repeated in cases of possible infection.

The control and treatment groups were compared according to all types of immunoglobulin trends in 30 days. The incidence rates of nosocomial infection, sepsis and mortality were calculated.

RESULTS

The properties of premature IVIG and control groups are shown in table I.

There was not a significant difference between preterm control and treatment groups according to the gestational age ($p>=0.05$), birth weight ($p>0.05$), maternal serum IgG ($p>0.05$) and cord blood serum IgG levels ($p>0.05$) statistically.

In our study, we observed a positive correlation between gestational age ($r=0.46$), birth weight ($r=0.42$) and preterm newborns' serum immunoglobulin G levels. However, we found a weak correlation between newborns' IgG levels and maternal IgG levels ($r=0.23$).

The cord blood IgG levels of preterm babies were significantly lower as compared to term babies ($p<0.001$, $t=11.46$).

The measurement of IgG levels on the second day showed significantly higher levels in the treatment group when compared to the control group ($p<0.001$, $t=6.00$). As the preparation we use in this study contains only trace amounts of IgM and IgA; we found comparable values of IgM and IgA in both groups on the 2^{nd} and 30^{th} days. This showed us that no endogenous suppression of immunoglobulin synthesis occurred in the treatment group. We also noticed a significantly higher mean level of IgG in the treatment group on day 30 ($p<0.001$, $t=3.82$) (Figs. 1, 2, 3).

When we divided control and treatment groups into two subgroups according to their gestational age (<32 weeks' gestation and >32 weeks' gestation), the IgG levels showed more striking differences ($p<0.01$, $t=3.79$). The birthweights of neonates below 32 weeks' gestational age averaged 1508.9 ± 291.5 g, while those over 32 weeks' gestation averaged 2067.6 ± 246g; the difference was statistically significant ($p<0.001$). However, as all the exitus cases (3 of 3) in the treatment group were under 32 weeks' gestational age, in the control group one of the exitus cases (1 of 3) was under 32 weeks, and two of them (2 of 3) were over 32 weeks' gestational age (Table II).

The most common organisms recovered from the cultures of the babies were Gram negative organisms. The distribution was as follows: Gram (-) bacilli 43 % (Pseudomonas aeruginosa 3 %, unidentified Gram (-) bacilli 8 %, Klebsiella pneumoniae 27 %, E. Coli 5%); Staphylococci 39 % (Staph. saprophyticus 11 %, Staph, epidermidis 16%, Staph.aureus 12%); Streptococci 15 % (S. pneumoniae 10 %, Group A β- hemolytic streptococci 3 %, S. viridans 2 %); and others 3 % (Bacillus subtilis 1%, Gram (-) diplococci 2%) (Fig. 4).

The infection patterns were similar in both groups. Five patients in the treatment group (20 %) and 6 patients in the control group (24%) developed nosocomial infection such as omphalitis, urinary tract infection and conjunctivitis.

All patients who died in both groups had late-onset sepsis and its complications. No death was observed in groups earlier than 5 days that might be attributable to early sepsis. One in the treatment group, had documented sepsis with urine cultures yielding E. Coli and Staph. saphrophyticus. The others were judged to have sepsis on clinical and laboratory findings.

Three of the twenty-five (12 %) babies in the treatment group died of sepsis and its complications, while 3/25 (12 %) died in the control group. We found no statistical difference between the two groups in the occurrence of nosocomial infection, sepsis and mortality. Also the IgG therapy did not affect the duration of the hospital stay (mean 14.28 ± 7.84 days versus 13.21 ± 6.72 days in the control group) and antibiotic requirements (p> 0.05, t=0.518). There was not a correlation between mortality and the IgG levels.

The IVIG administration was well tolerated by all infants. We have not seen any side effects or complications attributable to IVIG infusion.

Table I: The characteristics of groups

				SERUM IMMUNOGLOBULIN LEVELS (g/L)												
groups				maternal			cord			2nd day levels			30th day levels			notes
		gestation in weeks	birth weight (gr)	IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	
IVIG	ave	31.80	1608.40	9.49	2.04	1.56	5.66	0.15	0.13	7.83	0.16	0.18	7.19	0.23	0.37	ex=3
preterm	stdev	1.85	318.01	2.86	1.18	0.90	1.60	0.02	0.06	1.89	0.03	0.08	3.06	0.06	0.18	n=25
Control	ave	31.84	1878.80	8.60	1.64	1.72	5.14	0.15	0.15	4.73	0.15	0.18	4.37	0.21	0.33	ex=3
preterm	stdev	2.32	461.63	1.93	0.59	0.96	1.81	0.05	0.34	1.76	0.03	0.07	2.06	0.06	0.07	n=25
Term	ave	37.36	3016.79	10.41	2.13	1.90	11.39	0.16	0.10	7.84	0.14	0.12	8.38	0.27	0.36	ex=0
babies	stdev	1.22	447.45	2.63	0.94	1.23	2.24	0.04	0.05	2.28	0.03	0.06	3.71	0.05	0.18	n=25

ave: average, stdev: standard deviation, ex: exitus, n: number of patients

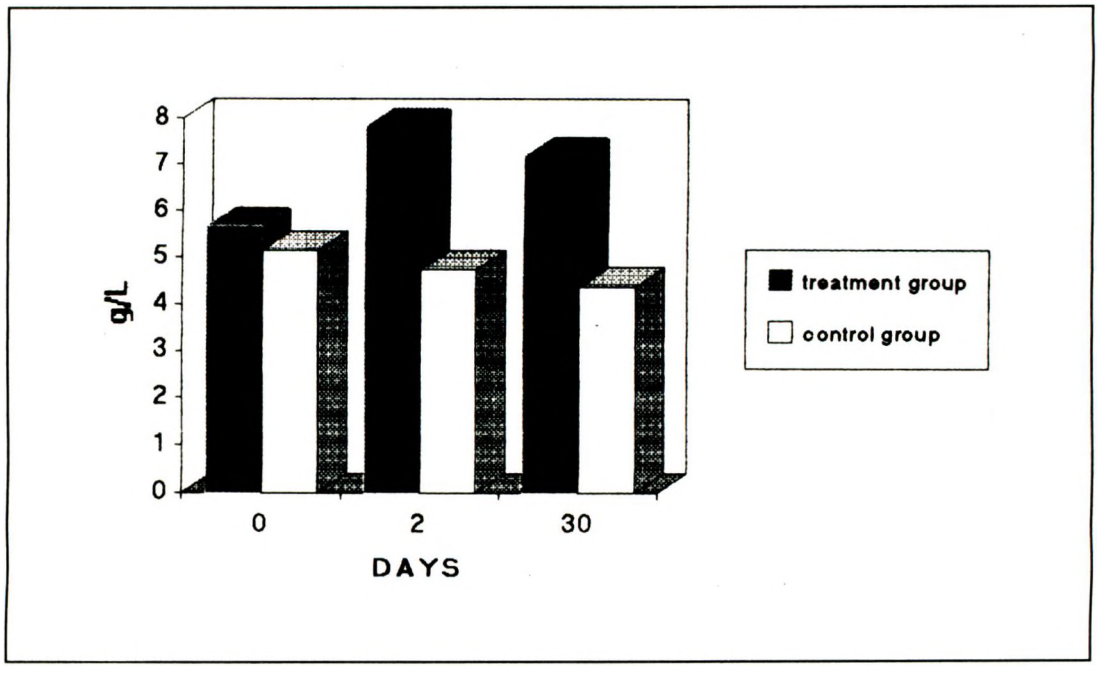

Fig. 1: Serum IgG levels of control and treatment preterm groups

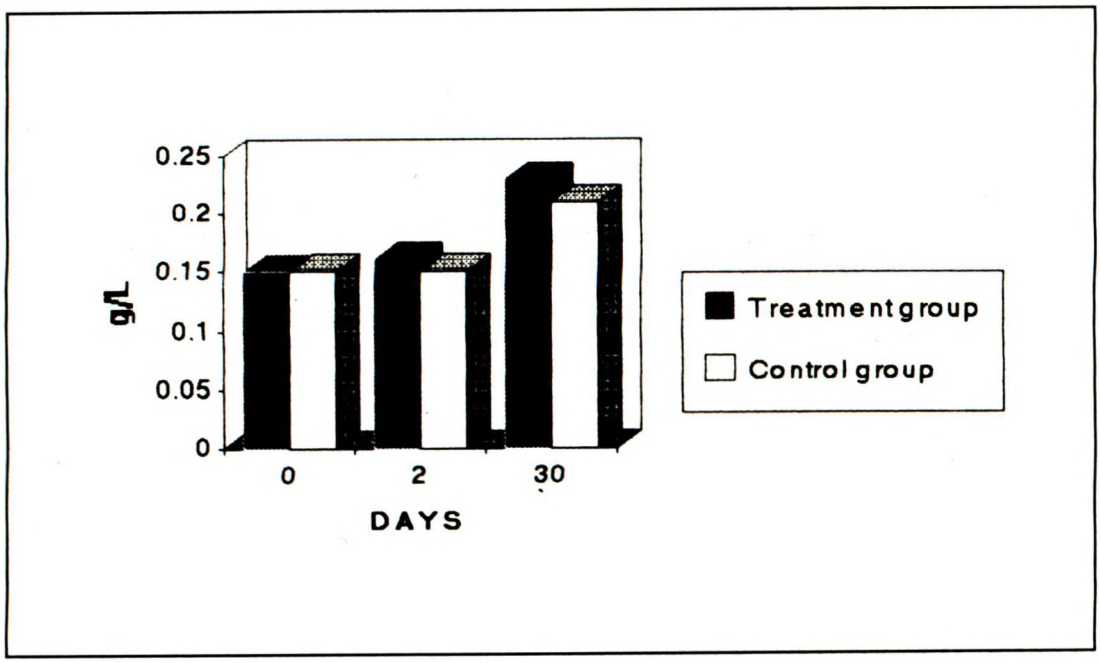

Fig. 2: Serum IgA levels of control and treatment preterm groups

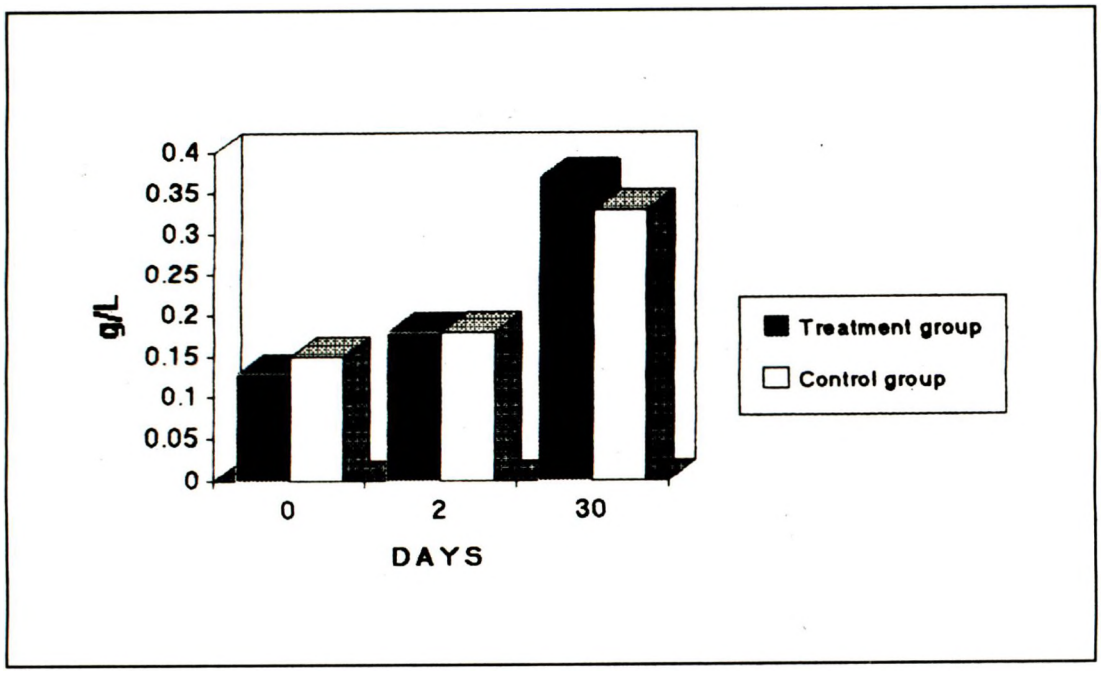

Fig. 3 Serum IgM levels of control and treatment preterm groups

Table II: The characteristics of subgroups

				SERUM IMMUNOGLOBULIN LEVELS (g/L)												
groups				maternal			cord			2nd day levels			30th day levels			notes
gest. in weeks		gestation in weeks	birth weight (gr)	IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	IgG	IgA	IgM	
IVIG	ave	30.53	1464.67	10.51	2.24	1.89	5.27	0.14	0.13	8.15	0.15	0.17	7.59	0.25	0.42	ex=3
<32	stdev	1.19	272.71	2.54	1.40	0.96	1.35	0.02	0.04	1.89	0.03	0.07	2.85	0.07	0.18	n=15
IVIG	ave	33.70	1824.00	7.97	1.75	1.06	6.25	0.16	0.14	7.38	0.17	0.18	6.74	0.21	0.32	ex=0
>32	stdev	0.48	260.61	2.73	0.72	0.51	1.82	0.02	0.08	1.88	0.03	0.08	3.38	0.06	0.17	n=10
control	ave	30.29	1556.43	9.21	1.66	2.00	4.17	0.14	0.08	3.74	0.15	0.18	2.74	0.23	0.34	ex=1
<32	stdev	1.98	311.76	2.02	0.62	1.10	1.52	0.03	0.05	1.32	0.03	0.07	0.79	0.05	0.05	n=14
control	ave	33.82	2289.09	7.82	1.62	1.37	6.37	0.16	0.23	5.99	0.15	0.19	6.44	0.18	0.33	ex=2
>32	stdev	0.40	233.30	1.57	0.58	0.63	1.37	0.06	0.51	1.45	0.03	0.06	0.97	0.08	0.08	n=11

ave: average, stdev: standard deviation, ex: exitus, n: number of patients

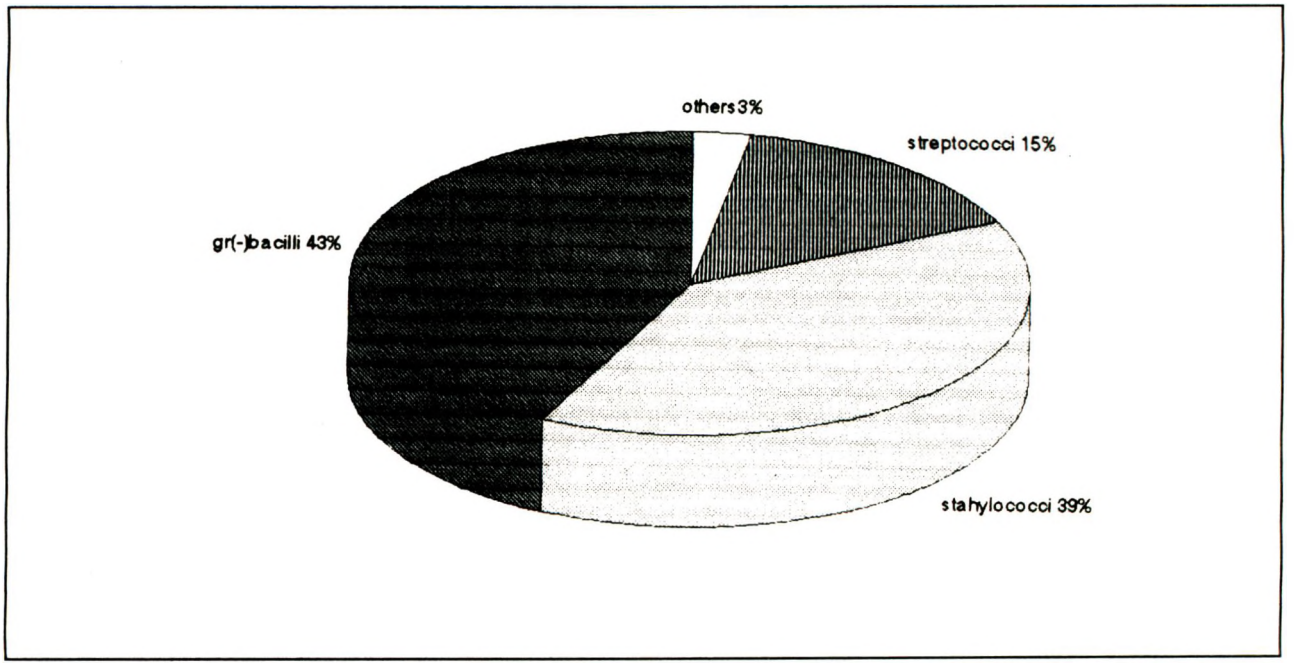

Fig. 4 Distribution of microorganisms recovered from cultures of preterm infants

DISCUSSION

Advances in neonatal care during the last decade have resulted in an increased survival rate for premature neonates. As a result, a considerable amount of preterm babies resides in neonatal intensive care units for a long period of time where they meet serious nosocomial infections.

The immune system of the prematures is immature at birth yet its development is completed within the following weeks or months. The immune functions,

particulaly anti-bacterial defense mechanisms are also suppressed in preterm infants as well as profound hypogammaglobulinemia. In these infants both the classical and alternate pathways of complement activation are highly deficient (5) and granulocyte functions such as chemotaxis and bactericidal activity are suppressed. This suppression lasts approximately one week in the term infant (6), but may be one and a half months in preterms, especially when born before 34 weeks' gestation (3).

The term newborns are under the protection of maternal immunoglobulins transferred from the mother but the preterm newborns lack this opportunity. IgG is the only type of immunoglobulin that crosses the placenta (7). Premature infants (especially < 34 weeks gestation) have low levels of serum IgG because the significant amount of IgG is transferred in the third trimester (8). Transplacentally acquired antibodies are also limited to the mother's previous exposure to specific pathogens. Therefore, preterm newborns have both a qualitative and a quantitative immunoglobulin deficiency. In our study we also observed that the immunoglobulin levels of the neonates show a good correlation to the gestational age and birth weight. However the correlation to the maternal immunoglobulin levels was not significant, showing the active transfer of IgG while IgM and IgA did not cross the placenta. We also observed that the critical cut-off gestational age might be 32 weeks. The babies born before this time showed a profound hypogammaglobulinemia extending to 1 month period. The babies especially ≥ 34 weeks of gestation have values lower than but comparable to those of term babies that make us think that the prophylaxis beyond this period may not be feasible.

What makes immunoglobulins so important in defense is their role in opsonisation of bacteria with polysaccharide capsules (group B streptococcus, streptococcus pneumoniae, E. Coli, etc.). This group of bacteria is well known for their role in neonatal sepsis and meningitis. Intravenous immunoglobulin products are shown to possess opsonic antibodies for several of these bacterial pathogens (9, 10).

The antibiotic era resulted in a major improvement in the management of sepsis. Also modalities such as granulocyte transfusion, exchange transfusion and some other adjunctive therapy modalities improved the outcome of the newborn babies. Despite these improvements, infection continues to cause high morbidity and mortality in these hypogammaglobulinemic preterm infants (1). In a study, nosocomial infection rates as high as 15 % to 30 % were reported in babies whose birth weights were less than 1500 grams (2). Here, we found an overall mortality rate of 12 % (6 of 50 preterm babies) despite improved intensive care facilities.

So one may easily think of preventing sepsis instead of treating it. On this basis, it seems reasonable to claim that supplementation of human intravenous immunoglobulin might be of some help for preterm infants.

Chirico demonstrated that the half life of IgG infused in the neonate is 7-10 days (4). On this basis, most treatment schedules were designed with weekly injections of 0.5 g/kg. This treatment in preterm infants allows prompt achievement of serum immunoglobulin levels similar to those observed in term infants (11). Under the light of this current knowledge, we designed our treatment protocol as to give 0.5 g/kg/dose IVIG every 10 days until the babies were one month old. We thought that it is a high-risk period for a preterm neonate.

The use of IVIG as an adjuntive therapy in neonatal sepsis and in prevention of infection in preterm babies was extensively studied. However conflicting results were achieved.

Haque et al. and Chirico et al. found significant decreases in the incidence of culture-proven sepsis and in the number of deaths in IVIG - treated versus control infants (4, 12). Stabile et al. found a comparable incidence of sepsis in the IVIG group compared to control subjects (13). In a large study group (more than 300 preterm babies with birth weights < 1500 garms) Clapp et al. found a significant decrease in the incidence of culture-proven sepsis in the IVIG group, although there were the same number of deaths in both groups (11). In our study we observed the same pattern of infection in both treatment and control groups and found no difference between mortality rates of both groups.

In addition to the examples above, some benefit was obtained by administration of prophylactic IVIG to preterm infants in some trials (14), but as the study designs and criteria for infections differ greatly, these data cannot be assessed clearly. The antibacterial properties of various immunoglobulin preparations change a lot and it is very difficult to decide which is appropriate against the microbial flora causing the nosocomial sepsis regionally despite the fact that some pathogens are ubiquitous. Unfortunately we had no data showing the type - specific immunoglobulin content and the opsonic capacity of the preparation we used. This might explain why we had the same rates of mortality in both the treatment and the control groups.

In conclusion, we found that the IVIG infusion caused a significant rise in IgG levels in the treatment group compared to the control group. We think that, especially preterm newborns born before 32 weeks of gestation are good candidates for this treatment. We did not observe a suppression of endogenous immunoglobulin synthesis during follow-up. However we did not see any improvement in the infection, sepsis and mortality rates. This shows us that the immune prophylaxis of these babies are still concerned, but the efficiency of the IVIG preparations must be reevaluated.

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