INTRAVENOUS IMMUNOGLOBULIN IN SYMPTOMATIC AND ASYMPTOMATIC CHILDREN WITH PERINATAL HIV INFECTION

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One hundred thirty-five children born to human immunodeficiency virus (HIV)-infected mothers were selected randomly to receive immunoglobulin (Gamimune-N, Miles Pharmaceutical Co) 200 mg/kg monthly for 1 year. All patients were seropositive by ELISA and Western blot at birth. At the time of the study, 15 symptomatic (P_2) and 57 asymptomatic (P_1) patients with evidence of viral infection (positive HIV culture or P_{24} antigen) received the immunoglobulin. Sixty-three indeterminate (P_0) patients with no evidence of infection served as the control. Mean age for infants in group P_2 was 32 months, 26 months for group P_1, and 11 months for group P_0.

Significant reduction in the frequency of bacterial infections (ie, otitis media, upper respiratory tract infections, urinary tract infections, and acute gastroenteritis) was seen in the symptomatic group compared with both the asymptomatic and the control groups. Growth as measured by weight and height >50th percentile was also markedly better in the symptomatic group than either asymptomatic or control patients. There was no significant difference in head circumference in all three groups. These results indicate that monthly intravenous immunoglobulin infusion (IVIG) appears to be beneficial to both symptomatic and asymptomatic HIV patients in reducing the frequency of bacterial infection and also enhancement of the immune response. However, symptomatic patients responded much better than the asymptomatic patients. (*J Natl Med Assoc.* 1997;89:543-547.)

Key words: human immunodeficiency virus ◆ intravenous immunoglobulin ◆ children

Several published reports have suggested that intravenous immunoglobulin (IVIG) in symptomatic human immunodeficiency virus (HIV)-infected children may result in immunologic improvement and reduction in frequency of bacterial infections.[1-7] Recent national multicenter studies also have confirmed the benefit of prophylactic use of immunoglobulin in symptomatic HIV-infected children and has shown significant increase in the time free from serious bacterial infections for those receiving such treatment with CD4>.2×10^9/L.[8-11] However, none of the published reports have looked at the use of immunoglobulin in asymptomatic HIV-positive children.

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Table 1. Characteristics of Study Group*

HIV Classification	No. Patients	Mean Age (Months)	Mode of Transmission	ELISA/WB	P_{24} Antigen	Maternal Risk Factor
P_0	63	11	Perinatal	+/+	–	IVDA
P_1	57	24	Perinatal	+/+	+	IVDA
P_2	15	36	Perinatal	+/+	+	IVDA

Abbreviations: HIV=human immunodeficiency virus, ELISA=enzyme-linked immunosorbent assay, WB=Western blot, and IVDA=intravenous drug abuse.
*N=135.

Because perinatal HIV infection always is associated with maternal transfer of anti-HIV-antibody, the benefits of immunoglobulin in asymptomatic patients in relation to their symptomatic counterparts among a perinatal HIV-infected population were evaluated at two pediatric clinics (Howard University Hospital and DC General Hospital, Washington, DC). This study was designed to determine whether the reported protective role of immunoglobulin in symptomatic patients was achievable in the asymptomatic, infected children. This was done by evaluating:

- frequency of bacterial infections,
- immunological response,
- improvement in growth and development, and
- enhancement of HIV disease through the use of IVIG.

METHODS

One hundred thirty-five children born to HIV-infected mothers comprised the study population. The patients were grouped (P_0, P_1, and P_2) according to CDC classification. Informed consent was obtained from their parents or legal guardians. Sixty-three children with a mean age of 11 months were in the P_0 (indeterminate) group, 57 HIV-positive asymptomatic children were in the P_1 group, and 15 symptomatic patients were in the P_2 group (Table 1).

All of the patients in the P_0 group had a positive enzyme-linked immunosorbent assay (ELISA) and Western blot, with no positive viral culture, or P_{24} antigen suggestive of infection. Both symptomatic and asymptomatic patients were ELISA and Western blot positive with either HIV culture positive or P_{24} antigen positive. The symptomatic patients also had lymphadenopathies, failure to thrive, and hepatosplenomegaly.

All P_1 and P_2 patients received immunoglobulin (Gamimune-N, Miles Pharmaceutical Co). P_0 patients did not receive any infusion. Immunoglobulin was given at a dose of 200 mg/kg every month at 28-day intervals for 1 year. At each visit, a complete physical examination including weight, height, and head circumference measurements was done. Blood samples were drawn for ELISA, Western blot, P_{24} antigen, CD4 cell count and HIV culture studies. Patients who missed three clinic appointments were removed from the study. A home visit policy was instituted to ensure punctuality to the clinic on the scheduled day, thus ensuring good compliance.

RESULTS

Study results indicate that immunoglobulin had a significant effect on patients with abnormal immune systems. While most of the primary infections recorded (Table 2) were minor, it is shown that IVIG had a significant role in reducing the frequency of such infections in both symptomatic and asymptomatic HIV-infected patients. Otitis media and upper respiratory, urinary, and gastrointestinal tract infections were the most frequently diagnosed illnesses.

Otitis media occurred 5.6 times more in the untreated indeterminate (P_0) group than in the treated symptomatic P_2 group and 3.8 times more in the treated asymptomatic P_1 group than the P_2 group. Upper respiratory tract infection was diagnosed 6.3 times more in the P_0 group than in the P_2 group and 4.8 times more in the P_1 group than in the P_2 group. Urinary tract infection was diagnosed 3 times more in the P_0 group than in the P_2 group and 3.3 times more in the P_1 group than in the P_2 group. Acute gastrointestinal tract infection occurred about 5 times more in P_0 patients than in P_2 patients and 3.8 times more in P_1 patients than in P_2 patients.

Table 2. Clinical and Laboratory Findings of the Study Groups

	P_0 (n=63)		P_1 (n=57)		P_2 (n=15)	
Infections						
Otitis media	252		171		45	
Upper respiratory infection	378		285		60	
Urinary tract infection	315		342		105	
Acute gastroenteritis	441		345		90	
Total	1386		1143		300	
Growth and Psychomotor Development						
Weight & height gain ≥50th percentile	33 (52%)		38 (67%)		13 (87%)	
Mean CD4 Count	**Before***	**After†**	**Before**	**After**	**Before**	**After**
$\times 10^9$/L	1.67	1.78	1.21	2.11	1.13	2.31
Change	+0.11		+0.90		+1.18	
Percent change	+6.6		+74		+104	

*Before intravenous immunoglobulin infusion.
†After intravenous immunoglobulin infusion.

Immunological response to the IVIG administration was greater in P_2 patients than either P_1 or P_0 patients. The percent change of CD4 count, before and after IVIG infusion, shows a +6.6% increment in CD4 count among the P_0 group, +74% in the P_1 group, and + 104% in the P_2 group. Improvement in growth and developmental parameters were better in P_2 patients than in either P_1 or P_0 patients.

DISCUSSION

The rationale for the therapeutic use of IVIG in symptomatic HIV patients has been based on various abnormalities of B-lymphocytes with functionally impaired antibody responses and recurrent bacterial infections.[12-17] Intravenous immunoglobulin contains a pool of specific antibodies that react with a variety of microbial agents and thus prevent occurrence of those specific infections. This study looked at two groups, symptomatic and asymptomatic HIV-infected patients, to see whether similar findings reported in symptomatic HIV children also can be seen in asymptomatic patients. Any major serious bacterial infections were unable to be documented. Most of the clinical infections recorded in all the groups were minor (otitis media, upper respiratory tract infection, urinary tract infection, and acute gastroenteritis with diarrhea).

The Figure shows the graphic representation of all types of infection among the three groups. A total of 300 episodes of infection were diagnosed among the symptomatic P_2 patients receiving immunoglobulin, 1143 among the P_1 asymptomatic patients, and 1386 among the P_0 intermediate group.

In both symptomatic and asymptomatic patients, significant benefits of IVIG were noted in decreasing the frequency of most commonly encountered pediatric ailments. The reduction was appreciated more markedly in the symptomatic patients than in the asymptomatic group. The reason for a significantly higher response in P_2 patients compared with P_1 patients is unknown. However, it is suspected that the higher level of response in P_2 patients may be related to the increased level of P_{24} antigenemia and the stage of the disease.

We postulated that by virtue of the stage of HIV infection coupled with low CD4 count and functionally impaired antibody created by B-cell defect, functional unimpaired antibody requirement by P_2 patients for adequate defense against microbial agents would be higher. Therefore, infusion of IVIG that contains a pool of specific antibodies in either asymptomatic or symptomatic perinatal HIV patients will result in increased defense activities against potential microbial agents. The level of the response therefore will depend on the extent of damage to the antibody-producing cells. The more the damage, the greater the response.

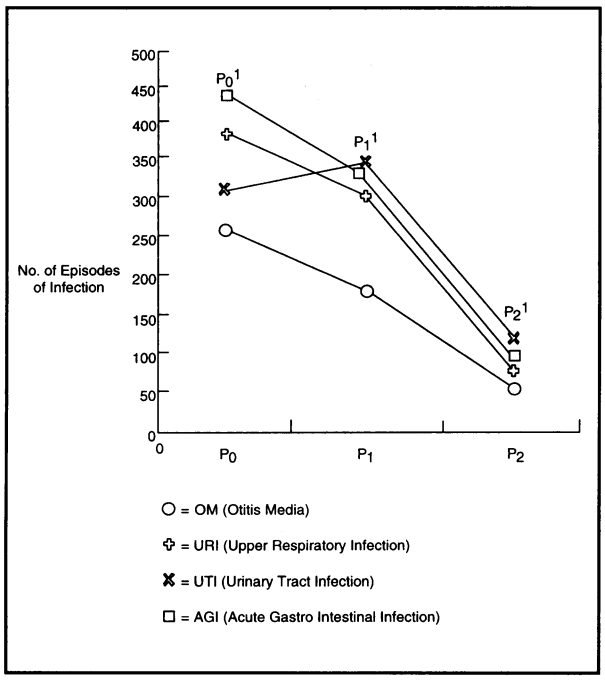

Figure.
Frequency of infection in relation to the stage of HIV disease. ([1]CDC HIV classification for children: P_0=indeterminate, P_1=asymptomatic, and P_2=symptomatic).

Although the level of immune complexes formed and the phagocytic activities in the treated group was not evaluated, we believe that some intrinsic immune enhancers are responsible for the beneficial effects of IVIG seen in these groups of patients. This might explain the remarkable response of both symptomatic and asymptomatic patients to IVIG administration.

We also have shown improvement of CD4 lymphocyte counts (Table 2) where P_2 patients had +104% change in CD4 counts compared with +74% and +6.6% for P_1 and P_0 patients, respectively. In addition, improvement was seen in both growth and motor development in the two groups while receiving immunoglobulin. There were no other opportunistic infections noted during the study period.

Progression of HIV disease in any of the IVIG-treated group was unable to be demonstrated, as has been suggested by other investigators.[18-20] None of the patients died during the study period. The major problem for IVIG therapy was the cost. Since the majority of these patients had no medical insurance, continuous utilization of this product was a big financial burden.

CONCLUSION

Intravenous immunoglobulin use in both symptomatic and asymptomatic children with perinatally acquired HIV infection resulted in fewer bacterial infections and improved CD4 cell counts. Similar studies on a much larger scale are needed to confirm these findings and to substantiate benefit of this product for asymptomatic patients.

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