Acta Paediatrica Academiae Scientiarum Hungaricae Vol. 9 (2), pp. 189—195 (1968)

Effect of Monthly Gamma-Globulin Administration on the Serum Gamma-Globulin Level of Premature Infants

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(Received September 29, 1967)

Staphylococcus aureus cross infections have become an everyday occurrence since more than a decade. Their prevention by means of gamma-globulin is now widely practised in newborn and premature babies, the principal sources of cross infection. The preventive value of repeated gamma-globulin administration seems to be evident from numerous clinical reports [1, 2, 14, 24, 27], although certain authors [15, 25] are somewhat sceptical in this respect.

Prolonged gamma-globulin treatment has at the same time raised a number of problems. It has been shown [19, 20] that repeated administration of gamma-globulin during the first year of life inhibits or delays the production of certain antibodies, while differences in the structure and, consequently, in the antigenic properties of the gamma-globulins lead to the production of anti-gamma-globulin antibodies in passively immunized infants [18, 26]. This induces sensitization and diminishes the therapeutic effect of the introduced gamma-globulin. The present study was designed to determine the effect of monthly administered gamma- globulin on its concentration in the blood of premature infants.

Material and Method

Two groups of premature infants of approximately equal body weight formed the material of this study. Members of the first group (test group in the following) received prophylactic gamma-globulin treatment, while those of the second (control) group received no such treatment. Table I shows the age distribution of the infants and the time of examinations. The first three examinations were carried out on one and the same individual in each of the groups, while later periods included some previously not examined individuals. The infants in the test group received 1 ml/kg of 10% gamma-globulin at birth and then at least four times at one-month intervals, and were not subjected to plasma or blood treatment. Members of the control group received none of these treatments. Blood was taken from the cephalic vein usually in the morning, and analysed in a fresh condition. Kjeldahlometric and paper-electrophoretic examinations of the blood samples were carried out in the usual manner in parallel experiments.

Results

Fig. 1 illustrates serum gamma-globulin levels in different periods.

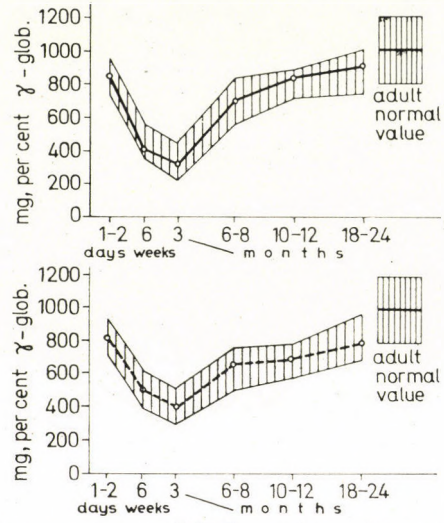

FIG. 1. Mean and extreme gamma-globulin values (mg per 100 ml) at different times. (Above: prophylactically treated infants; below: untreated babies)

TABLE I

Number and distribution of examined infants

Age	1—2 days	6 weeks	3 months	6—8 months	10—12 months	18—24 months
Treated with gamma-globulin	50	50	50	38	27	23
Untreated	50	50	50	32	29	26
Total	100	100	100	70	56	49

Compared with that of the test group, the curve of mean values descended steeper in the controls during the first six weeks of life, and its minimum at the age of 10 to 12 weeks was still lower than in the test group. When the values had started to rise, i.e. at the age between 3 and 6 months, the control curve rose quicker all along. Yet, the mean value had not reached the adult average even after two years; the serum-globulin level in the test group reached just the lowest limit of the adult value.

Fig. 2 shows the combined gamma-globulin curves of the two groups at different times. The serum gamma-globulin level was higher in the test group during the first three months; the difference between the two groups failed, however, to reach statistical significance ($p > 0.2$). The two curves

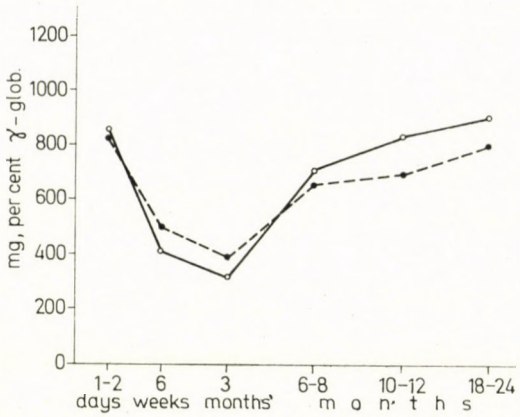

FIG. 2. Serum gamma-globulin level in treated and untreated infants during and after prophylactic treatment of the test group

intersected at the age of about 6 months (i.e. after the termination of prophylactic treatment) so that the mean gamma-globulin level had, at the age of one year, become higher in the controls than in the members of the test group ($\simeq 0.05$). The difference between the two groups was still considerable after 18 to 24 months ($p > 0.1$).

DISCUSSION

Few reports have dealt with the effect of repeated gamma-globulin administration on the biosynthesis of antibodies and the serum gamma-globulin level. Besides, data published so far were based on a few cases, and the amount of introduced gamma-globulin showed great variations. The available data do not, therefore, allow to form a true picture of the effect produced by passive antibodies on the serum gamma-globulin level; besides, most observations refer only to the time following the termination of gamma-globulin administration. STEEN [25], who administered 2×0.5 ml/kg of gamma-globulin two-weekly to 10 premature infants from the age of 3 weeks, found in the first four months a higher serum level than in untreated babies, whereas the situation was the opposite between the 6th and the 13th month, i.e., after prophylactic treatment had ended. AMER. et al [1] administered to a large number of prematures 3 ml/kg in the first week and then 1.5 ml/kg at monthly intervals over 8 months, while the controls received identical doses of 5% serum albumin. At the age of one year the serum gamma-globulin level was higher in the controls (0.72 ± 0.27 g per 100 ml) than in the treated group (0.62 ± 0.22 g per 100 ml). BARTOS [3] studied a few cases with hepatitis in which a single dose of 8 ml/kg was administered and found no difference in the serum gamma-globulin level between treated and untreated patients. NEJEDLA [19],

observing 10 mature infants who had received 0.2 ml/kg of gamma-globulin monthly until the age of 12 months, found that their serum level was not essentially different from that of untreated controls; it was only in the second month of life, i.e., after the first administration of gamma globulin, that its level in the serum of the controls became temporarily much lower.

The present results support the findings of AMER et al. [1] and those of STEEN [25] according to whom the serum gamma-globulin level of individuals systematically treated with exogenous gamma-globulin does not reach the control value after the age of 12 months. Examinations, carried out by us at different intervals, proved on the other hand that in the test group the serum gamma-globulin level was higher during the time of prophylactic treatment, a fact which calls for the regular control of the effect of exogenous gamma-globulin in the early and the later phase alike.

It would seem obvious that the initially higher serum gamma-globulin level in the test group was due to the exogenous supply. It was, however, demonstrated by MARTIN DU PAN et al [16] and HÄSSIG [11] that intramuscularly administered gamma-globulin is absorbed very slowly and that much of the absorbed amount was destroyed by proteolysis. It follows that the relatively small absorbed quantity cannot produce significant changes in the amount of circulating gamma-globulins. This is the more probable as, according to the results of JANEWAY and GITLIN [9, 12, 13], only half of the organism's total amount of gamma-globulins is circulating in the blood paths, while the other half is in the extravascular compartment. Resynthesis of amino acids liberated by proteolysis may be partly responsible for the observed elevation of the intravascular gamma-globulin level, a possibility suggested by considerations concerning the proteins of mother's milk. Although it has been demonstrated [10, 18, 28] that the immune proteins of colostrum and mother's milk are not absorbed from the gastrointestinal tract, it is commonly known that breast-fed babies show an increased resistance to infections and not only to local intestinal infections. DÓBIÁS et al. [7], showed that the serum anti-alpha-haemolysin level increased in neonates if they were fed colostrum rich in antibodies. Again, CSORBA and JEZERNICZKY [4] found that in the first three months the decrease in the serum gamma-globulin level was less in breast-fed than in artificially fed babies. It seems probable that the amino acids of the protein of mother's milk are built up in the newborn organism into autologous proteins.

The low serum gamma-globulin level after the termination of prophyalactic treatment may be interpreted as follows.

(1) Infants treated with gamma-globulin are often considerably less susceptible not only to major but also to minor superficial infections. The absence of serial antigenic stimuli may, in itself, lead to a reduction

in the serum gamma-globulin level, or, else, the frequent infections suffered by subjects lacking the protection of gamma-globulin may accelerate the rate of endogenous gamma-globulin synthesis, a phenomenon observed in earlier investigations [4].

(2) It has repeatedly been demonstrated [6, 19, 20, 21, 22] that the presence of passive antibodies inhibits the production of the organism's own antibodies.

(3) Repeated administration of indifferent gamma globulins induces in the recipient the development of anti-gamma-globulin antibodies [8, 26] which interfere with the independent production of antibodies and the synthesis of gamma-globulins. It is, however, known that a certain time of latency is required for the recognition of antiglobulin antibodies after repeated blood and plasma transfusions as well as after exchange transfusions and the introduction of gamma-globulins. Consequently, it is only in a later phase, usually between 1 to 3 years of age, that the presence of anti-gamma-globulin antibodies might be responsible for the low serum gamma-globulin level of subjects treated with gamma-globulin; since, moreover, the production of these antibodies is not general [26] their responsibility is a partial one even in the latter phase.

(4) The question as to whether repeated introduction of gamma globulins accelerates the catabolism of endogenous gamma globulins still awaits elucidation. Acceleration of this kind, too, may influence the serum gamma-globulin level.

We suggest that the slowly increasing rate of gamma-globulin synthesis observed in individuals systematically treated with exogenous gamma-globulin, is mainly due to the absence of serial antigenic stimulation. The significance of such stimulation is clearly borne out by our earlier observation [4] that newborn babies in the deepening phase of hypogammaglobulinaemia, after superficial staphylococcal infection showed an enhanced production of gamma-globulins so that soon thereafter their serum level was sufficient for ensuring immunity.

The present investigations, in harmony with the observations of other authors, call for a thorough study of the individuals who were subjected to gamma-globulin treatment. Until the question of the still unclear consequences has been settled, it would be necessary strictly to define the range of indications of prophylactic treatment, the cases in which the treatment is justified, as well as the time, duration, the most adequate amounts and the number of doses. It is only natural that seriously threatened prematures in the first three months of life are in the greatest need of substitution, for at that age not merely the serum level of gamma-globulin but also its total circulating amount is reduced [5].

Summary

Gamma-globulin in doses of 1 ml/kg has been administered to premature

infants monthly over a period of 6 months, and the serum gamma-globulin level was studied by paper electrophoresis at the age of 1 and 2 days, 6 weeks, 3, 6, 12 and 24 months, and compared with the corresponding data of equally aged control subjects. The serum gamma-globulin level was higher during treatment but after its termination the level decreased below that of the controls. Factors that may influence the serum gamma-globulin level of prophylactically treated infants are analysed.

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