

## THE EFFECT OF VITAMIN A ON IMMUNOGLOBULIN LEVELS DURING OPERATIONS INVOLVING CARDIOPULMONARY BYPASS

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*SUMMARY : Effect of open and closed heart surgery on the serum levels of Ig A, Ig M and Ig G were carried out in hundred patients. In sixty cases undergoing cardiopulmonary bypass (CPB) serum Ig A and Ig M levels were found to be decreased in regard to baseline values. The mean Ig G level decreased in off bypass more significantly than hemodilution. In this study the rate of regeneration of immunoglobulins during post-bypass period was also determined. At early post-bypass 8-72 hours, serum levels of Ig A, IgM and Ig G were significantly lower than their baseline concentrations. On the other hand, on late post-bypass 10-20 days, Ig A and Ig M exceeded the baseline values, while Ig G only reaching its preoperative concentration. The rate of regeneration of Ig G, however, was slower than that of Ig A and Ig M. In order to investigate the effect of vitamin A, it was administered for ten days in twenty cases prior to open operations. While the baseline values of Ig A and Ig M in patients with vitamin A supplement, were higher than in those without vitamin A the baseline concentration for Ig G was almost the same. In patients with vitamin A, the serum levels of Ig A, Ig M and G firstly decreased in off bypass and then, in post-bypass period increased in a similar fashion but almost always remaining significantly above that of patients without vitamin A. In twenty cases having closed operations, three main immunoglobulin levels retained the same value. Thus, it may be concluded that operations involving CPB cause a significant quantitative decrease in the levels of Ig A, Ig M and Ig G not only off bypass but also at early post-bypass period and it is possible to prevent this fall partially with use of and adjuvant such as vitamin A.*

*Key Words: Cardiopulmonary bypass, closed heart surgery, immunoglobulins, adjuvant, vitamin A.*

### INTRODUCTION

Cardiopulmonary bypass (CPB) with maintenance of the circulation by a pump oxygenator in which blood is subjected to mechanical trauma and exposed to such polymeric surfaces as a result of hemolysis of red blood cells, reduced bypass levels of proteins associated with diminished function of leukocytes and serum opsonic activity (1-7, 11-18). To investigate the relationship between CPB and host defense functions in patients undergoing open heart surgery, this study was carried out to determine the influence of CPB procedure on three main classes of immunoglobulin levels (Ig A, IgM and IgG) as well as the effect of an adjuvant such as vitamin A on these kind of immunoglobulins.

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### MATERIALS AND METHODS

This study was carried out in the Department of Thoracic and Cardiovascular Surgery of Hacettepe University School of Medicine. One hundred patients in whom immunoglobulin levels were assessed were included in this study and were divided into three groups. In Group I sixty patients undergoing operations involving CPB are included. In Group II, twenty patients were administered vitamin A in the amount of 30 000 IU for ten days before the surgery. Group III consisted of twenty patients undergoing closed heart surgery which made up the control group.

The operation procedure consisted of median sternotomy for open heart surgery and left lateral thoracotomy for closed heart surgery. The patients were premedicated with 1 mg/kg meperidine hydrochloride intramuscularly half an hour before the operation. Induction of anesthesia following preoxygenation was accomplished in all patients with intravenous thiopentone sodium 4-6 mg/kg. Patients then ventilated manually via mask following loss of consciousness. Endotracheal intubation was performed

Table 1: Level of Ig A in patients undergoing open cardiac operations.

| Time                    | Patients I (undergoing open operations) (n: 60) | Patients II (given Vitamin A before open operations) (n: 20) | p Value | Hematocrite value (n: 20) |
|-------------------------|---|--|---------|---------------------------|
| Baseline                | 258.38±7.59                                     | 294.40±9.62  | p<0.05  | 41.00±1.01                |
| Off Bypass              | 181.50±5.93                                     | 208.20±6.64  | p<0.05  | 28.65±0.73                |
| At 8 hours post bypass  | 206.36±6.64                                     | 236.70±5.82  | p<0.01  |                           |
| At 72 hours post-bypass | 223.88±5.82                                     | 251.55±8.37  | p<0.05  |                           |
| On 10 days of operation | 272.65±6.85                                     | 301.75±9.92  | p<0.05  |                           |
| On 20 days of operation | 280.43±6.80                                     | 315±9.54   | p<0.05  |                           |

Normal range 40-420.

The values are expressed in milligrams per deciliter.

with intravenous suxamehonium. Anaesthesia was maintained with a mixture of oxygen, nitrous oxide and halothane. Adequate dosage of pancuronium or suxamehonium was administered during the operation in order to provide muscle relation.

Patients in Group I and II who underwent extracorporeal circulation were given heparin 3 mg per kilogram of body weight. Also 50 mg heparin was added to the priming solution. Cardiopulmonary bypass was instituted with a roller pump and a disposable bubble oxygenator with a built in heat exchanger. A nonpulsatile perfusion technique was used. The systemic temperature was cooled to + 28 to +30°C then additional topical hypothermia with iced slush was applied. Immediately after aortic cross-clamping +4°C potassium cardioplegia was administered for myocardial protection. Neither blood was used during the operation and nor antibiotics were administered to the patients or to the priming solution during the course of this study. As soon as patients were off bypass protamine administration was started.

Venous blood samples were collected from each patients before the operation (baseline), off bypass or end of the surgery in closed cases, at 8 and 72 hours post-bypass or operation in closed cases (both early post-bypass hours), on 10-20 days post-bypass or operation in closed cases (both late post-bypass days). Blood samples were obtained as near to the puncture site to avoid denaturation and stored at -70°C. The determination were assessed using Behring Werke partigen diffusion plates, including the standard reference serum were expressed in milligram per deciliter, by standard procedure by Fahey (10).

Hematocrite values were obtained baseline and off bypass with a Coulter-Counter S in 20 patients undergoing operations involving CPB. Serum concentration of immunoglobulins was

Figure 1: Ig A levels during open and closed heart operations. Ig A levels in Group I (open operations) (open circles), dropped steeply off bypass and increased in progressively at early post-bypass hours exceeding baseline value on late post-bypass days. In Group II (after vitamin A in open operations) (closed squares), Ig A decreased in off bypass and increased in post-bypass period in a similar fashion, but almost always remaining higher than the corresponding values for Group I. In Group III (closed operations) (open squares) the values retained the straight trend.

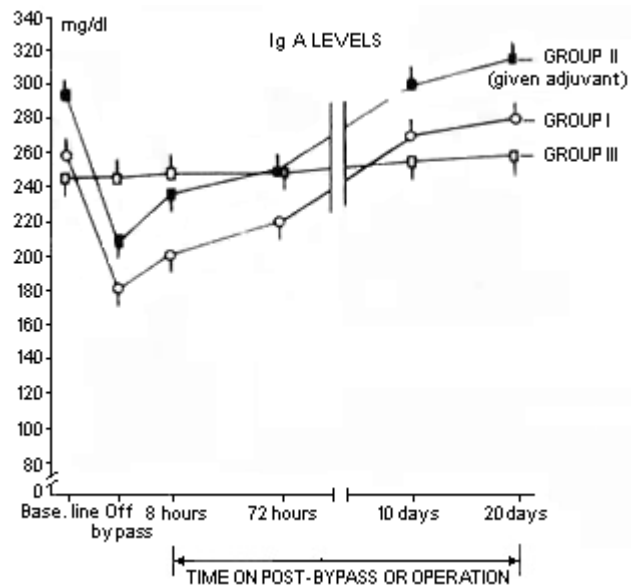


Table 2: Level of Ig A in patients undergoing open and closed cardiac operations.

| Time                                 | Patients I (undergoing open operations) (n: 60) | Patients III (undergoing closed operations) (n: 20) | p Value |
|--------------------------------------|---|---|---------|
| Baseline                             | 258.38±7.59                                     | 246.15±7.90   | p>0.05  |
| Off Bypass or operation              | 181.50±5.93                                     | 245.75±6.39   | p<0.01  |
| At 8 hours post bypass or operation  | 206.36±5.38                                     | 248.30±6.80   | p<0.01  |
| At 72 hours post-bypass or operation | 223.88±5.82                                     | 249.25±7.47   | p<0.05  |
| On 10 days of operation              | 272.65±6.85                                     | 256.65±6.60   | p>0.05  |
| On 20 days of operation              | 280.43±6.80                                     | 259.20±6.10   | p>0.05  |

Normal range 40-420.

The values are expressed in milligrams per deciliter.

Table 3: Level of Ig M in patients undergoing open cardiac operations.

| Time                    | Patients I (undergoing open operations) (n: 60) | Patients II (given Vitamin A before open operations) (n: 20) | p Value | Hematocrite value (n: 20) |
|-------------------------|---|--|---------|---------------------------|
| Baseline                | 124.75±4.53                                     | 153.85±7.30  | p<0.001 | 41.00±1.01                |
| Off Bypass              | 85±2.81   | 103.85±3.24  | p<0.001 | 28.65±0.73                |
| At 8 hours post bypass  | 91.98±2.74                                      | 111.20±4.97  | p<0.001 |                           |
| At 72 hours post-bypass | 103.03±3.05                                     | 124.00±5.58  | p<0.01  |                           |
| On 10 days of operation | 128.98±4.46                                     | 173.75±8.16  | p<0.001 |                           |
| On 20 days of operation | 131.58±4.37                                     | 178.20±8.33  | p<0.001 |                           |

Normal range 36-153.

The values are expressed in milligrams per deciliter.

corrected for hemodilution according to the formula : Immunoglobulin level (corrected) = Immunoglobulin level (measured) X baseline hematocrite volume/off bypass hematocrite volume. In statistical analysis, results are expressed as mean values ± standard error of the mean unless indicated otherwise. Differences between means were considered significant if the p value less than 0.05 as determined by Student t test.

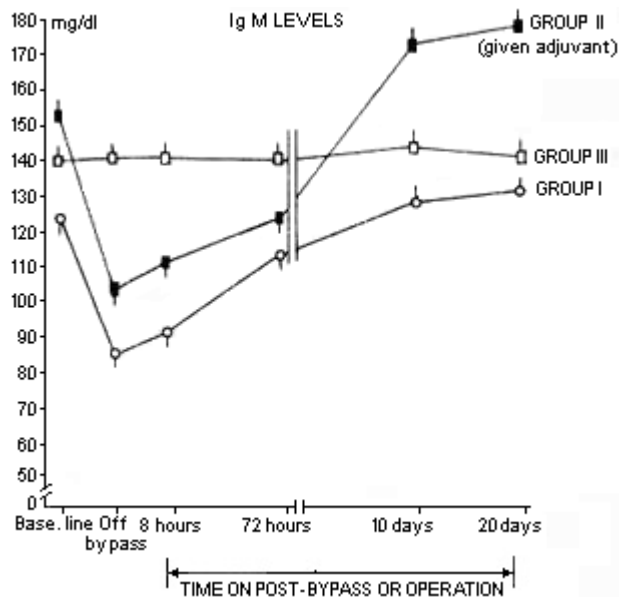
Table 4: Level of Ig M in patients undergoing open and closed cardiac operations.

| Time                                 | Patients I (undergoing open operations) (n: 60) | Patients III (undergoing closed operations) (n: 20) | p Value |
|--------------------------------------|---|---|---------|
| Baseline                             | 124.75±4.53                                     | 140.00±5.90   | p>0.05  |
| Off Bypass or operation              | 85.00±2.81                                      | 141.35±5.91   | p<0.001 |
| At 8 hours post bypass or operation  | 91.98±2.74                                      | 141.60±5.70   | p<0.001 |
| At 72 hours post-bypass or operation | 103.03±3.05                                     | 140.00±5.79   | p<0.001 |
| On 10 days of operation              | 128.98±4.46                                     | 144.10±5.40   | p>0.05  |
| On 20 days of operation              | 131.58±4.37                                     | 141.10±4.86   | p>0.05  |

Normal range 36-153.

The values are expressed in milligrams per deciliter.

Figure 2: Ig M levels during open and closed heart operations. Ig M levels in Group I (open operations) (open circles), dropped steeply off bypass and increased in slowly at early post-bypass hours, returning to baseline value on late post-operative days. In Group II (after vitamin A in open operations) (closed squares), Ig M decreased in off bypass and increased in post-bypass period in a similar fashion, exceeding baseline on late post-operative days, higher than the corresponding values for Group I. In Group III (closed operations) (open squares) the values retained on a straight trend.



RESULTS

In Group I sixty patients (undergoing operations in volving CPB without vitamin A (Tables 1,3,5 and Figures 1,2,3) the mean baseline levels of IgA, IgM and IgG as well as hematocrite values were within normal range. Since complete hemodilution applied during the surgery, the hemodilution rate in the perfusion system was found 30 per cent due to hemotocrite changes. The level of main classes immunoglobulins (IgA, IgM, IgG) followed the changes in the hemotocrite values. Off bypass, the decrease in IgA and IgM levels were attributed to hemodilution changes. Following correction for hemodilution, IgG showed a profound decrease more than IgA and IgM, in the rate of 19 percent (p<0.05). At early post-bypass 8-72 hours, whereas values of three classes of immunoglobulins progressively elevated, these levels were still lower than the baseline concentration. On the late post-bypass 10-20 days, although the values of IgA and IgM exceeded the baseline, IgG reached only the baseline concentration.

Table 5:Level of Ig G in patients undergoing open cardiac operations.

| Time                    | Patients I (undergoing open operations) (n: 60) | Patients II (given Vitamin A before open operations) (n: 20) | p Value | Hematocrite value (n: 20) |
|-------------------------|---|--|---------|---------------------------|
| Baseline                | 1131.25±32.16                                   | 1250.20±40.17  | p<0.05  | 41.00±1.01                |
| Off Bypass              | 586.30±16.64                                    | 681.25±20.71   | p<0.01  | 28.65±0.73                |
| At 8 hours post bypass  | 724.18±20.60                                    | 839.85±22.55   | p<0.01  |                           |
| At 72 hours post-bypass | 846.83±23.86                                    | 923.95±30.85   | p>0.05  |                           |
| On 10 days of operation | 1128.08±24.73                                   | 1261.80±35.72  | p<0.01  |                           |
| On 20 days of operation | 1157.36±24.32                                   | 1295.55±35.96  | p<0.05  |                           |

Normal range 600-2200.

The values are expressed in milligrams per deciliter.

Table 6:Level of Ig G in patients undergoing open and closed cardiac operations.

| Time                                 | Patients I (undergoing open operations) (n: 60) | Patients III (undergoing closed operations) (n: 20) | p Value |
|--------------------------------------|---|---|---------|
| Baseline                             | 1131.25±32.16                                   | 1117.85±37.75                                       | p>0.05  |
| Off Bypass or operation              | 586.30±16.64                                    | 1104.45±34.04                                       | p<0.001 |
| At 8 hours post bypass or operation  | 724.18±20.60                                    | 1129.8±27.46  | p<0.001 |
| At 72 hours post-bypass or operation | 846.83±23.86                                    | 1163.60±30.22                                       | p<0.001 |
| On 10 days of operation              | 1128.08±24.73                                   | 1144.95±26.83                                       | p>0.05  |
| On 20 days of operation              | 1157.36±24.32                                   | 1159.40±29.71                                       | p>0.05  |

Normal range 600-2200.

The values are expressed in milligrams per deciliter.

In Group II twenty patients (Vitamin A administered prior to operations involving CPB) (Tables 2,4,6 and Figures 1,2,3), the mean baseline IgA, IgM and IgG levels were significantly higher than in Group I patients. Those values also at first decreased in off bypass and later, showed a gradual increase in the same pattern of changes, but almost always remaining higher than those corresponding values for Group I. Present results showed

that during post-bypass period, the highest increase was noted in IgM level followed by IgA. The least increase was observed in IgG level while showing no difference between 72 nd post-bypass hours and baseline value, in contrast on late post-bypass days it also exceeded both the baseline concentration as well as those values for Group I.

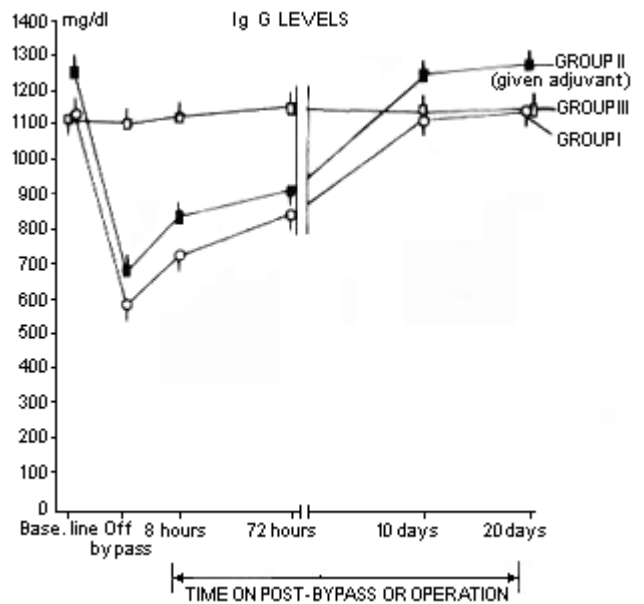
In Group III twenty patients, having closed operations (Tables 2,4,6 and Figures 1,2,3) the levels of ±IgA, M and IgG retained the same baseline value during both early and late post operative period. When Group I and III were compared with, for three main classes of immunoglobulins, the difference between off bypass and early post-bypass hours were of importance (p<0.05 - 0.01), on late post-bypass days the difference were insignificant (p>0.05).

DISCUSSION

It is generally recognized that in patients undergoing operations involving CPB, the host defense system is tem-

Figure 3: Ig G levels during open and closed heart operations. Ig

G levels in Group I (open operations) (open circles), reduced steeply off bypass and increased in progressively at early post-bypass hours, returning baseline value on late post-bypass days. In Group II (after vitamin A in open operations) (Closed squares), Ig G decreased in off bypass and increased in post bypass period in a similar fashion, but always higher than corresponding values for Group I. In Group III (closed operations) (open squares) the values retained on a straight trend.



porarily impaired (1-7, 11,18). As a part of host defense system, in this study the influence of CPB on levels of three main classes of immunoglobulins were carried out. It was previously reported that serum levels of immunoglobulins were reduced in open heart surgery (11,16,18). Our present findings have confirmed these data and have shown in addition that the low IgA and IgM concentrations were the result of hemodilution. It was interesting that the quantitative change in IgG level which was more significant than hemodilution was also different from those for IgA and IgM. The greater reduction in IgG compared with IgA, IgM provided that IgG is actively consumed during CPB (11). In addition to this conception, it has been proposed that the air-liquid interface of the oxygenator was a possible etiologic factor contributing to denaturation and aggregation of IgG (12). In fact, it has also been suggested that IgG may be cleared or denatured through some mechanism other than hemodilution (18).

In this study other interesting result has been obtained that the regeneration of IgG was slower than that of IgA and IgM during early and late post-bypass period. In the studies previously reported that the immunoglobulin levels for the late post-bypass days were not revealed (11,12,16). Another illustrative point in our study was the evaluation of stimulating effect of an adjuvant such as vitamin A upon which regeneration of immunoglobulins in operations involving CPB is improved it has been previously reported that vitamin A has reduced the morbidity and mortality rate in children with measles and also has a stimulating effect on immune defense system after thermal injury (8,9,13). For the first time in this field, in patients with vitamin A supplement, the three classes of immunoglobulins remained significantly higher than the baseline value and reduced less "off bypass" as well as demonstrative higher increase in post-bypass period as compared with cases without vitamin A. Other prospective studies are required in evaluating the effect of vitamin A on the immunoregulatory system is of clinical significance and whether prophylactic administration is beneficial in operations involving CPB.

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