THE EFFECT OF VITAMIN A ON COMPLEMENT LEVELS DURING OPEN HEART SURGERY

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SUMMARY: Complement level (C_3) measurements and the effect of an adjuvant on this complement level were carried out in a hundred patients undergoing open and closed heart surgery, at the end of bypass and after correction for hemodilution, a significant, abrupt fall in the complement level was observed. Later, the complement level began to rise gradually in the early post-bypass period of 8-72 hours, to exceed the baseline value later. Vitamin A was administered to twenty patients preoperatively in order to establish its adjuvanicy on the complement level. Off bypass and during the early post-bypass period, the complement level in patients with vitamin A showed a higher baseline value and less decrease compared with those without vitamin A. However in the late post-bypass period, the difference was significant in both groups of patients. In twenty patients having closed heart surgery, the complement level did not show any significant difference between baseline and post-bypass period. Thus, it may be concluded that open heart operations cause a significant quantitative decrease in the complement level and it is possible to reduce this fall partially by administration of vitamin A.

Key Words: Cardiopulmonary by-pass, closed heart operations, adjuvant, vitamin A, complement, hemodilution.

INTRODUCTION

Cordiopulmonary bypass (CPB) as a means of extracorporeal circulation by a pump-oxygenator has become an established modality for the support of patients during operations involving CPB (1-7, 11-14, 20). It is generally recognized that in patients undergoning CPB, the host defense system is temporarily impaired (1-7). The decrease in host resistance against invading or endogenous microorganisms can lead to postoperative infections (1-7). It has been suggested that the observed higher infection rate in patients undergoing CPB may on partly the result of CPB procedure which is associated with hemolytic anemia, reduced level of serum opsonic activity, denaturation of circulating blood proteins with diminished function of leukocytes and lymphocytes (1-7, 11-13, 16-20). This study was carried out to determine the influence of both the cardiopulmonary bypass mechanism and of an adjuvant such as vitamin A on the complement level, in order to investigate the relationship between cardiopulmonary bypass and host defence mechanism in patients undergoing operations involving CPB.

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 the complement levels were assessed were included in this study and were divided into three groups. In Group I, sixty patients undergoing open heart surgery

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were included. In Group II, twenty patients were administered vitamin A in a dose of 30000 IU for ten days before the operation. Group III consisted of twenty patients undergoing closed heart surgery and 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 anaesthesia following preoxygenization was accomplished in all patients with intravenous sodium thiopentone 4-6 mg/kg. Patients then ventilated manually via masks following loss of consciousness. Endotracheal intubation was performed with intravenous suxamethonium. Anaesthesia was maintained with a mixture of oxygen, nitrous oxide and halothane. Adequate dosage of pancuronium or suxamethonium was administered during the operation in order to provide muscle relaxation.

Patients in Group I and II who underwent extracorporeal circulation were given heparin in a dose of 3 mg per kilogram of body weight. In addition 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 +28 to +30°C then additional topical hpyothermeia with iced slush was applied. Immediately after aortic cross-clamping, +4°C potassium cardioplagia was administered for myocardial protection. Blood was not used during the operation and antibiotics were not administered preoperatively to the patients or to the priming solution during the course of this study. As soon as the patients were off the bypass, protamine administration was started.

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

Hematocrit values were obtained baseline and off bypass with a Coulter-Counter S in twenty patients undergoing operations involving CPB. Serum concentration of complement level was corrected for hemodilution based on the following formula: Complement level (corrected) = Complement level (measured) x Baseline hematocrit volume of bypass hematocrit volume.

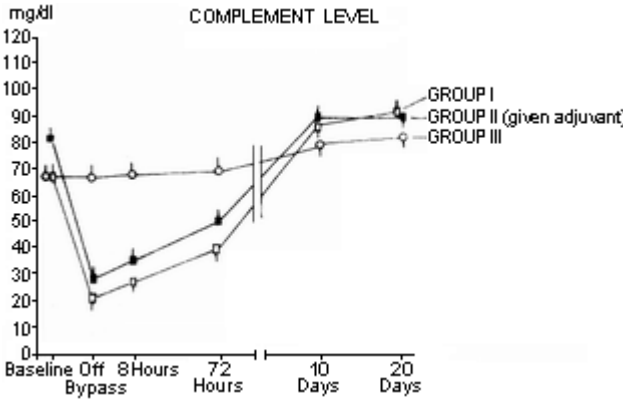

Figure 1: Complement levels during open and closed heart operations. Complement levels in Group 1 (open heart operations) (open squares), dropped steeply off bypass and increased slowly during early post-bypass hours, exceeding baseline value on late post-bypass days. In Group II (after vitamin A in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

Table 1: Level of Complement in Patients Undergoing Open Cardiac Operations.

Time	Group I Patients (undergoing open operations) (n=60)	Group II Patients (given Vitamin A before open operations) (n=20)	p value	Hematocrit value (n:20)
Baseline	68.31± 2.73	82.25 ± 3.18	p<0.001	41.00 ± 1.01
Off Bypass	21.20 ± 0.06	28.65 ± 1.11	p<0.001	28.65 ± 0.73
At 8 hours Post-bypass	27.33 ± 1.17	35.55 ± 1.43	p<0.001	= early post-bypass hours
At 72 hours Post-bypass	39.21 ± 1.59	49.00 ± 2.03	p<0.01	
On 10th day post-operation	85.33 ± 2.68	88.20 ± 2.76	p>0.05	= late post-tbypass days
On 20th day post-operation	89.55 ± 2.66	88.25 ± 2.78	p>0.05	

Normal range 55-120

The values are expressed in miligrams per deciliter.

In statistical analysis, results were expressed a mean values ±standard error of the mean unless indicated otherwise. Differences between means were considered significant if p value was less than 0.05 as determined by Student t test.

RESULTS

In the sixty patients in Group I (undergoing CPB without vitamin A) the complement level dropped abruptly off bypass then rose gradually during post-bypass period in a parabolic fashion (Table 1, Figure 1). Although complete hemodilution was carried out in CPB, the degree of dilution in the perfusion system was approximately 30 per cent as shown by the hematocrit values. Thus, the off bypass period, following the correction for hemodilution, the complement level fell significantly at by rate of 39 per cent ($p<0.001$). Later a slow regeneration was observed. Although the complement level was significantly less than the baseline level at early post-bypass 8-72 hours, it signficnatly exceeded the baseline value on late post-bypass 10-20th days ($p<0.001$).

In the twenty patients in Group II (administered vitamin A before open operations) the complement level also dropped off bypass, below the baseline value (Table 1, Figure 1). It then rose during early post-bypass (8-72 hours), reaching the baseline level on late post-bypass (10-20th days). Complement level for Group II patients is also presented by a parallel line but almost always higher than the values for Group I patients ($p<0.05$-0.001). A significant difference in baseline, off bypass and early post-bypass values were noted between Group I and II patients ($p<0.05$-0.001). However, on late post-bypass 10-20th days the difference was not significant ($p>0.05$).

In the twenty patients in Group III, (having closed heart surgery), the complement level demonstrated an almost straight line during the operative and post-operative periods compared with the parabolic fashion in Group I and II patients. When Group I and II were compared, no difference was noted between baseline values, while the difference between off bypass and post-bypass period were significant ($p<0.05$).

DISCUSSION

In patients undergoing open heart surgery, decreased host defense may significantly increase the risk of infections (1-7, 20). Since complement plays an essential role in the host defense mechanism, complement plays an essential role in the host defense mechanism, complement levels were determined in patients involving CPB surgery in this study. Off bypass, following the correction for hemodilution, the decrease in the complement level was of importance. Parker *et al.* also observed a decrease in the complement level involving CPB surgery (18). However, in this study neither measurement in the post-bypass period nor correlation between complement level and hemodilution were carried out. The degree of reduction of complement level could not be fully explained by hemodilution. It also suggested blood loss and complement consumption which was in agreement with earlier reports on complement activation during CPB (11-13, 15).

Following termination of bypass the increase in complement level may be associated with "going off hemodilution", blood transfusion and the administration of protamine sulfate which activates the complement system as well as the stimulator effect of the perfusion system upon the complement components (13,15,20). Most complement factors react as acute phase reactants which might explain the rapid restoration of complement values relative to the hematocrit values at early post-bypass hours (20).

Table 2: Level of Complement in Patients Undergoing Open and Closed Cardiac Operations.

Time	Group I Patients (undergoing open operations) (n:60)	Group II Patients (undergoing closed operations) (n:20)	p value
Baseline	68.31± 2.73	67.85 ± 2.48	p>0.05
Off Bypass or operation	21.20 ± 0.96	66.90 ± 2.14	p<0.001
At 8 hours Post-bypass or operation	27.33 ± 1.17	67.50 ± 2.17	p<0.001
At 72 hours Post-bypass or operation	39.21 ± 1.59	68.30 ± 2.17	p<0.001
On 10th day post-operation	85.33 ± 2.68	81.65 ± 2.68	p<0.01
On 20th day post-operation	89.55 ± 2.66	84.00 ± 1.63	p<0.01

Normal range 55-120

The values are expressed in miligrams per deciliter.

In order to increase the host defense mechanism in patients involving CPB, an adjuvant such as vitamin A were administered in a group of patients prior to surgery. The adjuvanicy of vitamin A was first clearly recognized by Dresser (8). Recent studies revealed that high doses of vitamin A reduced morbidity and mortality in children with measles (9). Other studies showed that immunosuppression resulting from thermal injury had been prevented by supplement of vitamin A in cellular and humoral immunoresponse (14). For the first time in the literature in patients given vitamin A, the complement level during baseline, off bypass and at early post-bypass hours increased significantly compared with patients who were not given vitamin A. The result of this resent study indicates that CPB cause a significant decrease in the complement level and it is possible to reduce this fall partially with the use of vitamin A. The stimulating effect of vitamin A on the immune system is yet unclear and requires further study. The clinical importance of the adjuvanicy of vitamin A still remains to be determined.

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