Serum and Urinary Fibrin/Fibrinogen Degradation Products in Patients with Korean Hemorrhagic Fever;

With Particular Reference to Disseminated Intravascular Coagulation and Acute Renal Failure

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ABSTRACT

Korean hemorrhagic fever is a disease with an acute onset of severe hemorrhagic tendency and acute renal failure. Acute renal failure may be produced by inducing intravascular coagulation in experimental animals, and also coagulation mechanisms may play a pathogenetic role in certain human renal diseases. One of the clinical consequences of DIC is serious ischemic tissue damage due to capillary flow blocking by fibrin deposits. The kidney is particularly vulnerable to ischemic effects. For the detection of intravascular coagulation, FDP assay is known as a more sensitive and reliable test than are other coagulation studies. Therefore, from September, 1973 to January, 1974, the serum and the urine of the selected patients with Korean hemorrhagic fever who had a typical clinical course were subjected to study. The alterations of the serum and urinary FDP concentrations, and the other hematologic, blood chemistry, and urinary examinations were studied in a total of 177 examples of each febrile, hypotensive, oliguric, diuretic, and convalescent phase. Both the serum and urinary FDP concentrations were significantly higher than normal. This data indicates that DIC is detected in Korean hemorrhagic fever, where it may play a major pathogenetic role. And the urinary FDP concentration more closely reflects the severity of renal lesions in this disease than does the serum FDP concentration and the blood urea nitrogen level. It can be assumed that the concentration of urinary FDP can be used as a therapeutic criteria, and is correlated to the intensity and the prognosis of the disease. Also the possibility of improvement following anticoagulant treatment may be proposed. It appears that acute renal failure in this disease has a close relationship to DIC. In its pathogenesis it can be assumed that disruption of the renal cortical perfusion plays

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a major role in this Korean hemorrhagic fever.

Korean hemorrhagic fever (hemorrhagic nephroso-nephritis, or hemorrhagic fever with renal syndrome) is a disease characterized by acute onset of a severe hemorrhagic tendency and acute renal failure. The etiology of this disease is yet unknown, but is suspected to be a viral infection.

Intensive investigation of the pathogenesis of acute renal failure has been done, but still the exact mechanism involved remains unclear. Four pathophysiologic mechanisms, however, have been recognized as primary factors in the pathogenesis of acute renal failure (Clarkson, et al., 1970; Bullock and Shapiro, 1974). Acute renal failure may be produced in animals by inducing intravascular coagulation and Robson (1965) and Hardaway (1966) suggested that such a mechanism might contribute to renal failure in man. There has been little direct evidence to support this postulate. However, there is experimental evidence for the participation of a coagulation process in renal diseases (Thomas and Good, 1952; Robbins and Collins, 1961; Vassalli and McCluskey, 1964; Halpem, et al., 1965).

The proposed etiology of disseminated intravascular coagulation (DIC) can be classified into three categories. Plasma finally produces fibrin/fibrinogen degradation products (FDP), which participate in the hemorrhagic diathesis. Therefore, detection of these fragments is a sensitive method of diagnosing DIC (Colman, et al., 1972). DIC may lead to three clinical consequences: a potential bleeding tendency; serious ischemic tissue damage due to the deposits of fibrin in the capillary; and red cell damage (Rapaport, 1972). Recently the concentration of serum FDP has been found, not only to reflect the activity and severity of proliferative renal lesions (Stiehm and Trygstad, 1969), but also to be raised in the other non-primary renal conditions such as deep vein thrombosis and DIC (Merskey, et al., 1967; Ruckley, et al., 1970). Clarkson, et al. (1971) reported urinary FDP concentration was a reliable and sensitive index of activity, progression and natural history of active proliferative glomerulonephritis. Therefore, FDP assay is a more sensitive and reliable test for the detection of intravascular coagulation, as well as of the intensity of proliferative renal lesions, than are other coagulation studies (Stiehm and Trygstad, 1969). Recently, McKey and Margaretten (1967) summarized the histopathologic evidence for the frequent occurrence of DIC in various exanthematous viral diseases and certain hemorrhagic fevers caused by arboviruses. However, there is only one of the reported cases of Korean hemorrhagic fever in which it is suggested that DIC had played an important role in the morbidity and mortality of this disease (Dennis and Conrad, 1968). Quite recently, Cho and Choi (1973) have found a rise with an interesting alteration of serum FDP concentration, analyzing 27 examples of patients with Korean hemorrhagic fever in all phases.

The mortality rate of Korean hemorrhagic fever is still high, and the pathogenesis and the mechanisms of this disease are still unclear. Therefore, to study the exact pathogenetic mechanisms of acute renal failure in this disease is very essential and important. Therefore, to study the alterations of the
concentration of FDP, not only in the urine but also in the serum, seems to be very important in order to measure the disease intensity and to correlate it to prognosis, and also to detect the evidence of DIC and the relationship to acute renal failure. Furthermore, there is the possibility of benefit in selection of patients for anticoagulant therapy alone or in combination with steroid and immunosuppressive drugs.

The present study is designed to detect the presence of FDP, and to compare the alternations of FDP concentration, both in the serum and in the urine, with particular references to DIC and acute renal failure, and furthermore, to establish prognostic and therapeutic criteria for improvement in the treatment of Korean hemorrhagic fever.

MATERIALS and METHODS

A. Materials

From September, 1973 to January, 1974, the serum and the urine were used from selected patients with Korean hemorrhagic fever, who were admitted to the Epidemic Hemorrhagic Fever Research Center in Capital Armed Forces General Hospital, ROK Army and had a typical clinical course. The patients were divided as follows:

- Febrile phase: 38 cases
- Hypotensive phase: 26 cases
- Oliguric phase: 46 cases
- Diuretic phase: 35 cases
- Convalescent phase: 32 cases

B. Methods

For general information, routine peripheral blood examinations, including hemoglobin, hematocrit, and white blood cell counts, and routine urinalysis, including specific gravity and proteinuria, were measured.

Platelets were counted by phase contrast microscopy (Brecher and Cronkite, 1950). Measurements of prothrombin time and partial thromboplastin time were performed by a fibrometer using the Hyland kit.

Serum and urinary FDP were measured in all patients periodically during each phase. FDP was measured both for serum and urine by the staphylococcal clumping test of Hawiger (1970). Twelve or 24-hours urine samples were used.

RESULTS

The findings of hematology are summarized in Table 1, blood chemistry in Table 2, and urinalysis in Table 3. Also the alterations of blood urea nitrogen level with clinical severity are summarized in Table 4, and Fig. 1. Particularly the platelet count was markedly decreased in the febrile and hypotensive phases, but was increased more than normal in the oliguric phase and then gradually returned to normal. The alterations of the blood urea nitrogen level and creatinine were similar. The blood urea nitrogen level began to increase more or less in the febrile and hypotensive phases, and showed the highest level in the oliguric phase, and later gradually decreased in the diuretic phase and returned to normal in the convalescent phase. As shown in Fig. 1, the blood urea nitrogen level in the diuretic phase was higher than in both the febrile and hypotensive phases.

The concentration of serum FDP and its concentration in relation to clinical severity are shown in Figures 2 and 3. The concen-
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Table 1. Hematologic finding

<table>
<thead>
<tr>
<th></th>
<th>Febrile</th>
<th>Hypotensive</th>
<th>Oliguric</th>
<th>Diuretic</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hg. (gm%)</td>
<td>14.1±3.5</td>
<td>13.7±2.7</td>
<td>14.2±3.1</td>
<td>12.8±2.4</td>
<td>13.4±2.9</td>
</tr>
<tr>
<td>Hct. (%</td>
<td>38 ±4.2</td>
<td>47 ±5.1</td>
<td>52 ±4.7</td>
<td>39 ±3.5</td>
<td>38 ±4.1</td>
</tr>
<tr>
<td>Leukocyte (/mm³)</td>
<td>15,850±1,400</td>
<td>16,720±1,600</td>
<td>23,110±2,100</td>
<td>11,280±1,300</td>
<td>7,290±900</td>
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<tr>
<td>Platelet (/mm³)</td>
<td>32,700±3,600</td>
<td>86,400±5,600</td>
<td>427,000±16,800</td>
<td>236,000±7,100</td>
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Table 2. Blood chemistry findings

<table>
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<th>Hypotensive</th>
<th>Oliguric</th>
<th>Diuretic</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. U. N. (mg%)</td>
<td>49.8±6.4</td>
<td>53.7±6.4</td>
<td>137.6±15.7</td>
<td>68.9±5.1</td>
<td>24.2±3.4</td>
</tr>
<tr>
<td>Creatinine (mg%)</td>
<td>5.1 ±0.9</td>
<td>5.8±1.1</td>
<td>11.7±2.2</td>
<td>5.4±0.7</td>
<td>2.5±0.4</td>
</tr>
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<td>Prothrombin time (%)</td>
<td>64 ±12.1</td>
<td>72 ±11.4</td>
<td>78 ±8.4</td>
<td>89 ±10.8</td>
<td>100 ±5.2</td>
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<tr>
<td>Partial thromboplastin time (sec.)</td>
<td>84 ±5.2</td>
<td>62 ±4.7</td>
<td>58 ±8.2</td>
<td>41 ±4.7</td>
<td>38 ±2.5</td>
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Table 3. Findings of urinalysis

<table>
<thead>
<tr>
<th></th>
<th>Febrile</th>
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<th>Diuretic</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.G.</td>
<td>1.029±0.01</td>
<td>1.016±0.003</td>
<td>1.009±0.005</td>
<td>1.050±0.003</td>
<td>1.005±0.002</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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</table>

Table 4. B. U. N. level to the clinical severity

<table>
<thead>
<tr>
<th></th>
<th>Febrile</th>
<th>Hypotensive</th>
<th>Oliguric</th>
<th>Diuretic</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>35.4±4.1</td>
<td>39.2±3.8</td>
<td>74.8±5.8</td>
<td>58.1±4.9</td>
<td>22.4±3.1</td>
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<tr>
<td>Moderate</td>
<td>49.2±5.3</td>
<td>62.4±5.7</td>
<td>127.2±7.9</td>
<td>89.2±7.4</td>
<td>26.4±3.4</td>
</tr>
<tr>
<td>Severe</td>
<td>54.7±4.8</td>
<td>68.9±5.6</td>
<td>178.5±8.2</td>
<td>105.7±9.4</td>
<td>27.2±4.1</td>
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</table>

Fig. 1. B. U. N. level to the clinical severity
Feb.: Febrile phase
Hypo.: Hypotensive phase
Olig.: Oliguric phase
Diar.: Diuretic phase
Conv.: Convalescent phase
Mod.: Moderate

The concentration of urinary FDP and its concentration related to the clinical severity are also shown in Figures 4 and 5.

The normal range of serum FDP concentration by the staphylococcal clumping test was positive from 1:2 to 1:4 dilution. The majority of the patients showed a higher concentration than normal. The highest level of three cases in the febrile, hypotensive and oliguric phases came from expired subjects. The normal range of urinary FDP concentration was also positive from 1:2 to 1:4 dilution. Higher concentrations than normal of serum FDP were shown in almost all of
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The patients, but they were significantly higher in the febrile and hypotensive phases. In the oliguric phase, both serum and urinary FDP concentrations were highest and positive in the same dilution. These serum and urinary FDP concentrations, particularly in the febrile and hypotensive phases, were very much higher than the level of blood urea nitrogen in the same phases. Moreover, the three highest concentrations of urinary FDP in the febrile and hypotensive phases were from expired subjects.
DISCUSSION

Disseminated intravascular coagulation (DIC) is found in a wide range of clinical conditions in which fibrin thrombi form in the microcirculation throughout the body. Such DIC is not a primary disease but rather a secondary complication of some underlying disorder which seriously deranges normal hemostasis. In a severe condition of DIC, there may occur two serious effects: severe hemorrhagic tendency; and ischemic tissue injury.

The etiology of DIC can be classified into three categories: (1) endothelial cell injury which activates the Hageman factor and the intrinsic clotting system; (2) tissue injury which activates the extrinsic clotting system; (3) red cell or platelet injury with the release of coagulant phospholipids. These initiating mechanisms result in a final common product, thrombin, which cleaves fibrinogen, activates factor XII, aggregates platelets, releases platelet constituents, and triggers secondary fibrinolysis. Plasmin produces FDP, which participates in the hemorrhagic diathesis. Therefore, detection of FDP is a reliable method of diagnosing DIC (Colman, et al., 1972).

DIC can be produced in the experimental animal (Rabiner and Friedman, 1968). Procoagulant stimuli may act at different steps to produce clinical intravascular clotting. Intravascular clotting can be caused by gram-negative endotoxins in many animal species, and endotoxemia is well known as a major cause of DIC (Davis, et al., 1960; Rodriguez-Erdmann, 1965; Lerner, et al., 1965; Forman, et al., 1969; McGrath and Stewart, 1969). Considerable evidence has implicated the antigen–antibody reaction as another mechanism for initiating both experimental and clinical intravascular clotting (Robbins and Stetson, 1959; Blomback, et al., 1967). Non-infectious complications of obstetrics, a certain tumor, promyelocytic leukemia, massive tissue trauma, and prostatic or pulmonary surgery are related to the extrinsic clotting pathway (Boggust, et al., 1963; McGehee and Rapaport, 1968; Friedman, et al., 1969; Hand, et al., 1969; Colman, et al., 1972).

Extensive endothelial damage presumably exposes the blood to tissue thromboplastin activity from endothelial cells. Thus the combined effects of factor XII (Hageman factor) activated by collagen in the basement membrane of the vascular wall, platelet aggregates, and the platelet activated factor II (Spaet and Cintron, 1965; Wilner, et al., 1968) trigger intrinsic clotting.

There are reliable methods to define intravascular coagulation: (1) fibrin deposit by histopathologic or immunofluorescent methods; (2) accelerated fibrin catabolism; (3) decreased level of plasma coagulation factors such as fibrinogen, prothrombin, factor II, and platelets; and (4) rise of FDP in the serum. The increased level of FDP in the serum, has been a constant feature in documented cases of intravascular coagulation studied by Merskey and co-workers and others (Rodriguez-Erdman, 1965: Merskey, et al., 1966; Hillman and Phillips, 1967; Merskey, et al., 1967). Therefore, FDP assay is a more sensitive and reliable test for the detection of intravascular coagulation than are other coagulation studies (Stiehm and Trygstad, 1969).

There are reports for the frequent occurrence of DIC in various exanthematus viral
diseases and certain hemorrhagic fevers caused by arboviruses (McKay and Margaretten, 1967), and another reports indicated that Argentine hemorrhagic fever is closely related to the consumption coagulation disorders (Agrest, et al., 1969). Kim (1972) reported, however, that there was no morphologic evidence of DIC on analyzing 27 autopsied and 22 renal biopsied cases. Quite recently, Cho and Choi (1973) have found a rise with interesting alteration of serum FDP concentration in their preliminary study by the staphylococcal clumping test, analysing 27 examples of the patients with Korean hemorrhagic fever in all phases, and they (1974) presented the pathophysiologic mechanisms in the Annual Symposium of the 38th Parallel Korean-American Medical Society, Seoul, Korea.

In this present research, in order to detect and evaluate the relationship between Korean hemorrhagic fever and DIC, and to study the pathogenesis of acute renal failure in patients with Korean hemorrhagic fever, alterations of the serum and urinary FDP concentrations were subjected to study. With a total of 177 examples of both urine and serum, as shown in our results, platelet count was markedly decreased in number less than 32,700 in febrile phase, and 86,400 in hypotensive phase; prothrombin time and partial thromboplastin time were prolonged in the early phases, and return to normal in the convalescent phase. All these findings are consistent with abnormal values for DIC. The specific and reliable test for DIC is FDP assay and in our study, the concentration of serum FDP and alterations of its concentration related to the clinical severity in each phase showed significant marked increase in the early phases. Moreover, the three expired samples showed peak concentration level of serum FDP. These indicate that DIC is defined in Korean hemorrhagic fever, where it may play a significant role.

DIC may lead to three clinical consequences: the consumption of platelets and clotting factors plus the antihemostatic properties of FDP creates a potential bleeding tendency; deposits of fibrin may block capillary flow in an organ with resulting serious ischemic tissue damage; damage of red blood cells may occur. The kidney is particularly vulnerable to such ischemic effect; lesions may vary in severity from reversible tubular necrosis to complete, irreversible, even bilateral renal cortical necrosis. Manifestations of ischemic tissue damage following intravascular clotting may be viewed as clinical equivalents of the Shwartzman reaction in the experimental animal (Hjort and Rapaport, 1965).

Numerous investigations for the pathogenesis of acute renal failure have been done, but the exact mechanism is still not proved. Four pathophysiologic mechanisms have been proposed as primary factors in the pathogenesis of acute renal failure: (1) tubular obstruction by casts and debris; (2) passive back diffusion of glomerular filtrate; (3) renal interstitial edema; and (4) alterations in renal hemodynamics resulting in loss of an effective filtration pressure (Clarkson, et al., 1970: Bullock and Shapiro, 1974). From the clinical and etiological standpoints, acute renal failure is divided into three categories: prerenal, renal, and postrenal. Prerenal causes are marked hypovolemia, impaired cardiac function, peripheral vasoconstriction, increased renal vascular resistance and bilateral renal vascular obstruction. The most common and character-
A characteristic form of acute renal failure has renal causes divided into ischemic and nephrotoxic (Strauss and Welt, 1971).

There is experimental evidence that not only is participation of the coagulation process observed in certain renal diseases (Thomas and Good, 1952; Robbins and Collins, 1961; Vassalli and McClusky, 1964 and 1965; Halpern, et al., 1965), but also that acute renal failure may be produced by inducing intravascular coagulation (Robson, 1965; Hardaway, 1966). Moreover, in certain forms of human renal diseases, there are reports that coagulation mechanisms may play a pathogenetic role: glomerular fibrin deposit by light microscopy (Gitlin, et al., 1957), and by immunofluorescent methods (Paronetto and Koffler, 1965; Koffler and Paronetto, 1965; McClusky, et al., 1966; Wadle and Taylor, 1968; Humair, et al., 1969); a report of DIC (Monnens and Schretlin, 1967): the benefit of anticoagulant therapy in certain renal diseases (Piel and Phibbs, 1966; Kincaid-Smith, et al., 1968; Herdman, et al., 1970): the evidence of fibrin deposit in the kidney during acute tubular necrosis (Koffler and Paronetto, 1966). Much of the naturally formed fibrin in vivo is removed by fibrinolysis in which an insoluble fibrin monomer is converted to soluble peptide fragments known as FDP.

Using renal arteriography and xenon washout studies, Hollenberg and associates (1968) proposed to establish definitely that renal cortical ischemia is a constant pathophysiologic feature of acute renal failure in man. However, the mechanism responsible for the preferential cortical ischemia remains obscure. Among the number of hypotheses suggested are the following: (1) afferent arteriolar vasoconstriction; (2) the "no flow" phenomenon; (3) activation of depression of various intrarenal humoral substances, such as catecholamines, resulting in cortical vasoconstriction; and (4) low fibrinolytic activity and intravascular clotting. Recently, attention has been directed to the possibility that disruption of normal renal cortical perfusion may be the common etiology of acute renal failure.

In patients with acute ischemic renal failure, Clarkson, et al. (1970) have studied coagulation and fibrinolysis, together with electron microscopic examination of renal biopsy material during the oliguric phase, and interpreted the studies as consistent with coagulation abnormalities in association with marked intraglomerular capillary thrombosis. In his case, moreover, recovery of renal function was found to be associated with resolution of intraglomerular coagulation, correction of coagulation abnormalities, and the excretion of a large amount of FDP into the urine. They have also suggested that intraglomerular coagulation is likely to play an important role in contributing to the prolonged depression of renal function in acute ischemic renal failure and it may be partly responsible for the tubular necrosis invariably observed in this condition. Quite recently, Cho, Bang and Choi (1975) have examined immediate renal necropsied material from a patient who expired with Korean hemorrhagic fever in the oliguric phase, and found intraglomerular and peritubular fibrin deposits by immunofluorescent and electron microscopic examinations, in association with the highest serum and urinary FDP concentrations and abnormalities of DIC, the latter of which are similar to the results obtained in this study. In their findings, the morphologic findings and abnormalities for DIC and FDP
alterations appear well correlated.

Accelerated catabolism representing intravascular coagulation has also been found with the onset of acute renal failure, in terminal uremia, in malignant hypertension with vascular damage, in chronic nephritis with refractory hypertension, and in rapidly progressive glomerulonephritis and immune complex type nephritis. After the onset of acute renal failure, accelerated catabolism persists until the recovery phase, and may be a post-traumatic response, a reaction to acidosis and to the tissue damage and to subclinical infection. Fibrin plays a part in the pathogenesis of acute renal failure due to sepsisemia, trauma, malignant hypertension, obstetric accidents, and mismatched transfusion, and may well be the cause of tubular necrosis (Wardle, 1973).

There are recent reports that the serum FDP concentration has been found to reflect the activity and the severity of proliferative renal lesions (Stiehm and Trygstad, 1969), and other non-primary renal conditions, such as deep vein thrombosis and DIC, may be associated with a rise in serum FDP (Merskey, et al., 1967; Ruckley, et al., 1970). However, Clarkson, et al. (1970) reported that urinary FDP concentration was a reliable and sensitive index of activity, progression and natural history of active proliferative glomerulonephritis, and was of potential value in the differential diagnosis of glomerulonephritis. They thought it predominantly showed lysis of intraglomerular fibrin deposits.

Quite recently (Uttley, et al., 1974), evidence has been suggested that urinary FDP correlated with total urinary protein in proliferative glomerulonephritis but not in nephrosis, nor did it correlate with serum FDP in either condition. Thus, it was concluded that the determination of urinary FDP in clinical practice is an indicator of activity and of possible response to treatment in the management of active proliferative glomerulonephritis in children. Moreover, Ambrus, et al. (1974) have shown in children with renal diseases that increased serum FDP levels suggest DIC with fibrinolysis or another processes resulting in increased fibrinogen catabolism, and increased urinary FDP levels indicate that renal fibrin deposition, fibrinolysis, and increased glomerular permeability to FDP. In their series, the highest levels of serum and urinary FDP were found in the hemolytic uremic syndrome.

In our study, the majority of the patients showed a significantly higher concentration of urinary FDP than normal, and moreover, urinary FDP concentration was higher than serum FDP concentration in the early febrile and hypotensive phases. Also three expired examples showed the highest concentration of urinary as well as serum FDP. Thus, the urinary FDP concentration appears more closely to reflect the clinical severity of renal lesions in this disease than do the serum FDP concentration and the blood urea nitrogen level. These results of this study indicate that DIC is detected in Korean hemorrhagic fever, where it may play a major pathogenetic role, and may have close relationship to acute renal failure. Therefore, it appears that the concentration of urinary FDP can be used as a therapeutic criterion, and is correlated with the intensity and prognosis of the disease, and furthermore, the possibility of improvement following anticoagulant treatment should be considered. All these findings appear to be well supported by the previous investiga-
tions in certain forms of acute renal failure by Clarkson, et al. (1970). Therefore, it appears that acute renal failure in this disease has a close relationship to fibrin deposits in the kidneys and DIC. In pathogenesis it can be assumed that disruption of renal cortical perfusion plays a major role in this disease.

There is a report of five theoretical categories in the treatment of DIC (Colman, et al., 1972), and recently Kincaid-Smith, et al. (1968) reported considerable improvement in six consecutive cases of irreversible oliguric acute renal failure, histologically due to glomerulonephritis or obstructive lesions in the arterioles and glomeruli, following a continuous high-dose infusion of heparin, given in addition to steroids and immunosuppressive drugs. Therapy of DIC may be considered as the therapy of the underlying disease, inhibition of the effects of thrombin with heparin, replacement of clotting factors and correction of other processes which may hinder the clotting function. Heparin interrupts the process by preventing activation of the clotting mechanism (Colman, et al., 1972).

Donadio and Holley (1974) have reported that acute renal failure, microangiopathic hemolytic anemia, and intravascular coagulation occurred in a 27 year-old woman during the second week after elective cesarian section of a term pregnancy and clinical and renal functional recovery were complete after treatment with heparin.

REFERENCES


Colman, R.W., Robboy, S.J. and Minna, J.D.: Disseminated Intravascular Coagulation (DIC):


Byung Ro Kim, Sang Ho Cho, In Joon Choi and Dong Sik Kim


