Use of Intravenous Mannitol in Postperfusion Oliguria-Anuria

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Previous experience indicates that renal failure following cardiopulmonary bypass can lead to morbidity and mortality. Doberneck and associates have indicated that a satisfactory technical operative procedure may be nullified by acute renal failure. These authors report the incidence of acute renal failure after open-heart operation using extracorporeal circulation as 3 per cent in a thousand patients. There was an associated mortality of 86.7 per cent in 30 patients experiencing postperfusion oliguria, azotemia, and hyperkalemia.

In order to evaluate our experience with renal failure following cardiopulmonary bypass, and the influence of intravenous mannitol on oliguria-anuria experienced during this procedure, the following investigation was carried out.

Methods

To date, we have performed 158 open-heart procedures for repair of congenital and acquired cardiac lesions. Of these, 33 patients had associated deep hypothermia (10 to 22 C.), with and without complete circulatory occlusion. The remaining 125 patients had moderate hypothermia (30 to 32 C.) throughout the bypass procedure. A disposable disk oxygenator-heat exchanger system and 360-degree spring-loaded pump were used.

No specific preoperative preparations or evaluation of renal function were undertaken other than routine urinalysis and measurement of blood urea nitrogen (BUN) and serum electrolytes. All patients were in the usual preoperative fasting state, begun at midnight prior to operation. Anesthesia was induced by sodium pentothal and maintained in most instances with nitrous oxide and oxygen, fluthane (0.5 to 1 per cent), and succinylcholine.

In adults, a Foley catheter was inserted prior to anesthesia; children were catheterized immediately after induction of anesthesia. The rate of urine flow was monitored by continuous collection of urine in a graduated cylinder. In the early phase of the study, the urinary flow during the entire operation was collected as a single specimen. Because of the occurrence of oliguria during the operation, we began monitoring the urine flow at 15-minute intervals throughout the entire operative procedure (fig. 1). In all instances, postoperative urinary flow was monitored at hourly intervals. All patients who developed oliguria, defined here as 0.25 ml./min. (360 ml./day) or less for two hours or longer, received a priming dose of 50 ml. of 20 per cent mannitol (10 Gm.). If urine flow did not increase within 30 minutes, a second dose of 10 Gm. was administered. If no response was obtained within an hour, no further mannitol was administered. When urine flow increased to 0.5 ml./min. or more, mannitol infusion was titrated against urine flow to maintain urinary flow at approximately 1 ml./min. Administration of 20 per cent intravenous mannitol at 0.5 to 1 ml./min. was usually adequate to provide a urinary flow of 1 to 1.5 ml./min. In no instance was more than 140 Gm. of mannitol administered in 24 hours. Amounts beyond 200 Gm. in 24 hours are not recommended because of the possibility of producing circulatory overload, clinical symptoms resembling water intoxication, hypernatremia, or irreversible renal tubular damage.

In this study, we have applied the principle of acute functional renal failure as proposed by Barry. Barry defines acute renal failure as the sudden inability of the kidneys to vary urinary volume and content appropriately in response to homeostatic needs. He classifies it into two major parts: functional renal failure, which is precipitated by extrarenal factors and is immediately reversible by arresting the renal action of these factors, since no organic lesions are present; and organic renal failure, which may be preceded by functional failure, but is not immediately reversible by arresting action of the extrarenal precipitating factors. Renal failure is maintained by organic renal lesions. Barry suggests that mannitol infusion may prevent the progression of functional to total organic failure.

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In an attempt to circumvent the rare, but fatal, problem of postperfusion hypothermic renal failure, we began to apply the above principle to the oliguric-anuric state associated with cardiopulmonary bypass. For purposes of clarity, renal failure is considered functional when: (1) urine flow is 0.25 ml./min. or less for two hours or longer; (2) oliguria is progressive and becomes associated with biochemical changes characteristic of renal failure, i.e., azotemia, hyperkalemia, and acidosis; (3) oliguria is reversible; and (4) oliguria is not associated with any demonstrable renal tubular changes characterized by degenerative changes of hypoxic nephrosis and/or acute tubular necrosis as demonstrated by light microscopy. When these criteria occurred in association with demonstrable tubular degenerative changes, organic renal failure was considered to be present.

Results

In the 158 patients studied, 19 were found to fulfill our criteria of acute renal failure. Seventeen patients fell into the functional group, and 2 into the organic; 7 were children and 12 adults (table 1). None of these patients demonstrated abnormal findings in the urine or serum BUN level preoperatively. The oliguria-anuria was most common in interventricular septal defects (six patients) and mitral insufficiency (four patients) (table 1). However, organic renal failure followed aortic valvulotomy in patient E.S., and repair of interventricular septal defect in patient C.Z. Deep hypothermia was utilized in eight patients with complete circulatory occlusion ranging from 4 to 45 minutes. High flow rates were utilized even at lower temperatures to avoid the development of metabolic acidosis.2

The onset of oliguria in relation to the anesthesia and bypass was important (fig. 2). Five patients had onset of oliguria shortly after anesthesia: one prior to the pump, three coincidental with the pump, six in the immediate postperfusion period, and four during the first 48 hours after operation. The duration of the oliguric-anuric period varied from 2 to 45 hours. In four children, the oliguria (0.05 to 0.15 ml./min.) lasted from 2.5 to 16 hours and ended with spontaneous diuresis. In the remaining three children, who died, the oliguria persisted in two until death and was reversed in patient D.D. with the use of mannitol. In the adult group, nine patients received mannitol, with good diuretic response (1 ml./min. or more) in eight; three died in functional renal failure.

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### Table 1

**Summary of Nineteen Patients Who Developed Renal Failure Associated with Cardiopulmonary Bypass**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Patient</th>
<th>Age (years)</th>
<th>Lowest temperature (°C.)</th>
<th>Period of occlusion</th>
<th>V (ml/hr) Duration of oliguria (hours)</th>
<th>Mannitol</th>
<th>Result of mannitol</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.V.S.D.</td>
<td>C.Z.</td>
<td>6</td>
<td>29</td>
<td>Perfusion</td>
<td>0.09/12</td>
<td>None</td>
<td></td>
<td>Hemoglobin casts in collecting tubules, hypoxic nephrosis—mild</td>
</tr>
<tr>
<td></td>
<td>S.S.</td>
<td>5</td>
<td>13.7</td>
<td>40 minutes</td>
<td>0.03/16</td>
<td>None</td>
<td>Spontaneous diuresis</td>
<td>RUN—11 to 28 mg., %; K—5.2 to 5.6 mEq./L., survived</td>
</tr>
<tr>
<td></td>
<td>M.S.M.</td>
<td>3</td>
<td>9.7</td>
<td>21 minutes</td>
<td>0.15/21</td>
<td>None</td>
<td>Spontaneous diuresis</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>R.S.</td>
<td>3</td>
<td>23</td>
<td>9 minutes</td>
<td>0.08/2.5</td>
<td>None</td>
<td>Spontaneous diuresis</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>C.S.</td>
<td>38</td>
<td>15</td>
<td>45 minutes</td>
<td>0.1/14</td>
<td>Yes</td>
<td>Spontaneous diuresis</td>
<td>Osmotic tubular change, proximal convoluted tubules</td>
</tr>
<tr>
<td></td>
<td>R.H.</td>
<td>17</td>
<td>21</td>
<td>4 minutes plus perfusion</td>
<td>0/2.25</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Survived</td>
</tr>
<tr>
<td>I.A.S.D.</td>
<td>B.C.</td>
<td>36</td>
<td>13</td>
<td>21 minutes</td>
<td>0.13/4</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Fibrin thrombi in glomerular capillaries, Osmotic tubular change</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>P.D.</td>
<td>4</td>
<td>28</td>
<td>Perfusion</td>
<td>0.20/12</td>
<td>None</td>
<td>Spontaneous diuresis</td>
<td>Osmotic tubular change, survived</td>
</tr>
<tr>
<td></td>
<td>V.R.</td>
<td>50</td>
<td>30</td>
<td>Perfusion</td>
<td>0.10/5.6</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Died of septicemia, no autopsy</td>
</tr>
<tr>
<td></td>
<td>M.P.</td>
<td>2.3</td>
<td>35</td>
<td>Perfusion</td>
<td>0.08/15</td>
<td>None</td>
<td></td>
<td>Hypoplastic normal kidney, renal infarcts, Osmotic tubular change</td>
</tr>
<tr>
<td></td>
<td>D.D.</td>
<td>3.5</td>
<td>15</td>
<td>24 minutes</td>
<td>0.1/2</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Died of hemorrhage—lungs, Osmotic tubular change</td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>H.B.</td>
<td>29</td>
<td>30</td>
<td>Perfusion</td>
<td>0.10/12</td>
<td>None</td>
<td></td>
<td>Died of atelectasis, partial autopsy</td>
</tr>
<tr>
<td></td>
<td>M.B.</td>
<td>31</td>
<td>30</td>
<td>Perfusion</td>
<td>0.02/34</td>
<td>None</td>
<td></td>
<td>No autopsy</td>
</tr>
<tr>
<td></td>
<td>M.N.</td>
<td>27</td>
<td>25</td>
<td>Perfusion</td>
<td>0/8</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>D.C.</td>
<td>20</td>
<td>31</td>
<td>Perfusion</td>
<td>0/2.5</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>F.R.</td>
<td>40</td>
<td>32</td>
<td>Perfusion</td>
<td>0/2</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Survived</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Aortic stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Died heart block, hypoxic plus osmotic tubular change with hemoglobin casts</td>
</tr>
<tr>
<td></td>
<td>E.S.</td>
<td>47</td>
<td>10</td>
<td>4 minutes plus perfusion</td>
<td>0/45</td>
<td>Yes</td>
<td>No response</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>M.B.</td>
<td>30</td>
<td>28</td>
<td>Perfusion</td>
<td>0.05/2</td>
<td>Yes</td>
<td>Diuresis</td>
<td>Died of ventricular fibrillation, Osmotic tubular change</td>
</tr>
<tr>
<td>Pulmonary embolectomy</td>
<td>W.F.</td>
<td>51</td>
<td>28</td>
<td>Perfusion</td>
<td>0.03/7</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

V = urine flow rate in ml./min.; I.V.S.D. = interventricular septal defect; I.A.S.D. = interatrial septal defect.
Figure 2

Graph illustrating urinary flow, ml./min., as plotted against time of onset of oliguria. Origin of arrow indicates degree of oliguria; length of arrow indicates duration of oliguria; height of arrow indicates degree of diuretic response.

Discussion

Oliguria-anuria and acute renal failure following open-heart operations have been attributed to various factors, including transfusion reactions, polybrene, inadequate and prolonged perfusions, and deep hypothermia with circulatory occlusion. In the present study, it became apparent that the onset of oliguria-anuria in cardiac patients was related not only to the pump perfusion, but also to the induction of anesthesia. This is accounted for by the further decrease in an already lowered cardiac output in patients with mitral stenosis, mitral insufficiency, and aortic insufficiency. The three patients (fig. 2) who developed oliguria-anuria during pump perfusion were all cooled to deep levels of hypothermia (13 to 21 C.) and had complete circulatory arrest for 4 to 21 minutes. The urinary flow was found to drop with the lowering of temperature and would not improve, despite mannitol, until rewarming. Those patients who developed renal failure in the post-perfusion and early postoperative periods were found to have the following in common: (1) episodes of hypotension during and after operation; (2) the use of vasopressors, specifically norepinephrine, to combat shock; (3) cardiac arrest in two patients; and (4) only two patients, E.S. and C.S., had an elevated free plasma hemoglobin level (120 to 300 mg. per cent), compared with an average of 50 mg. per cent in the remaining 17 patients.

The first patient in this group who received mannitol was E.S. (fig. 3). He had an aortic valvulotomy under deep hypothermia (15 to 10 C.) for two hours during which the mean arterial blood pressure was between 30 and 40 mm. Hg. Serum hemolysis was 290 mg. per cent at the completion of perfusion. He had severe oliguria (0.18 ml./min.) during operation, followed by 45 hours of total anuria, renal failure, and death. Such an episode of renal ischemia, elevated plasma hemoglobin...
level, and oliguria has been reported to produce acute tubular necrosis in dogs. One of us (Dr. Borges) had been using intravenous 20 per cent mannitol for the production of urinary flow in the treatment of postoperative oliguria-anuria. The intravenous administration of 140 Gm. of mannitol to E.S. after 15 hours of anuria was unsuccessful in interrupting his anuria and preventing organic renal failure. The delay between the onset of anuria and the initiation of mannitol therapy was felt to be of paramount importance in his failure to respond to mannitol titration.

Since then, eight other patients have received mannitol between 2 and 14 hours after the onset of oliguria-anuria, with an average waiting period of five hours. The response was immediate and diuresis between 0.50 and 2.50 ml./min. was obtained (fig. 1). Titration of mannitol was then maintained to keep the urinary flow at 1 ml./min. or higher, as described under Methods. There was no hyponatremia, circulatory overloading, or convulsions. Six other patients with oliguria-anuria (0 to 0.1 ml./min.), for an average period of 35 minutes, were also given mannitol, but were excluded from this study because they did not fulfill the criteria of functional renal failure. It is interesting to note that four children who had functional renal failure for a period varying from 2.5 to 21 hours recovered spontaneously, in contradistinction to three adults who had oliguria from 7 to 34 hours and died in renal failure.

An attempt was made to evaluate renal function during cardiopulmonary bypass by determination of glomerular filtration (endogenous creatinine clearance) and renal plasma flow (para-aminohippurate clearance) in two patients; however, the lack of a steady urinary flow throughout the operation rendered the clearance meaningless. Nevertheless, Barry et al. have demonstrated that mannitol infusion increases renal plasma flow and restores glomerular filtration rate and urinary flow rate in diseased kidneys. In addition, it has been
shown, experimentally, to protect the kidneys against pigment, epinephrine, and mallet trauma. If this is so, then hypertonic mannitol infusion would seem to be a direct attack on the immediate cause of acute renal failure, namely, renal ischemia and the more remote factors of hypoxia, interstitial edema, tubular collapse, tubular cast obstruction, and intracapillary thrombosis found in experimental acute renal failure. One or all of these factors may be operating during cardiopulmonary-bypass operations. We therefore believe that the use of mannitol in open-heart operations is indicated when functional renal failure is demonstrated.

Summary

We have applied the principle of acute functional renal failure in the management of the oliguric-anuric state encountered in 19 of 158 patients undergoing open-heart operations. Mannitol was administered to nine patients who experienced acute renal failure, with successful diuresis and restoration of kidney function in eight.

Acknowledgment

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