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Analysis of Anesthetic-Related Morbidity in Human Recipients of Renal Homografts

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KIDNEY transplantation in humans has in the last decade changed from a promising clinical investigation to a practical reality. A common denominator in the preoperative condition of the recipient is terminal renal failure, which often is exacerbated by concomitant diseases. The consequent problems encountered during the anesthetic management of patients undergoing kidney homograft operations have been documented by many authors.[1-14]

The early reports[2,9,14] from our center were based on experience with the first 50 patients in our series. Since then, the total number of renal transplantations at the University of Colorado Medical Center has increased to 285.† In the present communication, the intraoperative management of 260 of these patients is described, as well as the anesthetic complications encountered.

CLINICAL MATERIAL

Sex.—Two hundred thirty-nine patients, of whom 80 (31 percent) were females and 180 (69 percent) males, received 260 kidneys. Eighteen patients had a second and 3 patients had a third transplant.

Origin of Kidneys.—There were 254 homografts and 6 heterografts. Of the former, 2 were from identical twins, 221 from

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†Up to June 1, 1970.

living donors (usually relatives), and 31 from cadaveric donors.

Preoperative Physical Status.—Recipient physical condition, evaluated at the time of transplant, showed no patients in A.S.A. class I, 20 in class II (7.7 percent), 150 in class III (57.7 percent), and 90 in class IV (34.6 percent).

Age.—Most of the recipients were in the second, third, and fourth decades. The oldest was 57 and the youngest was 3 years of age (average 27.2 years).

Preanesthetic Medication.—Forty-four patients, all class IV, received no preanesthetic medication. The others received anticholinergic drugs, with or without narcotics, phenothiazines, and barbiturates.

Duration of Anesthesia.—The longest surgical procedure lasted 780 minutes and the shortest was 150 (average 329 minutes). In slightly more than three-fourths of the cases, splenectomy and bilateral nephrectomy were performed at the same time as the renal transplant. For this reason, the period of anesthesia was not a reflection of the time required for homograft insertion.

Anesthetic Technics.—A typical scheme of the anesthetic management of 1 of these patients is shown in figure 1. Anesthesia was intravenously induced by ultrashort-acting barbiturates in 197 patients and by inhalation in 25 cases. These 222 patients (85.4 percent) received inhalation anesthetic agents for maintenance. In addition, subarachnoid block with tetracaine and epinephrine was given to 14 recipients (5.4 percent), but had to be supplemented by inhalation agents either because of discomfort, lack of anesthesia, or protracted surgical procedures. For similar reasons, epidural blocks administered to 22 patients (8.4 percent) were unsatisfactory and general anesthesia was eventually administered to them. Only in one instance each were

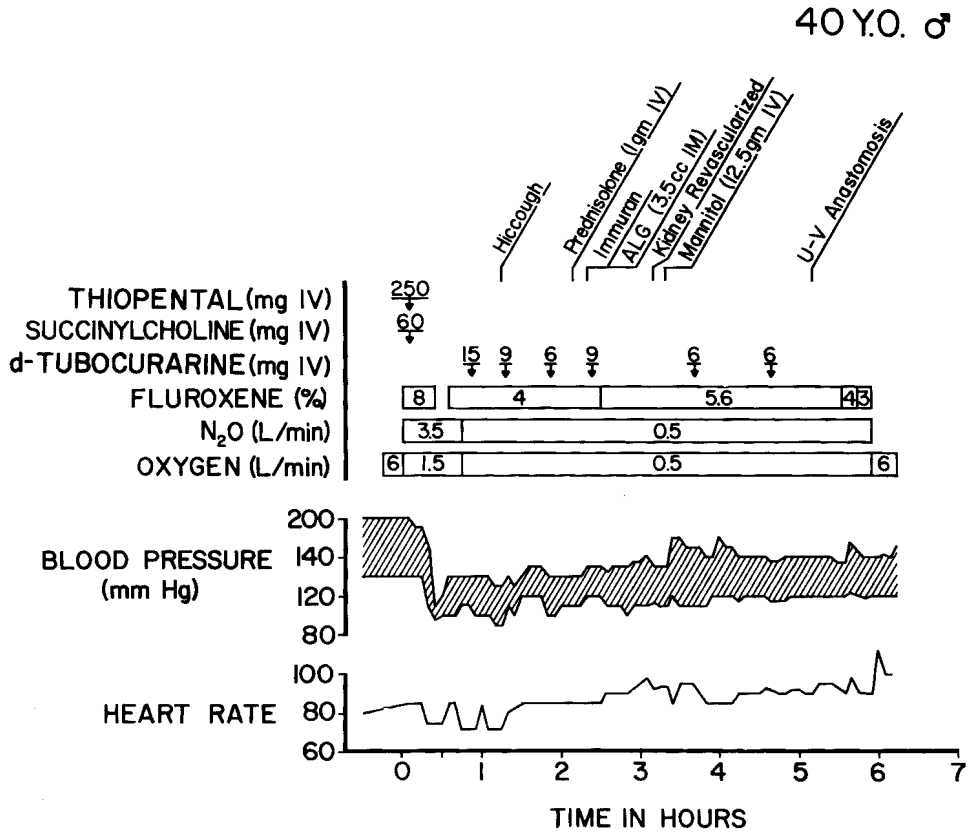

FIG. 1. Typical intraoperative management of a kidney transplant recipient, as shown in a scheme of an anesthetic record, demonstrating the changes of arterial pressure, heart rate, and temperature during operation. Anesthetic agents, muscle relaxants, and other data are shown at corresponding times of administration. Notice initial fall of blood pressure after induction of anesthesia.

epidural (0.4 percent) and spinal (0.4 percent) blocks solely adequate for the whole operation.

The technic and anesthetic agents (table 1) were selected by the staff anesthesiologist and resident participating in each case, according to the individual patient, the contemplated operative procedure, and the judgment of the anesthesiologists involved.

Muscle Relaxant Drugs.—Muscle relaxants were used during 239 of the 260 transplants. Succinylcholine alone was used to obtain muscle relaxation in 33 instances (13.8 percent); in 24 of these, a single dose was given to facilitate endotracheal intubation; in the other 9 cases, repeated injections were given. An initial dose of succinylcholine was followed by the subsequent administration of d-tubocurarine in 89 patients (37.2 percent) and of gallamine triethiodide in 8 cases (3.3 percent), 102 patients (42.7 percent) receiving d-tubocurarine exclusively and 7 patients (3 percent) receiving gallamine alone.

TABLE 1
Main Inhalation Anesthetic Agents Used in the Management of Renal Transplant Recipients

	Number	Percent
Halothane	142	55.0
Fluroxene	87	33.6
Methoxyflurane	23	9.0
Nitrous oxide +narcotic + relaxant	4	1.6
Cyclopropane	2	0.8
Total	258	100.0

Blood and Fluid Replacement.—During the surgical procedure, an effort was made to limit fluid intake to the estimated daily requirement to 10 ml./kg./24 hr. However, these considerations were individualized. The average amount of fluids actually administered before the arrival of the homograft was 472 ml. of either 5 percent dextrose in lactated Ringer's solution or acetate, or 2.5 percent dextrose in 0.25 percent saline solution. After revascularization of the homograft, fluids were given in amounts approximately equal to the urine produced.

Recipient patients came to the operating rooms with hematocrit values ranging between 15 and 38 percent, averaging 24 percent. The average estimated blood loss from the transplant was about 175 ml. The total blood loss varied mainly according to the extent and number of other surgical procedures performed concomitantly. When bilateral nephrectomy and splenectomy were simultaneously performed, an extra blood loss of about 625 ml. occurred. After the laparotomy and groin incisions had been closed, the anesthesiology team noted on two occasions that blood transfusions were needed to maintain the arterial blood pressure, despite replacement of adequate urine output; the peritoneal cavity was re-explored and bleeding, from the splenic and renal vascular pedicles, was found.

ANESTHETIC COMPLICATIONS

Arterial Hypotension.—Most patients were hypertensive before premedication or

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anesthesia; subsequently, falls of systolic blood pressure exceeding 25 percent of the preanesthetic reading were observed in 145 recipients (55.7 percent). Twenty-eight (19.3 percent) of these episodes occurred during or within 10 minutes of induction, 102 (70.3 percent) were within the 1st hour after induction, and 15 (10.3 percent) were after the 1st hour.

It may be significant that the peak incidence of hypotension during the 1st hour of anesthesia usually corresponded to the time when the diseased kidneys, as well as the spleen, were being excised. These falls in blood pressure did not have the same significance as in ordinary surgical cases because the original levels were so often abnormally high. When hypotension was defined as a systolic blood pressure of 90 mm. Hg or below, the incidence of the complication was only 21 (8 percent); 14 of these episodes occurred during or within 10 minutes of induction and the other 7 were afterward.

Cardiac Arrhythmias.—These were diagnosed by esophageal stethoscope and/or by electrocardiogram monitoring. Seven patients, 5 male and 2 female, had dangerous arrhythmias. In 6 instances, halothane was the main anesthetic agent, cyclopropane being used in the other case. Asystole occurred in 2 of these patients, 1 hour and 7 hours, respectively, after induction. Preoperative serum potassium in both these recipients was above 6 mEq./L. The cardiac arrests were treated with 100 percent oxygen, closed cardiac massage, insulin and glucose infusion, and the administration of bicarbonate. A spontaneous heart beat was restored, and in both cases a subsequent diuresis helped to correct the electrolyte imbalance in the following hours.

In another recipient in whom preoperative serum potassium was below 2.5 mEq./L., bigeminal rhythm was observed. Premature ventricular beats were noted at various times during the procedure in 4 other patients who had postdialysis and preoperative plasma potassium concentrations of between 5 and 6 mEq./L. (table 2).

TABLE 2
Incidence of Cardiac Arrhythmias

Sex	
Males	5
Females	2
Anesthetic agent	
Cyclopropane	1
Halothane	6
Type of arrhythmias	
Cardiac arrest	2
Bigeminy	1
Premature ventricular beats	4

Hiccups. — This complication occurred during the surgical procedure in 14 patients (5.4 percent), 11 male and 3 female. The main anesthetic agent being used was halothane in 8 cases, fluroxene in 3, methoxyflurane in 2, and nitrous oxide in the other. The muscle relaxant drug in 12 of these 14 cases was d-tubocurarine, the other 2 receiving gallamine or succinylcholine.

Prolonged Muscle Paralysis.—Ten renal recipients received nondepolarizing relaxants and at the end of the surgical procedure failed to regain muscle strength and adequate respiratory function despite adequate doses of anticholinesterase-type drugs. This complication was observed in 3 of 15 patients (20 percent) who received gallamine (with or without succinylcholine) and in 7 of 191 recipients (3.6 percent) to whom d-tubocurarine was given with or without the previous administration of succinylcholine (table 3). The preanesthetic serum potassium concentrations in these 10 recipients ranged from abnormally high through normal to pathologically low.

TABLE 3
Incidence of Prolonged Muscle Paralysis

Muscle relaxant drug	Number of patients	Number of prolonged weakness	Percent	Significance
Gallamine	15	3	20	$p = <0.01$
d-Tubocurarine	191	7	3.6	
Total	206	10 (all males)	4.8 (of all cases)	

Changes in Body Temperature.—In 89 cases, intermittent or continuous temperature determinations were obtained; such measurements have been made more systematically since one of the cardiac arrests alluded to earlier. In this patient, the serum potassium was 7.8 mEq./L. when asystole occurred. At the same time, the esophageal temperature was noted to be 39.8° C. (103+° F.). Moderate intraoperative hyperpyrexia has been frequently observed in recent cases in which it has been specifically looked for by continuous monitoring. It may be that the use of intramuscular antilymphocyte globulin, which is often pyrogenic,[15,16] contributes to the incidence of this complication.[17]

Liver Injury.—Abnormalities in hepatic function have frequently been detected in the post-transplantation period.[18] It has not been possible to say what contribution, if any, anesthesia has made to these findings, since immunosuppressive agents, especially azathioprine, instituted just prior to operation, have known hepatotoxic effects. One patient died of acute yellow atrophy following renal transplant, but it is probable that in this case azathioprine, rather than any anesthetic agent, was primarily responsible (fig. 2).

The Question of Methoxyflurane Anesthesia. — Crandell and coworkers[19,20] observed nephrotoxicity from methoxyflurane and recommended that this agent not be used in patients with renal disease. These reports prompted us to investigate the fate of 23 kidney recipients operated upon from a few weeks to 5 years ago. All 23 patients obtained good homograft function and 19 of them are still alive.

Other Complications.—In 6 patients, alopecia appeared, after operation, in the area covered by the straps of the rubber head harness.

Sudden onset of respiratory wheezing was audible during the anesthetic procedure in 4 cases. Two episodes of what was diagnosed as bronchospasm subsided spontaneously, whereas 2 others required administration of aminophyllin.

DISCUSSION

During the 8 years of existence of the renal transplantation program at the University of Colorado, a wide range of anesthetic technics and agents have been employed by many different members of the faculty and resident staff. As a consequence,

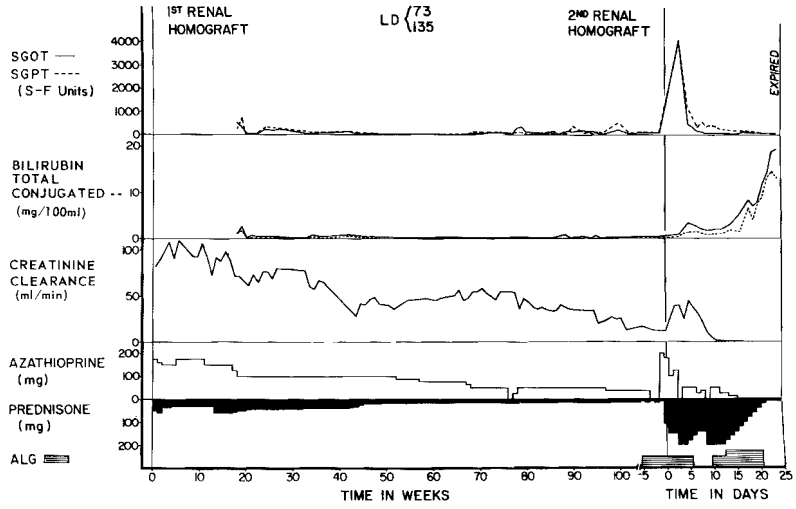

FIG. 2. Course of a 26-year-old man who had the first kidney homograft implanted with obvious improvement of creatinine clearance. For immunosuppression, he received azathioprine and prednisone. Five month later, he developed low-grade jaundice and slight elevation of transaminase. The azathioprine dose also reduced but the homograft eventually failed 2 years after implantation. For reimplantation, four large doses of azathioprine were given before and after operation, with subsequent and immediate rise of transaminases and serum bilirubin. He died shortly thereafter of hepatic and renal failure. The main anesthetic agent in both operations was fluroxene. This complication was subjective evidence of azathioprine hepatotoxicity. (By permission of the author, T. E. Starzl, and the publisher, W. B. Saunders Company.)

some practices were followed which are no longer considered acceptable.

An example is the use of gallamine triethiodide, a muscle relaxant eliminated almost exclusively by the kidney.[21] Albeit prompt function of the new kidney followed transplant in the few patients given this drug, prolonged paralysis was observed in 20 percent of them. In contrast, protracted paralysis was a problem in only 3.6 percent of patients given d-tubocurarine, which has both renal and hepatic pathways of detoxification and excretion.[22,23] (See addendum.)

Although succinylcholine is hydrolyzed by pseudocholinesterase of hepatic origin,[24] its repeated administration may result in prolonged muscle paralysis (dual block);[25,26] however, Sarmina's group[12] used succinylcholine infusion in renal recipients without apparent complications. Whether this complication is more likely in such patients has not been determined; in our experience, we have observed it in 2 anephric patients during thoracic surgery.

One more unsettled aspect of the use of succinylcholine in this type of patient has been raised by isolated case reports[14,27] of very low levels of plasma cholinesterase in patients who developed cardiac arrest after intravenous injection of the relaxant. This was thought to be related to the loss or breakdown of the enzyme during hemodialysis. However, Desmond and Gordon[28] and Thomas and Holmes[29] found that inconsistent changes of serum cholinesterase values were produced by dialysis. A possible explanation might be a concomitant degree of unnoticed hepatic insufficiency which produced decreased cholinesterase levels. Further clinical observations will be necessary to ascertain whether renal recipients tend to develop hypopseudocholinesterasemia or whether some therapeutic agents given in these cases might also have anticholinesterase action.

In the beginning phases of our program, *conduction anesthesia* was thought to offer a special advantage. However, for reasons that may have been as much psychologic as pharmacologic, it was almost alway necessary to add general anesthesia during the course of operation. Consequently, epidural and subarachnoid anesthesia have not been used recently. Instead, inhalation anesthesia combined with muscle relaxants is now almost always employed after induction with ultrashort-acting barbiturates.

As was first emphasized by Virtue,[2] the *choice of inhalation anesthetic* in renal transplant recipients is probably not usually critical, provided there is thorough familiarity with the potential side-effects of the agent. However, it may be that any agents in which there is a suspicion of hepatotoxicity should be avoided. In our series, halothane was the most commonly used inhalation agent. A number of the patients who received this anesthetic had liver function abnormalities after kidney transplant, and 1 died from acute yellow atrophy. The tendency was to ascribe these postoperative findings to one or other of the immunosuppressive drugs, but the anesthetic may have been a contributory factor.

It has already been made clear that one of the specific risks associated with renal homotransplantation is the use of anesthetic agents whose excretion is primarily through the kidney. However, the use of such agents is considerably less dangerous for the actual homograft procedure than for other operations performed in the essentially anephric state, such as thymectomy, nephrectomy, splenectomy, the insertion of dialysis shunts, and procedures for the control of pre-existing peptic ulcer disease or other intra-abdominal pathology. If any of the foregoing ancillary procedures are carried out before, and independent of, transplantation, *the factor of renal failure* is present throughout. In contrast, renal transplant almost always culminates in prompt relief of uremia. Despite this, it is best to approach the actual transplantation with the assumption that there will not necessarily be prompt urine excretion and that the azotemia may in fact not be relieved at all. If this attitude is taken, it should also serve as a stimulus to more complete preoperative preparation of such patients.

The need for excellent conditions of *body fluids and electrolytes* hardly needs stating, since alterations of the blood biochemical indexes are the rule in patients with long-standing renal failure. High blood urea and creatinine levels are consistently present. The most frequent aberrations are hyperkalemia, hypermagnesemia, hypercalcemia, and hypernatremia. Elevated serum potassium concentrations do not necessarily represent high intracellular values;[30] nevertheless, they may produce definite electrocardiographic alterations and either be exacerbated by the administration of succinylcholine or sensitize the digitalized heart.

A recently conducted study[31] of 12 patients undergoing bilateral nephrectomy, splenectomy, and renal transplant in the same session showed that patients with high predialysis potassium levels (>6 mEq./L.) tended to develop hyperkalemia and electrocardiographic changes, even though the postdialysis potassium determinations had been within normal limits. Consistently, plasma potassium values fell after revascularization of the homograft. This finding further supports other authors' observations;[4-6,10,13] as a whole, it is concluded that continuous electrocardiographic surveillance is in order in anesthetized patients with renal failure. Serial plasma potassium determinations are also recommended if predialysis values exceeded 6 mEq./L.

The incidence and onset of arterial hypotension deserves further comment. Although analyzed by the usual criterion, blood pressure falls of 25 percent of the preanesthetic value, hypotension may have been more relative than absolute in these patients. Hypertension was a common preoperative finding; it is, therefore, not surprising that after induction of general anesthesia in an apprehensive, underpremedicated patient, the initially elevated reading decreased to a more normal level. The frequency of this event during the 1st hour of anesthesia further substantiates this premise. Hypotensive episodes below levels that might have compromised perfusion of vital organs were rare.

The immediate lowering of blood pressure is probably due to a moderate depressive effect of the anesthetic agents upon the cardiovascular system with little or no mediation of the renal humoral mechanism. This contention is based on observations made during our clinical experience, since it has repeatedly been noted that when a uremic patient is made anatomically anephric, the blood pressure returns nearly to its preoperative high levels, only to trend frequently toward normality after successful renal transplant. This latter phenomenon has also been noticed in other patients after homograft function, even when both diseased kidneys have been left in situ.

Uremic patients usually have low *hematocrit* values, representing a normocytic, normochromic anemia, varying in degree according to the severity and duration of renal failure. This is basically due to two factors, *decreased erythropoiesis and hemolysis*. The effect on erythropoiesis is related to the decrease in renal mass and hence decreased ability to respond to a drop in red blood cell mass with increased erythropoietin production.[32] This in turn is reflected in bone marrow hypoplasia and decreased iron utilization, which occur in uremia.

Satisfactory chronic hemodialysis is associated with a gradual but slowly progressive improvement in *hematopoiesis*.[33] Red blood cell survival as measured with ^{51}Cr varies inversely with the level of azotemia. In some patients with acute renal insufficiency, there may be a predominance of hemolysis. However, in more chronic cases of renal failure, there is impaired erythropoiesis. Consequently, anemia develops gradually with a compensatory expansion of plasma volume. Attempts to bring the hematocrit to normal levels by rapid transfusions may be not only futile but even dangerous.

In this series, preoperative hematocrit values ranged from 15 to 38 percent, with an average of 24 percent. Under other circumstances, these low values might have been unacceptable; however, in our experience and in that of others,[34,35] patients with chronic anemia tolerate anesthesia remarkably well, probably because they have a normal or higher than normal plasma volume.[36] It is, therefore, recommended not to set a specific rule as to an acceptable hematocrit but rather to evaluate each patient individually.

The arrival of a renal homograft in *presensitized recipients* may carry certain other dangers to life that have yet to be fully characterized. In 1 of our patients[37] in whom preformed antigraft antibodies were present, there was joint effusion, hyperpyrexia, and rapid cessation of homograft function. Intraoperative febrile states may arise from a number of causes, including infection, the use of antilymphocyte globulin,[15,17] and blood transfusions. However, if sudden fevers are observed shortly after revascularization, the possibility of an immediate immunologic reaction involving the homograft must be strongly considered. In such an event, acute aberrations in coagulation may follow and may require joint management by the anesthesiologists and an expert in coagulation disorders.[38]

SUMMARY

In the anesthetic management of 260 cases of renal transplant, most recipients were in the young but poor-risk category.

The choice of anesthetic agent was partly determined by the realization that the preexisting anephric state might not be promptly relieved. Violation of this general rule, as with the administration of the muscle relaxant, gallamine, was followed by an increased incidence of pharmacologic complications. Conduction anesthesia was generally found unsuitable for renal transplant, since supplementary general anesthesia was too often required.

The anesthesia-related intraoperative and postoperative complications in this series included hypotension, cardiac arrhythmias (with two cardiac arrests), temperature changes, failure of anesthetic detoxification, and hyperpyrexia. The reasons for many of these complications as well as precautions to prevent them in future cases are discussed.

Addendum. A recent report (Anesth. & Analg. 50:11-16, 1971) demonstrated that anephric patients may receive gallamine as long as the dose is curtailed.

ACKNOWLEDGMENT

Drs. Robert W. Virtue, David S. LeVine, and Ted F. Gingrich, among many other staff members of the Anesthesiology Division of the University of Colorado Medical Center, actively participated in the administration of anesthesia to this group of patients.

Generic and Trade Names of Drugs

Succinylcholine chloride—Anectine, Sucostrin
Tubocurarine
Gallamine triethiodide—Flaxedil
Halothane—Fluothane
Methoxyflurane—Penthrane
Fluroxene—Fluoromar

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