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Anesthesia for heart transplantation at ChulalongkornHospital: results of a 9-year experience

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The anesthetic records of 25 heart transplant recipients were reviewed. Data collected included demographic characteristics, physical status, results of preoperative investigations, anesthetic agents and complications which may have been related to anesthetic management. Careful administration of midazolam and high doses of narcotics (morphine or fentanyl) was the preferable induction agents, and pancuronium was muscle relaxant of choice for maintenance. During maintenance fifteen patients (60%) received nitrous oxide, 15 patients (60%) received fentanyl, 11 patients (44%) received morphine and all 25 patients (100%) were supplemented with midazolam. Few recipients received volatile anesthetic agents. Isoproterenol was required to support ventricular performance and dopamine was the second most frequently used inotrope. The average anesthetic time was 277.68 ± 93.41 minutes, average cardio pulmonary bypass time was 99.52 ± 26.96 minutes, and average postoperative intubation time was 20.54 ± 10.95 hours. Common postperfusion problems were hypotension and cardiac arrhythmias. No mortality was associated with anesthetic management.

Key words: *Anesthesia, Anesthetic, Heart transplantation.*

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สมรัตน์ จารุลักษณานันท์, อรนุช เกี่ยวข้อง, นิชรี มะกรสาร, ศิริพร แจ่มใส, สิริประภา สิงหปรีชา. การให้ยาระงับความรู้สึกผู้ป่วยรับการผ่าตัดเปลี่ยนหัวใจ ณ โรงพยาบาลจุฬาลงกรณ์: ประสบการณ์ช่วงเวลา 9 ปี. จุฬาลงกรณ์เวชสาร 2539 มิถุนายน; 40(6): 465-475

การศึกษาแบบพรรณาย้อนหลังของการให้ยาระงับความรู้สึกในการผ่าตัดเปลี่ยนหัวใจ รวม 25 ราย ในโรงพยาบาลจุฬาลงกรณ์ นับตั้งแต่รายแรกของประเทศไทยในปี พ.ศ. 2530 โดยศึกษาจากแฟ้มประวัติผู้ป่วย บันทึกการให้ยาสลบ โดยทำการบันทึกข้อมูลด้านประชากรศาสตร์ของผู้ป่วยเข้ารับการผ่าตัดเปลี่ยนหัวใจ สภาวะทางกายภาพของผู้ป่วยและผลการศึกษาทางห้องปฏิบัติการก่อนการผ่าตัด ชนิดของยาระงับความรู้สึก ตลอดจนภาวะแทรกซ้อนซึ่งอาจเกี่ยวข้องกับการให้ยาระงับความรู้สึกในระหว่างผ่าตัดและหลังผ่าตัด ในหออภิบาลผู้ป่วยวิกฤตการนำสลบนิยมใช้ midazolam ร่วมกับ narcotics ได้แก่ morphine หรือ fentanyl ใช้ pancuronium เป็นยาหย่อนกล้ามเนื้อ ผู้ป่วย 15 ราย (ร้อยละ 60) ได้รับก๊าซ nitrous oxide, 15 ราย (ร้อยละ 60) ได้รับ fentanyl 11 ราย (ร้อยละ 44) ใช้ morphine เป็นยาสลบหลัก โดยใช้ midazolam เสริมทางหลอดเลือดดำทุกราย มีเพียง 3 รายได้ยาสลบชนิดสูดดม ยากระตุ้นหัวใจหลักได้แก่ Isoproterenol Dopamine เป็นยากระตุ้นหัวใจและหลอดเลือดที่นิยมใช้รองลงมา ระยะเวลาให้ยาระงับความรู้สึกเฉลี่ยเท่ากับ 277.68 $\pm$ 93.41 นาที, ระยะเวลาเฉลี่ยของการใช้เครื่องปอดและหัวใจเทียมได้แก่ 99.52 $\pm$ 26.96 นาที และระยะเวลาที่คาท่อช่วยหายใจนับตั้งแต่เสร็จการผ่าตัด จนถอดท่อช่วยหายใจเท่ากับ 20.54 $\pm$ 10.95 ชั่วโมง โดยร้อยละ 80 ของผู้ป่วยได้รับการถอดท่อช่วยหายใจ ภายใน 24 ชั่วโมงหลังการผ่าตัดภาวะแทรกซ้อนที่เกิดขึ้นบ่อย หลังเลิกใช้เครื่องปอดหัวใจเทียมได้แก่ภาวะความดันโลหิตต่ำ ภาวะระดับโปแตสเซียมในกระแสเลือดต่ำ และภาวะหัวใจเต้นผิดจังหวะชนิดต่างๆ ภาวะแทรกซ้อนที่พบบ่อยช่วงหลังผ่าตัดในหออภิบาลผู้ป่วยวิกฤต ได้แก่ ภาวะปัสสาวะน้อย ภาวะระดับโปแตสเซียมในกระแสเลือดต่ำ ภาวะความดันโลหิตต่ำ และภาวะหัวใจเต้นผิดจังหวะชนิดต่างๆ ไม่พบการตายจากการให้ยาระงับความรู้สึก

Since the first human heart transplantation by Christian Barnard in 1967,[1] its success as a treatment has been established for selected patients with end-stage cardiomyopathy. Its consistent long-term success required several developments in the following decade. These developments included (1) technical refinements, (2) improved graft preservation techniques, (3) maintenance of the recipients during transplantation (4) better understanding of the physiology of the transplanted organs, (5) understanding of immunology and development of immunosuppressive drugs, and (6) solutions to some of the legal and logistic problems.[2] By early 1980, further elucidation of the problems of infection, rejection, hemodynamic management, organ preservation and the availability of rabbit antithymocyte globulin and then cyclosporin for effective immunosuppression without frequent drastic side effects ushered in the modern era of thoracic organ transplantation.[3] The historic first human heart transplantation in Thailand and Southeast Asia was performed in 1987. That and additional experience at Chulalongkorn Hospital encouraged the establishment of cardiac transplant centres in Thailand. Anesthetic techniques have evolved along with surgical experience in cardiac transplantation. We review our clinical experience concerning the anesthetic techniques and agents used at Chulalongkorn Hospital over these first 9 years.

Methods

The charts and anesthetic records of 25 recipients between July 1987 and June 1996 were reviewed and data were extracted concerning demographic characteristics, physical status, results of preoperative investigations, anesthetic agents and techniques, postoperative management, including respiratory care and postoperative analgesia, and complications which may have been related to anesthetic management. These complications included intraoperative arrhythmias, systemic arterial hypotension, prolonged postoperative intubation, oliguria etc. Systemic arterial hypotension was defined as decreasing >30 percent of mean arterial blood pressure. Prolonged postoperative intubation was considered when intubation was required for more than 24 hours after transplant. Oliguria was defined as a volume of urine output of <0.5 millilitre per kilogram of body weight per hour.

Results

Demographic data

The eighteen (72%) male and 7 (28%) female recipients ranged in age from 12 to 60 years. Distribution of ages among recipients is shown in Table 1. The primary diagnoses of the recipients were: idiopathic cardiomyopathy 52% (13 cases); ischemic cardiomyopathy 32% (8 cases); valvular heart disease 8% (2 cases) and congenital heart disease 8% (2 cases).

Preoperative evaluation

The physical status of the recipients were New York Heart Association Class III 36% (9 cases), Class IV 36% (9 cases) and unknown 28% (7 cases) because of a lack of records. Twenty percent (5 cases) required pharmacological inotropic support before surgery.

Table 1. Age distribution of recepients.

Age (years)	Cases	Percentage
10-19	2	8
20-29	1	4
30-39	5	20
40-49	11	44
50-59	5	20
60-69	1	4

Preoperative cardiac catheterization data demonstrated marked left ventricular dysfunction in 5 cases (20%), and echocardiography demonstrated cardiac indices less than 0.5 in 7 cases (28%). Six cases (24%) were investigated preoperatively by both cardiac catheterization and echo-cardiography. Neither cardiac catheterization nor echocardiographic data could be found in the remaining 7 cases (28%).

Anesthetic management

Eighty eight percent (22 cases) received no premedication and 12% (3 cases) received midazolam as a preoperative medication. A blood pressure cuff and electrocardiographic leads were applied to all recipients on arrival to the operating room. Intravenous cannulas were inserted, and percutaneous cannulation of the radial artery provided direct arterial pressure monitoring and blood gas analysis. The venous pressure was monitored via a catheter in internal jugular vein or subclavian vein. The summary of monitoring during anesthesia is displayed in table 2.

For induction, fentanyl combined with midazolam were used in 15 recipients (60%) and morphine combined with midazolam in the other 10 recipients (40%). Supplemental doses of thiopental were used in 5 cases (20%) to accelerate induction. Variations of induction technique are displayed in table 3. Succinylcholine was used in 17 recipients (68%) to facilitate intubation and pancuronium bromide was used in the other 8 recipients (32%). Sixteen patients (64%) had nasotracheal intubation and 9 patients (36%) had orotracheal tubes. Anesthesia was maintained with narcotics (fentanyl and/or morphine) and supplemented with midazolam in all cases. Pancuronium provided complete muscular paralysis throughout the procedure in all patients. Patients were ventilated with either 100 percent oxygen or 50 percent of nitrous oxide and oxygen. The adequacy of ventilation and acid base status were assessed by intermittent analyses of arterial blood gas. Intraoperative agents used are summarized in table 4.

Table 2. Intraoperative monitoring during cardiac transplantation.

Monitoring	Cases	Percentage
Mean arterial pressure	25	100
Arterial blood gas	25	100
Central venous pressure	25	100
Electrocardiography	25	100
Temperature	25	100
Urine output	25	100
Accelerated Clotting Time	17	68

Table 3. Induction techniques used for cardiac transplantation.

	Cases	Percentage
Fentanyl + midazolam	13	52
Fentanyl + midazolam + thiopental	2	8
Morphine + midazolam	7	28
Morphine + midazolam + thiopental	3	12

Table 4. Anesthetic agents used in cardiac transplantation.

Agent	Cases	Percentage
Fentanyl	15	60
Morphine	11	44
Midazolam	25	100
Thiopental	5	20
Dehydrobenzperidol	6	24
Nitrous oxide	15	60
Halothane	3	12
Isoflurane	1	4
Pancuronium	25	100

Heparin (3 milligrams per kilogram) was administered prior to aortic and caval cannulation. Perfusion pressure was maintained between 50 and 100 torr. Moderate hypothermia with temperatures between 29 and 32 degree celcius was routinely employed. After suturing of the heart was completed, the transplanted heart commenced beating either spontaneously or after defibrillation.

Average recipient ischemic time was 85.52 ± 30.93 minutes; this varied from 50 to 160 minutes. Cardiopulmonary bypass time varied from 50 to 166 minutes with an average bypass time of 99.52 ± 26.96 minutes. During weaning from the bypass, and in the early post-bypass period, patients were given 100% oxygen.

Isoproterenol infusion was used in all but one case to maintain adequate heart rate and cardiac performance. Epicardial pacemaker wires were routinely applied to the heart and used when needed to maintain cardiac rate. Intravascular volume deficits during the post-bypass period were poorly tolerated; the central venous pressure or left atrial pressure was used to maintain the proper volume. Other vasoactive agents used are displayed in table 5. Protamine was slowly infused while the arterial pressure was being carefully monitored. Antibiotics and methylprednisolone were routinely used in all patients. Intravenous furosemide was used to ensure adequate urine output and potassium chloride was supplemented when needed.

Table 5. Vasoactive agents used during cardiac transplantation.

Agents	Cases	Percentage
Isoproterenol	24	96
Dopamine	18	72
Calcium chloride	16	64
Sodium nitroprusside	13	52
Adrenaline	7	28
Dobutamine	3	12
Nitroglycerine	2	8

The average anesthesia time was 277.68 ± 93.40 minutes which varied from 90 minutes to 435 minutes. On completion of the operation, all patients were transferred with continuous cardiac monitoring to an isolation area of the intensive care unit. Manual positive pressure ventilation with oxygen via a self-inflating bag was provided during transfer. Vasoactive agents, especially isoproterenol infusion,was maintained during this time in the intensive care unit.

Postoperative care

Twenty patients (80%) were extubated within 24 hours. Postoperative intubation time varied from 6 to 48 hours with an average time of 20.54 ± 10.95 hours. Five patients (20%) were extubated after 24 hours postoperatively.

Seventeen patients (68%) received morphine for postoperative analgesia. Ten patients (40%) received intermittent doses of morphine, and another 7 (28%) received morphine infusion. Three patients received only oral acetaminophen and 5 patients (20%) did not receive any analgesics. The duration of stay in the intensive care unit varied from 34 to 408 hours with an average ICU time of 178.48 + 78.98 hours. Six patients (24%) received isoproterenal for less than one week and 18 patients (72%) received it for more than one week.

Complications

Intraoperative and postoperative complications in the intensive care unit were summarized in table 6. There were no gross neurological deficits after transplant. Before being extubated, two patients were reoperated on within the first postoperative day so as to stop bleeding. Two patients (8%) were reintubated. For one, this was during cardiopulmonary resuscitation because of a heart block and required further mechanical ventilatory support. The other was reintubated because of pulmonary congestion. No mortalities occurred during the postoperative intensive care periods.

Discussion

There has been substantial improvement in heart transplant survival resulting from refinements in patient selection, improved postoperative care and the introduction of cyclosporin[4]. One and 5 year survival rates after orthotopic heart transplantation in adults from 1985 through 1990 are 81% and 69% respectively.[5] Causes of death are most commonly due to technical or primary cardiac complications soon after transplantation. However, after 1 month these complications are rapidly surpassed by infectious etiologies and rejection.[5] Anesthesia for cardiac transplantation can be successfully performed with a number of anaesthetic agents. A review of major anesthetic related complications revealed no death or permanent injury associated with anesthesia error or choice of anesthetic agent.[5] Ozinsky, reporting on the first heart transplantation, described the use of a slow thiopental infusion for induction. Orotracheal intubation was facilitated by succinylcholine and anesthesia was maintained with intermittent halothane.[6] Keats and associates used halothane or meperidine with nitrous oxide and oxygen. Muscle relaxation was provided by d-tubocurarine and gallamine.[7] Fernando and associates used combinations of diazepam and morphine for induction and maintenance anesthetic agents, either alone or in combination with 50 percent nitrous oxide inhalation. Waterman and Bjerke demonstrated that rapid sequence induction with fentanyl, etomidate and succinylcholine by defasciculation with curare can result in minimum cardiovascular changes.[9] In our study, careful administration of midazolam and high doses of narcotics were routinely used in induction to ensure amnesic effect.

Table 6. Complications.

Complications	Cases	Percentage
Intraoperative		
Hypotension	24	96
Hypokalemia (K<3.5 mEg/L)	13	52
Cardiac arrhythmias		
- Ventricular arrhythmias	7	28
- Sinus bradycardia	1	4
- Heart block	1	4
Metabolic acidosis (treated by sodium bicarbonate)	2	8
Hyperkalemia (K>5.5 mEg/L)	1	4
Intensive care unit		
Urine output <0.5 ml/kg/hr	22	88
Hypokalemia (K<3.5 mEq/L)	14	56
Hypotension	10	40
Cardiac arrhythmias		
- Ventricular arrhythmia	9	36
- Heart block	7	28
- sinus bradycardia	2	8
- cardiac surrest	1	4
Metabolic acidosis (treated by sodium bicarbonate)	6	24
Hyperkalemia (K > 5.5 mEg/L)	2	8
Reintubation	2	8

Anesthesia for heart transplantation requires adequate preparation. In addition, because most heart transplants are emergency cases, organization and planning are highly advantagious. The initiation of antibacterial and immunosuppressant protocols often begins in the preoperative period. Cyclosporin (10 to 18 ug/kg) is routinely administered orally before anesthesia and surgery. Therefore, full stomach conditions should always be considered. Premedication is best reserved for the patient whose anxiety or other symptoms indicate that

the risk is outweighed by the benefit. Excessive preoperative sedation may cause undesirable cardiac depression,[10] but H2 antagonists or nonparticulate antacids can be prescribed to decrease the risk of aspiration.

Anesthesia equipment should be clean, if not sterilized, because of the higher risk for infectious complications in these immunocompromised patients. Invasive and routine monitoring are necessary. In our cases, central venous access was most often obtained via the left jugular vein so as to leave the right internal jugular vein undisturbed for future endomyocardial biopsies. In this study, pulmonary artery catheters were not used. The use of the pulmonary artery catheter is controversial.[11] Risks associated with its use include infection and trauma to surgical anastomoses after transplant. Because many heart transplant recipients demonstrate no need for pulmonary artery catheters postoperatively, the risks outweigh the benefits of placing them in all patients. High dose opioids were routinely used for induction in our institute so pancuronium was the preferred muscle relaxant. Pancuronium will counter the central and vagal opioid-induced negative chronotropic effects by its vagolytic and mild sympathomimetic property. The severity of pre-existing left ventricular dysfunction may enhance the known depressant effects of the volatile anesthetics. However, low concentrations of volatile agents can be safely used to supplement narcotic anesthesia in transplant recipients with less severely impaired ventricular function.[4]

Nitrous oxide was avoided, especially during the post cardiopulmonary bypass period. This was due to possible adverse effects including potential increases in PVR or SVR and increased risks of enlarging an inadvertent air emboli.

The institution and management of CPB is quite similar to that used in other cardiac surgical procedures. Adequate heparinization is essential. Rewarming is usually begun during anastomosis of the atria. Adequate rewarming (rectal and nasopharyngal temperature >34°c) and sinus rhythm should be achieved before weaning from CPB.

Isoproterenol infusion which stimulates the beta receptor increased heart rate, decreases right ventricular afterload (PVR), and thus improves stroke volume and cardiac output.[12] All but one of recipients received isoproterenol infusion to decrease pulmonary vascular resistance and prevent bradycardia episode. There was only one recipient who did not receive isoproterenol infusion because the transplanted heart was too sensitive to isoproterenol. Because of the loss of parasympathetic innervation, the transplanted heart has an intrinsic sinus rate that is slightly faster (90-110 in beats per minute) than the average heart rate. Cardiac output augmentation in the transplanted heart is more dependent on increases in stroke volume than on heart rate increases.[13] Thus, maintenance of adequate preload is critical. In our cases, β-agonists such as dopamine and epinephrine were often used to augment graft myocardial contractility as it recovered from postischemic depression. Responses to catecholamines may be unpredictable.[14] Furosemide was frequently used to maintain good urine output. A conven-

tional dose of protamine was used to neutralize the heparin following cardiopulmonary bypass. Blood products were used according to laboratory coagulation profiles and the clinical setting.

In the intensive care unit, monitoring and management of hemodynamics were similar to that required for other patients following cardiopulmonary bypass. A key goal is maintenance of an adequate heart rate because of bradydysrhythmias. Usually, slow junctional or secondary to varying degrees of sinoatrial or atrioventricular nodal dysfunction are common. Weaning from mechanical ventilation and tracheal extubation is the next goal. Eighty percent of our recipients were extubated within 24 hours. One recipient needed reintubation and cardiopulmonary resuscitation because of bradydysrhythmia and cardiac arrest. The other was reintubated because of pulmonary congestion. Two recipients were reoperated on before first extubation to stop bleeding. All patients had no serious adverse outcome in the intensive care period.

All recipients were anesthetized by a high dose narcotic base technique so they required only small amounts of analgesics. Twenty percent of the recipients received no analgesics.

Hypotension (especially at the beginning of cardiopulmonary bypass),hypokalemia and cardiac arrhythmias were frequent in the intraoperative period. Oliguria, hypokalemia, hypotension and cardiac arrhythmias were common during the intensive care. Surveillance of these complications are crucial for prompt treatment to prevent morbidity and mortality.

Conclusions

Anesthetic experience and techniques have evolved along with surgical experience in cardiac transplantation at Chulalongkorn Hospital. Anesthetic management with a high dose narcotic technique, which is similar to that used in other cardiac surgical procedures;is appropriate for this group of patients. The anesthesiologist should keep in mind that the patient undergoing cardiac transplantat is one with severely impaired venticular function, and isoproterenol is an important cardiac stimulant for this procedure. Since infection remains a major cause of morbidity and mortality in these immunosuppessed patients, aseptic techniques must be used.

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