MEDICAL HISTORY AND CONTINUE EDUCATION
A Liver Transportation Model

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Abstract

Medical history and ethics have a great role in advance medical research and clinical practices, through studying health and medical situations along the human history, to detect the gabs between our knowledge and the ongoing inventions of various sorts. Closing these gabs and managing the new tools brought to us by these discoveries such as surgical scopes helped the current investigators to create better diagnosis, medical and surgical systems. Such efforts lead us to better care and better prognosis regarding current patients for current medical conditions and effective care. This study discusses the role of medical history in exploring new events and procedures as well as its application on our daily health situations, for example, a liver transplant model, to meet the upmost urgent need of a liver recipient.

التاريخ الطبي واخلاقيات لها دور كبير في تقدم البحث الطبي والممارسات الطبية المختلفة، من خلال دراسة الصحة والظروف الطبية خلال التاريخ الانساني للتعرف على الفجوات بين ما نعرفه والابتكارات المتواصلة في مختلف المجالات. مثل هذه الفجوات والتعامل مع الادوات الجراحية الجديدة المتاحة لنا بفعل الاكتشافات الحديثة مثل المناظير الجراحية ساعدت الباحثين لإيجاد تشخيصات أفضل، وانظمه صحية وطبيه انجح. هذه الجهود ادت بنا الى رعاية وعلاج أفضل فيما يخص المريض اليوم من أوضاع صحية ورعاية فعاله. هذه الدراسة تناقش دور التاريخ الطبي في اكتساب نماذج وخبرات جديدة وكذلك تطبيقها على مواقف حياتيه يوميه جديدة، كمثال. زرع فص كبد، نظرا للاحتياج الشديد لمرضى الفشل الكبدى.

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Introduction: Medical achievements along the human history shows that the discovery of the natural history of the diseases, management procedure, is not simple task, it took years to discover the key of this event or this procedure. For this reason, some faculty of medicine established special department of medical history, such as Faculty of Madison, University of Wisconsin-Madison, USA, since 1950.[1]

The acute chest pain of ischemic heart disease has been early described in the history of medicine; while Hippocrates,460-370 B.C., recorded the relation between the occupation and incidence of angina pectoris, Sarton G, 1959.[2] Beside Ibn Sina, 980-1036 A.D., in his "Al Kanon" gave full account of the pain of angina pectoris.[3]

Sclerosis of the coronary arteries in this disease was described by Fothergill in about the year 1748. By the end of seventeenth century, Parry wrote one of the earliest accounts of angina pectoris, which he attributed to disease of coronary arteries. The first clear description of angina pectoris appeared in1802 appeared by William Heberden, Major R H 1954.[4] Moreover, Heberden discussed factors that can participate attacks, how to prevent them and mentioned the value of opium in their management, Bishop L F, 1967.[5]

HISTORY OF LIVER TRANSPLANTATION

It is almost impossible to discuss the history and development of liver transplantation without mentioning the names of Thomas Starzl and Roy Calne, two of the surgical founders of liver transplantation, who have both published autobiographies, have produced a beautifully non-technical history in Art, Surgery and Transplantation, Ismael A, 1990.[6]

Liver Transplantation Events[6,7]

YEAR DESCRIPTION

1955 Firsts article in the literature on auxiliary liver transplantation (C Stuart Welch)

1956 First article on orthotopic liver transplantation (Jack Cannon) 1958-1960 Formal research programs on liver replacement at Harvard and Northwestern

1960 Multi-visceral transplantation described, the forerunner of composite grafts

1963 Development of the azathioprine-prednisone cocktail (kidneys first, then livers)

1963 First human liver transplantation trial (University of Colorado)

1964 Confirmation of the portal venous blood hepato-trophic effect; defined the problem of auxiliary liver transplantation

1963-1966 Improvements in preservation, in situ and ex vivo 1966 Introduction of anti-lymphocyte globulin (kidneys, then livers)

1967 First long survivals of human recipients (1967-1968), treated with azathioprine, prednisone and anti-lymphocyte globulin

1973-1976 Principal portal hepato-trophic substance identified as insulin

1976 Improved liver preservation (5-8 hours) permitting long-distance procurement

1979d Systematic use of arterial and venous grafts for vascular reconstruction

1979 Cyclosporine introduced for kidneys and liver

1980 Cyclosporine-steroid cocktail introduced for kidneys

1980 Cyclosporine-steroid cocktail for livers

1983 Pump-driven venovenous bypass without anticoagulation

1984 Standardization of multiple organ procurement techniques

1987 University of Wisconsin (UW) solution for improved preservation

1989 FK 506 steroid immunosuppression

1990 Alaa Ismail, TRANSPLANTATION OF LIVING LIVER GRAFT IN DIFFERENT POSSIBLE SITES, Sci. Med J. Cai Med. Synd., Vol. 2, No.3, July 1990

1992 Discovery of chimerism as explanation of hepatic tolerogenicity

1992 Baboon to human xenotransplantation

Transplantation of Living Liver Graft in Different Possible Sites, Model

Orthotopic replacement of the diseased liver by a whole liver obtained from a heart-beating cadaver is the standard technique for liver transplantation. A main obstacle is the shortage of liver donors compared to the long waiting list of recipients. In some countries in which brain death is not yet accepted as a legal criterion for organ retrieval the liver graft is simply not available. For infants the shortage of pediatric donors was particularly critics. Because of the rapid expansion of liver transplantation for treatment of numerous patients with acute or chronic liver diseases. Potential sources of organs such as non-heart-beating human cadavers or non-human donors are under investigations. Another source of liver grafts could result from the fact that the liver is composed of two half-liver which can be surgically divided. Each half-liver has its own portal vein, hepatic artery and bile duct. Partition of the liver may allow the obtaining of two grafts from a liver retrieved in a cadaver donor and of one graft from a living donor. In several centers, the technique has been markedly improved by the use of reduced size grafts

from older heart-beating cadaver donors. The experimental study was conducted to assess the feasibility of resecting segment II and III from a living donor and implanting it in three different sites in the abdominal cavity of the recipients.8-13,14,15,16,17

Animals and Methods

The study was done on 30 adult mongrel dogs weighting 12-16KG. Sodium pentobarbital was used for the induction of anesthesia which was maintained by endotracheal intubation and halothane.

The experiment was designed to evaluate three possible sites for partial liver transplantation.

1. Auxiliary heterotopic partial liver transplantation of a bisegmental graft from a living donor in the splenic bed (Fig. 1&2).

2. Auxiliary heteropic partial liver transplantation of bisegmental graft from a living donor in the right paravenebral gutter (Fig. 3).

3. Orthotopic non auxiliary partial liver transplantation of bisegmnetal graft from living donor.

The investigator used another 30 dogs for liver donation. The technique of resection was standardized as described by Couinaud13 for the three types of recipient operations. Investigator resected segment II and III with its left hepatic vein (Fig. 1).

Preservation was done by flushing and cooling the graft via its portal vein and hepatic artery using 4C" Ringer's lactate solution. Then, the graft was stored in cold Euro-Collins solution at 4 Centigrade.

Donor Operation

According to Houssin et al., 1988[14] the donor operation was performed through a midline incision. The round ligament, falciform ligaments were divided. Using an operative microscope, the terminal 2cm of the left hepatic vein were dissected from the surrounding parenchyma and encircled. Then, the upper left portion of the hepatic artery, hepatic duct and portal vein was achieved. According to the particular animal, two to three glissonian pedicles going from the horizontal portion of the left glissonian pedicle to the quadrate lobe were ligated and divided, as well as one or two short pedicles going to the Spigelian lobe. Then, without clamping the vascular structures going to the left part of the liver, the liver capsule was incised along a line between the right side of the round ligament and the right side of the end of the left hepatic vein. The transaction was done step by step using a Kelly clamp with ligature or coagulation of each pedicle; it was conducted posteriorly and slightly to the left ending in front of the right border of the caudate portion of the Spigelian lobe. This technique allowed us to maintain normal blood to the left part of the liver during transection of the parenchyma.

Finally, the left branches of the hepatic artery and portal vein and left hepatic vein clamped and divided. After a warm ischemia time of less than 2 min, the graft was flushed and cooled via the left portal branch and the left hepatic artery using 200ml of 4 centigrade Ringer's lactate solution and them immediately transplanted. In the donor, the stumps of the left portal branch, and left hepatic duct were either ligated or sutured. Before the abdomen was closed without drainage, inspection of the remaining liver revealed in all cases a small area of congestion on its left and anterior part, close to the transaction plane.

1. **Technique of auxiliary heterotopic partial liver transplantation in the splenic bed:**

The donor and recipient operation were done simultaneously. The liver graft was flushed cooled via its portal vein and its hepatic artery using 4C* Ringer's lactate solution during operation. The graft was implanted in the splenic bed of the recipient after removal of the spleen and leaving a long stump of the splenic artery and vein. The splenic vein was flushed by 1/10.000 heparinized saline solution before its clamping to prevent splenic vein thrombosis. The liver graft was rotated 180' in the frontal plane so that the end of the hepatic vein was in down ward position, also the graft was rotated 180" in the vertical plane so that the cut surface of the graft is facing medially. The graft was implanted in the splenic bed by anastomosing its left portal branch end-to-end to the splenic vein using 6-0 prolene continuous suture. The hepatic artery was anastomosed end-to-end to the splenic artery using 6-0 prolene continuous suture. The hepatic vein was anastomosed end-to-end to the proximal end of the left renal vein after its thorough dissection and ligation very bear to the kidney hilum. The hepatic duct of the graft-was implanted end-to-side on a Roux-ewn-Y in a jejunal loop. The portal vein of the recipient was narrowed to half of its diameter to allow blood to flow to the graft. At the end of the operation careful hemostasis was done and the abdomen was closed by ordinary technique. The dogs were then extubated as soon as it awoke.

2. **Technique of auxiliary heterotopic partial liver transplantation in the right paravertebral gutter:**

The recipient operation was done through a midline incision. The harvesting procedure itself was standardized in all types of operations. The right paravertebral gutter was dissected carefully to find a bed suitable for the size o the graft. Mobilization of portal vein and exposure of the infra-hepatic inferior. Vena cava is essential step. Then the graft was placed in the space after its rotation 180' in the frontal plane so as to bring the hepatic vein downward and hepatic pedicle upward. The hepatic vein of the graft was anastomosed end-to-end side to the right anterior surface of the inferior vena cava below the site of the right renal vein. The portal branch of the graft was anastomosed end-to-end to the portal vein of the recipient. The hepatic duct was implanted end-to-side as a Roux-en-Y in a jejnal loop. The dogs were infused by 750 ml lactated Ringer's solution, because of the dissection of the P.C. gutter.

3. Technique of Orthotopic Partial Liver Transplantation:

The recipient operation started by complete dissection of the liver and total hepatectomy without its vascular supply, i.e. leaving the vessels in its place after their clamping. The investigators clamped and transected the hepatic veins while the recipient I.V.C. was clamped above and below the liver which is preserved in continuity. The confluence of the three hepatic veins was left opened while the small hepatic veins.

The graft was implanted by anastomosing the hepatic vein end-to-side of the I.V.C. at the site of the recipient veins, using 5-0; prolene suhire. The hepatic artery of the graft was anastomosed to the recipient hepatic artery end-to-end using 5-0 prolene suture. The portal vein was anastomosed end-to-end to the recipient portal vein, using 6-0 prolene suture. Then the clamps the investigatorsre removed and bleeding or biliary leakage were managed. Then, the duct was reconstructed as end-to-side choledo-chojejunostomy using a Roux-en-Y loop with insertion of a T tube. The dogs were infused by 500 ml lactated Ringer's solution and 500 ml plasma expanders because of the ooze occurred during dissection and removal of the liver.

Table (1): Complications after the different types' liver transplantation

Type of Complications	Type of Operations		
	APLT in splenic n=10	ALPT in right paravertebral gutter n=10	Partial LTX n =10
Bleeding	2/10	3/10	3/10
Sepsis	1/10	2/10	1/10
Graft necrosis	1/10	1/10	--
Venous thrombosis	2/10	--	--

ALPT= Auxillary Partial Liver Transplantation
LTX=Orthotopic Liver Transplantation

Table (2): Mortality and its causes in the three different types of partial liver transplantation

Type of Operation	Cause of death				
	Bleeding	Sepsis	Graft Necrosis	Venous Throm-bosis	% of mortality
APLT in splenic bed	2	1	1	2	60%
APLT in right para vertebral gutter	1	2	-	-	30%
Partial LTX					

Table (3): As Regard the Donor most operations were successful

Type of infusion	Type of Operation		
	APLT in splenic bed	ALPT in right paravertebral gutter	Partial LTX
Ringer's Lactate solution	500 ml	750	500 ml
Plasma expanders	--	--	500 ml

Results:

As regards the donor most operations were successful: Seven dogs out of thirty died. Four cases died either at the end of operation or two days after due to acute anemia resulting from repeated hemorrhagic episodes during transection of the liver parenchyma and in availability of blood transfusion. The other three died from 4-10 days after operation due to severe intra-abdominal infection – 23 dogs were alive 3 months after operation Three of these twenty-three dogs were systematically killed. No abdominal complications were noted. The remaining right part of the liver was slightly enlarged as compared with the time of surgery. The surface, color and consistency of the livers were normal. Histological examination of the liver was normal.

The investigator started immune oppressive drugs to all the recipient dogs during operation and the dose was calculated according to the body weight. Nineteen

recipient dogs remained alive three months after operation. The investigators did scarification of three dogs one from each group after 3 months. No abdominal complications. The graft of normal color and consistency, and histologically the graft were normal. The remaining dogs are living their normal life. The mortality rate was 20% in dogs submitted to partial Orthotopic liver transplantation of living graft. One dog died of hemorrhage out of three dogs who developed post-operative bleeding. The causes of bleeding were: congestion of the graft in one case leading to subscapular hemorrhage, leakage from the vena cava anastomosis in the second case, and bleeding from the cut surface of the liver graft in the third who died immediately. Another dog died 3 days' post operatively due to intra-abdominal infection.

Discussion: There are some problems facing liver transplantation. Two of them are; the availability of the graft and the second is lack of room inside the abdominal cavity specially in children. In countries where the brain death is not yet accepted, the problem is much more. So, the investigators aimed in this study to solve these problems by using a bisegmental liver graft from a living donor from the study of Welch and Co-studiers in 1955.[21] In 1965 Absolon[1] did the first auxiliary heterotopic liver transplantation.

In this study, the results of the donor operation is encouraging. The technique was harmless to the donor and his remaining liver, in spite of doing transection without clamping any vascular structure, to avoid the warm ischemic damage of the graft's parenchyma. These results go with the results of Houssin et all, in 1988.[14]

In this study, the investigators implanted the graft in 3 sites. The first site is auxiliary heterotopic in the splenic bed. In this site, there is enough space for the graft after splenectomy, the stumps of the recipient vessels after rotation of the graft 180 in horizontal plane. Also, the use of heparin locally in splenic vein is important which is a common complication after splenectomy. The portal vein of the recipient is narrowed to the half of its diameter to oblige the portal blood to flow to the graft. So, in this site for implantation, it is easy to find space for the graft, but there is high incidence of vascular thrombosis. In this group, two dogs died from bleeding due to non-availability of blood transfusion. High incidence of venous thrombosis due to the long splenic vein and stagnation of blood inside it.

The second site is implantation in the right para-colic gutter. In this group, there was much difficulty to dissect a space for the graft with much bleeding and dogs were infused by 750 ml lactated Ringer's solution which saved two dogs out of three developed bleeding during operation. But two cases developed severe, abdominal sepsis and died because of the dissection of the para colic gutter which helped in wide spread of infection.

In the third site which is orthotopic non auxiliary; expecting bleeding during hepatectomy of the recipient liver, the dogs were infused by 500 ml plasma expanders. This amount of infusion saved 2 I.V.C., only clamping of the portal vein before hepatectomy without excision of the recipient I.V.C.[14,18,19,20,21]

In conclusion, the study presents a technique for obtaining a liver graft from a living donor in an attempt to transplant these grafts either heterotopic ally or orthotopically. The heterotopic implantation met with difficulty in the right para colic gutter to find an adequate space for the graft. As regard the implantation in the splenic bed it met with the problem of venous thrombosis and hence the graft necrosis. In the orthotopic non auxiliary partial liver transplantation of a bi-segmental liver graft with conservation of the vena cava of the recipient would probably be preferable, its only problem is bleeding which can be corrected by blood transfusion.

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Fig. 1: Orthotopic non auxiliary partial liver transplantation of bisegmnetal graft from living donor[6]

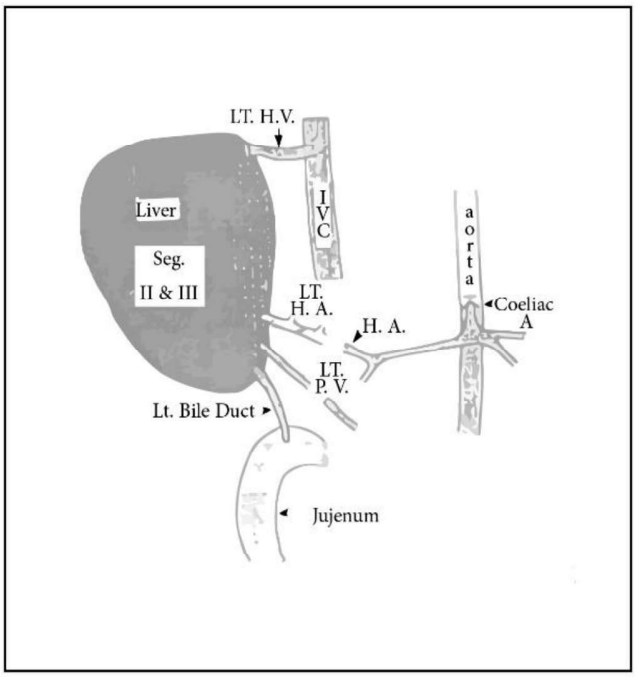

Fig. 2: Anatomy of hepatobiliary tree[6]

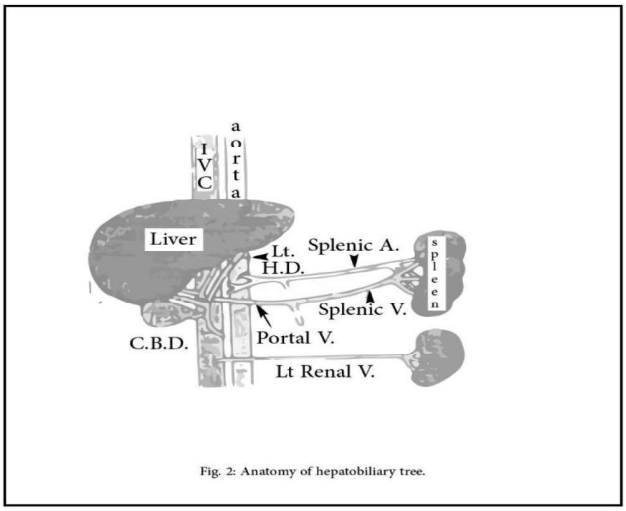

Fig. 3: Auxiliary heteropic partial liver transplantation of bisegmental graft from a living donor in the splenic bed[6]

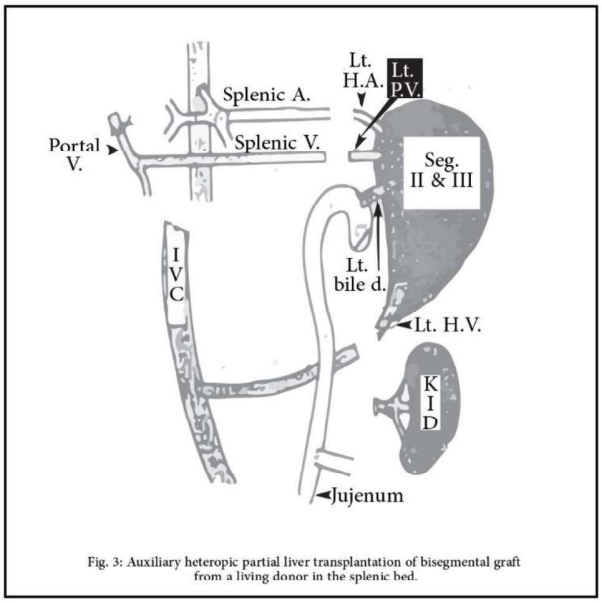

Fig. 3: Auxiliary heteropic partial liver transplantation of bisegmental graft from a living donor in the splenic bed.

Fig. 4: Resection of segmental graft of the liver[6]