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COMPARATIVE STUDIES ON PARTIAL AUXILIARY LIVER AUTO AND HOMOTRANSPLANTATION IN DOGS

(With 10 Figures & 2 Tables)

By

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دراسات مقارنة على الأزدراع الجزئى لكبد من نفس الحيوان أو من حيوان أخر من نفس الفصيله فى الكلاب

على حسين ، محمود ناصف ، حسين البدوى ، محمد على
أحمد صالح ، جمال أحمد ، عبد المنعم الخطيب

أجرى هذا البحث على عدد ٢٥ كلباً سليماً من سلالة خليط يتراوح وزنها من ١٠ – ٢٥ كيلو جرام ولقد قسمت هذه الحيوانات إلى ثلاث مجموعات كالأتى :-

المجموعه الأولى :- أجرى عليها عملية أزدراع الكبد الجزئى من نفس الحيوان وأشتملت على خمس كلاب وكان الغرض من هذا الأختيار دراسة الأزدراع الجزئى للكبد الأضافى مع تقليل عوامل المناعه وتأثيرها

المجموعه الثانيه :- أجرى أزدراع الكبد الجزئى الأضافى دون عمل توصيله بين الوريد البابى والوريد الأجوف السفلى (١٠ حيوانات).

المجموعه الثالثه :- أجرى أزدراع الكبد الجزئى الأضافى من حيوان أخر من نفس الفصيله مع عمل توصيله بين الوريد البابى والوريد الأجوف السفلى فى نفس وقت العمليه (١٠ حيوانات).

أجريت عمليات المجموعه الثانيه والثالثه بعد أخذ جزء من الكبد وما يتصل به من شريان ووريد من حيوان وزرعه فى حيوان أخر . ثم توصيل الشريان الكبدى للجزء المزروع بالشريان الحرقفى الخارجى أو بالشريان الحرقفى الداخلى . كذلك تم توصيل الويد الكبدى بالوريد الأجوف السفلى . ولخروج العصاره الصفراويه تم توصيل الحوصله المراريه بالصائم. أعطيت الكورتيكوستيرويدات فى كل من المجموعه الثانيه والثالثه لتكون كابحه للمناعه. تم تسجيل الصفات التشريحيه والمجهريه للكبد المزدرع فى المجموعات المختلفه.

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SUMMARY

The present work was done on 25 clinically healthy mongral dogs, weighing between 10-25 kg. b.w. The dogs were divided into three groups. The first group was subjected to partial auxiliary autotransplantation. The immunological factors were behind this choice. The second group, homotransplantation with portocaval shunt. The third group was subjected to partial auxiliary homotransplantation and portocaval shunt. The postmortem and histopathological examination were studied.

INTRODUCTION

Liver transplantation has been developed in the last 30 years. Canine liver grafts were shown to function after transplantation to the pelvis by *FONKALSRUD* et al. *(1967)*. Several techniques have been described for canine liver transplantation by *MOORE* et al. *(1960); El-GUINDY* et al. *(1969); STARZL and PUTNAM (1969) and STARZL* et al. *(1982)*.

The first attempt at liver allotransplantation in man was mad by *STARZL (1964)* at University of Colorado, the 3-year-old recipient with extrahepatic biliary atresia died of haemorrhage on the day of transplantation. The addition of cycloporine immunosuppression as well as liver preservation and surgical techniques have recently improved the prospects for clinical liver transplantation *(STARZL* et al., *1982 and ABRAHAM* et al., *1989)*.

The established indications for liver transplantation include nearly all irreversible liver failure states confronting the practicing clinician. The broadly defined disease categories that may prompt consideration for transplant stated by *JENKINS (1987)* are:- primary biliary cirrhosis, chronic active hepatitis, sclerosing cholangitis, fulminant/subfulminant hepatic necrosis, primary hepatic neoplasms, hepatic veno-occlusive disease, metabolic disorders, alcoholic cirrhosis (inactive), biliary atresia, polycystic disease and failed prior transplantation.

The aim of the present study is to evaluate the technique for partial auxiliary liver transplantation and to study the fate of auto and homograft of liver through post-mortem and histopathological examinations.

MATERIAL and METHODS

These experimental studies were performed on 25 clinically healthy mongral adult dogs of both sexes, weighing 10-25 kg. The animals were divided into 3 groups (table 1).

Table 1: Partial auxiliary liver transplantation.

	procedure	No. of cases
Group I	Autotransplantation.	5
Group II	Heterotopic (auxiliary) transplantation.	10
Group III	Heterotopic (auxiliary) transplantation with porto-caval shunt.	10

Animal Preparation:

The dogs of all groups were withheld of food and water 12 hours before operation and prepared for aseptic surgery. They were premedicated with intramuscular injection of chlorpromazine HC1 in a dose of 1 mg/kg.b.w. General anaesthesia was induced and maintained through intravenous cannulation by injection of thiopental sodium until the main reflexes were abolished.

Surgical Technique:

Group I: Partial auxiliary transplantation of the left lateral, left central and right central lobes together with gallbladder.

The abdomen was opened by a midline incision and continued at its upper end by right Kocher's incision. After exposure of the whole liver, the left central, left lateral and right central lobes were dissected from the right half of the liver with good venous and arterial blood supply. The common bile duct and hepatic duct were dissected and elevated with a sling of silk No.3. The hepatic artery proper was isolated and gently retracted to expose the dorsal aspect of the hepatoduodenal ligament. The arterial branch or branches of the right half of liver can be seen arised from the common hepatic artery before it bifurcates into the hepatic artery proper and gastroduodenal arteries (Fig.1).

Ligation and division of the hepatic artery with preservation of good stumps were done. The bile duct was transected between two ligatures. The portal vein at the liver hilum provides a large branch to the right division and the

arches to the left supplying the remainder of the liver (left branches). By caeeful dissection, the vein was ligated and divided. Cannulation of the portal vein and perfusion of cold (4°C) lactated Ringer's solution with 2000 IU heparin was performed. By downward traction on the liver, the falciform ligament was divided. The medial extension of the coronary ligament, the left triangular ligament was incised taking care to avoid the left phrenic vein and secure the small vessels. Ligation and division of the hepatic veins were carried out with separation of the graft.

Graft Preparation:

The graft was taken to the back table to be prepared for transplantation. The perfusion was continued by cold lactated Ringer's solution until complete wash of the graft occured and the fluid returned clear from the hepatic veins (Fig.2). Further dissection of the arterial and venous stumps by removing the areolar tissues encircling them was performed (Fig.3).

Graft Application:

The inferior vena cava and right iliac artery were dissected and vascular clamps were applied (Fig.4). End to side anastomosis were performed between the hepatic vein of the graft to the inferior vena cava and between hepatic artery and external iliac artery. The anastomosis were done by using prolene 6/ 0. The clamps were released firstly from inferior vena cava then other arterial clamps (Fig.5). Biliary drainage was achieved by cholecystojejunostomy (Fig.6). Complete haemostasis was carried out and the abdomintal wound was closed in two layers after insertion of drains.

Post-operative care:

The animals recieved hydrocortesone 100 mg intravenously followed by another 100 mg intramuscularly. Dexamethasone 4 mg was given i.m daily. Antibiotic (penicillin and streptomycin) 1 gm/ 12 hours was given before, during and after the operation. I.V. fluid (glucose-saline) was given for 3 days then the animal was allowed to recieve oral fluids.

Group II: Heterotopic partial auxiliary transplantation without porto-caval shunt.

The same technique as in group I was performed to obtain the liver graft from the donor and implanted into the recipient. The same post-operative care was applied.

Group III: Heterotopic partial auxiliary homotransplantation with porto-caval shunt.

The same technique for dissection and implantation in the

first and second groups was performed in addition to porto-caval shunt.

RESULTS

The clinical results of the present work were summarised in table 2.

Table (2): Transplantation, Results and time of procedures.

Case No.	Type of transplant.	Time of operation		Length of survival		Cause of death.
		hr.	min.	hr.	min.	
1	Auto-	6	20	00	00	Barbiturate toxicity.
2	transplant.	6	00	01	00	Barbiturate toxicity.
3		7	00	02	00	Barbiturate toxicity.
4		6	00	00	00	Shock reaction.
5		5	50	12	00	Technical error.
1		5	00	72	00	Peritoneal sepsis.
2		5	30	48	00	Hge.
3		4	45	72	00	Sepsis.
4		4	00	48	00	Hge.
5	Heterotopic	4	30	72	00	Sepsis.
6	transplant.	5	30	48	00	Thrombosis & necrosis.
7		4	50	48	00	Thrombosis & necrosis.
8		4	30	06	weeks	Post-mortem exam.
9		5	00	01	week	Post-mortem exam.
10		5	30	02	weeks	Post-mortem exam.
1		7	00	02	00	Barbiturate toxicity.
2		6	00	03	00	Barbiturate toxicity.
3		8	00	14	00	Barbiturate toxicity.
4	Heterotopic	6	00	12	00	Failure of anastomosis.
5	transplant.	5	50	24	00	Failure of anastomosis.
6	+	4	50	48	00	Pulmonary infection.
7	porto-caval	6	50	96	00	Pulmonary infection.
8	shunt	5	30	70	00	Peritoneal sepsis.
9		6	00	07	days	Peritoneal sepsis.
10		5	00	72	00	Peritoneal sepsis.

Post-Mortem Examination:

The blood vessels at the site of anastomosis were patent in all survived dogs except in 3 where thrombosis observed with atrophy of the graft. Portal vein was thrombosed in 2 dogs. Biliary leakage was seen in one dog due to disruption of the cholecystojejunostomy.

Rejected livers in 3 cases were grossly hypertrophied with rounded edges and mottled green areas while in successful dogs, the livers were grossly normal (6 cases). The livers were ususlly covered by thick fibrinous pseudocapsule unnder which lymphatic collection was frequently present particularly between lobes.

The iliao-hepatic artery was thrombosed in 3 dogs, stenosed without thrombosis in other 2 dogs and functioning in the remaining dogs. When vessels were thrombosed, grafts were shrunken and atrophied. They were generally softer and spongier than normal.

The porto-caval shunts and hepatic vein-inferior vena cava anastomosis were patent and functioning in the sucesseful group (6 cases).

Histopathological Findings:

The microscopic pictures of the survived cases showed that the grafts were remarkably preserved showing only slight congestion with presence of blood cells in central vein and peripheral blood sinusoids (Fig.7). The cases of thrombosis (3 cases) the grafts showed atrophic changes as evidenced by decreased lobular size in smaller cells. They showed also necrosis, scar tissue and collapsed reticulin frame work (Fig.8).

Considerable acute and chronic inflammatory reaction and only minimal residual hepatic tissue could be detected (Fig.9). Classical rejection with portal inflammatory cell infiltration with varying degrees were seen in 3 cases. Inflammatory cells were occasionally seen around central veins and scattered patchy areas of focal necrosis. Mononuclear cells aggregation were found among these cases. Aggregation of lymphocytes with an attempt for follicle formation was observed (Fig.10).

DISCUSSION

Long term survival with good liver function had been achieved both in experimental work and then in human with orthotopic transplantation. From the physiolgical point of view orthotopic transplantation is the most ideal. The preceding hepatectomy, space is made in the recipient's upper abdomen so that the graft can be implanted in its anatomical place, with

the ordinary anatomical arterial, portal vascularization and venous outflow. This method may be the most ideal theoretically, but in practice it is quite the opposite. The great risk associated with hepatectomy and the entire dependence of the recipient on the good functioning of the graft immediately after operation make the results of orthotopic transplantation not so encouraging.

In the first group, a trail to avoid immunological problems through autotransplantation to test the technique. The death rate among this group was very high because of the prolonged time of operation, anaesthetic agents and blood loss.

In heterotopic transplantation, the graft has an auxiliary function and at least the first temporary loss of function of the graft through ischaemia before and during transport is not harmful to patient. Besides heterotopic transplantation has the additional advantage of being much simpler operation than is required in orthotopic transplantation *(VAN DER HEYDE and SCHALM, 1968)*. Loss of function of the grafts within few days and complete atrophy within weeks in the present study was recorded also by *MARCHIORO* et al. *(1965)*. Time of survival ranged between 1 and 6 weeks but sepsis, thrombosis and atrophy of the grafts were the main cause of the death (Table 2). The common causes of death recorded by *MARVIN* et al. *(1972)* in hepatic transplantation were sepsis and thrombosis.

HALGRIMSON et al. *(1966)* reported that the demonstrated protective action of a porto-caval shunt on transplanted liver may be due to its known damaging effect on the host's own liver with constant stimulation of graft function, and not due to specific portal trophic factor which becomes available to the graft as a result of shunt. Accordingly in our study the models with porto-caval shunt showed no atrophy and better function of the graft. These results were similar to that recorded by *MARVIN* et al. *(1972)*.

The anastomosis with iliac artery was suitable and showed no technical difficulties and where the hepatic artery was narrow or injured, the portal vein was easily used instead. The venous out flow of the graft was via end to side anastomosis of the left hepatic vein and inferior vena cava. This was also supported by *VAN DER HEYDE and SCHAIM (1968)*. The histopathological changes as stenosis, focal necrosis and chalestasis are non-specific alterations and can be seen in various illnesses. Infiltration particularly of portal triads by large number of lymphocytes was the change most relied upon to judge the liver as rejected. These microscopical changes were also recorded by *BEAUDOIN* et al. *(1970)*. The corticosteroids used in the present study was valiable but not

able alone to prevent rejection completely. JAIN et al. (1991) mentioned that acute rejection could be managed in the first week by a large dose of the conventional immunosuppressive drugs.

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LEGENDS

Fig. 1 : Visualization of the lobulated liver and dissection of common bile duct, hepatic artery and portal vein.

Fig. 2 : Three lobes of liver prepared for transplantation by complete wash using Ringer's solution until the fluid returned clear from hepatic vein.

Fig. 3 : Further dissection and removal of the areolar tissue that encircling the blood vessels.

Fig. 4 : Dissection of the inferior vena cava and iliac artery in right iliac fossa of the recipient.

Fig. 5 : After releasing of vascular clamps the graft became congested with blood.

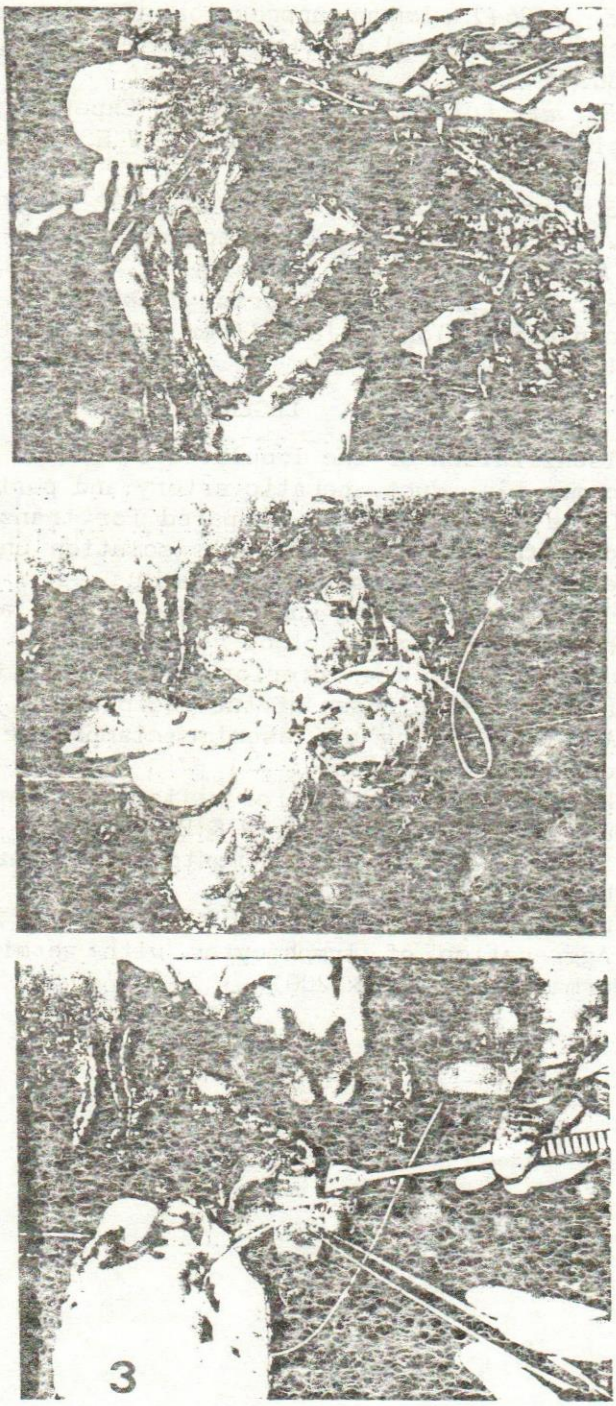
Fig. 6 : Cholecystojejunostomy for biliary drainage.

Fig. 7 : Marked liver congesion (H & E x 200).

Fig. 8 : Decreased cellular elements with area of necrosis (Reticular stain x 200).

Fig. 9 : Inflammatory cellular reaction (H & E x 200).

Fig. 10: Aggregation of lymphocytes with germinal center formation (H & E x 200).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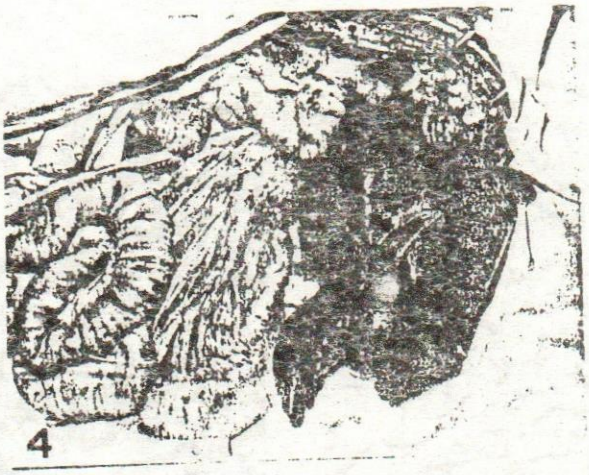

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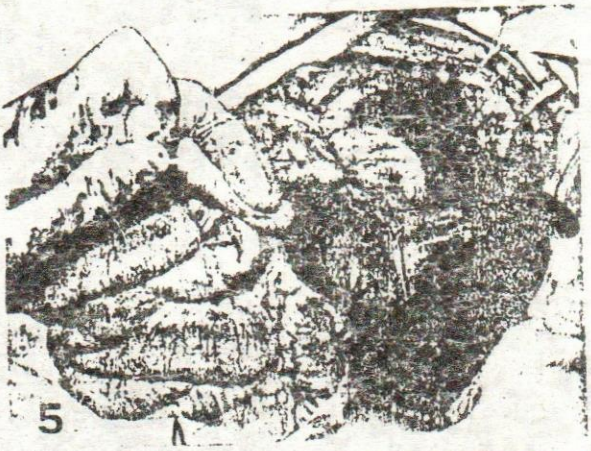

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