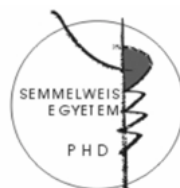


Investigation of Some Factors That Have Affect on Survival of Combined Liver-Kidney Transplantation

Doctoral theses

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Introduction

During the last decades the transplantation become widely accepted treatment of end stage organ dysfunction. It is not an extremity, but part of daily routine in Hungary too. The transplantation works with continuous collaboration of surgeon, anesthesiologist, radiologist and all specialties for full rehabilitation of patients.

Relatively early, at the beginning of transplant era born the need of combined organ transplant. Kelly et al. did the first combined organ transplantation in 1966. They transplanted kidney and pancreas in one setting in a young diabetic male with diabetic nephropathy. In the next decades different combinations of organs were transplanted, but most relevant clinical importance were archived in combined liver-kidney, heart kidney and liver-intestine transplantations. Margreiter et al. published the first combined liver-kidney transplantation (CLKT) in 1984. Although there were important differences in indications and survival, the first reviews were published in 1997 and became the gold standard.

The development of surgical technique, the personalized immunosuppression, the knowledge of immune system and update of ICU therapy were necessary for good clinical results. Professor Andor Szécsényi did the first liver transplantation in Hungary at 1st Dept. of Surgery in Semmelweis University.

Professor Ferenc Perner started the liver transplantation program in 1995 at the new Transplantation and Surgical Department of Semmelweis University. The department did 372 liver transplantations between January 1995 and June 2008. It was necessary to do 7 CLKT-s during these 13 years, since statistically in every 50th -70th liver transplantation there is need for combined transplant. The daily practice of combined organ transplantation became a milestone in surgery in Hungary.

The aim of the study

The aim of doctoral theses is to analyze the present situation of CLKT-s in Hungary and to investigate those factors that have effect on patient survival. Namely:

1. Is there any difference in patient selection and indication for combined liver-kidney transplantation in Hungary and other countries?
2. Is there any difference in operating technique in Hungary and other countries?
3. What is the effect of MELD system on CLKT-s?
4. What kind of preoperative parameters have effect on long-term patient survival?
5. Has the combined transplantation protective effect on acute rejection compared to single organ transplantation?
6. What is the importance of humoral immune response after CLKT-s?
7. What is the dynamics of intraoperative cytokine release? Is it possible to decrease cytokine release for protective effect?

Methods and Results

Four different studies were used to answer the above-mentioned questions. For better understanding the methods and results are discussed at different studies.

Combined Liver-Kidney Transplant Protocol

There were 372 liver transplantations at Transplantation and Surgical Department of Semmelweis University between January 1995 and June 2008. According statistics in every 50th-70th single liver transplant should be combined liver-kidney transplant. Also well known, that the learning curve is necessary before reaching the optimal results. In 1999 the first CLKT patient was lost on 21st postoperative day. It was obvious, that this failure couldn't be reason to stop the program as the next patient was waiting for CLKT. After the first case we made detailed literature analysis to make a safer protocol for the forthcoming patients. The results of these analyses were significant changes in our protocol.

1. In every CLKT were done afterward, we used continuous veno-venous hemofiltration (CVVH). This gave us the possibility to control the volume load of patients.

2. If the patient had huge portal hypertension, we used biopump. This gave us the possibility to control and decrease portal pressure, resulting decrease of intraoperative bleeding. Piggy back and cross-clamping techniques were used at acceptable portal pressure cases, when hepatectomy was easier.
3. All the patients got intraoperative Doppler examination to check the portal and arterial circulation. In case of any circulation failure complete reconstruction was done. It meant arterial or portal reanastomosis as well as use of vascular conduit.
4. After transplantation of the liver the operation was continued if the liver recovered well and the hemostasis was appropriate. The continuation of transplantation of the kidney was safe in these circumstances.
5. The CVVH treatment was continued in the ICU until the volume balance made it necessary. The daily routine became the Doppler examination of both transplanted organs. We tried to start less nephrotoxic immunosuppression regime, and prevent toxic drug levels.
6. Nor OKT3, nor ATG induction treatment was successful at our patients. In all cases the result was uncorrectable thrombopenic bleeding (OKT3 at first patients) or intraoperative bleedings (ATG at two patients) We had much better results with IL-2 receptor blockers (basiliximab, aclizumab) without any complication.
7. This aggressive surgical treatment meant reoperations in case of smallest bleedings or infections. But it also meant use of cautious antibiotic regime..
8. The postoperative outpatient care mean that the patients checked up weekly in the first three months, afterward in every second week, later in every month. In outpatient exams we check the drug levels as well as we take care to prevent the immunosuppressive treatment side effects.

6 patients underwent CLKT according our new protocol in the abovementioned period. All patients are alive, and underwent rehabilitation. Laboratory test are in acceptable ranges, there is no need for organ replacement therapy. Long term survival is appropriate (first patients is 11 years, the last mentioned is 3 years after CLKT). The indications for CLKT in our patients were appropriate to international standards.

MELD score in combined liver-kidney transplantation

In 2002 US started to use the MELD score for allocation of deceased donor livers. The results were dramatic in number and survival of CLKT patients. The results were significant better in liver transplantation but had negative effect in CLKT. While number of operation increased to 320 from the previous 100-120 operations/year, the 1 year survival decreased 87% (2002) to 76% (2005) and the death hazard risk ratio increased 1.4 fold among CLKT patients. Before use of MELD system the CLKT patients were stable, in good physical condition, but MELD preferred high score patients who were high risk in poor condition. The result was, that very often critical condition patient underwent CLKT, for whom organ transplantation was not salvage. In spite of dramatic US results the European data were unknown. This was the reason why I started a European Transplant Society (ESOT) and European Transplant Registry (ELTR) approved study. This was an internet-based questionnaire to understand the results of using MELD score in Europe. On this base:

1. I developed an internet based secure server system. Each transplant center can reach this server and can build own database of CLKT patients
2. On the bases of ELTR address list I contacted all European liver transplant centres and ask voluntary collaboration to fill database with CLKT-s made between 1984-2007.
3. Data mining was done on the basis of transplant indication, immunosuppressive regime, and patient and graft survival. The change of survival according year of transplantation also was analyzed.

I compared data to UNOS and ISHLT relevant data. All statistical analysis were made by using IBM SPSS 19 statistical software (IBM Corporation, Route 100 Somers, NY 10589, USA).

Results

1525 CLKT-s were made in Europe between 1984 and 2007 in 126 centers. Database was filled by 24 centers (19%) for 165 patients (10,8%) These patients were 105 male

(63,6%) and 60 female (36,4%). Among them 99 patients (60%) got renal replacement treatment (RRT) before transplantation. The RRT was hemodialysis in 81 pts, peritoneal dialysis in 14 and booth modality in 4 pts. Duration of RRT was more than 3 months in 92 pts, between 3 months and 6 weeks in 5 pts and less then 6 weeks in 2 pts.

Operative details were: piggyback technique in 51 cases, cross clamping is 52 cases and by using veno-venous bypass 62 cases. In 139 cases the combined liver-kidney transplantation were done in one setting. Intraoperative RRT were used in 9 pts. (5,5%). Immediate kidney function was observed in 122 pts. while 27 pts. got HD treatment, 13 pts. CVVH treatment and 3 got other RRT method in early postoperative period.

Induction treatment was used in 59 patients, which was mainly IL2Ra (51 pts). At the end of first week the typical immunosuppression was steroid (140 cases), which was eliminated by the end of first year at the majority of patients (used by 75 pts). At that time CNI were the typical immunosuppression. At the end of 5th year only 39 pts got steroid as a part of CNI based immunosuppression.

In the whole cohort 12 pts. (7,3%) had biopsy proven kidney rejection. The onset time of kidney rejection was in the 1st month in 4 cases, between the 1st and 3rd month in 4 cases and after 3 month in one case. Repeated kidney rejection was observed in three cases. Kidney retransplantation rate was 3,6% (6 pts). Cause of loss of kidney was acute rejection in one case, chronic rejection in one case and unknown origin in 4 cases. Median RRT free period was 50 months.

Biopsy proven acut liver rejection was found in 19 cases: 8 cases within the first month, 7 cases between the 1st and 3rd month. There are no data of rejection time in 4 cases. Liver retransplantation was done in 8 cases: 1 for recurrent disease, 1 for acute rejection and 6 for other causes. Cumulative survival curve is seen on Fig.1.

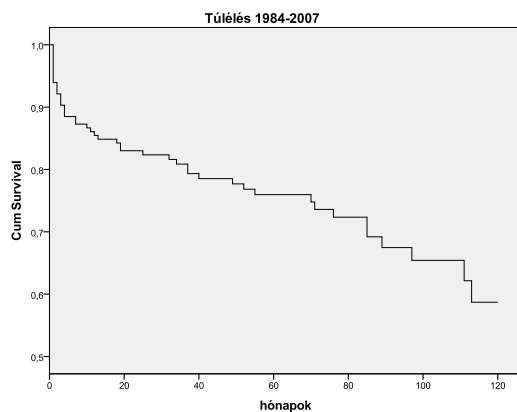


Fig.1 Cumulative survival. Timeline in month (n=165)

If we compare patient survival according the time of CLKT (before 2004 and after 2004) the same significant decline is seen as in UNOS data. (Fig.2) The reason to choose 2004 for cutting year was, that at that time MELD was generally used in different European transplant centers and dividing this way the groups were comparable ($p=0,79$) and homogenous in all other parameters.

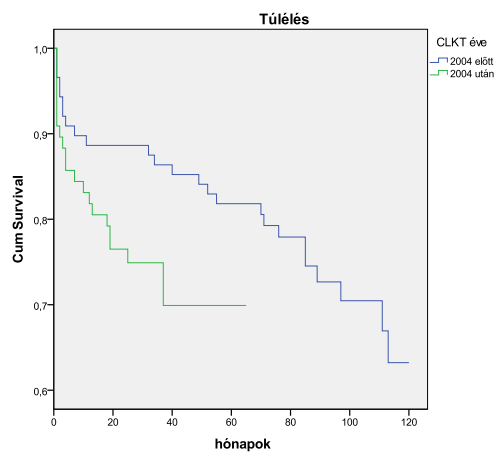


Fig.2 Survival according date of transplant (n=88 CLKT before 2004, n= 77 CLKT after 2004) $p=0,04$ Timeline in month

The median MELD score was 22. The “kidney part” of MELD was at maximum value, but the patients were in worse condition than suggested by the score. The transplantation was in appropriate time according to the score, but the physical condition of patients was poor. Decreasing liver function together with poor kidney function and/or RRT will cause this decline in survival. According to previous publications, the hepato-renal syndrome is not (or only in very strict circumstances) an indication for CLKT. Since the MELD score “kidney part” has a maximal value, the score does not reflect the real state of patients, and the result will be a decreasing survival.

In a multivariate regression model, the investigated parameters were: date of transplantation (before or after 2004), recipient age and body weight, primary liver and kidney disease, need and time of RRT, operative parameters, preoperative serum creatinine, bilirubin, and INR and MELD score, onset of acute rejection, induction treatment, RRT-free postoperative period. Significant parameters are shown in Table 1.

	f	sign	importance
CLKT year	141.506	0.000	0.214
Postop. RRT	14.608	0.000	0.118
Primary kidney disease	5.807	0.004	0.116
Type of op techn.	6.80	0.01	0.112
Liver acute rejection	5.52	0.02	0.111
Primary liver disease	4.825	0.03	0.110
Preop. Se. Creatinine	4.031	0.047	0.110

Table 1. Significant parameters of survival

The answer for decreasing survival can be the change of survival according to the preoperative serum creatinine level, which is very demonstrative. (Fig.3)

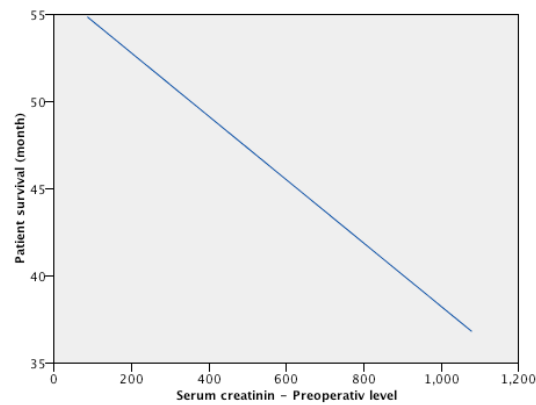


Fig.3. Patient survival and preop. Serum Creatinine level (Se Creat $\mu\text{mol/l}$)

On the basis of abovementioned results the MELD score, as it is not eligible for patient selection for CLKT. The patient selection based on in surely not reflects the real condition of patients, and does not give optimal chance for transplantation. At least ethically questionable whether transplant a kidney to a hepato-renal syndrome patient is appropriate, is it not a loss of a kidney. Transplant a liver in time will result increase of kidney function and not an indication for CLKT. MELD score was originally developed for forecasting survival of TIPS patients. It works well at cirrhotic patients for selection for liver transplantation, but not appropriate to handle emergency situation and tumor patients. It is not eligible for selection CLKT patients too. I think it would be very important to fulfill the European database, and on the basis of results to develop a new score system.

Immune mediated hemolysis in organ transplantation

We investigated the frequency, origin and specificity of antibodies after the first 150 liver transplant patients. Among these patients the late hemolytic transfusion complications and passenger lymphocyte syndrome (PLS) are well represented. Before transplantation protocol immune hematological examinations are done (ABO and Rh phenotype, Kell antigen and irregular antibody screening). If there is transfusion on the waiting list, these entire tests are repeated after 2 weeks. Every patient underwent obligatory compatibility pretransfusion tests (ABO, RhD, antibody

screening, two steps papain and LISS-indirect antiglobulin test, together with direct antiglobulin test). In this study the pretransplant antibody positive patients were excluded. In the patients who had extra transfusion need in postoperative periode and there was no evidence of bleeding, the test were repeted. In case of positive antibody test the titer was examined weekly. The liver graft was ABO identic in 86% and compatible in 14%. Rh matching was identic in 77% RhD neg recipient/RhD pos donor in 14% and RhD pos recipient/ RhD neg donor in 9%.

We found in 23 cases blood group specific antibodies after transplantation. (Table 2) It is well known, that liver patients often got blood transfusion before transplantation, and generally the blood consumption of the liver transplantation also above the average. This makes the chance of alloimmunisation higher.

Tx No	Tx	Recipients	Donor	Tx utáni antitest	Dg.	Kor
66	1999. 2. 24.	A-	A+	a-E	HCV	61,8
88	2000. 1. 26.	A-	O+	a-A(d)-PLS	Budd Chiari	22,4
25	1996. 9. 19.	A+	A+	a-ce	ACUT	14,1
97	2000. 5. 4.	A+	O-	a-A(d)-PLS? , a-K	HCV	43,8
61	1998. 9. 21.	B-	B+	a-D	HCV	46,9
79	1999. 8. 20.	AB+	A+	a-B(d)-PLS , a-E	HCV	48,4
49	1998. 4. 25.	B+	B+	a-E	HCV	43,4
53	1998. 5. 30.	O+	O+	a-E, a-Jka	HCV	43,7
55	1998. 6. 14.	A+	A+	a-E	HCV	46
67	1999. 3. 24.	B+	B-	a-Jka, a-K	HCV	49,4
6	1995. 9. 29.	O+	O+	a-E /95.10.10.	ACUT	32,9
72	1999. 5. 13.	A+	A+	a-E	AIH	42,9
113	2001. 2. 18.	B+	B-	a-DCE(d)-PLS , auto-e, a-Jkb	PSC	51,6
145	2003. 1. 16.	O+	O+	a-Jkb	PSC	49,4
139	2002. 8. 18.	AB+	O+	Non specif. autoat	HCV	46,9
138	2002. 8. 1.	O+	O+	a-E	ALD	54,2
129	2002. 1. 30.	B+	B+	a-E, a-Jka	HCV	43,3
157	2003. 6. 1.	A+	A+	a-E, a-Cw, a-Kell	PSC	48,4
140	2002. 9. 3.	A+	A+	a-E, a-c(d??)	Wilson	34,4
126	2001. 11. 18.	A+	A+	a-E	HCV	41,4
154	2003. 5. 11.	A+	A-	a-E	HCV	37,5
120	2001. 5. 18.	O+	O-	a-E, a-Cw, a-Jkb	Cryptogen	39,8
137	2002. 6. 7.	A+	O+	a-A(d)-PLS?	ALD	46,4

2.táblázat Autoantibodies after transplantation

All antibody producing patients were anemic, and there was clear-cut indication of transfusion. As the patients were antibody negatives before transplantation, the antibody production is result of intraoperative transfusion. Fig 17 shows the appearance time after transplantation. Most of the antibodies were detected between postop days 8-14, but there was new antibody production on postop day 56 too. Nine from the 23 patients produced more then one autoantibody. The lifetime of transfused red blood cells is up to 120 day, so the immunization can appear any time in this interval. We have found 5 PLS patients: 4 on ABO mismatch 1 on Rh mismatch (anti-DCE). The frequency and specificity of antibodies were: anti-D (n=1), anti-E (n=15), anti-c (n=1) anti-ce (n=1) anti-Kell (n=4), anti-Cw (n=2) anti-Jka (n=3) and anti-Jkb (n=3). If we compare survival of antibody producing and non-producing group, the difference is significant. (Fig.4)

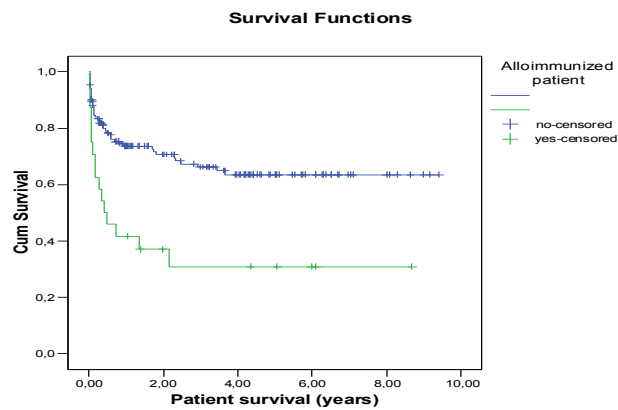


Fig. 4 Survival of alloimmunised (n=23) and non-alloimmunised (n=127) patients

On basis of our results the post-transplant compatibility rule has been modified: all transplanted patients got Rh phenotype and Kell compatible blood product even if they have no alloimmunisation. Further better results can be waited if the immune hematological tests made in time. This makes very important the post-transplant immune monitoring.

Intraoperative immunology of transplantation

The transplanted organ undergoes extreme influences during revascularization. The vascular endothelium meets the recipient's lymphocytes. The cytokine release and following cytokine storm and the treatment of this storm have crucial impact on patient and graft survival. The generally used steroid shot –in the anhepatic phase at liver transplant and before revascularisation at kidney transplant – mostly prevents the cytokine storm, and protects the transplanted organ. But hemodynamic instability is often seen.

There are very few publications on intraoperative immunological “shock” of liver transplanted patients, and there are no publication on prolonged, multiple cytokine release of multiorgan transplantation. According to our best knowledge our publication was the first in 2003 on intraoperative cytokine release of our 2 CLKT patients.

Patients and methods

We investigated the changes of inflammatory parameters (PCT, CRP) and cytokine (TNF α and IL-6) at 2 CLKT patients in the pre-, intra-, and 5 days postoperative period. There were no major surgical complications (arterial or venous failure, liver or kidney function delay) in the postoperative period. Also we had no infection at the patients in the study period. The liver reperfusion was done by 400 ml blood; samples were taken from every 100 ml.

We have found no difference in regional and systemic CRP levels. CRP started to increase shortly after the end of operation, and remained in elevation to the 2nd postoperative day. PCT increase started at reperfusion of the liver and had a second peak at the kidney reperfusion. In uncomplicated cases these peaks are results of cytokine caused inflammatory response. Immunosuppressive drugs, like steroids can decrease the IL-6 type PCT induction but have no effect on TNF alpha induction so there are no significant differences in PCT levels. The use of ant-thymocyte globulins or OKT3 can result 10 fold PCT level increase without infections. During liver transplantation always there is an inflammatory response due to surgical intervention and reperfusion syndrome. As the inflammatory response spread over, nonspecific complications can be observed even on the first postoperative day. Without treatment it can lead to infectious complications. The peak concentration of PCT measured at

1-2 day after operation and normalized within the next week. In case of complications the rejection had no effect on PCT level but infection caused significant increase.

The CLKT as operation affects only few patients in Hungary. The patient number is too low for statistical analysis. But up to now this was the only study which examined the reperfusion cytokine storm in high resolution. Both patients recovered without any complications. Their results can be basis of further investigations.

Conclusion

1. I could be member of the team who made the first long term survival CLKT in Hungary. The first successful operation followed by 5 further CLKT-s operated by me. Our protocol confirm to international standards in patient selection and indications. Our 7 patients practically covered the whole field of indication so we could demonstrate competence of our therapeutic protocol
2. We have appropriate practice and skill in all type of transplant surgical technique published before.
3. The developed European CLKT Registry data confirmed –according to previous US data- that survival of CLKT patients decreased after using MELD score. In spite of improving surgical technique, ICU treatment and immunosuppression the results of CLKT became worse. On the basis of our results we can declare that use of MELD score inappropriate for CLKT patient selection.
4. On the basis of new European CLKT Registry the immediate kidney graft function, the cholestatic primary liver disease, and use of vena-venous bypass have positive predictive value, high preoperative serum creatinine level negative predictive value on survival of CLKT patients.
5. On the basis of new European CLKT Registry the biopsy proven acute rejection of liver and kidney was lower then in previous publications of solitary liver transplantation or kidney transplantation. We had no acute liver rejection among our patients.
6. We published first PLS case observed in CLKT patient. The rare cases reflect the importance of humoral immunity of transplanted patients. These areas were less investigated before. On basis of our results we confirmed the negative impact of alloimmunisation of transplanted patients on survival.

7. We published first the changes of inflammatory factors during multiorgan transplantation based on high-resolution sampling. These results are the basis of understanding intraoperative immunology, and through this knowledge the fundamentals of better patient care.

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