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## The early and long term function and survival of kidney allografts stored before transplantation by hypothermic pulsatile perfusion. A prospective randomized study

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### Summary

#### Background:

A prospective evaluation of the influence of methods of kidney storage prior to transplantation on long-term graft function has not been shown so far. A retrospective study undertaken in 415 patients in our department showed the benefit of machine perfusion (MP) on long-term results. The aim of the present study was to assess prospectively the long term function and survival of paired kidney allografts retrieved from the same donor, comparing the influence of cold storage (CS) and MP.

#### Material/Methods:

74 recipients included in the study received kidneys from 37 cadaveric donors. Kidneys were randomized to storage by CS or MP. There were no significant differences between the groups as to age, gender, duration of ESRD treatment, PRA titres, HLA compatibility and immunosuppressive regimens.

#### Results:

At 10 years follow-up recipients of CS-stored kidneys returned to dialysis treatment twice as frequently as recipients of MP-stored kidneys (50% vs. 25%,  $p=0.02$ ).

#### Conclusions:

Kidney storage by MP improves graft survival and reduces the number of patients who return to dialysis treatment at long-term post-transplant.

#### Key words

**long term function • machine perfusion (MP) • prospective randomized study • kidney transplantation**

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## BACKGROUND

The survival of transplanted organs is limited by its chronic dysfunction or death of the recipient. Long-term function of transplanted kidneys is influenced by donor-dependent factors (age, gender, cause of death, homodynamic instability, metabolic and hormonal changes preceding death or associated with brain death), duration and mode of organ preservation (cold storage, machine perfusion, type of preservation medium) and recipient-related factors (tissue compatibility, acute rejection, delayed graft function, reperfusion injury, underlying disease and co-morbidities, gender, infection, medications).

Continuous Hypothermic Pulsatile Perfusion (MP-machine perfusion) has been used as the kidney preservation method in our Center for over 10 years. The mode of organ preservation prior to transplantation is among the factors affecting early graft function. MP allows for wider use of kidneys injured by preagonal donor metabolic and hemodynamic instability [1] and results in superior rate of immediate kidney transplant function as compared to cold-stored grafts [2]. Several reports indicate that MP permits an extension of preservation time [3]. Machine-perfused kidneys may be treated during perfusion by medication administered into the perfusate and by modification of flow parameters. MP is also thought to reduce the risk of donor-recipient HCV transmission [4]. Analysis of perfusion data including vascular flow and resistance as well as biochemistry of perfusion medium allows for an evaluation of ischemic organ damage prior to transplantation [5]. Thus it is possible to reduce the risk to allogenic kidney graft recipients by discarding kidneys which will not function when transplanted. Recently Eurotransplant begun prospective, randomized study comparing the effect of simple cold storage vs. machine perfusion of deceased donor kidneys before transplantation on the early graft function. Preliminary results presented at the last ESOT meeting showed beneficial effect of perfusion storage. In this paper we are presenting a prospective analysis of early and long term function and survival of paired kidney allografts taken from the same donor, comparing the influence of CS and MP.

In our recently published study [6] based on a retrospective analysis of 415 patients who received deceased donor kidneys we documented, that Machine perfusion of kidney allografts leads to superior graft survival, reduces the number of

patients returning to dialysis and results in superior graft long term function.

In this paper we present long term results of prospective randomized study comparing two modes of storage (cold storage vs. machine perfusion) of kidneys procured from the same donor.

## MATERIAL AND METHODS

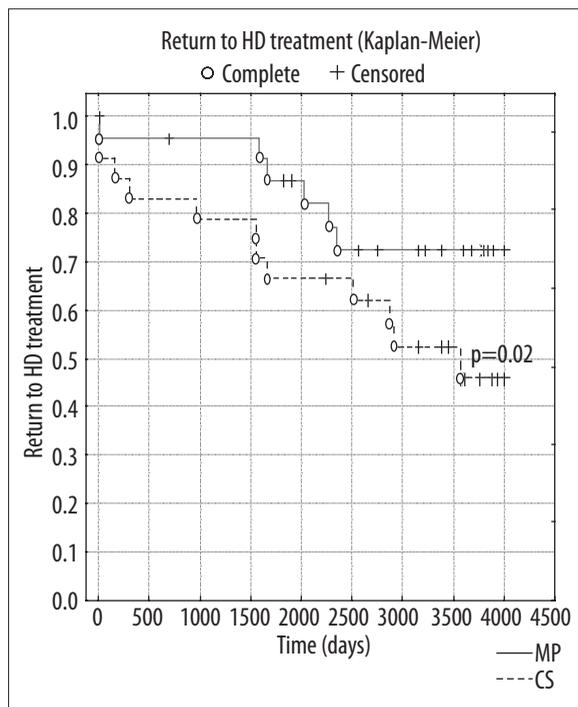
There were 37 deceased donors, 5–70 years (mean 36 years), predominantly males (66%), hospitalized in ICU for 1–18 days (mean ICU stay  $4.8 \pm 12$  days). Causes of death included CNS trauma ( $n=18$ , 66%), cerebral vascular incidents ( $n=8$ , 32%) and others, such as CNS tumors, asphyxia ( $n=11$ , 29.8%). Donor serum creatinine concentration ranged between 0.5 mg/dl and 6.8 mg/dl (mean  $1.4 \pm 2.83$  mg/dl). Vasopressors, most commonly dopamine, were administered at an average dose of  $8.1 \pm 8.14$   $\mu$ g/kg/min. Twenty four of the donors belonged to the extended criteria category.

Seventy four kidneys were procured, immediately prior to surgery the donors were administered lidocaine 2 mg/kg, heparin 10000 i.u. and broad-spectrum antibiotic. One kidney from each donor was stored using continuous pulsatile, hypothermic perfusion (MP), the other in simple hypothermia (CS). After bench surgery kidneys stored by MP were placed in a sterile disposable cassette (MOX 100DCM Disposable Cassette, Waters Instruments) of the perfusion unit (MOX-100 m<sup>2</sup> Transport Unit, Waters Instruments Inc., Rochester) filled with 1000 ml of perfusion fluid – MPS II. To ensure constant fluid temperature (60°C) a cooling bath was used (Model 900 Constant Temperature Circulator, Fisher Scientific, Pittsburgh). Electrolyte and pH monitoring of perfusion fluid and subsequent bacteriology cultures were performed during and after every perfusion procedure. A constant flow of 1Hz frequency (60 pulses per minute) was set. The starting perfusion pressure was set at 50 mmHg systolic.

During MP (at 1,2,3,4 hours and 4-hourly afterwards) the following parameters were monitored: systolic-diastolic pressure, mean perfusion pressure, flow per minute, vascular resistance, pH, pO<sub>2</sub>, pCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup> (ABL 330 Radiometer, Copenhagen), Na<sup>+</sup>, K<sup>+</sup> (Ionometr EF Fresenius) and osmolarity (Osmometr 800 cl). Depending on the results of monitored parameters relaxing agents (papaverine, verapamil) were administered

**Table 1.** Return to haemodialysis treatment.

Preservation method	Graft survival	Return to dialysis	% of patients with creatinine <2 mg/dl at 5 years	Patient survival
CS, n=37	43.0% (16)	50.0% (18)	40.5% (15)	83.7% (31)
MP, n=37	68.2% (23)	25.0% (9)	54.0% (20)	86.5% (32)
P	0.08	0.02	ns	ns

**Figure 1.** Return to haemodialysis treatment in the period of over 10 years.

to influence resistance, bicarbonate and CO<sub>2</sub> insufflations to correct pH, mannitol in cases of low osmolality. Results of perfusion parameters analysis were published previously [5].

Seventy four end stage renal failure patients received kidney transplant. In each pair of recipients one kidney was cold stored (CS), the other one machine perfused (MP). The average age of recipients in the MP group was 37±12 years and 40±15 years in the CS group. The cold ischemia time was 27.5 h in CS group and 34.5 h in MP group. Triple immunosuppression was most commonly used (cyclosporine, azathioprine and encorton), in selected cases justified by the recipients' immunological status a fourth agent was added.

## RESULTS

The early graft function in both groups of patients was comparable. Delayed graft function oc-

curred in 17/34 patients from CS group, and in 11/34 patients from MP group. It should be noted however, that the ischemia time in MP group of patients was longer. Acute rejection (within first 6 month) occurred in similar ration in both group of patients.

Recipients of kidneys stored in CS prior to transplantation returned to dialysis twice as frequently as patients with MP kidneys (50% vs. 25%, p=0.02; Table 1). Graft survival of MP-stored kidneys was superior to CS-stored organs (68.2% vs. 43%, p=0.08) although this difference did not reach statistical significance. Kaplan-Meier analysis shows return to haemodialysis treatment in the period of observation over 10 years (Figure 1).

Kidney biopsies of the surviving patients showed that Kidneys preserved by cold storage are more frequently affected by chronic rejection and interstitial fibrosis [7].

## DISCUSSION

This paper, to our best knowledge, is the first publications showing results of prospective and randomized study of Machine Pulsatile Storage of kidneys prior transplantation.

## CONCLUSIONS

Storage of kidneys by machine perfusion may improve graft survival by limiting chronic changes in renal allografts, and reduces the number of patients who return to dialysis treatment at long-term post-transplant.

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