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Pulsatile machine perfusion compared to cold storage in kidney preservation

Comparaison entre la machine à perfusion et le stockage sur glace pour la conservation des reins

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La transplantation rénale est un traitement accepté pour les patients en phase terminale d'insuffisance rénale. Les donneurs pour transplantations rénales sont habituellement des donneurs vivants ou des donneurs en état de mort cérébrale. Cependant, l'utilisation d'organes provenant de donneurs alternatifs comme les donneurs à cœur arrêté (DCA) ou les donneurs limites, pourrait augmenter le nombre d'organes disponibles étant donnée la pénurie actuelle de greffons.

Les organes provenant de donneurs à cœur arrêté subissent une période d'ischémie chaude suite à leur prélèvement après arrêt cardiorespiratoire, ce qui pourrait affecter la fonction rénale après la transplantation. Des dommages d'origine ischémique pourraient continuer à affecter le greffon après son prélèvement dû à l'arrêt de la circulation vasculaire. Par contre, il est possible de réduire ces dommages en plaçant le greffon dans des conditions hypothermiques.

La technique usuelle de conservation des organes consiste d'abord à infuser une solution de conservation dans le greffon, puis à le placer dans la glace. Des machines à perfusion, imitant la circulation artérielle et maintenant une certaine vasodilatation, ont été développées offrant ainsi de meilleures possibilités pour conserver intact la fonction rénale. Le dommage ischémique causé entre le moment du prélèvement et celui de la transplantation rénale peut retarder le retour à un fonctionnement normal de l'organe transplanté. La reprise retardée de la fonction rénale (RRF) peut durer de quelques jours jusqu'à un à deux mois. La RRF est associée à une hospitalisation prolongée ainsi qu'à une utilisation temporaire de la dialyse, jusqu'à la reprise de la fonction rénale. Cette condition peut aussi entraîner des résultats cliniques plus faibles quant au devenir du greffon. La diminution de la fréquence et de la gravité de la RRF est l'objectif visé par les techniques améliorées de conservation.

Nous avons fait une revue systématique de la littérature pour identifier les études comparatives entre la conservation du rein avec machines à perfusion et la conservation du rein à froid. Un rapport d'évaluation des technologies, incluant une meta-analyse, a été trouvé. Dix études

additionnelles ont aussi été identifiées mais seulement deux pouvaient être incluses dans la mise à jour de notre meta-analyse.

Nous avons démontré une réduction de 22% du taux de la RRF avec la machine à perfusion par rapport à la conservation à froid (risque relatif (RR) 0.78 , intervalle de confiance (IC) 95% : 0.67 , 0.92). Aucun bénéfice à long terme, incluant la survie du patient ou du greffon, n'a été trouvé suite à l'utilisation de la machine à perfusion par comparaison à la conservation à froid.

Le taux de base de la RRF au Centre Universitaire de Santé McGill (CUSM) est environ 27% et est associé à un séjour moyen de 16 jours d'hospitalisation supplémentaires (incluant des sessions d'hémodialyse aux deux jours) par rapport aux patients sans RRF. Environ 80 transplantations rénales sont réalisées chaque année au CUSM, dont 60 de donneurs décédés. Si la machine à perfusion était utilisée lors de 30 transplantations par année, ceci pourrait résulter en une réduction de 1.77 (95% IC : 0.63 , 2.88) cas de RRF par année (0.059/transplantation , 95% IC : 0.0209 , 0.096). Il est peu probable que l'utilisation de la machine à perfusion occasionne une augmentation du nombre de transplantations réalisées chaque année au CUSM.

Le coût de cette machine est de $14,800 par unité ($29,600 pour deux unités) et le coût du matériel associé est de $750 /transplantation ($22,500 pour 30 procédures), pour un montant total de $52,460 pour la première année et de $22,500 pour les années subséquentes. Avec une amortissement du coût de la machine sur 8 ans, une ***réduction du coût total*** d'environ $20,940 par année (95% IC: $37,860 , $3,810) peut être envisagée avec la machine à perfusion par rapport à la conservation du rein à froid. Si des fonds extérieurs étaient disponibles pour défrayer le coût des deux machines à perfusion, une réduction du coût total d'environ $25,230 par année (95% CI: $42,180 , $8,070) pourrait être considérée selon nos analyses de coût-efficacité.

Un rapport d'évaluation des technologies publié en 2003 a aussi trouvé des évidences quant à un coût-efficacité favorable, mais la pauvre qualité des données tempère quelque peu cette conclusion. Nous reconnaissons que les études disponibles, incluant les plus récentes, ont des

faiblesses méthodologiques et que des études additionnelles seraient utiles. Les études randomisées en cours pourraient ajouter plus d'évidences supportant ou non l'utilisation de cette technologie. Malgré les incertitudes en regard de l'efficacité de cette technologie, l'implication financière peu élevée pour le CUSM supporte une recommandation positive quant à son adoption.

RECOMMANDATION

Les évidences disponibles nous suggèrent que l'utilisation de la machine à perfusion peut résulter en une réduction des coûts tout en impliquant un coût d'investissement relativement faible. L'Unité d'Évaluation des Technologies recommande donc au CUSM l'adoption de cette technologie. Puisque les évidences supportant son utilisation ne sont pas parfaites, nous recommandons que les résultats cliniques de son utilisation soient suivis prospectivement et soient comparés à ceux des transplantations utilisant des reins conservés à froid.

Les résultats des études randomisées en cours pourront nous apporter plus d'information sur le rôle de cette technologie. Dans cette perspective, les recommandations de ce rapport devront être réévaluées à la lumière de ces nouvelles données.

EXECUTIVE SUMMARY

Kidney transplantation is an accepted treatment for patients with end-stage renal disease. Donors for kidney transplantations usually are living or brain dead donors, however, the use of organs from alternative donors such as non-heart-beating donors (NHBD) and extended criteria donors (ECD) may increase the number of organs available given the present shortage of organs.

Organs from NHBD undergo a period of warm ischemia as they are harvested after cardiac arrest, which may affect the graft function after the transplantation. Ischemic organ damage may continue after its harvest due to the loss of vascular circulation. Keeping the organ in hypothermic conditions has been used to reduce ischemic damage. The usual cold storage technique infuses a preservation solution and keeps the organ on ice. Pulsatile machines that mimic the physiological arterial circulation, maintaining arterial vasodilatation, have also been developed and offer the potential of enhancing kidney preservation. Ischemic injury that occurs between harvesting and implantation may delay the return of function in the grafted organ. Delayed graft function (DGF) may last for a few days to one or two months. It is associated with prolongation of hospitalization and the temporary use of dialysis, which must continue until the transplanted kidney function is recovered. It is also linked to poorer long term graft outcomes. Reduction in the frequency and severity of DGF is the objective of better renal preservation techniques.

We performed a systematic literature search to identify studies comparing the clinical outcomes of machine perfusion and cold storage. One technology assessment report that included a comparative meta-analysis was identified. An additional 10 studies were identified but only two were eligible for inclusion in our updated meta-analysis. We found a cumulative 22% reduction of DGF risk with machine perfusion compared to cold storage (RR 0.78, 95% confidence interval (CI): 0.67 , 0.92). No long-term clinical benefits, such as graft or overall survival, with machine perfusion compared to cold storage were identified from the peer-reviewed literature search.

The baseline rate of DGF at the MUHC is approximately 27% and is associated with an estimated 16 additional days in hospital (with hemodialysis sessions every two days) compared to patients who did not experience DGF. Approximately 80 kidney transplantations are performed yearly at the MUHC, 60 from cadaveric donors and it has been proposed that

machine perfusion could be used in 30 transplantations/year. This could result in 1.77 (95% CI : 0.63 , 2.88) DGF events avoided each year (0.059 / transplantation 95% CI: 0.0209 , 0.096). It does not seem likely that the machine will cause an increase in the total number of transplantations performed annually.

The cost of the machine is $14,800/unit ($29,960 for two units), and disposable materials cost $750/transplantation, ($22,500 for 30 procedures), totaling $52,460 in the first year and $22,500 in subsequent years. With amortization of capital costs over 8 years, there would be a ***net cost saving*** of approximately $20,940 (95% CI: $37,860 , $3,810) annually. If external funding is available to cover the costs of the 2 units of the machine, our cost-effectiveness analysis indicates that an annual net ***cost saving*** of approximately $25,230 (95% CI: $42,180 , $8,070).

A 2003 technology assessment report also found evidence of cost-effectiveness but this was tempered by the poor quality of the efficacy data. We concur that present studies, including the most recent, have several methodological weaknesses and that additional evidence would be helpful. The results of ongoing RCTs with machine perfusion may provide additional evidence of the role of this technology. However, not withstanding the existing uncertainty about the effectiveness of this technology, the amount of capital at risk is small thereby supporting our positive recommendation.

RECOMMENDATIONS

The available evidence suggests that machine preservation technology is likely to be cost saving and moreover capital costs are relatively small. The TAU therefore recommends that this technology should be acquired. Since the evidence on which this recommendation is based is far from perfect it is further recommended that transplantation outcomes with machine perfusion should be prospectively recorded and compared with those from kidneys preserved by cold storage.

New data from ongoing RCTs may provide additional information on the role of this technology and this report and recommendations will need to be re-evaluated as this new evidence becomes available.

GLOSSARY

DGF – delayed graft function

HBD – heart-beating donors

NHBD – non-heart beating donors

ECD – extended criteria donors

Pulsatile machine perfusion compared to cold storage in kidney preservation

FOREWORD

In July 2006, Mr. Gary Stoopler, (Director, Administration) requested that the Joint Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) and Centre Hospitalier de l'Université de Montréal (CHUM) evaluate the clinical and economic impact of the use of machine perfusion for kidney preservation.

INTRODUCTION

Kidney transplantation is an accepted treatment for patients with end-stage renal disease [1 2]. Living or brain dead donors have usually been used in kidney transplantation[1]. However, given the shortage of available kidneys for transplantation and the increases in wait lists in different countries, alternative sources of organs are being proposed such as those from non-heart-beating donors (NHBD) and extended criteria donors (ECD) (i.e., donors older than 60 years or those with hypertension or diabetes) in order to increase the donor pool.

NHBDs and heart-beating donors (HBD) both consist of deceased donors, however their definition differs according to the criteria used to diagnose death, for HBD, brainstem death criteria are used, and for NHBD, cardiac criteria are used[3]. HBD are maintained with a ventilator and have a beating heart at the time of organ harvest, whereas NHBD have experienced cardiorespiratory arrest and therefore do not have a beating heart at the time of organ harvest[4].

Although NHBD has been used since the 1970's and constituted the only source of cadaveric donors until the establishment of criteria for brain death, most transplantation centres prefer to use HBD[1 3]. One reason being that, unlike HBD, organs from NHBD undergo a period of warm ischemia as they are harvested after cardiac arrest [3]. Warm ischemia time is defined as the period from the time the heart stopped beating until the organ is stored in hypothermic conditions. This period of warm ischemia, which is usually unknown, may affect the graft function after the transplantation[3]. However, if the warm ischemic time is known and is of short duration, organ damage may be reduced [3]. Proposed acceptable warm ischemic time has varied between 30-45 minutes in the literature but the age and general condition of the donor also influence the length of acceptable warm ischemic time [3] .

Ischemic organ damage may continue after its harvest due to the loss of vascular circulation[5]. Ischemia leads to a shortage of oxygen and nutrients, loss of metabolic activity which initiates a process of cellular damage with the degradation of compounds that are necessary for the cell metabolism, and the activation of degenerative enzymes[5]. This leads to the loss of structural and functional components of the cell[5] which may result in delayed function or even permanent organ dysfunction [6 7]. Preservation of the kidney from the time of harvesting through the period of tissue typing, matching and transplantation allows the maintenance of the organ functions after the transplantation and is expected to reduce the risk of post-transplant delayed graft function.

The maintenance of the organ in hypothermic conditions has been used as a means of suppressing the metabolic activity thereby reducing the damage[5]. Hypothermic kidney preservation systems available include cold storage and machine pulsatile perfusion[7]. With cold storage, the kidney is first infused with a preservation solution and then kept on ice[7]. The cold perfusion solutions commercially available are the EuroCollins, and the University of Wisconsin, histidine-tryptophan-ketoglutarate[3]. With machine perfusion, a cold oxygenated solution is delivered through the renal artery[8]. It mimics the physiological arterial circulation[8], supplies oxygen and nutrients and removes metabolic end products[7] potentially avoiding the initiation of a cell damaging cascade[7] and may decrease delayed graft function (DGF) which requires dialysis while waiting for the recovery of the transplanted organ[8] . Another purported advantage of machine perfusion is that it allows for testing the viability of the organ before the transplantation thereby avoiding the transplantation of an organ that would not achieve function[7].

PERFUSION MACHINES

Machine perfusion was used to preserve most kidneys in the 70's until the mid-80's when it was replaced by cold storage as studies showed comparable efficacy without the extra costs associated with machine purchase and operation as well as the avoidance of any risk of equipment failure[7]. However, with the idea of expanding the kidney donor pool in order to include NHBD and ECD donors [7] and the development of new preservation solutions there has been a renewed interest in the use of machine perfusion[7].

Two FDA-approved pulsatile perfusion machines are the LifePort™ pulsatile perfusion machine and the Waters RM3 machine®. Health Canada does not require formal approval before marketing but rather a Health Canada license (information from Health Canada). Other perfusion machines are mentioned in the literature but don't seem to be commercially available[9] [10]. RCTs are ongoing with the LifePort machine perfusion in kidney preservation in different countries (http://www.organ-recovery.com/opairs.php).

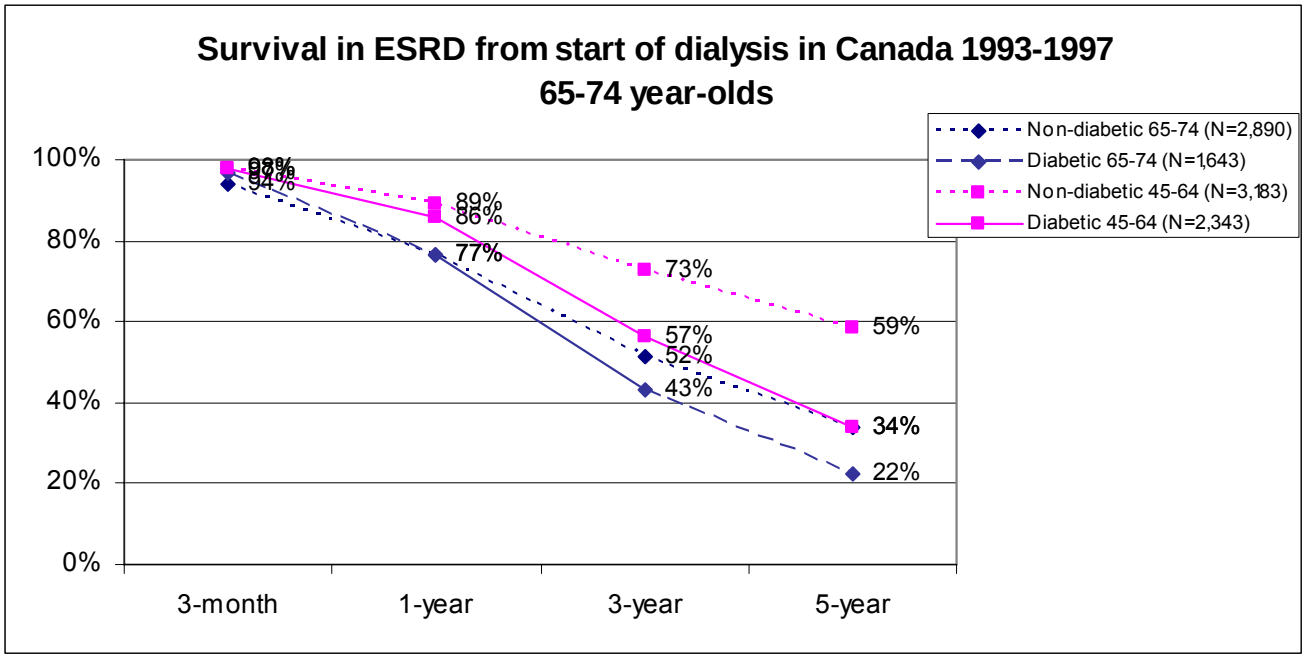
Machine perfusion has not yet been used in Québec centers (information from Dr. Steven Paraskevas). According to information from the manufacturer (Organ Recovery Systems) machine perfusion is being used in Saskatchewan. It is expected that machine perfusion will start to be used in the University of Toronto in ECD and NHBD in 2007.
According to the manufacturers, machine perfusion is being used throughout the US (Organ Recovery Systems, Waters Medical Systems).

END-STAGE RENAL DISEASE (ESRD) AND SURVIVAL IN CANADA

Kidney transplantation is the treatment of choice in most patients with end-stage renal disease (ESRD)[11] [12]. These patients need to undergo dialysis while waiting for a renal transplantation[11].
In Canada in 2002 there were 10,126 patients aged 45-74 registered on hemo- or peritoneal dialysis (2,165 in Québec) (source: Canadian Institute for Health Information 2002-2003 report)[13].

The survival in ESRD patients is low, especially in older age groups (Figure 1).

Figure 1 – Survival of ESRD patients – Canada 1993-1997



Source: Canadian Institute for Health Information 2002-2003 report[13]

KIDNEY TRANSPLANTATION IN CANADA

A 2003 Canadian Institute for Health Information (CIHI) study reported that although kidney transplantations from deceased donors (neurologic criteria) were being done in Canada, NHBDs were not being used, in contrast to the United States, Europe and Asia[14]. Recently, the Canadian Council for Donation and Transplantation (CCDT) published recommendations to guide the development of programs for donation from NHBD based on a discussion forum involving nationwide stakeholders held in February 2005[15]. Despite limited evidence, the CCDT recommends that machine pulsatile perfusion be used for organ preservation at institutions providing donation after cardiocirculatory death[15]. Despite the lack of prospective studies the CCDT authors believe, based on expert opinion, that machine pulsatile perfusion may improve organ viability[15].

In Canada in 2003 there were 997 kidney transplantations in adults, 557 (almost 2/3s) of which from deceased donors (HBD)[13]. In Québec, there were 261 kidney transplantations performed in adults during the same year, 218 from deceased donors (HBD)[13]. Between 1994 and 2003, Québec was one of the few Canadian provinces with a yearly trend to an increase in the number of kidney transplantations from deceased donors, 139 to 218 [13] . The unadjusted 3-month, 1-year, 3-year and 5-year adult patient survival following a first kidney transplantation in

Canada in 1998 was 98.5%, 95.1%, 90.9%, and 87.9% respectively for transplantations from deceased donors (n=528), and 99.7%, 99%, 96%, 93% respectively with living donors (n=301)[13]. Average age of recipients was 47.5 years (20.8% >=60 years) for transplantations from deceased donors and 43.4 years (12.3% >=60years) for transplantations from living donors[13].

By mid-year 2006 there were 2,810 adult patients waiting for kidney transplantation in Canada, 738 in Québec[16] and for the first time there were 2 kidney transplantations from NHBD, both performed in Ontario[17]. Statistics from the previous years do not indicate any such transplantation performed before 2006 [17]. The authors from a 2003 report from CIHI estimate that using NHBD would add 28 organ donors to the pool in Canada per year [14].

KIDNEY TRANSPLANTATION AT THE MUHC

Approximately 80 kidney transplantations are performed yearly at the MUHC, 60 from deceased and 20 from live donors. It is estimated that machine perfusion may be used in approximately 30 kidney transplantations annually at the MUHC mainly from organs from NHBD or ECD. It is unlikely that the use of the machine will increase the number of transplantations performed annually at the MUHC (information from Dr. Steven Paraskevas).

The baseline rate of DGF in patients receiving kidney transplantation from a deceased donor at the MUHC over the past 5 years was approximately 27% (average of 55 transplantations from deceased donors per year). DGF was defined as any patient requiring dialysis after a renal transplantation (information from Dr. Steven Paraskevas). Patients experiencing DGF use more hospital resources compared to patients without DGF due to a prolonged hospital stay, estimated at an additional 16 days, and a need for hemodialysis approximately every 2 days (information from Dr. Steven Paraskevas). A systematic literature review found that DGF was statistically associated with a 1.4 to 4.2 fold increase in risk of graft loss[7]. It is important therefore to evaluate the effect of machine perfusion on DGF and graft loss.

METHODS

Objectives

Our objective was to evaluate the impact of pulsatile machine perfusion on DGF and graft survival compared to cold storage. The value of kidney viability testing with machine perfusion was also evaluated.

Systematic Literature Review

A systematic literature review of all articles in patients published in English or French was performed using Medline and Embase databases. The International Network of Agencies for Health Technology Assessment (INAHTA) database was searched for health technology assessment reports and other publications without any restrictions for date or language of publication. Finally, the reference lists of the publications identified were also searched for additional relevant publications. The abstracts from the American Transplantation Congress from 2002-2005 and the World Transplantation Congress of 2006 were searched for relevant abstracts. Last search: March 16th 2007. Keywords: (machine or preservation AND perfusion or pulsatile AND kidney or renal).

Clinical studies, systematic reviews, economic analyses, and technology assessment reports comparing cold storage and pulsatile machine perfusion were selected. Case reports were excluded. Studies that attempted to control for baseline differences between the machine perfusion and cold storage groups either by comparing the outcomes in kidneys from the same donor preserved by a different system, or by randomizing the kidneys to the preservation system were included in our meta-analysis as this would minimize the risk of selection bias.

Study results were pooled in a random effects model meta-analysis to estimate the risk of delayed graft function and graft survival. Review Manager software version 4.2 from the Cochrane Collaboration was used.

Outcomes evaluated

DGF and graft survival rates were extracted from the studies identified using a standardized form. Delayed graft function was defined as dialysis requirement during the first week after transplantation[7 18 19], or anuria within 24 hours [19]. Graft survival failure was defined in one study as a non-functioning graft or death of the recipient [18]. The definition of these endpoints was not clear in other studies. The definition of delayed graft function used at the MUHC is any patient requiring dialysis after renal transplantation.

Other outcomes such as machine failure and kidney viability testing were also evaluated.

Effectiveness & Cost-effectiveness analysis

The mean DGF with cold storage observed in our institution over the past 5 years was used as an estimate of the baseline DGF risk in our cost-effectiveness analysis. We have used the DGF rates from transplantations from deceased donors (HBD) as this would be closer to the rate in transplantations from NHBD, than those using live donors. The clinical effectiveness for machine perfusion technology for the short-term measure, DGF, was available from our meta-analysis. Therefore we could only calculate the short-term cost-effectiveness of machine perfusion compared to cold storage, i.e., the cost / number of DGF events avoided.

Resource use and costs

The perspective of our institution was used in the base case analysis, which does not take into account physician fees. We have assumed that the machines would be used in 30 transplantations per year.

Resources included in the analyses:

- Equipment and/or disposable costs associated with the use of machine perfusion and cold storage
- In-hospital healthcare resources associated with DGF. Patients are discharged from hospital once the renal function is recovered.

Sources for unit costs were obtained from the proposal for purchase of machine perfusion by Dr. Steven Paraskevas, and from the departments of Finance, Nephrology, and Quality Management of the McGill University Health Centre.

Costs are reported in 2006 Canadian dollars. Costs obtained from other years were adjusted for inflation according to the Bank of Canada rates. Discounting for clinical or economic outcomes was not used as a short-term model of < 1 year was used.

The incremental cost and effectiveness of machine perfusion compared to cold storage and the 95% confidence interval were calculated through probabilistic sensitivity analyses, with 10,000 Monte Carlo simulations. For some model parameters a point estimate and a measure of data spread could be obtained from the literature, in these cases, a beta distribution was used for probability variables and a log-normal distribution was used for risk ratios in the probabilistic

sensitivity analyses. Otherwise a triangular distribution was used using a range that was considered plausible.

RESULTS

We identified one technology assessment report published in 2003 that evaluated the cost-effectiveness of machine perfusion compared to cold storage[7]. This 2001 systematic literature review included 20 controlled comparative studies published after 1971[7]. The studies used different machine models (Waters MOX 100, Belzer LI 400, Gambro, Nikison APS-02) and preservation solutions[7]. The studies consisted mostly of paired comparisons between kidneys from the same donor allocated to either machine perfusion or cold storage. The authors of the report considered the quality of the studies to be poor[7]. The method of allocation of kidneys to each preservation technique was most often unspecified and rarely randomized [7]. Information on important outcome predictors such as donor status, NHBD or HBD, cold ischemic time and the number of previous transplantations was often not available and information on drop-outs was also lacking[7].

We updated the 2001 systematic literature search by searching the literature after their October 2001 cut date. We identified 10 additional studies not included in the earlier review[18 19 20 21 22 23 24 25 26 27] but no new randomized controlled trials (RCTs). Most studies were comparative analyses of retrospectively collected outcomes data from kidney transplantation registries or databases with non-randomized methods of allocation of organ storage, increasing the possibility of selection bias. Only two of these studies attempted to control for potential baseline imbalances between the two groups by allocating one kidney from each donor to machine perfusion and one to cold storage [19 22]. One of these studies was published in an abstract format[22].

In most studies the data were analyzed by logistic and survival analyses for short and long-term outcomes respectively and at times adjustments for confounders were carried-out. The type of machine and preservation solution, and the study population were not always adequately defined. [22 25]. The studies included transplantations from HBD, NHBD and ECD.

Appendix 1 summarizes the characteristics of these studies.

Technical failure

None of the studies reported equipment or technical failure of machine perfusion.

Delayed graft function

Meta-analysis (Technology assessment report published in 2003)

The previous technology assessment report included fifteen studies in the delayed graft function meta-analysis. Delayed graft function was defined in most studies as need for dialysis during the first one to two weeks after the transplantation, but occasionally a decline in serum creatinine over the first 4 days after the transplantation was employed[7].

The meta-analysis included 591 patients in the machine perfusion group and 563 in the cold storage, 37.6% of the patients in the machine perfusion group experienced delayed graft function compared to 47.8% in the cold storage group[7]. The overall relative risk (RR) of DGF obtained was 0.804 , 95% confidence interval (CI): 0.672 , 0.961) with machine perfusion compared to cold storage[7]. Subgroup analyses yielded a RR of 0.847 (95% CI:0.653 , 1.098) from three NHBD studies and 0.718 (95%CI: 0.572 , 0.903) from five HBD studies[7]. In two studies using the University of Wisconsin solution, the RR was 0.703 (95% CI: 0.524 , 0.943).

Our Systematic literature search

Eight of the studies later identified evaluated the rate of delayed graft function [18] [19] [22] [23] [24] [25] [26] [27]. The unadjusted DGF rates with machine perfusion and cold storage reported in these studies and their respective odds ratios (ORs) if available are shown in table 1. More details in Appendix 2.

Table 1 – Unadjusted DGF rates and ORs with machine perfusion compared to cold storage

Study, year (N)	DGF rate machine perfusion	DGF rate cold storage	p-value	OR (95% CI)
Schold et al. [19], 2005 (N=907 pairs)	19.3%	26.4%	P<0.001	NR
Matsuoka et al. [18], 2006 (N=4,618)	25.8%	37.1%	P<0.001	0.51 (0.43 , 0.61)(adjusted)
Goldstein et al. [22], 2006 (N=9 pairs)	20%	64%	P=0.03	NR
Cho et al. [23], 2005 (N=4,960)	26%	36%	P<0.001	0.60 (0.51 , 0.70) (adjusted)
Shidban et al. [25],	15.3%	43.7%	P=0.09	NR

2004 (N=320)				
Jaccobbi et al.[24], 2003 (N=39,917)	NR	NR	NR	0.53 (adjusted) p<0.0001
Shidban et al. [26], 2004 N=320)	NR	NR	NR	0.53 (adjusted) p<0.0001
Meier-Kriesche et al. [27], 2002 (N=54,404)	NR	NR	NR	Cold ischemic time < 12 hours 0.57 (adjusted) statistical test result not reported

More details in Appendix 2.

Our Meta-Analysis

In addition to the studies included in the previous HTA report[7], only two studies [19 22] identified in our systematic literature search met the eligibility criteria to be used in our meta-analysis. In these additional studies, each kidney from each donor was sequentially allocated to either machine perfusion or cold storage [19 22].

Pooling the results of these 17 studies (Figure 2), we have estimated a 22% a relative risk reduction of delayed graft function with machine perfusion compared to cold storage (Relative risk (RR): 0.78, 95% Confidence interval (CI): 0.67 , 0.92). The absolute difference in the risk of delayed graft function was -11% (95% CI -17% , -4%) with machine perfusion compared to cold storage (Figure 2).

Results in transplantations from NHBD showed only a trend to a DGF risk reduction with machine perfusion compared to cold storage (RR 0.81, 95% CI: 0.60 , 1.08 ; RD: -0.16, 95% CI: -0.36 , 0.03), but there may have been insufficient power to detect a risk difference in any subgroup analyses (Figure 2).

Figure 2 – Meta-analyses - DGF

All patients (Risk ratio)

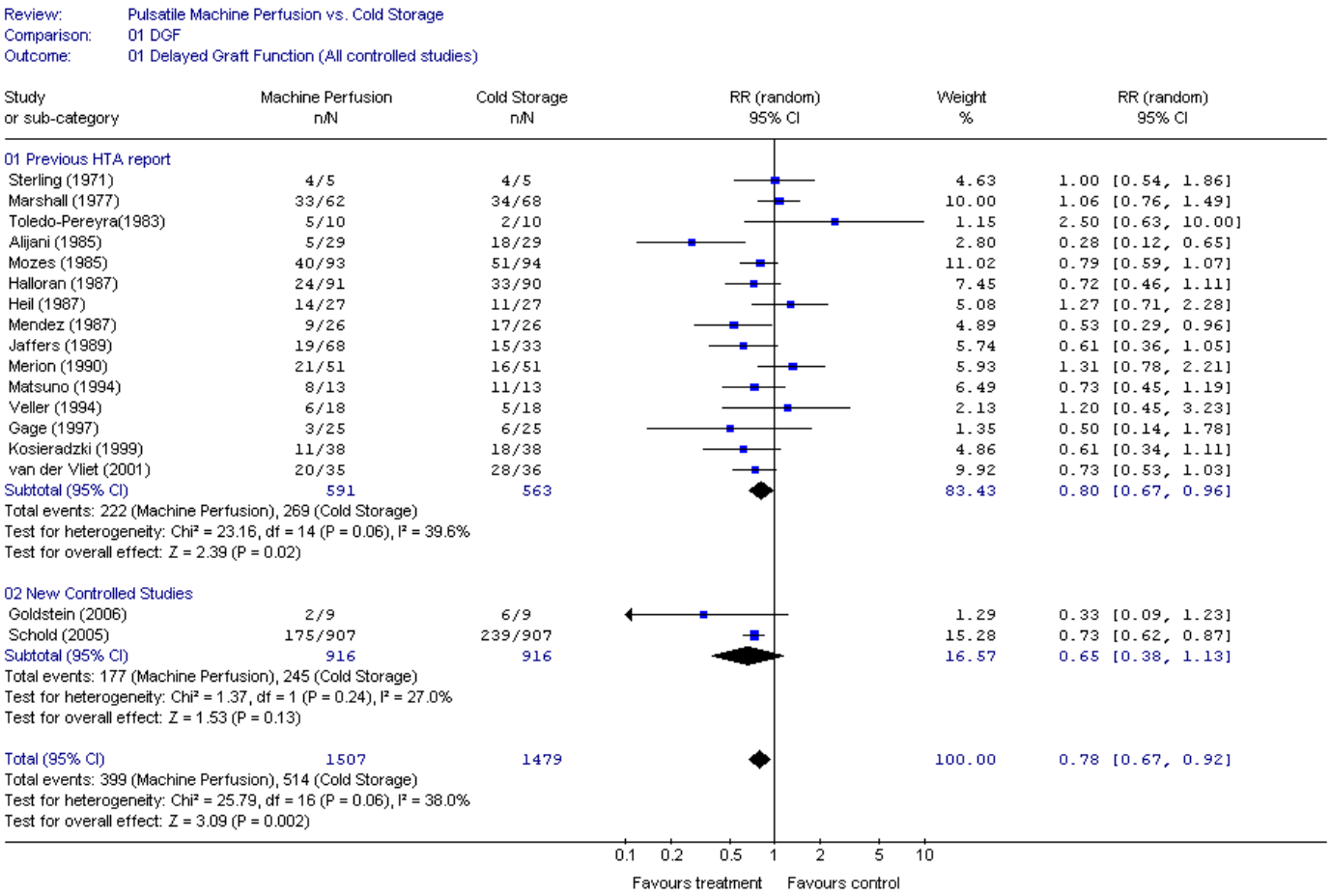
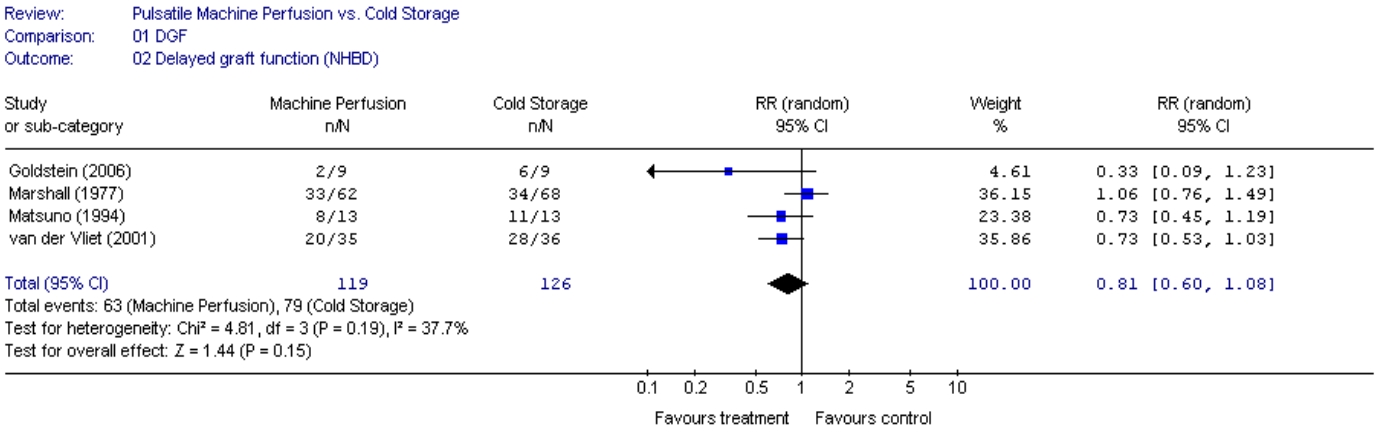


Figure 2 cont.

NHBD (Risk ratio)



All patients (Risk difference)

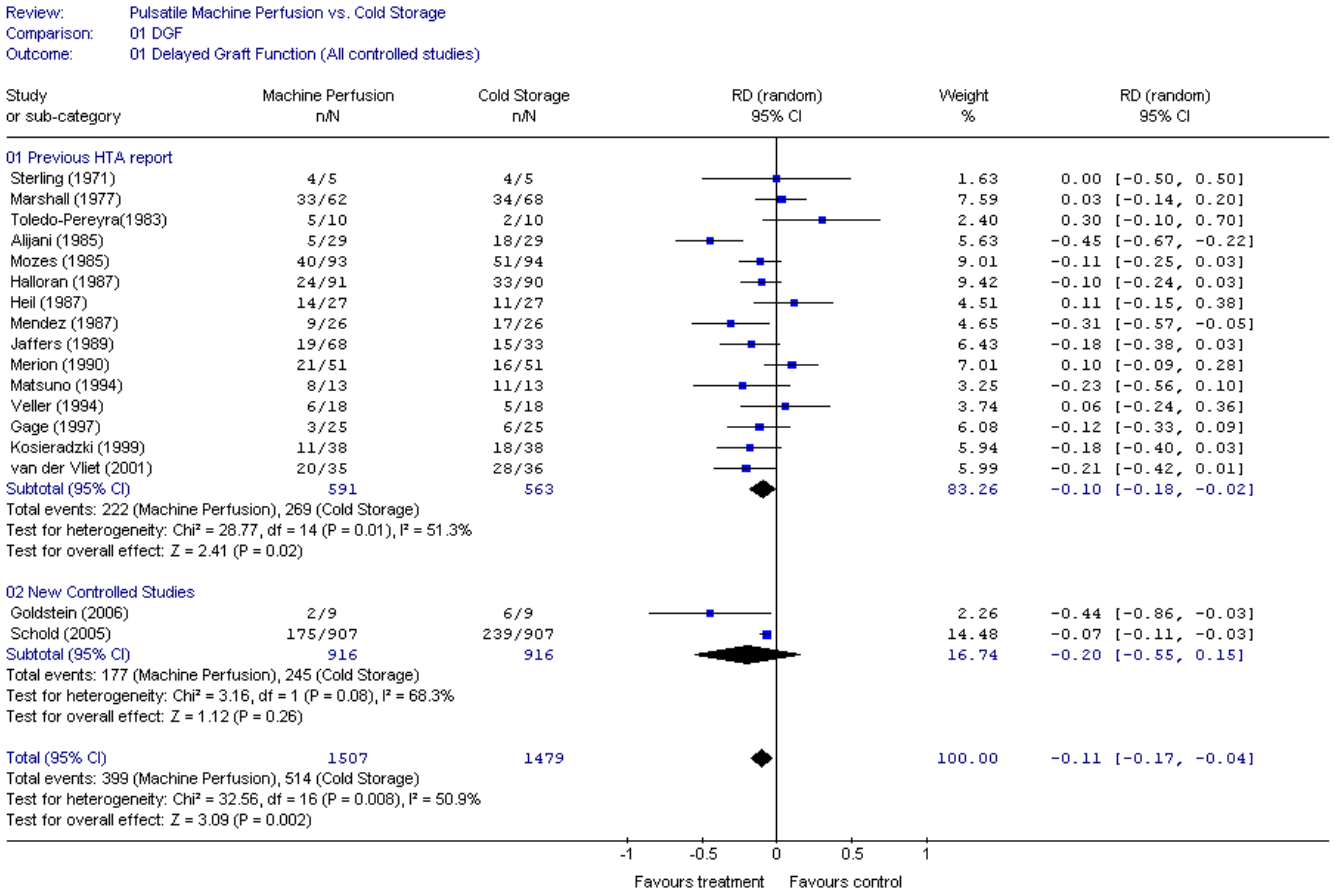
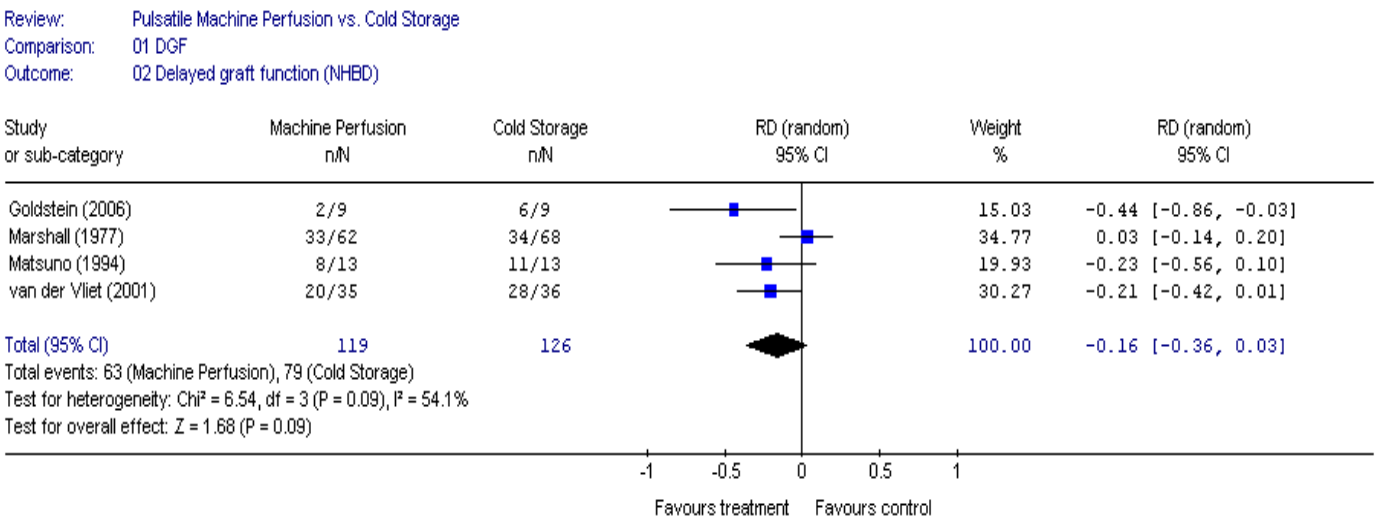


Figure 2 cont.

NHBD (Risk difference)



Long-term graft survival

Meta-analysis (Technology assessment report published in 2003)

Seven studies were included in the long-term graft survival meta-analysis from the technology assessment report published in 2003, totaling 235 patients in the machine perfusion group and 185 in the cold storage groups[7]. The pooled graft survival rates were 76.2% and 74.1% respectively, and the pooled RR was 1.025 (95% CI: 0.963 , 1.09) for machine perfusion compared to cold storage[7]. Based on these results the authors concluded that there is no evidence of improvements in graft survival with machine perfusion compared to cold storage, but the authors believe that this could be due to insufficient statistical power to detect such differences[7].

Our systematic literature search

Seven studies later identified compared the long-term graft survival among the two methods of kidney preservation [18 19 20 21 24 25 26]. Overall these studies didn't show any difference in graft survival (see appendix 2)

TAU Meta-Analysis

None of the studies identified through our systematic literature search met the criteria for inclusion in our meta-analysis, i.e., in general they did not control for systematic bias in treatment allocation. Therefore the results obtained in the previous HTA report were used to evaluate long-term graft survival.

Kidney Viability testing

Results from the technology assessment report published in 2003

The authors found little evidence in 26 studies that the viability of kidneys pre-transplantation could be predicted with machine perfusion[7].

Our systematic literature search

We did not identify any additional study that adequately evaluated the association between pre-transplant parameters tested with machine perfusion and transplantation outcomes.

Safety

No safety concerns were mentioned in the studies identified but, of course, the small sample sizes mean a small adverse event can't be completely excluded.

Comments – Clinical Studies

The technology assessment report from the UK included controlled studies comparing machine perfusion and cold storage, however they considered the studies to be of poor methodological quality [7]. Our systematic literature search yielded only two additional controlled studies. Only the studies that attempted to control for baseline imbalances between the two groups were included in our meta-analysis as this minimizes the occurrence of selection bias.

The technology assessment report from the UK concluded that there was no evidence of improvements in graft survival with machine perfusion compared to cold storage, although this could be due to insufficient power to detect such differences[7]. In the long-term survival analyses later identified, it was unclear if the results were adjusted for possible confounders. Similarly, it wasn't clear how censoring for losses to follow-up or deaths due to other conditions was done, and if these events occurred randomly. For these reasons, the results obtained should be

interpreted very carefully and in our opinion do not consist of sufficient evidence of improvements in survival with machine perfusion.

Published Technology Assessment Reports – Economic Analyses

The technology assessment report from the UK published in 2003 included a cost-utility analysis[7]. The authors found that although there were uncertainties involved, on average machine perfusion seemed to be the dominant strategy (less costly and more effective) in 80% of NHBD and approximately 50-60% of HBD donors[7]. This analysis differs from our economic analysis in that we evaluated the incremental cost/DGF avoided and not the cost/QALY, which is more problematic to meaure.

Comments: The authors estimated the long-term cost-effectiveness of machine perfusion compared to cold storage using short-term results on DGF from studies identified in through a systematic literature search, and modeled the correlation between DGF and long-term graft survivals based on observational studies, despite the existence of long-term studies comparing machine perfusion and cold storage. Moreover, the long-term graft survival benefit with machine perfusion compared to cold storage seen in published studies was not statistically significant (meta-analysis RR: 1.025, 95% CI: 0.96 , 1.09[7]).

An economic analysis published in abstract format provided the cumulative treatment costs in patients whose kidneys had been preserved using machine perfusion (n=227) and those whose kidneys were preserved by cold storage (n=188) between months 1 and 60 post-transplantation[28]. Cumulative costs with machine perfusion and cold storage respectively were US$ 3,730 vs. $2998 at 1 month, $4,514 vs. 3,785 at 2 months, $12,336 vs. $12,084 at 12 months, $15,040 vs. $15,059 at 16 months, $20,454 vs. $20,932 at 24 months, and $43,787 vs. $46,484 at 60 months[28]. The costs included machine perfusion equipment, post-transplantation hemodialysis, hospitalization costs, and costs of immunospressants[28]. Additional details were not available.

COST ANALYSIS

Equipment costs

Equipment and disposables are presented in table 2.

Table 2 – Cost of Equipment and Disposables (source of information: proposal for the purchase of pulsatile perfusion system for kidney transplantation by Dr. Steven Paraskevas)

	Unit Cost (CDN$)	**Number needed**	**Total cost**
Perfusion machine*	$14,980**	2	$29,960
Disposables (machine perfusion)	$750	30	$22,500
Total			$52,460 (1st year) $22,500 (subsequent years until the machine is replaced

* Based on the Lifeport® machine costs
** Costs with 20% discount, original cost per perfusion machine unit = $18,500 ($37,000 for 2 units)

Cold storages uses 2 liters of preservation solution, $350/liter, $700 in total (information from Dr. Steven Paraskevas).

Treatment costs due to DGF

Patients experiencing DGF remain in hospital on average 16 days longer than patients not experiencing DGF, and require hemodialysis approximately every 2 days until the kidney function is recovered (information from Dr. Steven Paraskevas).

Table 3 shows the estimated in-hospital costs associated with DGF.

Table 3 – Estimated in-hospital costs of DGF (2006 Costs in Canadian dollars)

	Additional resources / patient with DGF vs. no DGF§§	Unit costs (CDN$)	Additional expected cost/patient with DGF vs. no DGF	Source for costs
Per diem hospital costs *	16 days	$ 660.93	$ 10,575	Finance Department MUHC
Hemodialysis costs	8 sessions §	$ 276‡	$ 2,208	Dr. Paul Barre, Nephrology, MUHC
Medication use in-hospital (Details in Appendix 4)	16 days	$88.36/day	$1,414	Regie de l'assurance Maladie du

				Quebec (RAMQ)[29]
Kidney ultrasound	1.5/hospital stay	$11.96¶	$17	Quality Management, MUHC (Ms. Linda Maruska)
Kidney biopsy	0.5/hospital stay	$55.39¶	$27	Quality Management, MUHC (Ms. Linda Maruska)
Laboratory tests performed daily during hospital stay (Details in Appendix 4)	16 days	$60.39/day	$966	Quality Management, MUHC (Ms. Linda Maruska)
Total			$15,207	

§§ Information provided by Dr. Steven Paraskevas.

* Includes nursing, medical equipment and supplies. Source: Gilles Gaudet and Paul Tan (Finance Department MUHC), per diem cost for Patient Care Unit (PCU) Ross 3, $622.96 in 2003 ($660.93 corrected for inflation according to Bank of Canada rates).

§ Hemodialysis is done approximately every 2 days in patients with DGF until the recovery of renal function (estimated as 16 days).

‡ Hemodialysis costs include disposables, staff, equipment, and building costs (excludes physician fees).

¶ Values corrected for inflation according to Bank of Canada rates, $11.46 for 1 kidney ultrasound and $53.09 for a kidney biopsy, 2004-2005 fiscal year.

As can be seen in table 2, DGF is estimated to cost approximately $15,207 per patient experiencing the complication.

Cost-effectiveness analyses

A decision tree was used to calculate the incremental cost per DGF event avoided using machine perfusion compared to cold storage.

The mean incremental cost and effectiveness, and the 95% confidence interval were calculated through probabilistic sensitivity analysis. The variables and distributions used in these analyses are given in table 4.

As the perfusion machine at the MUHC may be provided with external funding two scenarios were considered in our analyses, one excluding and one including equipment costs. This also ensures a better generalizability of our results to other institutions.

Table 4 - Variables used in the probabilistic sensitivity analyses (costs/DGF event avoided)

Variable	Base case value (variation) distribution	Source
Clinical variables		
Baseline rate of DGF (cold storage)	0.27 (SD: 0.027) Beta distribution	Source for DGF rate: Dr. Steven Paraskevas
Relative risk of DGF with machine perfusion	RR: 0.78 (95% CI: 0.67 , 0.92) Log-normal distribution	TAU meta-analysis
Costs associated with kidney preservation		
Equipment cost (machine perfusion) per transplantation* Base case: Assuming that the machine would be used in 30 transplantations and for 8 years before it needs to be replaced	$138 ($114 , $178) Triangular distribution Extremes were calculated by varying the number if years of machine use from 6-10 years	Equipment cost/transplantation based on the unit costs of machine perfusion. Source: proposal for the purchase of pulsatile perfusion system, by Dr. Steven Paraskevas.
Disposables / transplantation	$750 (machine perfusion) $700 (2 liters of preservation solution, $350 each for cold storage)	Dr. Steven Paraskevas
Resource utilization and costs associated with DGF (compared to no DGF)		
Number of additional in-hospital days	16	Dr. Steven Paraskevas
DGF costs	$15,207	Table 3

*The equivalent annual cost of equipment (machine perfusion) was calculated by the amortization procedure using the formula: $K = E (((1 – (1+r)^{-(n-1)}) / r) +1)$ assuming that costs incurred at the end of the year[30]
K= equipment cost ($29,960) / E=equivalent annual cost / n=number of years (8 years) / r=interest rate (discount rate=3%)
Equivalent annual cost = $4,143 Equipment cost/procedure = $138 ($4,143/30)
The perspective of our institution was used in the base case analysis, which does not take into account physician fees or those costs incurred outside of the hospital.
SD=standard deviation

Cost-effectiveness analyses results

Table 4 shows the variables used in our analyses.

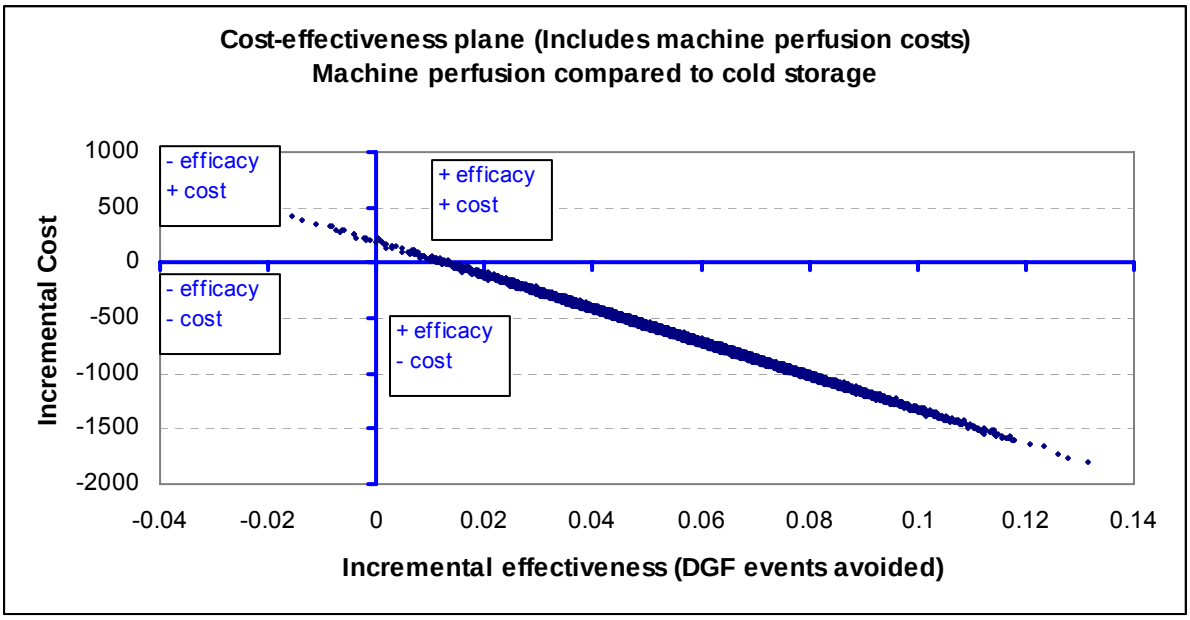
Including the machine perfusion costs, our probabilistic sensitivity analyses resulted in a mean 0.059 DGF episodes avoided (95% CI: 0.0209 , 0.0957), and mean ***cost saving*** of $698 (95% CI: $1,262 , $127) per transplantation with machine perfusion compared to cold storage. The

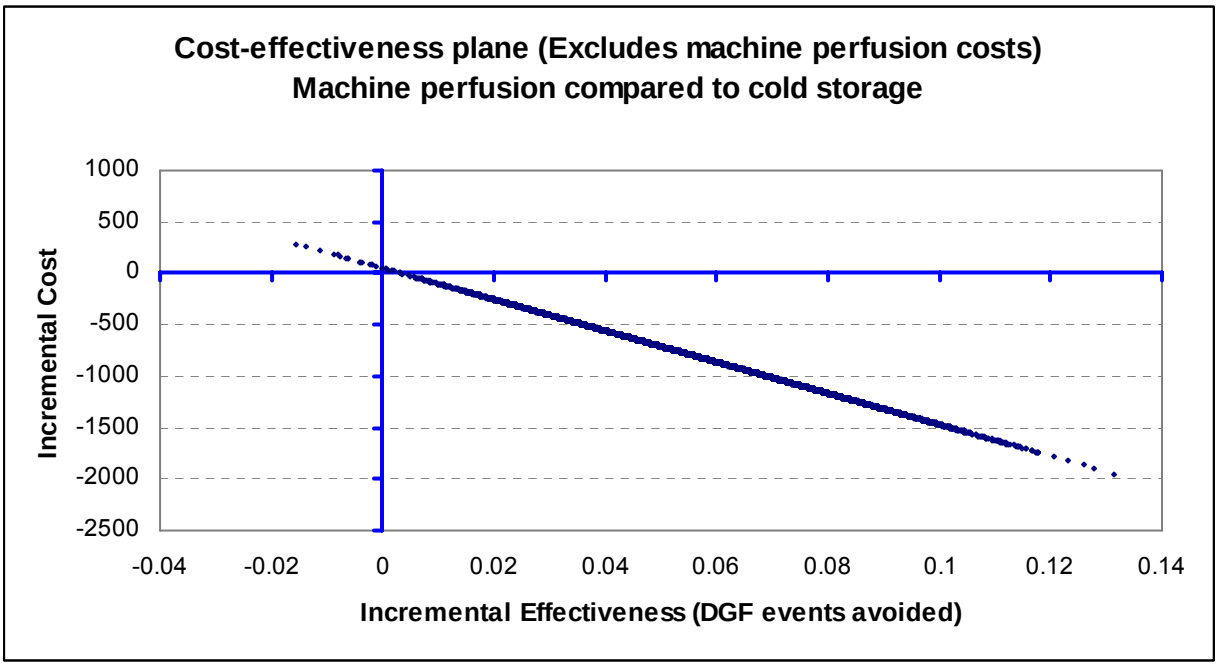
cost-effectiveness scatterplot obtained with the 10,000 Monte Carlo simulation (Figure 4) shows that in 99.8% of the simulations machine perfusion would have a higher effectiveness compared to cold storage, in 99.1% machine perfusion would be the dominant strategy, with both a higher effectiveness and a lower cost. There was a < 1% chance that machine perfusion would have both a lower effectiveness and a higher cost compared to cold storage.

Excluding the machine perfusion costs, our probabilistic sensitivity analysis resulted in a mean 0.059 DGF episodes avoided (95% CI: 0.0209 , 0.0957), and mean ***cost saving*** of $841 (95% CI: $1,406 , $269) per transplantation with machine perfusion compared to cold storage. The cost-effectiveness scatterplot obtained with the 10,000 Monte Carlo simulation (Figure 3) shows that in 99.8% of the simulations the machine perfusion would have a higher effectiveness compared to cold storage, in 99.7% machine perfusion would be the dominant strategy, with both a higher effectiveness and a lower cost. There was a < 1% chance that machine perfusion would have both a lower effectiveness and a higher cost compared to cold storage.

Incremental cost-effectiveness ratios were not used due to the difficulties in interpretation of negative ratios, and also the difficulties in calculating cost-effectiveness ratios when the incremental effectiveness approaches zero[31 32]. Instead, the cost-effectiveness plane (Figure 3) were produced as they show the distribution of the results according to positive or negative effectiveness and cost.

Figure 3 – Incremental cost and effectiveness scatterplot comparing machine perfusion and cold storage





DGF=delayed graft function

Conclusions:

Our analyses showed that machine perfusion is likely to improve DGF outcomes with lower costs compared to cold storage. Limitations involve the weak quality of the efficacy data

(although studies that attempted to control for baseline differences were privileged in our meta-analysis) such that possible selection biases can't be totally excluded.

DISCUSSION

The studies identified demonstrate a short-term beneficial effect for machine perfusion compared to cold storage in reducing DGF which is associated with prolonged hospitalization, supplemental hemodialysis and consequently additional costs. Weaknesses in study methodology do not permit the determination of the long-term effectiveness (graft survival / overall survival) of machine perfusion compared to cold storage.

The authors of a 2003 technology assessment report concluded that the studies comparing machine perfusion and cold storage available have a relatively poor quality and that therefore additional research is required to establish the short and long-term consequences of using this technology[7]. The additional studies identified through our systematic literature search presented similar methodological weaknesses as the ones included in the previous technology assessment report.

Two economic evaluations were identified in the literature, one included in the 2003 technology assessment report that concluded that the use of machine perfusion may be cost-effective[7]. The second economic analysis was published in an abstract format and therefore does not provide sufficient details about the cost-effectiveness of machine perfusion preservation[28].

Our cost-effectiveness analyses showed that use of machine perfusion compared to cold storage is likely to be cost-saving considering short-term outcomes. We agree with previous authors that additional evidence of the short and long-term effects of machine perfusion as well as its effects on the patients' quality of life would be helpful. The results of ongoing RCTs with machine perfusion may provide additional evidence of the role of this technology.

RECOMMENDATIONS

The available evidence suggests that machine preservation technology is likely to be cost saving and moreover capital costs are relatively small. The TAU therefore recommends that this technology should be acquired. Since the evidence on which this recommendation is based is far from perfect it is further recommended that transplantation outcomes with machine perfusion

should be prospectively recorded and compared with those from kidneys preserved by cold storage.

New data from ongoing RCTs may provide additional information on the role of this technology and this report and recommendations will need to be re-evaluated as this new evidence becomes available.

APPENDIX 1 – CHARACTERISTICS OF THE STUDIES IDENTIFIED (SYSTEMATIC REVIEW)

Study (year of publication) N Country	Type of donor	Comparative groups (number of patients)	Machine perfusion and solution used	Study design	Data collection period	Method of allocation of organ preservation method
Matsuoka[18] (2006) **N=4,618** **US**	Deceased or living donors: NHBD, HBD, ECD**	Cold storage (N=3,706) Machine perfusion (N=912)	Not specified	Retrospective Data from transplantation registry Multivariate analysis	2000-2003	Not specified
Schold[19] (2005) **N=907 pairs** **US** **Only paired analysis used as allocation may have done according to organ characteristics**	Deceased donors: NHBD, HBD, ECD***	Machine perfusion: 907 Cold storage: 907	Not specified	Retrospective Data from transplantation registry Multivariate analysis	1994-2003	Kidneys from African-American donors, with extended cold ischemia times, with history of diabetes and increasing donor age and from NHBD were more likely to be preserved with Machine perfusion
Kwiatkowski[21] (2006) (abstract) **N=415** **Poland**	Deceased donors	Continuous machine perfusion: N=227 Cold storage: N=188	Not specified	Retrospective data collection	1994-1999	Not specified

ECD=extended criteria donors / N=number of patients / HBD=heart-beating donor / NHBD=non-heart beating donor

*Donors older than 55 years

** ECD definition: deceased donors > 60 years, or living donors between 50-59 years with 2 of the following: hypertension, history of cerebrovascular accident, terminal serum creatinine > 1.5mg/dl

*** ECD definition: > 60 years, elevated creatinine levels (>1.5mg/dl), hypertension or diabetes history

Appendix 1 – cont.

Study (year of publication) N Country	Type of donor	Comparative groups (number of patients)	Machine perfusion and solution used	Study design	Data collection period	Method of allocation of organ preservation method
Montgomery[20] (2003) **N=287** **US**	Deceased non-ideal donors§	Machine perfusion: 140 Other method: (147?)	Not specified	Retrospective Data from transplantation database Unadjusted analysis	1996-2001	Not specified Kidneys were more likely to have longer cold ischemic time and lower terminal creatinine
Goldstein[22] (2006) (abstract) **N=18 (9 pairs)** **US**	Deceased donors	Machine perfusion: N=9 Cold storage: N=9	RM3 Waters Medical Systems Solution: Belzer MP	Retrospective data collection	2005-2006	Each kidney of each pair was allocated sequentially to cold storage and machine perfusion
Cho et al.[23] (2005) (abstract) **N=4,960** **US**	ECDs	Machine perfusion: 1,003 Cold storage: 3,957	Not specified	Retrospective Data from transplantation database Multivariate analysis	2000-2003	Not specified
Shidban et al.[25] (2004) (abstract **N=320** **US**	Deceased donors	Machine perfusion: 59 Non-machine pumped : 261	Machine : not specified Solution : University of Wisconsis	Retrospective for controls, not clear for machine perfusion group Unadjusted analysis	2001-2003	Not specified

§ kidneys where immediate function was expected

Appendix 1 Cont.

Study (year of publication) N Country	Type of donor	Comparative groups (number of patients)	Machine perfusion and solution used	Study design	Data collection period	Method of allocation of organ preservation method
Greenstein et al. [26] (2003) (abstract) N=10,562 US	Deceased	Initial Machine perfusion: 1,056 Non-initial machine perfusion: 9,506	Not specified	Adjusted analysis	1999-2001	Not specified
Jacobbi et al. [24](2003) (abstract) N=39,917 US	Deceased	Machine perfusion: 4,790 Non-machine perfusion: 35,127	Not specified	Retrospective Data from transplant registry Adjusted analysis	1995-2001	Not specified
Meier-Kriesche et al.[27](2002) (abstract) N=54,404 US	Deceased	Machine perfusion: 7,158 Cold storage: 47,400	Not specified	Retrospective	Not specified	Not specified

APPENDIX 2 RESULTS OF THE STUDIES IDENTIFIED (SYSTEMATIC REVIEW)

Study	Pre-transplantation characteristics	DGF	Graft survival	Survival	Rejection
Matsuoka[18] (2006) N=4,618 (MP=912 / CS: 3706) HBD, NHBD, ECD donors* Period: 2000-2003 Information from transplant database (US)	Recipient Age:: MP: 56±11.4 / CS: 54.5±12.3 Pre-tx dialysis: None: MP: 4.7% / CS: 5.2% Hemodialysis: MP: 79.8% / CS: 82.7% Donor Age: MP: 61.1±6.3 / CS: 59.8±6.1 Serum creatin. (mg/dL): MP: 1.2±1.1 / CS: 1.1±1 CVA: MP: 83.6% / CS: 85.2% Hypertension: MP : 63.3% / CS : 65.2% Donation after cardiac death : MP : 6.5% / CS : 0.9% Cold ischemia time (hours): MP: 18.9±8.1 / CS: 20.1 ±8.9	Dialysis within 1st week Adjusted OR: 0.51 (0.43 , 0.61) MP: 25.8% / CS: 37.1% (p=<0.001) Primary non-function: MP: 2.6% / CS: 3.2% (p=0.37)	Similar rates 1-3 years between MP and CS 1 year No DGF:>80% / With DGF: > 60% MP-DGF patients had a worse graft survival than CS-DGF patients Deaths with functioning graft were censored		In-hospital: MP: 6.8% / CS: 7.5% (p=0.46) 6 months: MP: 16% / 16.4% (p=0.8) 1 year: MP: 19% / CS: 18.9% (p=0.96)

*ECD donors: deceased donors > 60 years or living donors between 50-59 years old with 2 of the following: hypertension, history of CVA, terminal serum creatinine value > 1.5mg/dl

Appendix 2 cont.

Study	Pre-transplantation characteristics	DGF	Graft survival	Survival	Rejection
Montgomery et al. [20](2003) Deceased ECD* donors N=287 (MP=140 , CS=147) Period: 1996-2001 Retrospective study, non-random allocation of kidney to preservation technique	Kidneys in MP more likely to have longer cold ischemia and donors with lower creatinine clearance More details not provided		Equivalent between MP and CS although MP donors had poorer characteristics (Rates not provided) (Creatinine clearance was greater in MP at 2-4 years despite being lower at transplantation (statistical significance not reported)		
Kwiatkowski et al. [21](2006) (abstract) N=415 (MP=227 / CS=188) Period : 1994-1999 Retrospective study (5-10 years follow-up)	No information provided	-	MP: 155 (68.2%) / CS: 102 (54.2%)	MP: 189 (83.5%) / CS: 156 (83%)	-
Schold (2005)[19] Deceased donors (NHBD, HBD), ECD* Period: 1994-2003 N=907 pairs (MP: 907/ CS: 907) US Transplant database	-	DGF within 1st week or anuria within 24 hours Pair kidney analysis MP:19.3% / CS: 26.4% p<0.001	Paired kidney analysis 1-year MP: 89.8% / CS: 88.4% 6-year MP:64.4% / CS: 62%		

CS=cold storage / MP=machine perfusion
*ECD donors defined as: donor age <5 or >55 years, terminal creatinine > 1.5mg/dl, history of hypertension, cold ischemic time > 30 hours

Appendix 2 cont.

Study	Pre-transplantation characteristics	DGF	Graft survival	Survival	Rejection
Goldstein et al. [22](2006) (abstract) N=18 (9 pairs) (each kidney of each pair was allocated sequentially to CS and MP) MP: Waters RM3® with Belzer MP solution Period: 2005-2006	-	MP: 2 (22%) / CS: 6 (64%) p=0.03 Creatinine clearance at hospital discharge: MP: 46.2ml/min. / CS: 34.8 ml/min. (p=0.2)			
Cho et al.[23] (2005) (Abstract) N=4,960 (MP=1,003 / CS : 3,957) Period 2000-2003 ECD	Not available	MP: 26% / CS: 36% (p< 0.001) Adjusted OR: 0.60 (95% CI: 0.51 , 0.70) (p>0.001) Other DGF risk factors identified: cold ischemia time (>36 hours vs. < 24hours), OR 1.78 (95% CI: 1.32 , 2.39)	-		
Jacobbi et al. [24](2003) (abstract) **N=39,917** **US**	Not available	Adjusted analysis: OR: 0.53 (p<0.0001) No effect of machine perfusion on permanent non-function	Unadjusted analysis: RR: 1.14 (95% CI: 1.04 , 1.25)	-	-

CS=cold storage / MP=machine perfusion

Appendix 2 cont.

Study	Pre-transplantation characteristics	DGF	Graft survival	Mortality	Rejection
Shidban et al.[25] (2004) (abstract N=320 US	Donor age > 55: MP: 19 (32.2% / CS: 72 (19.6%) Cold ischemic time > 36 hours: MP: 7 (11.9%) / CS: 164 (62.8%) Preoperative recipient serum creatinine: MP: 8.6 / CS: 7.2	Unadjusted analysis: MP: 9 (15.3%) / CS: 114 (43.7%) P=0.09	1 year MP: 81.3% / CS: 85% (p=0.44)	1 year MP: 96.6% / CS: 95.7% (p=0.74)	
Greenstein et al. [26](2003) N=10,562 US	Not available	Adjusted analysis: OR: 0.53 (p<0.0001) Variables adjusted for: donor age, hypertension, diabetes, creatinine, NHBD, recipient age, sex, race, and cause of ESRD	Analysis: RR: 0.75 (p=0.02)		
Meier-Kriesche et al. [27](2002) (abstract) N=54,404 US	Not available	Adjusted analysis: Cold ischemic time 0-12 hours: OR: 0.57 (measure of variance or statistical significance not provided)	-	-	-

CI= confidence interval / (CS=cold storage / MP=machine perfusion / min=minutes / WIT=warm ischemia time

Appendix 3 – Pre-transplant organ evaluation

Study	Pre-transplant biopsy done ?	Pre-transplant organ evaluation through machine perfusion parameters ?	Results	Comments
Matsuoka et al.[18] (2006) N=4,618 Machine not specified	Yes (ECD kidneys)	No	> 10% Glomerulosclerosis: MP: 27.3% / CS: 18.1% p=0.002 Interstitial fibrosis MP: 48.5% / CS: 40.5% p=0.03 In kidneys with biopsies in transplant centers	Non-randomized allocation to preservation method may have been responsible for worse conditions with machine perfused kidneys compared to cold storage ?

ECD=extended criteria donors / CS: cold storage / MP: machine perfusion

APPENDIX 4 – UNIT COSTS INCLUDED IN THE COST-EFFECTIVENESS ANALYSES

Tables 4.1 and 4.2 show the daily used in-hospital of laboratory tests and medications. These resources are used in patients undergoing a kidney transplantation, including those experiencing DGF.

The information on types of laboratory tests and medications used by these patients was provided by Dr. Steven Paraskevas and Valérie Cass (Nurse, Transplant, MUHC).

Table 4.1 – Laboratory tests performed daily in-hospital (Source for unit costs: Ms. Linda Maruska, Quality Management Department, MUHC)

Laboratory test performed daily	**Unit Cost**	**Specimen handling fee**	**Total**
Complete blood count with differentials	$3.25	$1.00	$4.25
Alanine aminotransferase*	$0.40	-	$0.40
Alkaline phosphatase*	$0.35	-	$0.35
Billirubin*	$0.41	-	$0.41
Albumin*	$0.33	-	$0.33
Total protein*	$0.32	$1.00	$0.32 $1.00
Amylase	$1.39	$1.00	$2.39
Lipase	$3.25	$1.00	$4.25
Sodium*	$0.34	-	$0.34
Chloride*	$0.34	$1.00	$0.34 $1.00
Prothrombin time / partial thromboplastin time	$21.27	$1.00	$22.27
Tacrolimus drug levels measurement	$15.30	$1.00	$16.30
Cyclosporin drug leves measurement	$2.87	$1.00	$3.87
Total			**$57.82** **$60.32 (corrected for inflation according to the Bank of Canada)**

* Specimen handling fee added only once for this group of tests

Table 4.2 – Daily use of medications in-hospital

Medication, daily dose	**Unit Cost**	**Cost / day**
Mofetil mycophenolate 1,000mg BID	$4.124 / 500mg	$16.5
Prednisone 15mg/day	$0.022 / 5mg	$0.066
Ganciclovir (IV) 1.25 mg/kg/day	$41.214 / 500mg	$41.21 (assuming that one vial would be used for each patient)
Epoetin alfa 5000 U 3x/week	$71.25 / 5000 U	$30.54
Total		**$88.32**

Source for medication unit costs: Regie de l'Assurance Maladie du Québec (RAMQ) [29]

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