LAPAROSCOPIC DONOR NEPHRECTOMY – EVOLUTION OF TECHNIQUE AND DONOR OUTCOMES

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By

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STATEMENT OF ORIGINALITY

This dissertation has been produced from my own individual work at the University of Leicester Department of Surgery from 2004-2006

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Oral Presentations from data collected from this thesis

Laparoscopic versus short incision open donor nephrectomy – A randomised controlled trial
Kaushik M, Brook NR, Bagul A, Elwell R, Veitch PS, Nicholson ML
ASGBI 2009, Glasgow – Presented at the associations prestigious Moynihan prize session

Medium-term follow up of renal transplant recipients from a randomised controlled trial of laparoscopic versus open live donor nephrectomy
Kaushik M, Elwell R, Bagul A, Veitch P, Nicholson M
BTS 2009 Annual Conference, May 2009 – Liverpool

Randomised controlled trial of laparoscopic verus minimal access open donor nephrectomy
Kaushik M, Bagul A, Yates PJ, Elwell R, Nicholson ML
SARS – Cambridge, Jan 2007

Comparison of techniques of vascular control in Laparoscopic donor nephrectomy
Kaushik M, Bagul A, Yates PJ, Elwell R, Nicholson ML
World Transplant Congress – Boston; July 2006

Comparison of techniques of vascular control in Laparoscopic donor nephrectomy
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Postoperative complication profile and donor recovery rates in a consecutive series of 115 laparoscopic live donor nephrectomies
Kaushik M, Brook NR, Kay MD, Bagul A, Elwell R, Nicholson ML
BTS – Edinburgh, March 2006

Randomised controlled trial of open versus laparoscopic live donor nephrectomy
Kaushik M, Brook NR, Kay MD, Bagul A, Elwell R, Nicholson ML
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Poster Presentations

Right versus left laparoscopic donor nephrectomy
M Kaushik**,** A Bagul, PJ Yates, R Elwell, ML Nicholson
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M Kaushik, NR Brook, MD Kay, A Bagul, R Elwell ML Nicholson
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M Kaushik, PJ Yates, A Bagul, R Elwell and ML Nicholson
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M Kaushik, A Bagul, PJ Yates, R Elwell and ML Nicholson
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Postoperative complication profile and donor recovery rates in a consecutive series of 90 laparoscopic live donor nephrectomies
M Kaushik, NR Brook, SJF Harper, M Kay, A Bagul, R Elwell ML Nicholson
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Abstract

Background: The interest in living donor transplantation has been driven by the continuing fall in available cadaveric organs for transplantation. During the last five years there has been a substantial growth in living donor kidney transplantation in the UK but there is still considerable room for expansion in comparison with activity in Scandinavia and the USA. Traditionally kidneys have been harvested from donors via a loin incision with partial resection of the twelfth rib, which placed a considerable burden on the donors in terms of post-operative pain, absence from work, and morbidity.

Laparoscopic live donor nephrectomy developed in 1995, promised to reduce these burdens on the donors and reduce some of the disincentives to kidney donation. Several comparative studies have shown this new technique to hold promise in terms of less pain and faster inpatient and outpatient recovery.

However there were some concerns in procuring the kidneys with this technique, namely, increase in warm ischaemia times and the quality of graft.

Methods: This was addressed in the setting of a prospective randomised controlled trial of laparoscopic versus limited incision live donor nephrectomy. Live kidney donors were randomly assigned in a 2:1 ratio to laparoscopic (LDN n=56) or short incision open donor nephrectomy (ODN n=28). Quality of life was assessed using the Short-Form 36 questionnaire. Postoperative analgesia was by morphine PCAS. Pain scores were recorded using visual analogue and verbal response scales. Donor convalescence was self-reported using a prospective diary system. Our study was the first randomised control trial to present live donor transplant recipient data at a minimum follow-up of four years. There were no differences in renal function or allograft survival for kidneys removed by LDN (laparoscopic

donor nephrectomy) or ODN (open donor nephrectomy) at this point. The other aspect of this study is that this is the first study to compare respiratory function after LDN and ODN. During the evolution of LDN, the vessels are secured with various methods (endoclips, polymer clips and stapling device). These methods were compared with respect to complications and maximum length of vessels obtained. Technical modifications and improvement of techniques especially when comparing right and left donor nephrectomy are described.

Results: Postoperative morphine requirement was lower in the LDN group [median (range) 59 (6-136) vs ODN 90 (35-312)mg; p=0.01]. Donors in the LDN group returned to normal activities more quickly compared to the ODN group [median (range) days to: driving 21 (7-70) vs 28 (7-70); p=0.05), exercise 28 (7-77) vs 42 (14-84); p=0.001, return to work 42 (14-84) vs 66.5 (14-112); p=0.001].

When compared to the pre-operative baseline, norm adjusted physical component scores (PCS) fell significantly at 6 weeks in both the LDN (mean±SD 46.3±8.9 vs 55±6.9; p=0.001) and ODN groups (44.0±7.9 vs 52.7±9.0; p=0.008). Nonetheless, the bodily pain domain score of PCS was significantly better in the LDN group (57.5 to 49.5; p=0.0001). The mental component score also fell in the ODN group (48±10.2 vs 53.5±7.6; p=0.02). In contrast, there was no fall in the mental component score after LDN (mean±SD 51.9±7.2 vs 53.8±6.4; p=0.29).

Conclusions: In conclusion, our trial has shown that laparoscopic donor nephrectomy removes some of the disincentives to live kidney donation. This can be achieved without any additional morbidity in the recipient. This study provides high-level evidence to show that laparoscopic donor nephrectomy improves recovery back to the normal activities of daily life, is less painful than open surgery and improves the mental component of quality of life.

CHAPTER ONE: INTRODUCTION

1.1 Historical Aspects

Transplantation, the removal or partial detachment of a part of the body and its implantation to the body of the same or a different individual, has fascinated mankind for centuries. One of the most widely cited early examples is that of the Christian Arab Saints Cosmos and Damien around 300AD. They were reputed to have successfully replaced the diseased leg of a patient with that from a black man who had died several days earlier (Fig 1).

Fig 1 Depiction of saint Cosmos and Damian performing a transplantation of the leg

Since animal donors were used for the first kidney transplants attempted in humans (1902-1906), their rapid failure was inevitable.

The first experimental renal transplant was reported by Ullmann in March 1902. He transplanted kidneys into dogs using magnesium tube stents and ligatures to make the vascular anastomosis to the carotid artery and the internal jugular vein in the neck[1]. The same year the French surgeon Carrel reported his new technique of suturing blood vessels together using triangulation and fine silk suture material[2]. He successfully transplanted

kidneys and other organs into animals, utilizing this model to develop the technique of modern blood vessel surgery. This brilliant work resulted in a Nobel Prize in 1912.

Although important developments in the last half of the nineteenth century, such as the use of ether and other general anaesthetics and the acceptance of Lister's principles of antiseptic surgery, were important in the progress of transplantation, organ replacement is a development of the twentieth century. In 1947 Hoofnagle, Hume and Landssteiner at the Peter Brent Hospital in Boston obtained transient function of a kidney allograft. This patient was suffering from acute renal failure and this transient function may have helped her recovery. This event along with the development of dialysis machines, renewed interest in kidney transplantation. On December 23, 1954, a kidney was transplanted from one healthy identical twin to his twin who was dying of renal disease. The surgery was performed at the Peter Brent Hospital in Boston and John Merrill, Joseph Murray, and Hartwell Harrison led the clinical team[3,4]. The operation was successful, renal function was restored in the recipient and the donor suffered no ill effects. This was the first successful transplantation performed against a background of failure. For this reason it created enormous excitement, both in the media and among medical professionals, at a time when the pioneers of kidney transplantation were despondent about the possibility of any real clinical application.

The modern era of clinical transplantation began in Paris and Boston after the Second World War, and one highlight of postwar efforts was the small series of transplantations of cadaveric kidneys performed by David Hume (1917-1973)[4,5,6].
No immunosuppression was used, but some kidneys did function for days or weeks and one for several months – no doubt because of the immunosuppression resulting from the profound uraemia in the recipients[6]. Those pursuing immunosuppression in Boston and

Europe, now directed all their efforts at total body irradiation. Although such irradiation did achieve immunosuppression, however, it also produced profound marrow aplasia, which led to patients' deaths from overwhelming infections. By the early 1960s, it was clear that total body irradiation was not the solution[7]. Over the next 30 years, progress in histocompatibility typing, immunosuppressive therapy, and organ preservation, as well as the accumulation of clinical experience all contributed to the present status of transplantation, which now allows successful long term management of previously fatal renal disease in a majority of the more than 20,000 patients per year worlwide who receive renal allografts.

1.2 Living donor renal transplantation

Renal transplantation is the treatment of choice for the vast majority of patients with end-stage renal disease. It is widely accepted as the best form of renal replacement therapy. A successfully transplanted patient can avoid potentially complicated, time consuming and uncomfortable haemodialysis or peritoneal dialysis. Transplanted patients enjoy an improved sense of general well-being compared to dialysis patients; this is related to the fact that a transplant allows normal renal function and blood chemistry thus removing all the symptoms of uraemia. All dialysis methods are much less efficient at clearing the nitrogenous waste products of metabolism compared to transplantation and whilst they keep patients alive this is at the expense of a continuing degree of background uraemia that may lead to symptoms such as general malaise, fatigue, lethargy, anorexia, nausea, vomiting, hiccough, weight loss and urinary symptoms such as polyuria and nocturia. Dialysis patients are also more susceptible to anaemia and renal bone disease, but a successful kidney transplant reverses these conditions. The continuing decline in the number of cadaveric renal donors worldwide has led to a search for alternative sources of organs, to help bridge the widening gap between the number of patients on transplant waiting lists and the number of renal transplants being performed each year. Kidneys from non-heart beating donors (NHBD) in both a controlled and uncontrolled setting have shown promising results in some centres[8,9]. In the year between April 2007 and March 2008 the highest number of non-heart beating donor transplants took place in the UK – 429 transplants, a 36% increase from the previous year (UK transplant figures). The number of transplants from cadaveric and NHB donors have increased quite markedly in the last few years. The increase in non-heart beating donors will eventually reach a ceiling and many professionals in

the transplant field believe that expansion of the live donor programme is the best solution to the organ donor shortage as this pool is essentially unlimited.

The opportunity for planned transplantation before dialysis becomes inevitable, is an attractive option for patients and evidence suggests that there is improved graft survival in transplants performed pre-emptively, making it the treatment of choice[10]. The use of kidneys from living donors offers scope to achieve this and to maximise benefit to patients. Living donor kidney transplants are increasing – 589 in 2005-2006, 690 in 2006-2007 and 829 in 2007-2008 and now represent more than one in three of all kidney transplants. There has been an increase of 10% in the number of living related donor adult transplants and an increase of 47% in living unrelated donor adult transplants. For the first time in the UK this financial year saw unrelated living donor kidney transplants as a result of both altruistic living kidney donation and paired donation (or exchange). In 2007-2008, there were 4 paired donations (2x2 transplants) and 6 altruistic donors (UK transplant figures).

Figure 2 **Deceased donor kidney programme in the UK, 1 April 1998 - 31 March 2008**
Number of donors, transplants and patients on the active transplant list at 31 March

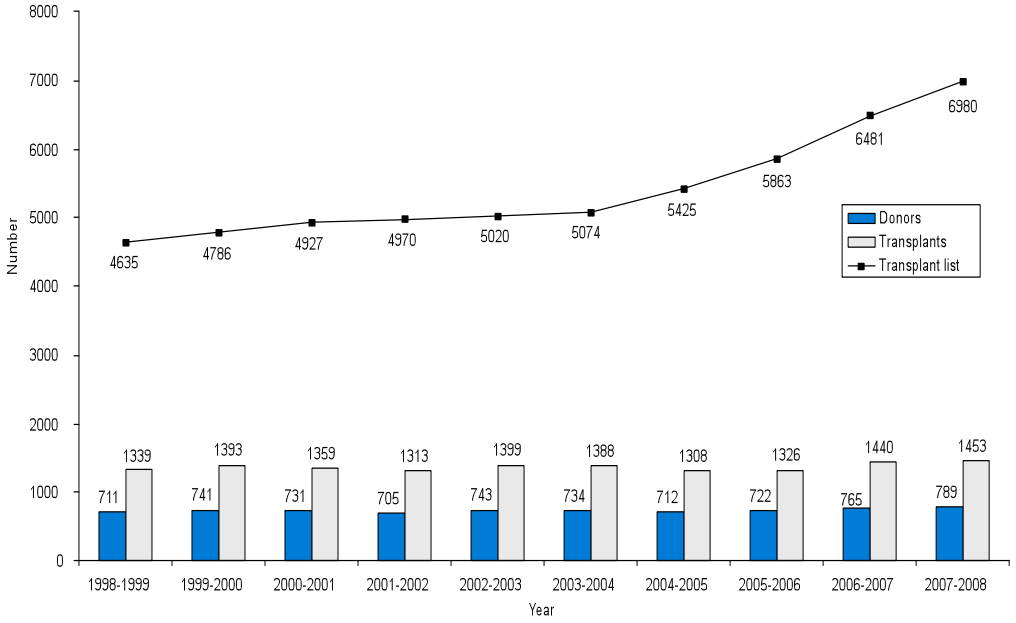
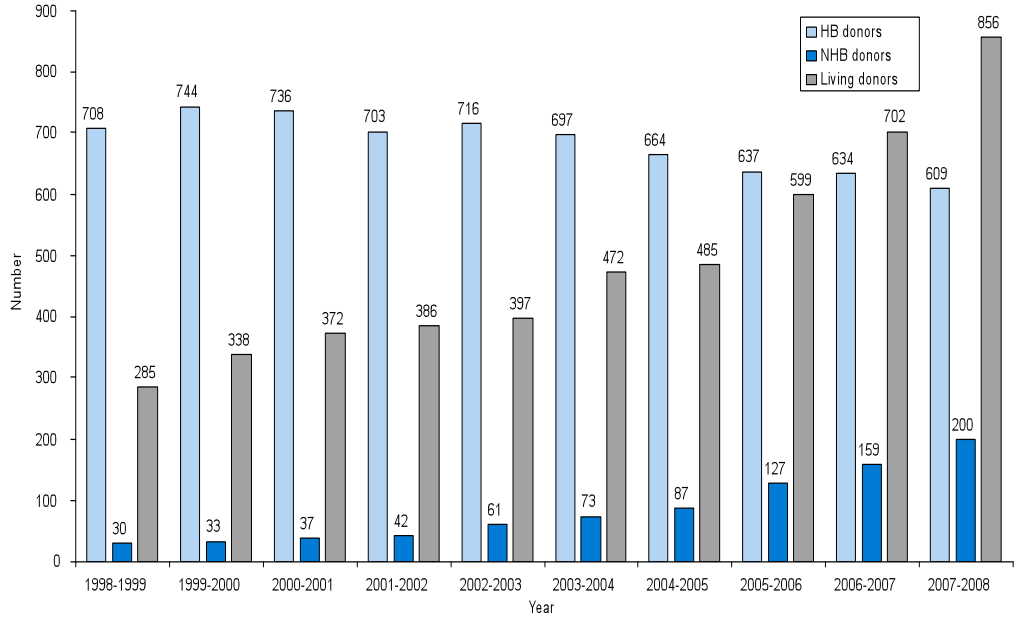


Figure 3 **Number of deceased and living donors in the UK, 1 April 1998 - 31 March 2008**



The increase in UK activity can be attributed to a number of factors including improved patient awareness, innovative surgical techniques with minimally invasive/laparoscopic nephrectomy surgery to minimise donor morbidity and acceptance that outcomes from living unrelated donors are equal to traditional genetically related sibling/parental pairings[11]. In addition, there has been increased funding for living donor programmes from the Department of Health via UK transplant, which has facilitated the appointment of dedicated living donor co-ordinators in transplant centres nationwide.

The main objections to living kidney donation are associated with the welfare of the donor; both through exposure to major surgery, which is not required for the purposes of improving the health of the donor, and the long term concerns of life with a solitary kidney.

1.3 Benefits and risks of live kidney donation

The benefits of live kidney donation are[11]:

1) The need for cadaveric donor kidneys far exceeding the supply.
2) The better kidney quality from living donors due to shorter ischaemia time, the lack of agonal phase and cytokines release that follow brain death.
3) The continuing improved results of kidney transplants from living donors in comparison with those from cadaveric donors in the cyclosporine era also. This appears to be true also for kidney transplants from unrelated living donors in spite of often complete incompatibility with recipients.
4) Pre-emptive transplantation, based on living donors, not only avoids the risks, cost and inconvenience of dialysis, but is also associated with better graft survival than transplantation after a period of dialysis, particularly within the live donor cohort.

Its risks are:

1) A healthy individual has to undergo a major operative procedure, and is exposed to the associated mortality and morbidity of a donor nephrectomy.
2) Long-term follow-up in kidney donors has shown that mild, non progressive proteinuria develops in about 33% and that the frequency of hypertension may increase[12].
3) Kidneys procured from live donors do not possess a Carrel aortic patch, which makes them technically more challenging to implant.
4) Financial loss to both the donor and the employer from time off work.
5) The ethical issues associated with donation, particularly from individuals without purely altruistic intentions.

1.4 Graft survival

Renal transplantation using grafts from live donors give superior results when compared to cadaveric and non-heart beating grafts. This could be attributed to shorter ischaemic times. The initial function rates for non-heart beating donor grafts, heart beating donor and live donor transplants are 6.5%, 76.3% and 93%[8] respectively. The one, three and five year survival rates of live donor grafts are 94-97%, 87-95% and 78-86% compared to 88-97%, 75-76.5% and 64-75% for cadaveric grafts[8, 13-16] respectively. This compares with a five year survival of 46-79% for NHBD grafts[8, 17.] Despite improved graft function, this does not confer improved patient survival[15] . Initial graft function rates are highest in live donor grafts (93% vs. 77% cadaveric vs. 7% non heart beating), and primary graft non function rates lowest (2% vs. 3% cadaveric vs. 7% non heart beating)[8] .

1.5 Mortality and Morbidity

Set against the undoubted advantages of live donor kidney transplantation is the necessity for the donor to undergo a major surgical operation entirely for the benefit of another individual, albeit a loved one with a debilitating chronic illness. The overall mortality in series of 3000 to 10,000 donors in the USA has been quoted to be 0.03% - 0.06%[17] . The most common causes of death were pulmonary embolism, myocardial infarction and cardiac arrhythmia. Overall, at least 17 live donors in the USA have died from causes relating to their nephrectomy. Severe complications occur with a frequency of 0.23%-4.4% (pulmonary embolus, re-operation secondary to bleeding, pneumothorax, splenic injury), and less severe complications in up to 15% (wound infection, chronic pain, incisional hernia)[18]. There have been at least two peri-operative deaths in the UK[19]. One was due to myocardial infarction and one due to pulmonary embolus.

Long – term morbidity is more difficult to quantify due to the selected population of medically fit donors, and for this reason live renal donors have better long-term survival, and lower incidence of end-stage renal failure than the general population[20]. Unilateral nephrectomy has been shown to increase systolic and diastolic blood pressure marginally, but, whether or not it increases the prevalence of hypertension in these groups is debated[21-24], but when compared against sibling controls, there is no increase [24]. It is also associated with non-progressive microscopic proteinuria[21, 24], and an initial decrease in glomerular filteration rate (GFR). However, the GFR improves steadily after this expected initial fall, and progressive deterioration in renal function does not occur [21].

Traditionally live donor nephrectomy was performed through a large incision in the loin, with removal of the twelfth rib (figure 4). This provided surgeons with excellent access to the kidney and its blood supply and this operation was believed to be very safe. Nonetheless, there is significant morbidity from flank incisions. Long term wound complications are common, with incisional hernia / bulge (figures 5, 6) occurring in 7%[25] , and significant bother relating to wound pain in 25%. These hernias are often impossible to repair and usually cause pain throughout the donor's life. This surgical approach was only abandoned in the UK in the last five or so years. Another study reported patient dissatisfaction in scar location (11.5%), unsightliness of scar (9.6%), and length of scar (5.8%) [26]. Of donors undergoing flank incisions, 86% of donors state that the decision to donate was their own, and less than 1% of donors regretted their donation. However, 34% stated that they took between 3 and 4 months to get over the procedure, 5% stating that they had never recovered fully [27].

The minimal incision open approach emerged as a less invasive alternative to the traditional flank incision. This is performed either by a loin incision, or by a shorter, laterally placed subcostal incision. A retroperitoneal approach is maintained, and rib resection is not required. (Figure 7). This modified technique has been shown to have benefits in terms of reduced analgesic requirements, shorter incision length, and shorter inpatient stay compared to the traditional operation [28]. Despite this improvement to technique, major open surgery remains a considerable disincentive to potential donors, particularly those who are in employment or have a young family to care for. Better alternatives were therefore sought.

1.6 Laparoscopic live donor nephrectomy

Laparoscopic donor nephrectomy (LDN) was introduced in the hope, of reducing some of the disincentives of live kidney donation. Since the initial report from Johns Hopkins Medical Centre in 1995 LDN has been widely adopted as the standard surgical approach by many transplant units worldwide [29]. LDN appears to be superior to the open approach with respect to postoperative pain, hospital stay and recovery time [30-33]. Laparoscopic and open donor nephrectomy have similar incidence of complications at around 1-2% [34]. The first procedure was performed on a forty-year-old male, as a purely laparoscopic procedure. The graft was removed via a 90mm infraumbilical incision and functioned immediately in the recipient. The donor was discharged on the first postoperative day [29]. Since then, LDN has enjoyed increasing popularity, with 84% of the US centres offering the procedure by 2000 [35], and over 200 centres worldwide offering the procedure [36]. This approach has been embraced less enthusiastically in the UK, with only 21% of UK centres performing live kidney transplants offering LDN in 2002 [37]. This is in part, due to lack of level one evidence of the benefits and safety of the procedure, and also the technical difficulty of performing this approach.

Two randomised trials of pure LDN versus the open procedure have been published to date [38, 39]. The first of these was a study of eighty donors, and failed to show significant benefit, lacked detailed donor / recipient outcome, and had a high rate of splenic injury (5%) in the laparoscopic group. This is in stark contrast to several other studies with either historical control groups, or non-randomised series. These have consistently demonstrated shortened inpatient recovery, less analgesic use, shorter hospitalisation, better cosmetic outcome, reduced blood loss, and more rapid return to normal activities compared to the open technique[40, 41]. These findings were supported by the second randomised trial, which compared 100 donors, and found that the

laparoscopic procedure was associated with less post-operative pain, shorter hospitalisation, less blood loss, and yet with comparable complication rates. The authors also concluded that the laparoscopic group had suffered less physical fatigue, and better physical function at one year post nephrectomy. However, these benefits were at the expense of a longer procedure, and significantly longer first warm ischaemic time [39].

Two additional randomised trials have compared a hand-assisted laparoscopic technique versus the open [42,43.] These concluded that donors undergoing hand-assisted LDN had a reduction in analgesia requirements, shorter hospitalisation, and shorter recovery. However, this was at the expense of a longer, more expensive procedure, shorter graft vessel length, and a prolonged first warm ischaemic time. More concerning was the 8% major complication rate of LDN in the Norwegian series[43]. These donors all required re-operation.

The impact of LDN on live donor activity in the US has been marked. In one major US transplant centre, the implementation of a formal live donor education programme, and introduction of LRD has doubled the number of live donor transplants performed [44]. Up to 25% of donors 2 years after the introduction of the new technique stated that they would not have donated if the open procedure was the only option [45].

The operative cost of LDN is greater than ODN (£1000 more), but when shortened hospitalisation and faster return to work are undertaken into consideration, overall costs are lower than ODN [46,47] . Additionally, when increased donor rates and a reduction in patients requiring dialysis are considered LDN begins to look like an attractive option.

1.7 Concerns over laparoscopic approach

The most pressing concerns regarding LDN are first, its safety for the donor, and the remainder, whether graft quality is compromised.

Major intra-operative complication rates are quoted at 2%, these consisted mainly of vascular injury (86%), the remainder bowel injury. Minor injuries occurred in 6.8%, including uncomplicated splenic laceration, liver laceration, pneumothorax, diaphragmatic injury, conversion for obesity, stapler misfire, airway difficulties, difficult extractions, cardiac arrhythmia and retained fragment of retrieval bag. Overall conversion rates are 1.6%, usually for haemorrhage [31]. Major post-operative complication rates are quoted as 2.3%. Complications include small bowel obstruction requiring re-operation, pancreatitis, retroperitoneal haematoma, atrial fibrillation, pneumonia and sepsis / ARDS, in descending order of frequency. Minor complications occurred in 16%, including atelectasis, pulmonary oedema, urinary retention / infection, epididymitis, ileus, incisional hernia, thigh numbness, back pain, upper airway oedema, late depression, pleural / pericardial effusion and abdominal pain [31].

A meta-analysis of comparative studies performed in 2003 commented that non-standardisation of reporting or grading of complications made comparison difficult between laparoscopic and open techniques. Quoted complication rates of 0-30% for LDN, and 0-35% for ODN illustrate this, however, none of the studies examined quoted statistically different complication rates between the two procedures [48].

Prolonged CO_2 pneumoperitoneum at 15mmHg or above has been shown in animal models to decrease renal blood flow by up to 70%, and potentiate renal dysfunction [49, 50].

This decrease in renal perfusion can be corrected with intraoperative intra-venous fluid administration, but calculated creatinine clearance remains impaired despite these measures[50]. These effects are temporary in the donor, but there is concern whether this insult, combined with laparoscopic manipulation, injures the donor organ, or even predisposes it to an increased risk of rejection[49, 50,51].

Laparoscopic technique prolongs the first warm ischaemic time from an average of 2 to 4 minutes. This probably accounts for the slight compromise in the immediate graft function with laparoscopically retrieved kidneys. This manifests itself as a higher serum creatinine at the time of discharge (49.2% VS 44.9% with serum creatinine greater than 1.4mg.dL. p=0.002). However, this effect seems to be temporary, with graft function at one year identical to that of kidneys retrieved from open nephrectomy[52, 53]. No differences in the rejection rates between the two approaches have been observed[53]. Long term graft function and graft survival comparative data is yet to be produced.

Initially, there was concern over the significant increase in the incidence of ureteric complications in recipients of laparoscopically retrieved renal allografts[54, 55]. This was thought to be secondary to denudation of the blood supply, following dissection and clip application prior to division. Fortunately this trend was reversed by a change in technique, involving a wider periureteric dissection (including the gonadal vein), and use of an endovascular stapling device[54]. With the introduction of this modification, ureteral complication rates between LDN and ODN are now comparable[31, 54-57]. Ratner *et al* also noted that the ureteric complication rate rose after introduction of the endocatch bag system for delivering the kidney from the abdominal cavity. This was thought to be secondary to the closure of the drawstring around the incompletely contained ureter, resulting in a denuding crush injury. Once this was recognised, ureteric complication rates were comparable to open procedure[57].

After initial resistance, right laparoscopic donor nephrectomy has emerged as an equivalent to the left sided procedure, and has the advantage of a shortened operative time[58-60]. This is at the expense of renal artery and vein length (up to 15mm loss of vein length if a linear stapler is used at the caval border), and hence a more technically challenging implantation[55, 61]. However, no differences in rates of vascular complications in the recipients have been noted[58-60]. Techniques have been described to overcome both of these problems. The use of a laparoscopic modified Satinsky caval clamp, minimises renal vein loss, but requires the cut border of the vena cava to be oversewn laparoscopically[61]. This is technically difficult and has the potential for catastrophic blood loss if the clamp slips. Interaortocaval renal artery dissection has also been described for enhancing renal artery length[62], but again carries potential risk of haemorrhage. Circumaortic left renal vein, which is present in 9% of donors, does not preclude left laparoscopic donor nephrectomy[63], the posterior limb is commonly the smaller limb and can be sacrificed without complications.

Recipient vascular and ureteric complication rates have been noted to be higher whilst the procedure was in its inception in those institutions[31, 55,57]. This learning curve effect has been noted in other laparoscopic procedures, and is inversely related to the number of cases performed[64]. Operative exposure to the procedure has been a more important factor, with a clinically measurable improvement in trainees after as few as 13 cases as participant, or 6 as operative surgeon (hand-assisted laparoscopic donor nephrectomy) [64]. This effect is independent of trainee experience, which highlights the need for either a period of observation / assistance in an experienced centre, or the presence of an experienced mentor. Ideally LDN should be performed with two proficient laparoscopic surgeons, as this has been shown to decrease both blood loss and operative time[65]. The reduction in operative time is is especially desirable in the setting because of the aforementioned concerns over the prolonged pneumoperitoneum[49, 50].

1.8 Donor Evaluation

The primary goal of the donor evaluation process is to ensure the suitability, safety and well being of the donor. This involves the identification of contraindications and unreasonable medical risks. In order to avoid important omissions, the evaluation of potential donors should be carried out according to an agreed, evidence-based protocol with which the donor assessment team is fully conversant. Investigations should be undertaken in a logical sequence so that the potential donor is protected from unnecessary procedures, such as invasive vascular imaging, until the appropriate time in the course of the assessment. There is good agreement regarding the routine screening tests that should be performed[66-68]. If several potential donors come forward, then all are tested for blood group compatibility and briefly assessed as to their suitability as a donor. HLA matching is then performed to select the best-matched individual. Once matching has selected the first choice donor, they are subjected to a full medical and social history, and a thorough physical examination. Blood pressure measurements are taken on three separate occasions, and any borderline values are investigated with 24 hour monitoring. In our centre, controlled hypertension is not considered a contraindication to donation as long as there is no evidence of end organ damage e.g. left ventricular hypertrophy on ECG and echocardiogram. Blood samples are taken for laboratory analysis (U&E, LFT, bone profile, glucose, FBC, HIV, Hepatitis B and C, syphilis, toxoplasma, CMV and EBV screening), and urine samples are tested for blood, glucose and protein.

A standard chest x-ray and 12 lead electro-cardiogram are also performed at this stage. Provided these tests and examination are normal, detailed imaging of the kidneys, their vasculature and collecting system are obtained. This information is most commonly obtained with spiral computed tomographic angiography and a delayed abdominal scout film, which confirms the

presence of two kidneys, their position, absence of pathology, and details of the renal vascular anatomy. Left kidneys are harvested preferentially due to their longer renal vein. In the presence of multiple renal arteries or complex venous anatomy on the left side, the right kidney is harvested. If there is bilateral duplex arterial supply, or bilateral complex venous anatomy, then a DMSA split function nephrogram is obtained, and the kidney with least function is removed for transplantation. It is a rare occurrence that the vascular anatomy is so complex in both kidneys that it is technically unsafe or unwise to proceed to donation.

The most common reasons for not accepting a donor, in descending order, are ABO blood group incompatibility, hypertension and / or renal disease, unwillingness of the donor to proceed, heart / lung disease, obesity, latent diabetes, or death of the recipient during work up[69].
Disincentives often cited by donors and potential donors are the risks of surgery itself, post-operative pain, prolonged hospital stay and recovery, potential loss of earnings due to time off work, long term risks of unilateral nephrectomy, long term morbidity from the surgery, and concerns that they would not be able to donate to one of their children, should this be necessary at some point in the future[45].

1.9 Surgical Techniques

Donor nephrectomy, traditionally is performed via a muscle-splitting flank incision, with the patient in a lateral decubitus position. A table bridge is implemented to open the space between the iliac crest and the subcostal margin. The incision is made overlying the twelfth rib and extended towards the umbilicus (approximately 150mm). Partial excision of the twelfth rib maybe performed to enhance exposure (figure 4).

On entering the retroperitoneal space, care is taken to preserve the integrity of the peritoneum, and is swept forward to expose the kidney and its surrounding Gerota's fascia. This fascia can be removed with the kidney '*en-bloc*' or can be incised, peeled away from the renal capsule, and left *in-situ*.

The operative procedure is maintained with retractors, and the ureter is identified at the lower pole of the kidney, slung and mobilised distally, ensuring that the ureteric blood supply is not disrupted. The renal vein is then identified as the most anterior structure at the renal hilum, slung, mobilised, and its tributaries, controlled, ligated and divided. The superior mesenteric artery, passing anteriorly over the vein as it descends from its origin, limits mobilisation of the left renal vein medially.

The renal artery is situated directly posterior to the vein, and is mobilised in a similar manner back to its origin at the aorta. Commonly, there is a small adrenal branch that needs to be controlled at this point. It is important not to dissect the renal artery at the renal hilum as the ureteric arterial branch may be damaged, rendering the ureter devoid of a blood supply.

Once the vessels have been isolated, the kidney is freed from its posterior retroperitoneal attachments; the ureter is ligated at the pelvic brim, divided and then decompressed with a small incision in its side wall. The renal artery, followed by the vein, are double ligated, and divided.

Ties are placed as far proximally as possible on the renal vessels to try and preserve maximal length for the anastomoses in the recipient.

Once the kidney is removed, it is immediately perfused with hyperosmolar citrate preservation fluid at 4^0C until the effluent runs clear (approx 500ml), and placed in a bath of iced preservation fluid. Typically one surgeon will perfuse the kidney whilst another inspects the renal bed and vascular pedicles for bleeding. The ligated vessel stumps are over sewn with a non-absorbable synthetic suture, and an absorbable subcuticular suture is placed in the skin.

A variation of the traditional open approach is via a more lateral placed incision, without resection of the tip of the twelfth rib (figure 7). This gives comparable operative exposure, but is associated with less post-operative pain and less wound morbidity[28].

Laparoscopic donor nephrectomy was first introduced in 1995[29]. The left laparoscopic nephrectomy is performed via a transperitoneal approach, with the patient in a modified left lateral decubitus position, again with a table break to open the space between the iliac crest and the costal margin (figure 8). A pneumoperitoneum is established with a Veress needle, placed at the level of the umbilicus, at the edge of the rectus sheath (on the same side as the kidney being removed), and the peritoneal cavity insufflated to a pressure of 15mmHg. Four ports are inserted for dissection, 2x12mm ports in the midline (above/below the umbilicus and 2 fingerbreaths below the xiphesternum), 1x12mm port at the insufflation site, and a 5mm port is inserted in the mid-axillary line, midway between the costal margin and the iliac crest (figures 8,10). The umbilical port is used to house the video laparoscope; the epigastric and iliac ports are used for dissection instruments. The colon is mobilised by dissection of the splenic / hepatic flexure, and division of the lateral peritoneal reflection. The colon is then retracted medially to expose the Gerota's fascia, which is incised to expose the underlying kidney. The hilum is exposed to reveal the renal vein anteriorly, and more inferiorly, the upper ureter. Great care must be taken to

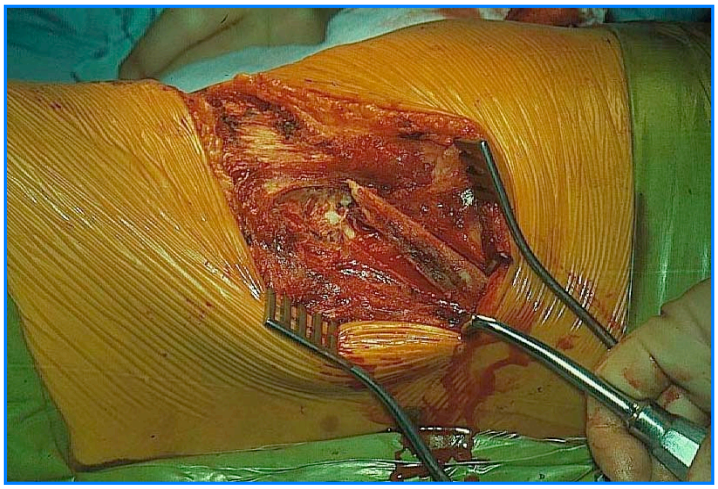
preserve the ureteric branch of the renal artery at the renal hilum. The ureter is dissected first, taking care to include the gonadal vein during mobilisation in order to maintain a good margin of peri-ureteric tissue. The ureter is followed to the pelvic brim, where it is divided with an endosvascular stapling device, and decompressed with a cut in the sidewall. The renal vein is then dissected free, and its gonadal, lumbar and adrenal tributaries secured with metal clips and then divided. The renal artery is dissected back to its origin from the aorta and topical papaverine is applied to relieve any vasospasm. The remaining fascial attachments are divided to free the kidney.

The kidney is then manouvered into an endocatch retrieval bag (Tyco Healthcare Ltd, Gosport, UK), inserted via a short Pfannensteil incision (figure 9). The pneumoperitoneum is maintained with a pursestring suture in the peritoneum. The renal artery and vein are divided using an endovascular stapling device, and the kidney removed via the Pfannensteil incision in the endocatch bag. The explanted kidney then has its staple lines excised, and is perfused in an identical manner to that for an open procedure. The purse-string suture is then tied, and the pneumoperitoneum re-established to inspect the renal bed. The Pfannensteil incision is then closed with a non-absorbable continous suture to the rectus sheath, and a sub-cuticular absorbable suture to the skin. Port sites are closed with interrupted absorbable sutures to the muscle/fascia, and non-absorbable interrupted skin sutures.

Right laparoscopic donor nephrectomies sometimes requires a modified approach to secure the renal vein. Port placement is a mirror image of that for the left side, and the technique for renal dissection remains unchanged. Once mobilised, a 6-10cm transverse incision is made in the right upper quadrant instead of a Pfannensteil, and control of the vena cava is maintained with a partially occluding vascular clamp. This allows the full length of the relatively short right renal

vein to be removed with the kidney. In these patients, the kidney is retrieved via the RUQ incision.

Kidneys are transplanted into the recipients via an extraperitoneal approach in the iliac fossa (figure 11). The vein is anastomosed end-to-side to the external iliac vein, and the artery is anastomosed end-to-end with the divided internal iliac artery. In those cases with multiple arteries, suitable branches of the internal iliac artery are utilised for anastomosis. The ureter is spatulated and anastomosed to the bladder as an extravesical onlay, over a double J stent.



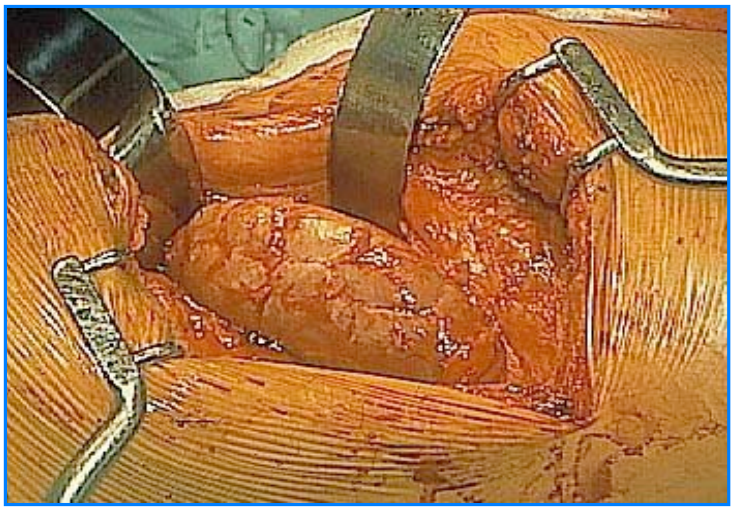


Figure 4 – Open donor nephrectomy with partial resection of 12th rib

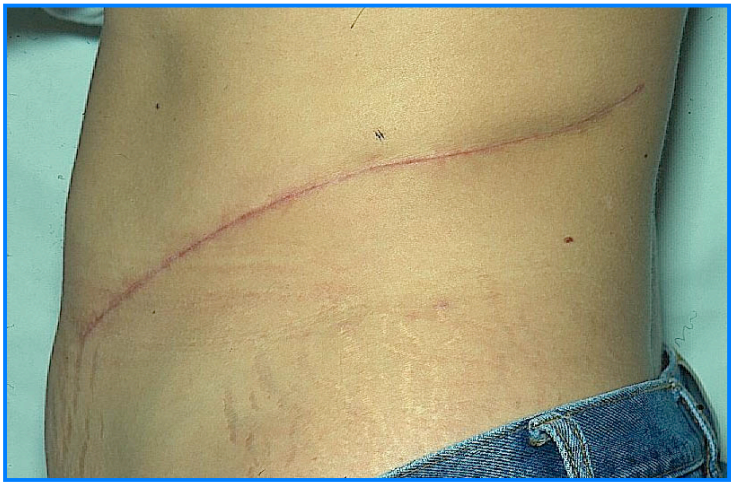


Figure 5 – Loin scar after open donor nephrectomy with rib resection

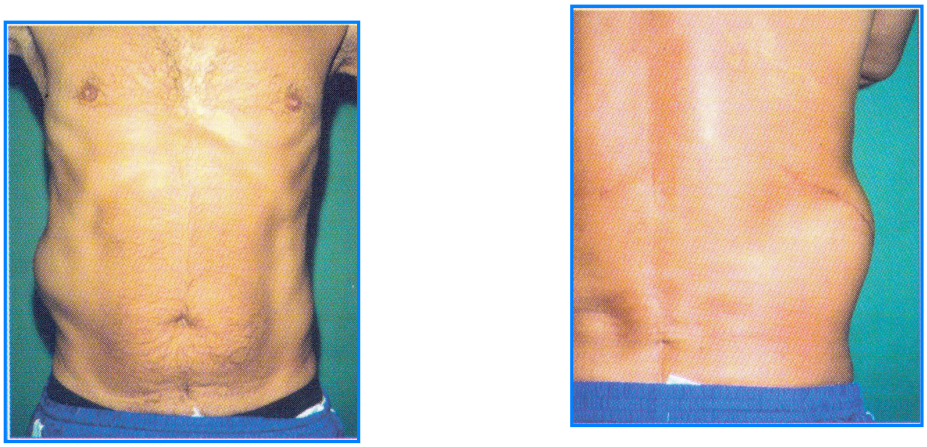
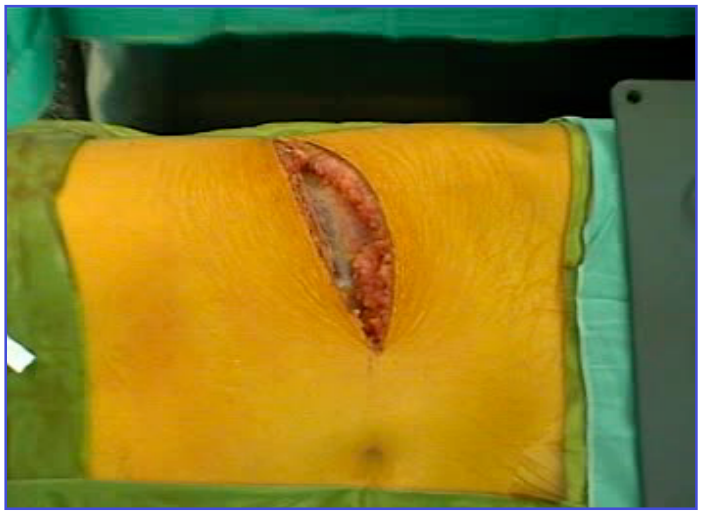


Figure 6 : Loin hernia (flaccid paralysis of the muscles) after open donor nephrectomy with rib resection



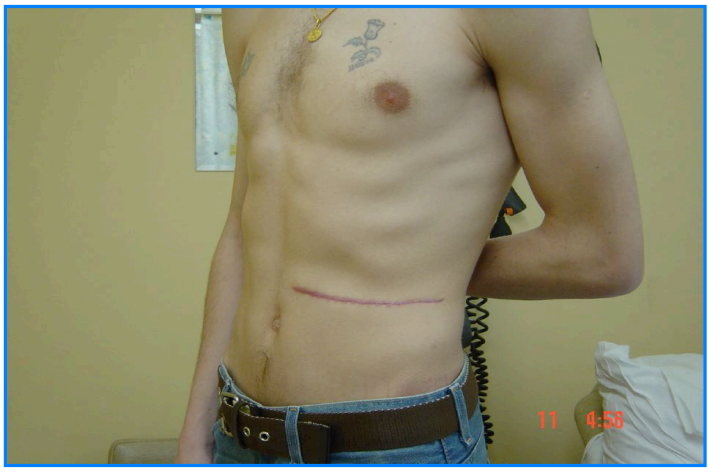


Figure 7: ODN without 12th rib resection

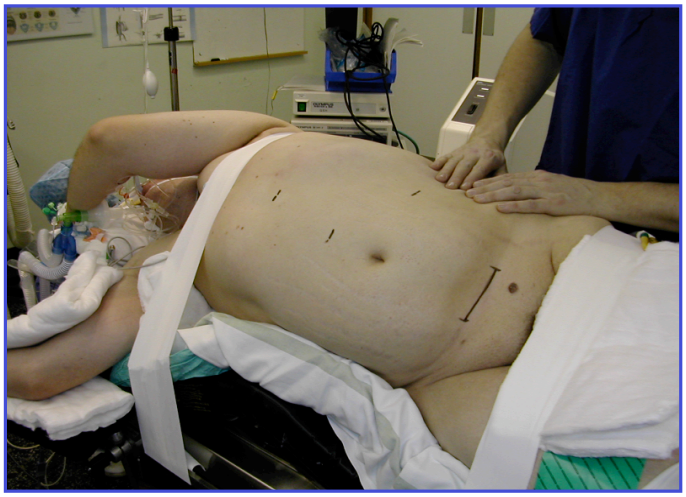


Figure 8 – Lateral decubitus position for left laparoscopic live donor nephrectomy, port sites and Pfannensteil incision marked

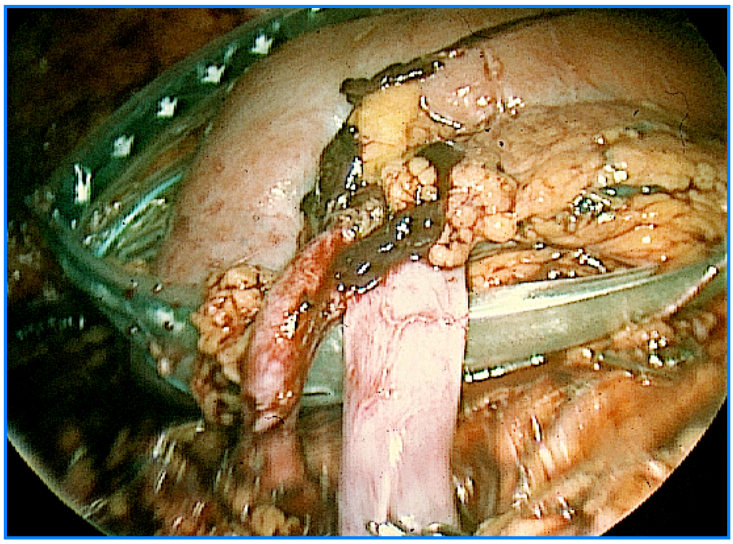
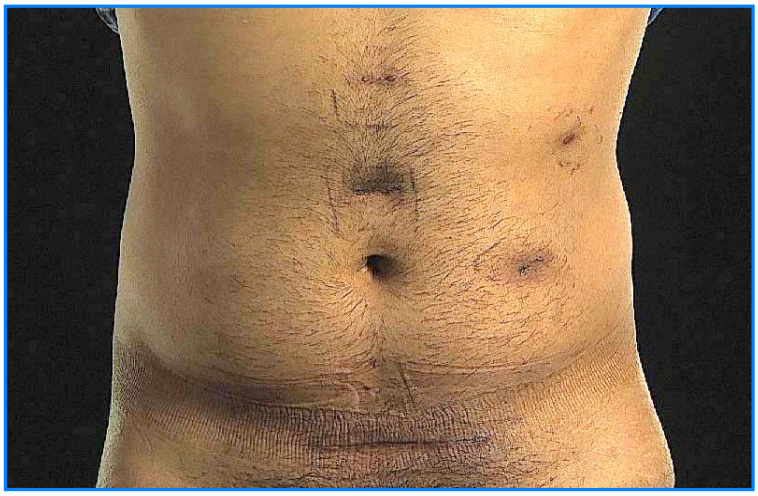


Figure 9 – Retrieving the kidney laparoscopically with endocatch



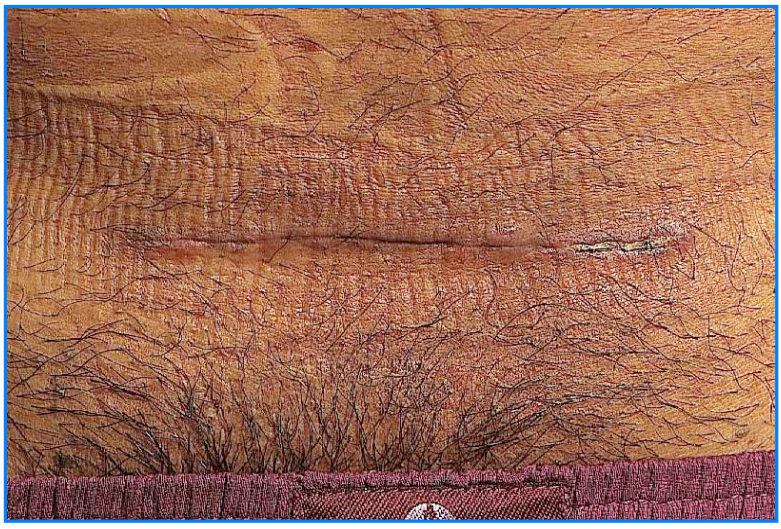
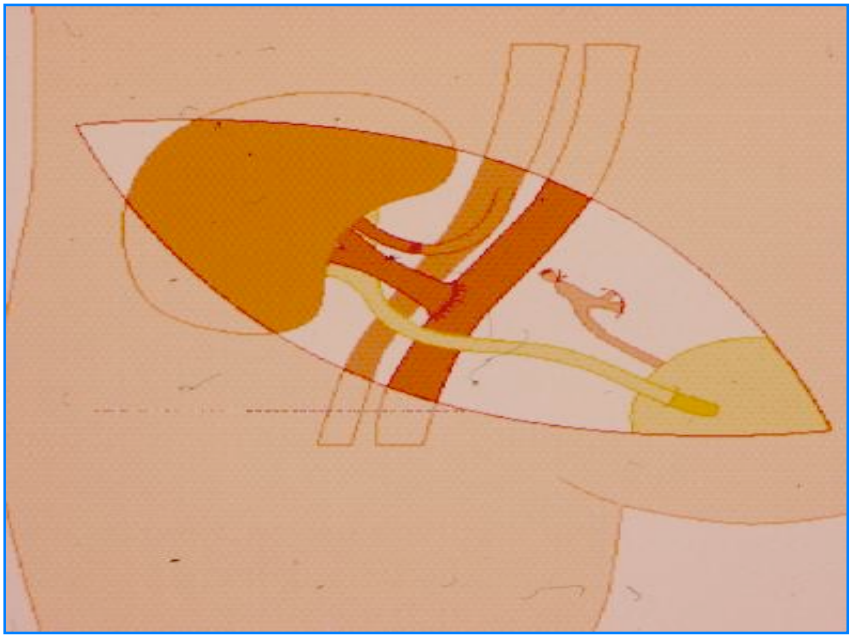


Figure 10 – Laparoscopic live donor nephrectomy incisions – 4 laparoscopic port sites and supra-pubic retrieval incision



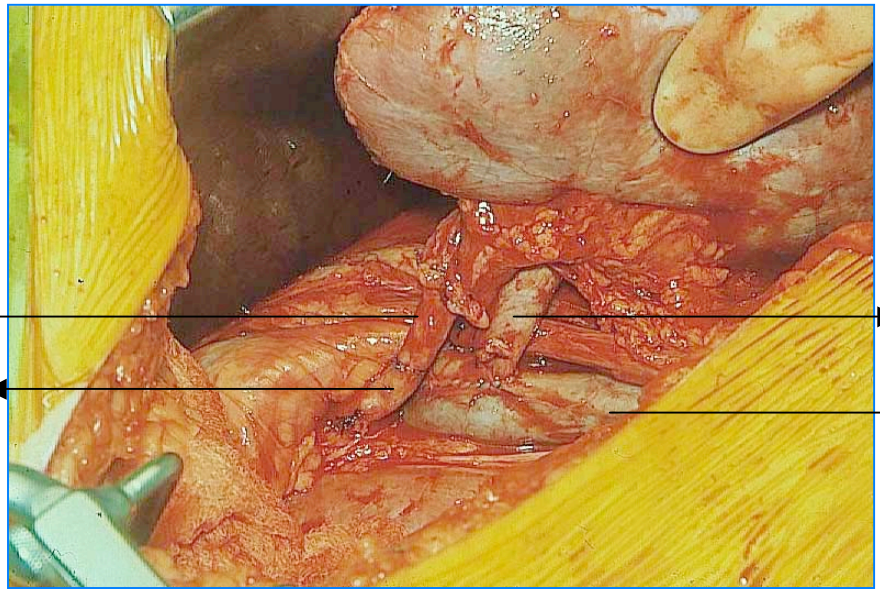


Figure 11 – Recipient renal transplant

1.10 Other new techniques

Hand-assisted laparoscopic donor nephrectomy is a variation of the pure laparoscopic procedure, where an airtight sleeve is utilised to allow one of the operators' hands direct access to the peritoneal cavity during dissection and retrieval. It has been shown to have the same advantages as the pure laparoscopic procedure compared to the open technique, but with the potential benefit of greater control over the vascular pedicle, shorter warm ischaemia, a shortened operative time when compared with the purely laparoscopic procedure[42, 70-73]. It is also considered to be an easier procedure to learn, especially to those with limited laparoscopic experience[70]. Potential disadvantages are the less cosmetic, commonly used peri-umbilical midline incision, pneumoperitoneal CO_2 leakage from the sleeve, and 'forearm claudication' in the surgeon.

A retroperitoneal laparoscopically assisted technique has been described, which potentially allows donor nephrectomy to be performed via a shorter sub-costal incision. The largest series reported by Yang et al, stated significantly shorter recovery, less analgesic requirements, and a shorter incision compared to the standard open donor nephrectomy[74]

Wadstrom *et al* has developed a technique combining hand-assistence with a retroperitoneal approach, arguing that this has the advantages of being able to control sudden haemorrhage but o might also protect against bowel injury by avoiding breaching the peritoneal cavity[75].

CHAPTER TWO: REVIEW OF THE LITERATURE

2.1 Effects of laparoscopic and open nephrectomy on donor postoperative recovery

The attraction of minimally invasive nephrectomy using laparoscopic methods is that this will reduce the surgical insult and so has the potential for more rapid donor recovery rates. This might result in shorter in patient stay, less postoperative pain and a quicker return to normal activities, including full time employment. At the same time, these advantages would have to be achieved without compromising the outcome of the recipient kidney transplant operation. In this section, the evidence in the peer-reviewed literature relevant to these concerns will be reviewed.

Various levels of evidence are available in the published literature (Table 2.1).

An objective systematic review of level II to IV has been published (Merline *et al*, 2000) [87] and since this time, higher-level evidence has become available. Considering this, in the short review presented here only the best evidence (Level I) will be considered.

Four randomized controlled trials have been published to date (Wolf *et al*, 2001[42]; Simforoosh *et al*, 2005[92];Øyen *et al*[43], 2005; Kok *et al*[39], 2006). The last two of these contain data addressing donor quality of life, which was separately published from the original Øyen trial by Andersen *et al* (2007) [104]. The quality of life aspects will be discussed later. The Wolfe[42] trial compared hand-assisted laparoscopic nephrectomy (n=35) with and open donor nephrectomy performed through a retroperitoneal loin incision without rib resection (n=35). Donors undergoing the hand assisted laparoscopic operation required less postoperative morphine (mean ± SD = 59±62 vs 111±96 mg; p=0.004), had a shorter postoperative stay (1.7±0.9 vs 2.6±0.7 days; p=0.0001) and returned to work more

Table 2.1: Hierarchy of research evidence

Level	Descriptor
I	Systematic review of all available randomised controlled trials
II	Evidence from at least one properly designed randomised controlled trial
III-1	Evidence from pseudo-randomised controlled trials (alternate allocation or some other not entirely random allocation)
III-2	Evidence from comparative studies with concurrent controls (non -randomised), case-control studies or interrupted time series with a control group
III-3	Evidence from comparative studies with historical controls, two or more single-arm studies or interrupted time series without a control group
IV	Evidence from case series

quickly (median 33 vs 43 days; p=0.037) when compared to donors in the open nephrectomy group. The operative time (206±32 vs 125±36 min; p=0.0001) and the warm ischaemia time to the kidney (183±122 vs 96±57 seconds; p=0.0001) were, however, longer in the laparoscopic operation compared to open surgery. There were no statistically significant differences in transplant failure or transplant renal function in the first 3 months between the two groups. The mean hospital cost of the laparoscopic operation was, however, 24% more expensive than the open operation. This study had some disadvantages. The sample size is relatively small and a significant number of patients were excluded. This means that the external validity was poor. In addition, much of the subjective recovery data were obtained by telephone interviews performed retrospectively.

The study reported by Simforoosh *et al* (2005) [92] from Iran compared the outcome of traditional open nephrectomy through a loin incision and without rib resection to laparoscopic nephrectomy (n=100 in each group). Although the latter method was not hand assisted during the dissection, the kidney was removed by hand through an 8-10 cm suprapubic incision. There were no differences in hospital stay between the two groups (mean open vs laparoscopic = 2.2 vs 2.26 days). Furthermore, there were no differences in parenteral analgesic requirements during hospitalization between the two groups. Donor satisfaction was scored using a 20-point linear analogue scale. The satisfaction score was higher following laparoscopic nephrectomy (19.6±1.0 vs 17.3±3.5; $p<0.001$). Donors in the laparoscopic group started driving their cars sooner (mean 11.6 vs 20.8 days; $p=0.004$) and returned to 'heavy activities' sooner (mean 34 vs 56.5 days; $p=0.002$) compared to the open operation donors. The operating time and warm ischaemic time were longer in the laparoscopic group but there were no differences in renal function or transplant survival in the recipients of kidneys removed laparoscopically or by open operation. Although this trial contains a large number of patients there is no description of the method of randomization and no postoperative pain scores. The data relating to postoperative analgesia does not mention which drugs were used. Finally, some outcome data was obtained by telephone interviews performed some time after discharge from hospital and this might affect the reliability of the recovery results presented.

The study published by Øyen *et al* (2005) [43] included 122 live donors randomized in an approximately 1:1 ratio into open (n=59) and laparoscopic groups (n=63). Further data from this trial was reported in a later publication examining donor postoperative pain in more detail (Andersen *et al*, 2006) [105]. The reason for this slight discrepancy in the numbers in each group was not discussed in the paper and the method of randomization was not described. Furthermore, only patients with single renal arteries who were donating the left kidney were included in the study. The issue with the left kidney is that it has longer blood vessels than

the right-sided kidney and this makes the left kidney easier to transplant. Open operations were performed through a conventional retroperitoneal flank incision without rib resection. There were some differences in the laparoscopic approach compared to previous studies. The kidney was removed through a midline incision in each case but for the last 46 cases, this was done by introducing a hand into the abdomen in the final stages of the operation. The Øyen study (2005) [43] showed no differences in hospital stay (laparoscopic vs open mean stay = 6.2 vs 6.7 days) but lower analgesic requirements in the first two days after surgery in the laparoscopic group (mean = 28.1 vs 36.4 mg morphine; p=0.016). Again, the first warm time (4.3 vs 1.4 min; p<0.01) and the total operative time (180 vs 140 min; p<0.01) were longer in the laparoscopic group. There was a relatively high incidence of serious complications in the laparoscopic operations in this series. There were two major haemorrhages from the renal artery during kidney retrieval and five re-operations: two for bleeding, one for a retained swab and two for intestinal perforation. The major complication rate following laparoscopic surgery was therefore 8% and the authors called into question the safety of this operation especially in obese patients who were more likely to have complications. There were no major complications in the open surgical group. An important disadvantage of this study was that recipient outcome was not analysed in any detail.

The fourth published randomized trial studied a total of 100 live donors in two separate centres in Holland (Kok *et al* 2006)[39]. The laparoscopic operation was without hand assistance but the open operation was different from previous work as it was through a 'mini incision' measuring some 10-12cm. As with the other trials warm time and operating time was longer in patients undergoing laparoscopic surgery. In terms of donor recovery, in-patient stay was shorter in the laparoscopic group (3 vs 4 days; p=0.003) and the laparoscopic donors required less postoperative morphine (median 16 vs 25 mg; p=0.005).

The methodological quality of clinical trials is most widely assessed using the Jadad Scoring system (Jadad *et al*) [106]. This is based on answering the following seven questions:

1. Was the study described as randomized (this includes words such as randomly, random and randomization)?
2. Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated etc)?
3. Was the study described as double blind?
4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy etc)?
5. Was there a description of withdrawals and dropouts?
6. Was the method used to generate the randomization sequence described but inappropriate (e.g. patients allocated alternately, or according to date of birth, hospital number etc)?
7. Was the study described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet with injection with no double dummy)?

The first five items on this list are indicators of good quality and score one point if the answer is yes. If the answer to any of these questions is no then that item scores zero. The two final questions address indicators of poor quality and if these are answered as yes then one point is subtracted from the overall score for the trial. If the answer to these is no then the score is zero. This means that the range of possible scores is from zero to five, with five representing the best quality trial.

Table 2.2 shows the Jadad scores achieved by the four randomized trials discussed using the system described.

Table 2.2 Jadad Scoring of four published randomized controlled trials

Question No.	1	2	3	4	5	6	7	Overall Score
Wolf *et al*, 2001	1	0	0	0	1	0	0	2
Simforoosh *et al*, 2005	1	0	0	0	0	0	0	1
Øyen *et al*, 2005	1	0	0	0	0	0	0	1
Kok *et al*, 2006	1	1	0	0	1	0	0	3

The overall quality of these trials doesn't appear to be very high using the Jadad scale but this is in part due to the fact that no attempt was made to blind the patients or the medical staff to the treatment allocation. This is completely understandable as it would be very difficult to blind both the staff and the patients to whether they underwent open or laparoscopic surgery, as the incisions are obvious and very different. The trial described by Kok *et al*[39] is the highest quality but the findings of the four trails in terms of donor recovery and recipient outcome (when measured) are broadly in agreement.

CHAPTER THREE: AIMS OF THE THESIS AND HYPOTHESES

3.1 Aims of the Thesis

This study described the evolution of laparoscopic donor nephrectomy at Leicester. Initial assessment of all the donors with a thorough medical check up was done and renal function was assessed by an isotope GFR. The donor then underwent spiral CT angiogram to assess the renovascular anatomy. There was no selection bias on the basis of body mass index or because of difficult vascular anatomy, although in general the left kidney was preferred to the right in view of renal vein length. All patients were given thromboembolic prophylaxis. Donors receive patient controlled analgesia postoperatively with morphine

- LDN (56 patients) were compared to ODN (28 patients); 2;1 ratio as ODN was the standard procedure before LDN was introduced. The following variables were compared (Chapter 4) –
    1. Operative times
    2. Amount of blood loss
    3. Amount and duration of postoperative analgesia requirements
    4. Comparing respiratory functions by measuring pre and post operative spirometry (to compare the % fall in pulmonary expiratory flow rate) and overnight pulse oximetry (to compare O_2 saturation)
    5. Number of days of inpatient stay
    6. Postoperative complications
- During the evolution of LDN, the vessels were secured with various methods (endoclips, polymer clips and stapling device). These methods were compared with respect to complications and maximum length of vessels obtained (Chapter 5).

- Technical modifications and improvement of techniques especially when comparing right and left donor nephrectomy were described (Chapter 6).
- This trial will also study the effects of kidney donation on the donors' subsequent quality of life (Chapter 7). Although the primary end points of such a study should be rate of recovery and quality of life in the donor, an important secondary outcome will be the results of the recipient kidney transplantation. This dissertation will address these issues.

3.2 Hypotheses

The hypotheses under test in this dissertation are:

1. Laparoscopic live donor nephrectomy leads to less postoperative pain, shorter in-patient stay, an improved recovery back to normal activities and better cosmetic results, when compared to traditional open donor nephrectomy.

2. Any benefits of laparoscopic donor nephrectomy over traditional surgery are achieved without greater morbidity in the kidney transplant recipient.

3. Laparoscopic live donor nephrectomy improves quality of life in the donor when compared to traditional open donor nephrectomy patients.

CHAPTER FOUR: COMPARISON OF LAPAROSCOPIC AND SHORT INCISION OPEN DONOR NEPHRECTOMY: A RANDOMISED CONTROLLED TRIAL

4.1 Introduction

One method of addressing the growing shortage of organs for kidney transplantation is the increased use of living kidney donors. Kidney transplants from living donors have many advantages. Set against the undoubted advantages of live donor kidney transplantation is the necessity for the donor to undergo a major surgical operation entirely for the benefit of another individual, albeit a loved one with a debilitating chronic illness. The traditional approach for open donor nephrectomy (ODN) is through an extra-peritoneal loin incision with or without resection of the twelfth rib. Mortality is approximately 0.03%, but long-term morbidity may be substantial, ranging from 15%-20% or higher [76,77]. Although the extraperitoneal flank incision results in lower morbidity than a midline transperitoneal approach, wound complications including infection and hernia formation occur in approximately 9% of patients with a flank approach[78]. Pneumothorax requiring pleural space drainage occurs in approximately 8% of patients. Chronic wound 'diastasis' of bulging and chronic incisional pain have been reported in up to 25% of patients, and return to normal activity may not occur for as long as 6 to 8 weeks after surgery [76,77]. These considerations are likely to deter a significant number of potential donors and have stimulated transplant surgeons to develop open nephrectomy techniques through shorter incisions[79-82].

Developments in minimal access surgery have led to the introduction of laparoscopically assisted donor nephrectomy (LDN)[29] and it has been suggested that this technique has the potential to overcome many of the disincentives to live kidney donation. It has significantly reduced the duration of donors hospital stay, the duration of postoperative convalescence, and has demonstrated favourable long-term outcomes[29,45,51]. There are however some concerns

regarding LDN. First, the duration of surgery is longer in the laparoscopic approach[40]. Second, there has been some concern about longer warm ischaemia times and its impact on the allograft obtained[40,52]. There is a transient delay in the recovery of graft function in the recipient after LDN and an increased incidence of delayed graft function during the first week[52]. Kidneys removed laparoscopically are subjected to longer first warm ischaemic times and the intra-abdominal insufflation of carbon dioxide is known to cause decreases in both renal blood flow and urine output and could have an adverse effect on post-operative respiratory function. There has also been reports of a high incidence of urological complications following the early experience of LDN[54]. Clearly, the laparoscopic operation could not be considered as an advance if it merely transfers morbidity from the donor to the recipient.

Enthusiasm for the use of laparoscopic assisted live donor nephrectomy is increasing around the world. The introduction of this procedure cannot , however, be supported purely by audit data and comparisons with historical control groups[51,54,83-85]. There is still a need to collect high-level evidence comparing the open and laparoscopic nephrectomy operations.

The aim of this study was to compare the safety and efficacy of short incision open donor nephrectomy (ODN) without rib resection and LDN in a single centre randomised controlled trial.

4.2 Patients and Methods

Local ethics committee approval was obtained for this trial (Leicestershire, Northamptonshire and Rutland LREC number 5906; University Hospitals of Leicester Research and development number 06104). The study was performed over a six-year period ending in 2008. The principal investigator for this trial was Prof ML Nicholson, Consultant Transplant Surgeon, University Hospitals of Leicester. The author, who co-ordinated the process in liaison with the transplant surgery and nephrology teams, worked up all potential live donors and their recipients. Standard donor work-up followed the guidelines produced by the British Transplantation Society (UK Guidelines for Living Donor Kidney Transplantation, second edition 2005 www.bts.org.uk). In brief, donors were seen at an initial visit where blood was taken for blood grouping and HLA tissue typing. This established whether or not a potential donor was both blood group and immunologically compatible to the potential recipient. If these tests were in order then the potential donor and recipient pair and any other interested parties or family members were invited to an information session. Leicester has a large ethnic community and renal failure is more common in certain of these ethnic groups due to higher incidences of hypertension and diabetes. In view of this, these sessions included interpreters when this was appropriate. The information sessions were organised by the author and consisted of two 45-minute power point presentations covering all aspects of live kidney donation and transplantation. The presentations included written information in the form of a copy of the power point presentation. A particularly important part of the information session related to the risks of donation, including mortality, surgical and medical complications and the consequences of living with one kidney. The surgical presentation described the traditional open and newer laparoscopic operations in some detail. It was made clear to potential donors that both of these operations had good safety profiles but there continued to

be uncertainty about the relative advantages of one procedure over the other. This 'uncertainty principle' was the basis of running the randomised controlled trial, which was presented as the best scientific way of deciding on the best practice. Interested donors and recipients then underwent a full medical history and clinical examination; this was carried out by a member of the transplant surgery team in conjunction with the author. Further baseline investigations included full blood count, urea and electrolytes, clotting screen, liver and thyroid function tests, bone profile, virology (including hepatitis B and C and HIV), urinalysis, chest x-ray and ECG. Some donors, for example those with hypertension, required additional tests such as 24 hour blood pressure monitoring, echocardiograms and stress ECG. All donors had their glomerular filtration rate (GFR) measured using an isotopic method. This test takes 4 hours and was performed by the author and her colleague. This gave an opportunity to further explore any concerns that the potential donor and their family had about the process. The isotope GFR test was used to screen out unsuitable potential donors on the basis of a lack of renal reserve. In general, the measured GFR had to be within the normal range for the age of the donor and leave sufficient renal function after removing a kidney so that the donor could live into their eighties without requiring renal replacement therapy themselves. If the GFR result was satisfactory, potential donors moved onto the final preoperative tests, which were a CT scan and an intravenous urogram to define the renal vascular and ureteric anatomy. The CT scan findings were also used to decide which of the two kidneys would be removed. For example, multiple arteries and short renal veins were avoided as these make the removal and transplantation of the kidney more technically demanding and also increase the complications rates. All potential donors who were unrelated, for example spouses, partners and friends, were referred to the Unrelated Live Transplant Regulatory Authority (ULTRA), a government appointed body initially created to prevent commercial trade in human organs. The Human Tissue Act 2004 was enacted in April 2005. The Act outlines the legal framework governing the removal, retention and subsequent

use of human tissue excluding gametes. The Act is drafted in wide terms, which are then qualified by excluding causes and definitions. The Secretary of State is given broad powers to amend the Act through Orders and Regulations. A person commits an offence if he removes any transplantable material from the body of a living person intending that the material be used for the purposes of transplantation, and gives or receives a reward for the supply of, or for an offer to supply. Unrelated donors were required to provide evidence of a longstanding emotional relationship with the potential recipient. This might have included photographic evidence, marriage certificates, mortgage documents and shared utility bills. In donor recipient pairs who did not co-habit for example friends, then testimonies were obtained from spouses, parents and employees. It is important to recognise that there will be many variations of 'informed consent' freely given, as there are donor-recipient pairs, and in very many situations the motives and autonomy of the donor will be beyond question. It is for this reason that independence between the clinicians responsible for the donor and the recipient is recommended – allowing for, in effect, a donor advocate. A similar role may be played by a living donor co-ordinator, or more formally by an 'independent third party', which may be embedded within the regulations associated with the Human Tissue Act 2004. Potential donors who had completed this complex work-up routine were therefore seen by an independent consultant nephrologist who checked that all the necessary components were completed and the volunteer was fit to donate.

All live kidney donors who successfully completed this work-up process during the period 2004-2008 were invited to take part in the randomised controlled trial. Donors accepting entry into the trial were consented for nephrectomy by either traditional open or laparoscopic nephrectomy. Renal transplant recipients were followed up for a minimum of four years before data analysis.

Inclusion Criteria

Patients were eligible for the trial if all of the following criteria were met:

1. Male or female live kidney donors of any race, aged 18 years or more.
2. Participants should have the ability to understand the presentation material provided.
3. Potential donors who did not express a clear preference for either open or laparoscopic surgery after attending the donor information session and having read the associated written information.
4. Donors willing and capable of completing the SF-36 at both the preoperative and 6 week post-donation time points.
5. Donors able to give signed written informed consent to the trial.

Exclusion Criteria

Patients were not considered to be eligible for the trial if any of the following criteria apply:

1. Donors expressing a clear preference for either open or laparoscopic surgery.
2. Donors who were unlikely to comply with the study requirements or unable to co-operate or communicate with the investigators.

Primary Outcome Measures of the Trial

1. The level of postoperative pain suffered and the total postoperative analgesic requirements.
2. Rate of recovery of the normal activities of daily living including shopping, driving a car, normal level of exercise, feeling able to return to work and actual return to work.

Secondary Outcome Measures of the Trial

1. Operative details including total operating time, first warm ischaemic time and blood loss.
2. Postoperative respiratory function measured by pulse oximetry and spirometry.
3. Time to the introduction of oral fluids and solid diet postoperatively.
4. Donor complication rates.
5. Duration of in-patient stay.
6. Cosmetic appearance of the wounds at 6 weeks post-donation.
7. Recipient transplant outcome: renal function measured by serum creatinine and estimated glomerular filtration rate.
8. Recipient transplant outcome: complication rates.
9. Recipient transplant Outcome: graft and patient survival.

Randomisation

Patients were randomised to LDN or ODN in a 2:1 ratio. This was a deliberate manoeuvre to keep the number of LDN being performed in the department at a high level. The randomisation sequence was computer generated and converted into a closed envelope system by a trial administrator who was independent from all other aspects of the trial. The list was generated from the Instat software statistics programme (GraphPad Software, San Diego California USA, Copyright 1992-1998 GraphPad Software Inc.). The consecutively numbered opaque envelopes contained a slip identifying the study number and the type of surgery to be performed. Patients were randomised on the day before the proposed surgery and there was no blinding of the randomisation outcome.

Pre and Peri-operative donor management

Following randomisation, and prior to theatre, patients underwent a physical examination, baseline spirometry , serum biochemical analysis, and overnight pulse oximetry. In addition, all donors received 1 litre of intravenous crystalloid fluid in the twelve hours before surgery, to maximise renal perfusion at the time of nephrectomy. A urinary catheter and an internal jugular central venous catheter were placed after the induction of anaesthesia to help guide intra-operative fluid replacement. An intraoperative diuresis was stimulated prior to division of the renal vessels and kidney retrieval by the administration of mannitol 0.5 g/kg iv. Donors received subcutaneous heparin pre-operatively but systemic anticoagulation was not employed prior to clamping the renal vessels.

Anaesthetic and Surgical techniques

All donors received a standardised general anaesthetic given by one of two consultant anaesthetists. Anaesthesia was induced with propofol 2.5-3 mg/kg and fentanyl 1-2μg/kg and maintained with isofluorane and 50% oxygen in air. Muscle relaxation was achieved with atracurium 1 mg/kg. Intravenous fluids were administered to maintain the CVP in the range 8-10 mmHg and systolic blood pressure above 100 mmHg. In order to reduce the effects of a learning curve, twenty laparoscopic live donor nephrectomies had been completed before the trial was initiated. The surgical team had 30 years collective experience of open donor nephrectomy.

Open and laparoscopic operations were both carried out with the patient in a modified lateral decubitus position with a slight break in the table. Open donor nephrectomy was performed using a retroperitoneal approach through an incision placed in the anterior portion of a line between the tip of the eleventh rib and the umbilicus. The length of the incision was minimised as much as possible and this was aided by the use of a fixed retraction system (Omnitract®) and by the use of laparoscopic instruments for dissection.

The laparoscopic operation was performed by using a pnemoperitoneum maintained at a pressure of 12-15 mmHg. Three 12mm ports were placed in a midline above the umbilicus, in the epigastrium and in the ipsilateral iliac fossa. A 5mm port was placed in the flank for hepatic or colonic retraction. Dissection was performed using a combination of diathermy and the harmonic scalpel.

In the vast majority of cases the kidney was retrieved using an Endocatch II® retrieval system placed through a 6-8 cm Pfannensteil incision made 1 cm above the pubis. However, in three of the right sided operations the kidney was removed directly through a 6cm transverse muscle cutting incision placed in the right upper quadrant. This modified approach was used when the right renal vein was very short because it allowed direct control of the vena cava with a side-biting vascular clamp, so that the full length of the vein could be harvested.

Retrieved kidneys were perfused at the back table using 500 ml hyperosmolar citrate solution held at 4°C and infused at a pressure of 100 cmH_2O. Kidneys were then weighed and their anatomical details recorded including the lengths of the renal artery, vein and ureter. Kidneys were then stored in iced hyperosmolar citrate solution until transplantation. The donor and transplantation procedures were performed sequentially in the same operating theatre. Wound lengths (skin incision) were measured at the end of each operation as it has been previously noticed that wounds of a marked fixed length can stretch during traction and manipulation.

Postoperative protocol

At the end of the operation, donors in both groups had their wounds infiltrated with 40ml of 0.25% bupivocaine. Postoperative pain relief was administered using a patient controlled analgesia system (PCAS) delivering 1 mg boluses of morphine with a 5-minute lock-out period. Pain scores were recorded hourly using the following scale:

0, No pain at rest and on movement

1, No pain at rest, slight pain on movement

2, Intermittent pain at rest, moderate pain on movement

3, Continuous pain at rest and severe pain on movement

The hospital's pain control team, who were independent from the transplant surgical team, managed the PCAS in all cases. Opiate analgesia was discontinued at the discretion of the patient and was then replaced by oral analgesia with tramadol or paracetamol.

In addition to this, patients recorded their pain at rest and on deep inspiration using a visual analogue scale (VAS). The VAS was created by printing a 100 mm line on a sheet of paper with the words 'no pain at all' written at the zero (left hand) end of the scale and 'worst pain imaginable' at the 100 (right hand) end of the scale. The patient was asked to draw a line to cross the scale at a point consistent with the level of their pain at that time. The distance from the zero end of the scale to the point on the line marked by the patient was measured in mm to give a pain score out of 100 and results were therefore presented and analysed as a percentage score. These visual analogue scores were made in the morning on the first and third postoperative days. Two VAS scores were made on each occasion: one recording pain at rest and the other recording pain on deep inspiration.

Thrombo-embolic complications are a major cause of death following living donor nephrectomy. As prophylaxis against venous thrombo-embolism all donors wore TED stockings and were administered subcutaneous heparin 5000 IU b.d until fully mobile. As anaesthesia was performed with muscle relaxation, the patient's leg muscle pump was inactive during surgery and this was countered by the use of intermittent pneumatic calf compression throughout surgery. As a third precaution, all donors wore thrombo-embolic deterrent stockings pre and post operatively until they were fully mobile. All donors were allowed to begin mobilisation on the first post-operative day and started eating and drinking at their own discretion. Donors made their own decision about fitness for discharge from the hospital. These decisions were not affected by the views of the medical and nursing team, except in the event of a complication when the medical staff intervened and the patient was

kept in the hospital until they were fit for discharge. This policy of non-interference with the donor's recovery and decision to go home was adhered to strictly. The time of introduction of free oral fluids and the first solid food, along with the length of hospital stay, were recorded along with any complications. The discharge letter to the general practitioner contained details of the nature and purpose of the trial and specifically requested that the GP should not try to influence the time taken off work or the time taken for the patient to resume other normal activities. All patients were encouraged to resume full activities as soon as they felt fit enough but were not given any advice on how long they might expect to remain convalescent. Patients were however advised that they should not resume driving their cars for a period of at least 2 weeks.

Respiratory function tests

A hand held enhanced mini spirometer was used to measure peri-operative respiratory function tests. Peak expiratory flow rate (PEFR) and forced vital capacity (FVC) were measured using an enhanced mini-spirometer on the day before surgery and on the first and third post-operative days. In all cases, the patient was asked to blow into the spirometrer as hard as possible and the patients were given three attempts. The results of the best attempt were recorded and used for analysis. Continuous pulse oximetry was performed in all donors during the first three postoperative days. Overnight arterial oxygen saturation (SpO_2) was recorded before surgery and on the first and third post-operative nights using an Edentrace digital recorder (Edentec, MN, USA). Data were analysed using the manufacturer's software to yield mean and minimum SpO_2 and for desaturations per hour (desaturation index), defined as a fall in $SpO_2 > 4\%$ from the mean for a period greater than 10 seconds[86]. Pulse oximetry

data were incomplete for 10 patients in the LDN group and 6 in the ODN group due to probe displacement or discharge from hospital prior to the third postoperative night.

Donor Follow-up

At the time of discharge each donor was given a diary sheet and asked to note the date on which the following activities were resumed: driving a car, shopping, resumption of their normal level of exercise (e.g. walking, running, swimming), feeling able to return to work and the time of their actual return to work. All donors were reviewed 6 weeks post-operatively. Wound cosmesis was assessed at this time using a 100 mm linear analogue scale with 'worst imaginable cosmetic appearance' written at the 0 end and 'perfect cosmetic result' written at the 100 end. . The patient scored a line through the scale as an assessment of their satisfaction with the appearance of the surgical scars at this time point.

Data collection and analysis

The author collected and recorded all data prospectively, entering this onto a computerised database that had been specifically designed for this study. Comparisons of outcomes were made on an intention to treat basis; patients randomised to open surgery but actually undergoing the laparoscopic operation were analysed in the open group and the single conversion from laparoscopic to open surgery was analysed in the laparoscopic group. Data are presented as mean ± SD and statistical analysis was performed using Instat® software for MacIntosh (Graphpad San Diego, USA, www.Graphpad.com). Normality testing was performed using the Kolmogorov – Smirnov test. Continuous variables were compared using

the student's t-test or the Mann-Whitney U test as appropriate. Categorical variables were compared using Fisher's exact test. $P<0.05$ was considered statistically significant.

Power calculations

A number of different errors can occur in statistical analysis of data. A type II error (beta error or false negative) occurs when a test fails to detect a difference between two treatments when in truth there is a difference. This type of error most commonly occurs when the numbers of patients being studied is too small. The power of a statistical test is the probability that the test will not make a type II error. Power analysis can be used to calculate the minimum sample size required to accept the answer given by that test with a specified degree of confidence. Power calculations for this study were kindly performed by Dr Suzanne Stevens PhD, Department of Cardiovascular Sciences, University of Leicester. The primary end points of the study were total post-operative morphine requirements and length of hospital stay. Trial size was calculated with respect to these end points by power calculations using data from previous local comparative studies. These revealed that 19 open and 38 laparoscopic operations would be required to detect a 40% difference in morphine dosage with a power of 90% and a statistical significance level of $\alpha=0.05$. In addition, 21 open and 42 laparoscopic procedures would be required to detect a 1.5 day difference in length of hospital stay with the same power and α. A total of 84 patients were enrolled into the study.

4.3 Results

Patients

A consecutive series of ninety-four eligible patients were invited to take part in the trial. After attending the standardised information session, 10 patients expressed a strong preference for a particular operative approach (7 laparoscopic and 3 open) and declined randomisation. There were no exclusions for any other reason including obesity or complex renal vascular anatomy. Eighty-four patients were randomised, 56 to the laparoscopic procedure and 28 to the open operation. After randomisation, three patients randomised to the open group subsequently declined to undergo open nephrectomy and therefore underwent the laparoscopic operation. In line with the intention to treat principle these three patients were analysed in the open group (Figure 1). Baseline donor demographics are presented in Table 1. The LDN and ODN groups were well matched with no statistically significant differences between donor or recipient characteristics in the two study groups.

Donor operation details (Table2, Graph 1)

The total donor operating time (from first incision to last skin suture) and the first warm ischaemic time (time from renal artery clamping to commencement of cold flushing) was significantly longer in the laparoscopic group. The estimated intra-operative blood loss was similar in the two groups. ODN wounds were longer than the LDN suprapubic retrieval incision.

Donor intra- and post-operative complications (Table 3)

One laparoscopic operation was converted to an open operation due to intra-operative bleeding from the renal artery stump. In this case the renal artery was controlled with 3 metal clips and divided without problems. However, the arterial clips were dislodged when an endovascular stapling device was closed around the renal vein but inadvertently included the arterial stump. This situation was managed by immediate conversion through a transverse muscle cutting incision and suture of the renal artery stump. Total blood loss was 2 litres and four units of packed red cells were transfused on-table. The donor recovered well and the kidney was successfully transplanted and demonstrated good initial and long-term function. There was also one intra-operative pneumothorax in the laparoscopic group, caused by a previously undiagnosed patent left sided pleuro-peritoneal canal. A chest drain was inserted intraoperatively and despite a persistent slow leak of the pneumoperitoneum, the operation was completed without conversion. There were no other intraoperative complications in the laparoscopic or open groups.

Overall postoperative complication rates per donor were lower in the LDN group and in particular, chest infections requiring treatment with antibiotics were not seen as often after this operation. One patient undergoing LDN had repeat laparoscopy for division of adhesions postoperatively at 8 weeks. Testicular swelling and thigh numbness also occurred more commonly after LDN but this difference was not statistically significant.

Postoperative pain and respiratory function (Table 4, Graphs 3-8)

Donors undergoing laparoscopic surgery used their PCAS for a shorter period of time and used a lower total dose of morphine than donors in the open group. Postoperative pain scores were also significantly lower in the laparoscopic group. There were significant decreases in PEFR and FVC in both groups post-operatively. In the laparoscopic group, there was a significantly lower fall in both PEFR and FVC on the first post-operative day. On day three, PEFR and FVC were still lower than pre-operative values in both groups but there were no significant differences between the LDN and ODN groups. The desaturation index was significantly lower in the LDN group compared to ODN on the third post-operative day.

Return to Normal Activities (Table 4, Graphs 9, 10)

Patients undergoing LDN resumed oral fluids and diet significantly more quickly than patients undergoing ODN. In-patient stay was also shorter after LDN (3.8 ± 1.0 vs 5.9 ± 1.7 days; $p<0.0001$). There was no significant difference in the time taken for patients to return to shopping between the two groups but patients in the LDN group started driving their cars and returned to their usual level of exercise activity quicker than patients in the ODN group. Patients in the LDN group felt able to return to work and actually returned to work significantly quicker than patients undergoing ODN. At the 6-week out-patient review donors in the LDN group scored the cosmetic appearance of their wounds more highly than the ODN group (linear analogue scores 73±15 vs 60±17; $p=0.0006$).

Recipient Demographics, Patient and operative details and Allograft survival and Renal Function (Tables 1,2,5, Graph 11)

Baseline recipient characteristics are presented in Tables 1 & 2. Transplanted kidneys in the two groups had similar features, apart from a longer length of the ureter being retrieved during the laparoscopic operation. There was only one urological complication in this series of transplants and this occurred after ODN. The patient developed an ischaemic stricture of the distal transplant ureter 3 months post-operatively. Native to transplant uretero-ureterostomy successfully treated this.

There have been three recipient deaths during follow-up, two in the laparoscopic group and one in the open donor nephrectomy group. All three patients died with functioning grafts. One death occurred two months post-operatively and was due to gastrointestinal infarction as a result of opportunistic infection with the fungus *rhizopus*. There were also two cardiovascular deaths occurring four months and 43 months post-transplant. Recipient (patient) survival at 1 year post-transplant was 96 percent (95% confidence intervals = 86 – 99) in the laparoscopic group and 100 percent (95% confidence intervals = 85 - 100) in the open group. Recipient survival at 5 years post-transplant was 94 percent (95% confidence intervals = 84 – 99) and 89 percent in the laparoscopic and open groups respectively. There was no statistically significant difference in transplant recipient survival over the first 5 years (log - rank Mantel - Cox test p = 0.204).

Transplant survival at 1 year after laparoscopic nephrectomy was 93 percent (95% confidence intervals = 82 – 98) and 100 percent in the open nephrectomy group (95% confidence interval = 85 – 100). At five years the transplant survival rates were 91 percent in the laparoscopic group (95% confidence interval = 80 – 97) and 86 percent in the open group (95% confidence

interval = 66 – 95). There were no significant differences in transplant survival between the two groups (p = 0.516; log - rank Mantel - Cox test).

There were no differences in renal allograft function measured by serum creatinine or estimated GFR using the Modification of Diet in Renal Disease method (Table 5).

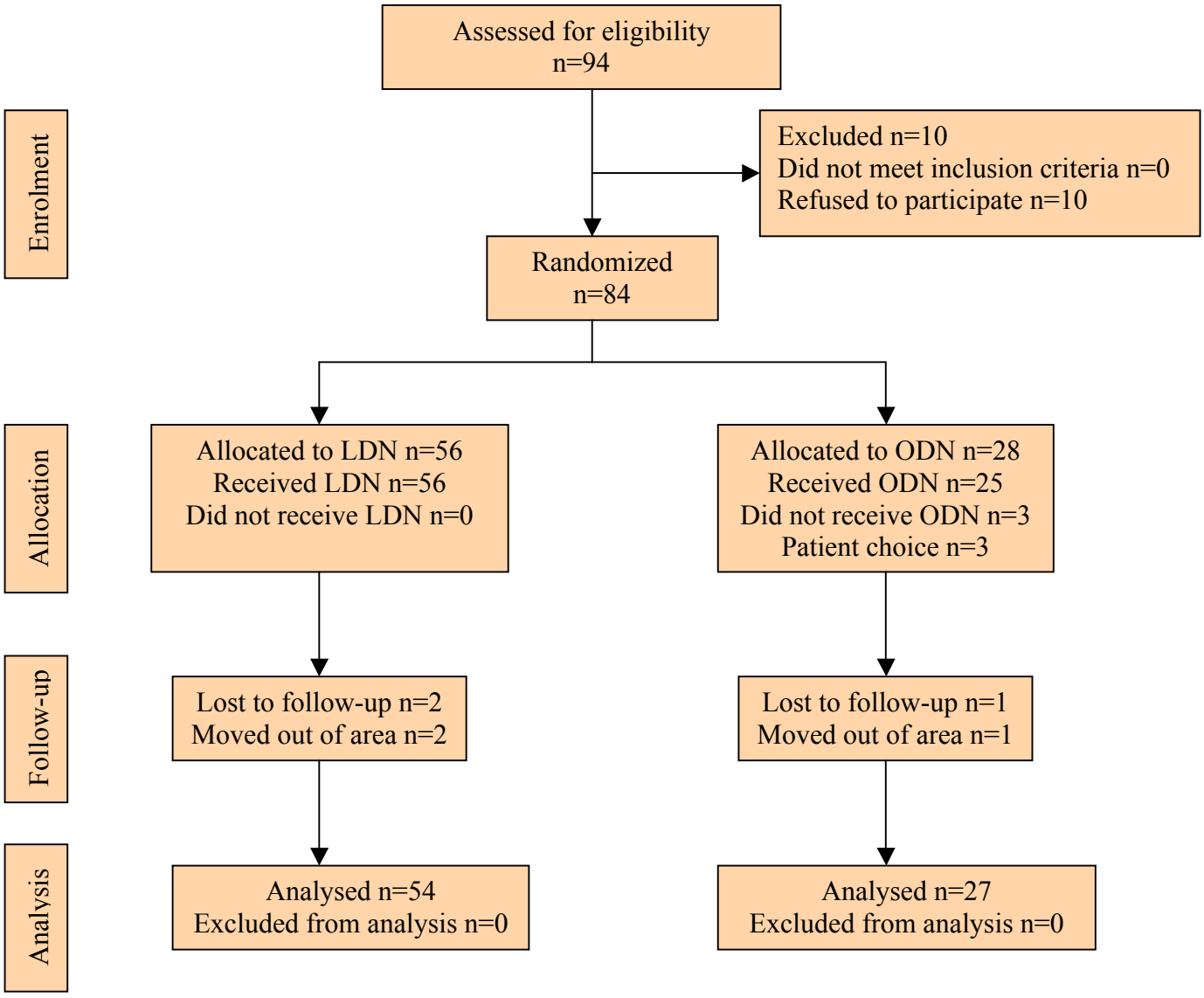


Figure 1: Trial profile. LDN, laparoscopic donor nephrectomy; ODN, open donor nephrectomy

Table 1: Donor and Recipient Demographics

	LDN (n=56)	ODN (n=28)	P Value
Donor			
N (%)	56 (67)	28 (33)	
M:F	20:36	14:14	0.243
Age	47 ± 12	45 ± 11	0.248
BMI (Kg/m²)	26.3 ± 5.0	25.6 ± 3.9	0.529
HLA A mis-match	0.70 ± 0.56	0.71 ± 0.60	0.935
HLA B mis-match	0.87 ± 0.68	0.75 ± 0.65	0.471
HLA DR mis-match	0.75 ± 0.63	0.82 ± 0.55	0.609
Donor related (%)	40 (71.4)	25 (89.2)	0.0963
Donor unrelated (%)	16 (28.6)	3 (10.8)	0.0963
Parental donor (%)	18 (32.1)	11 (39.3)	0.627
Side of operation R:L	12:44	6:23	1.000
Employed (%)	41 (73.2)	18 (64.3)	0.623
Recipient			
Sex (M:F)	30:26	14:14	0.819
Age (yrs)	38.5 ± 12.5	37.9 ± 12.8	0.8609
Anastomosis time (min)	28 ± 5	29 ± 7	0.388
Cold ischaemic time (min)	197 ± 30	179 ± 45	0.082
Kidney weight (g)	174 ± 47	184 ± 34	0.095
Artery length (mm)	30 ± 8	30 ± 8	0.691
Vein length (mm)	36 ± 11	31 ± 10	0.068
Ureteric length (mm)	118 ± 20	101 ± 18	0.002

Table 2: Operative details

	LDN (n=56)	ODN (n=28)	P Value
Donor			
Conversion to open	1	n/a	
Operation time (min)	168 ± 30	145 ± 27	0.0042
Incision length (cm)	8.5 ± 1.3	15.3 ± 3.3	<0.0001
Blood loss (ml)	280 ± 270	276 ± 269	0.717
Warm ischaemic time (min)	3.8 ± 1.1	2.2 ± 1.1	<0.0001
Wound length (mm)	79 ± 11	137 ± 33	<0.0001
Recipient			
Anastomosis time (mins)	28 ± 5	29 ± 7	0.388
Cold ischaemic time (min)	197 ± 30	179 ± 45	0.082
Kidney weight (mg)	174 ± 47	184 ± 34	0.095
Artery length (mm)	30 ± 8	30 ± 8	0.691
Vein length (mm)	36 ± 11	31 ± 10	0.068
Ureteric length (mm)	118 ± 20	101 ± 18	0.002

Values are mean ± S.D.

Table 3: Donor intra and post operative complications

Complication	LDN (n=56)	ODN (n=28)	P Value
Intraoperative			
Haemorrhage	1	0	0.3333
Pneumothorax	1	0	0.3333
Postoperative			
Wound infection	2	2	0.5977
Chest infection	5	8	0.0267
Thigh numbness	4	1	0.6606
Adhesions requiring surgery	2	0	0.5502
Testicular swelling / pain	3	0	0.2614
Incisional hernia	0	1	0.3333
Chronic wound pain	0	2	0.1084
Paralytic ileus	0	2	0.1084
Rectus sheath nerve entrapment	0	1	0.3333
Overall number of complications per donor	0.3 ± 0.5	0.6 ± 0.7	0.0327

Table 4: Donor post-operative pain, respiratory function and recovery

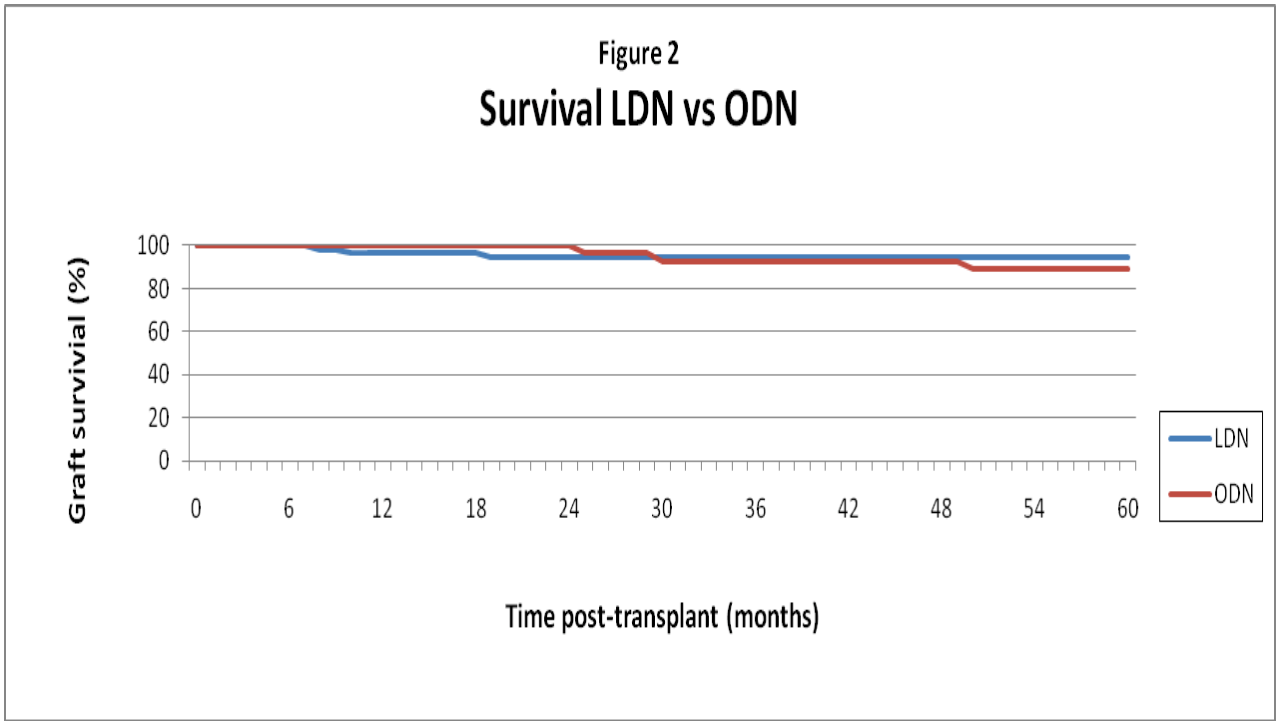
	LDN (n=56)	ODN (n=28)	P Value
PCAS dose (mg)	61 ± 35	111 ± 68	0.0006
PCAS duration (hr)	40 ± 18	55 ± 14	0.0001
PCAS Score (pain score)	0.51 ± 0.28	0.69 ± 0.40	0.038
% fall PEFR – day 1	37 ± 21	52 ± 18	0.0018
% fall PEFR – day 3	22 ± 25	35 ± 29	0.075
% fall FVC – day 1	44 ± 13	53 ± 17	0.0373
% fall FVC – day 3	27 ± 17	32 ± 14	0.1822
Desaturation index – day 3	2.4 ± 3.9	6.8 ± 9.6	0.0449
In-patient stay (days)	3.8 ± 1.0	5.9 ± 1.7	<0.0001
Resumption of oral fluids (days)	1.0 ± 0.2	1.5 ± 0.5	0.0013
Resumption of diet (days)	1.4 ± 0.6	2.6 ± 1.3	<0.0001
Shopping (days)	17.8 ± 10.8	17.7 ± 9.7	0.771
Driving (days)	23.4 ± 13.9	30.2 ± 15.1	0.053
Return to normal level of exercise (days)	25.4 ± 12.7	40.7 ± 16.1	<0.0001
Felt able to return to work	31.9 ± 15.9	50.1 ± 21.3	0.001
Actual return to work	39.1 ± 18.0	61.8 ± 28.1	0.0044

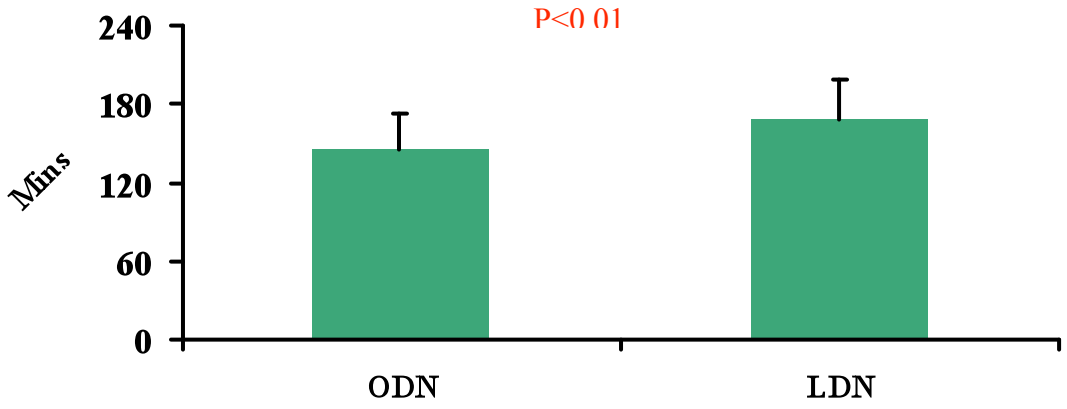
Values are mean ± S.D.

Table 5: Recipient Outcome

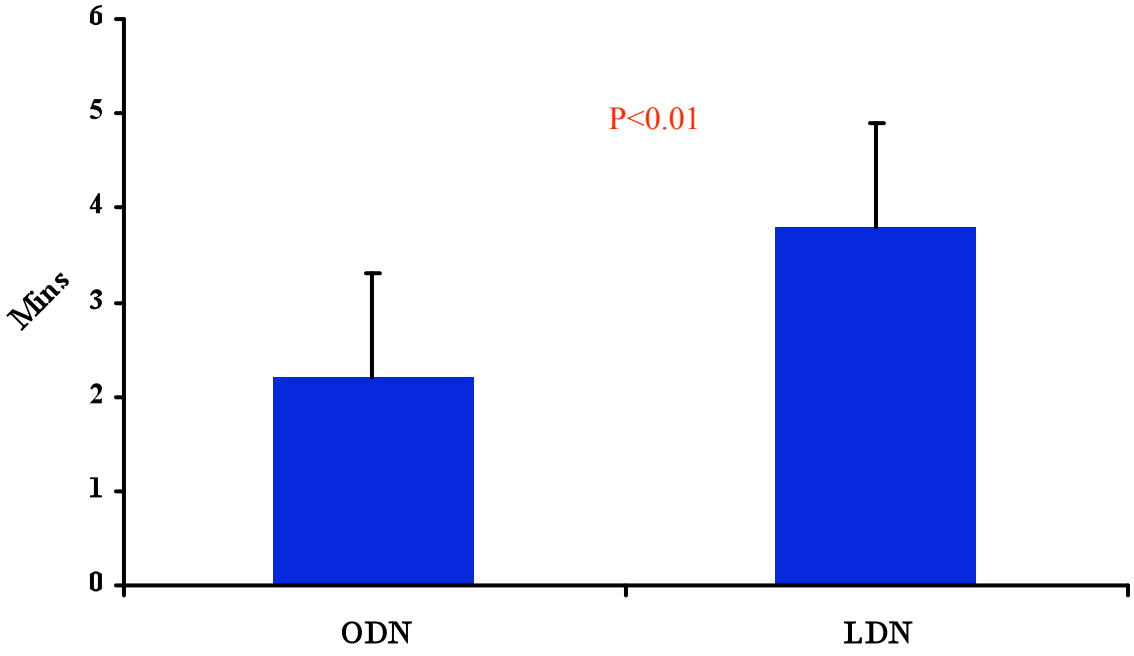
	LDN (n=56)	ODN (n=28)	P Value
Vascular thrombosis	0	0	1.00
Ureteric complication	0	1 (3.6%)	1.00
Delayed graft function	1 (1.8%)	1 (3.6%)	1.00
Biopsy proven acute rejection	15 (27%)	8 (29%)	1.00
Steroid resistant rejection	4 (7.1%)	1 (3.6%)	0.66
Lymphocele	0	1 (3.6%)	1.00
Patient survival at 1-year (95% confidence interval)	96.3 (86.4-99.3)	100 (84.9-100)	
Patient survival at 5-year (95% confidence interval)	94.4 (83.9-98.5)	89.3 (70.6-97.2)	
Allograft survival at 1-year (95% confidence interval)	92.9 (81.8-97.7)	100 (84.8-100)	
Allograft survival at 5-year (95% confidence interval)	91.1 (79.6-96.7)	85.7 (66.4-95.3)	
Renal Function			
Creatinine – year 1	128.7 ± 39.8	125.3 ± 34.8	0.6916
Creatinine – year 2	138.3 ± 54.2	132.0 ± 31.8	0.5257
Creatinine – year 3	167.7 ± 175.8	155.5 ± 161.6	0.7601
Creatinine – year 4	156.5 ± 106.5	154.6 ± 121.8	0.9466
Creatinine – year 5	141.2 ± 71.6	167.5 ± 165.1	0.4683
Estimated GFR			
1 year	53.2(13.9)	52.6(16.4)	0.872
5 years	47.4(15.3)	54.2(17.2)	0.218

Figure 2


Survival LDN vs ODN
Graft survivial (%)
100
80
60
40
20
0
0
6
12
18
24
30
36
42
48
54
60
Time post-transplant (months)
LDN
ODN

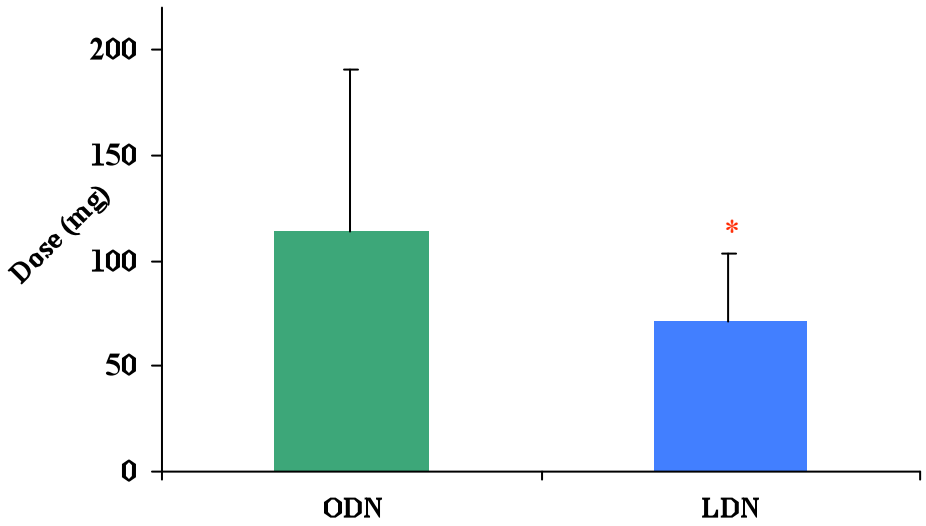


Graph 1 – Operating time (min)

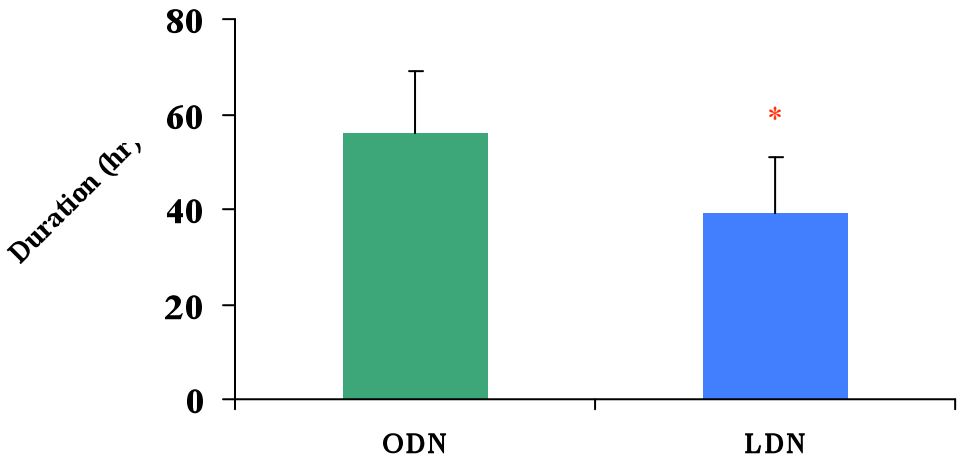


Graph 2 – 1st warm ischaemic time (min)

Values mean ± SD

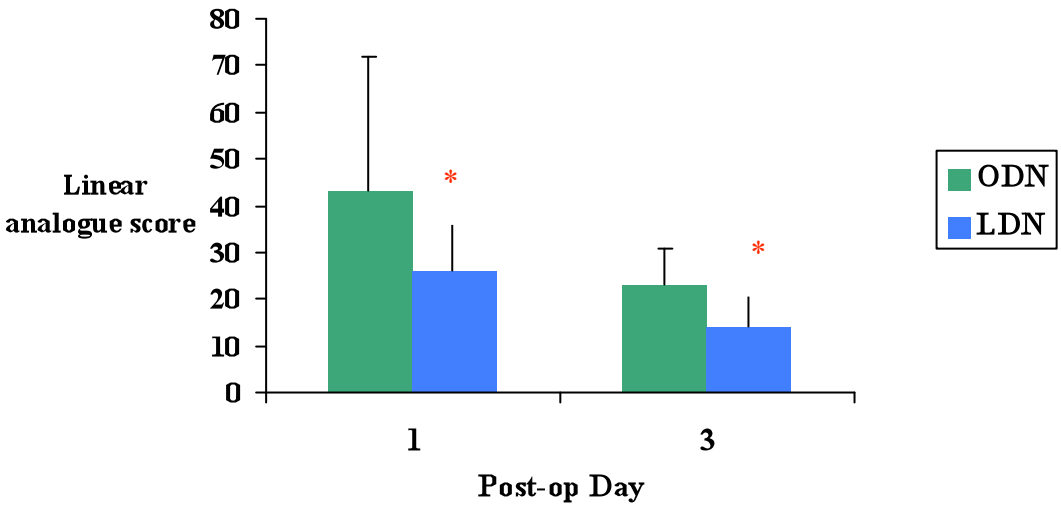


Graph 3 – Total morphine dose (*P<0.01 vs ODN)

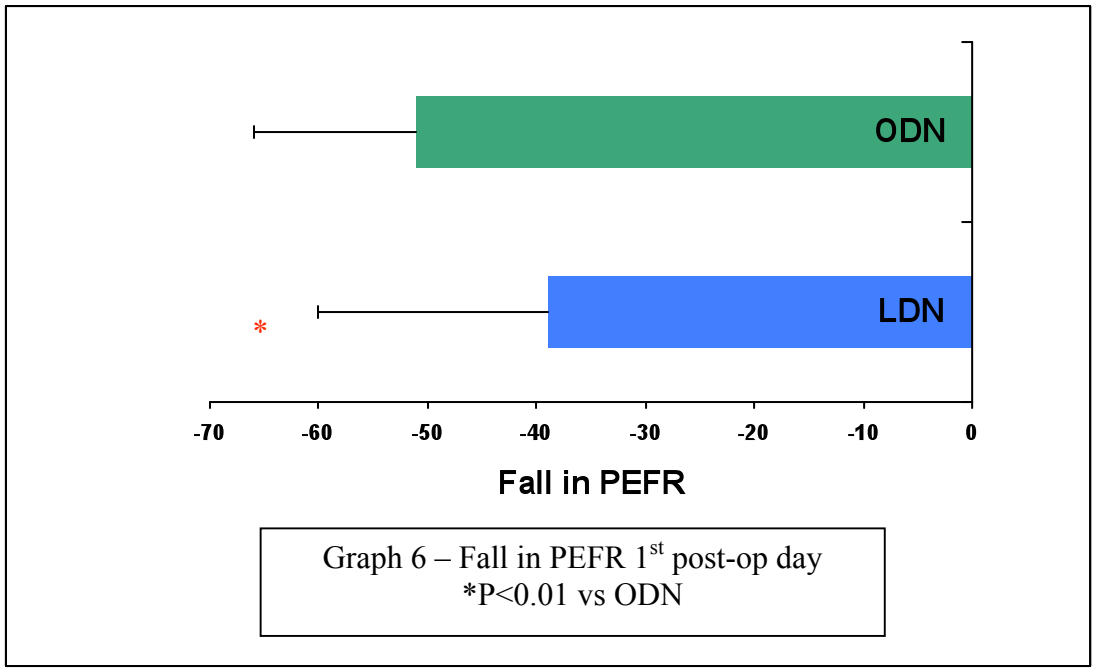


Graph 4 – Duration PCAS (*P<0.01 vs ODN)

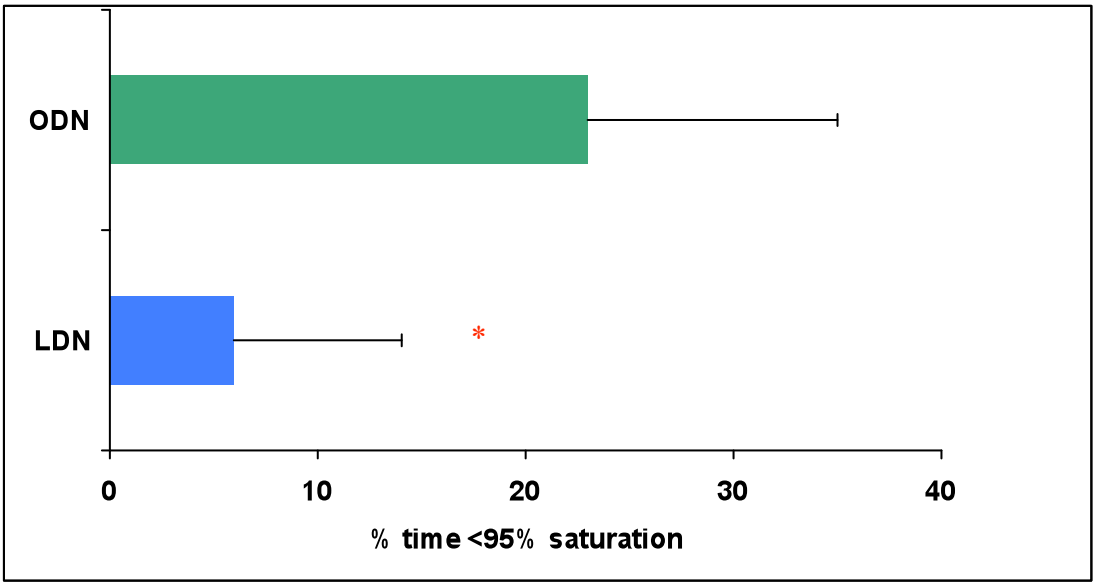
Values mean ± SD



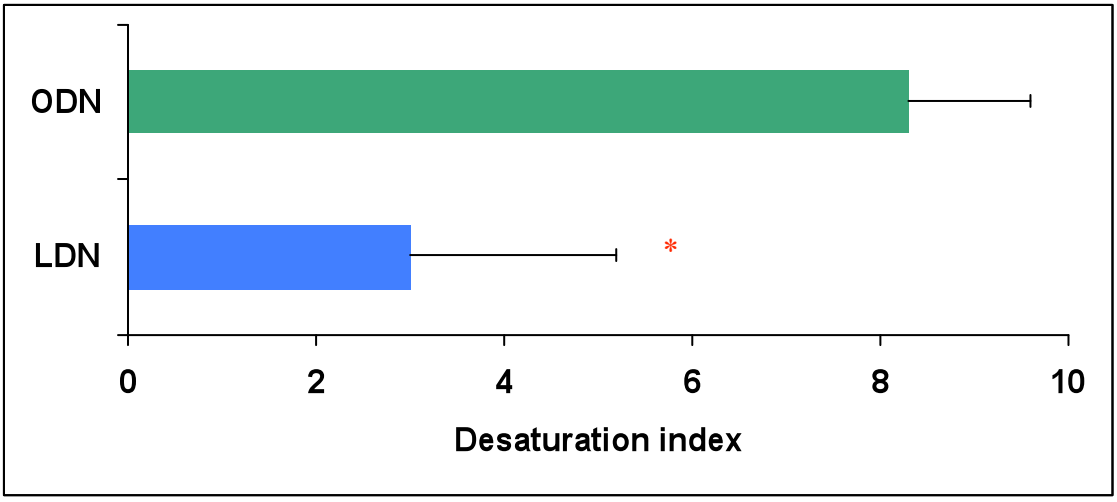
Graph 5 – Pain scores (*P<0.01 vs ODN)



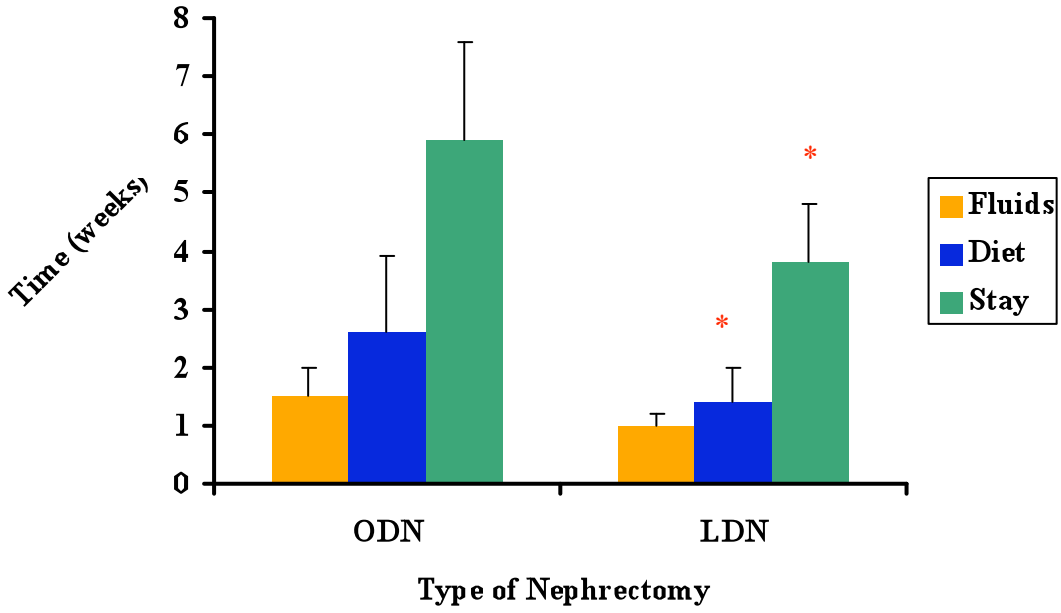
Graph 6 – Fall in PEFR 1st post-op day
*P<0.01 vs ODN



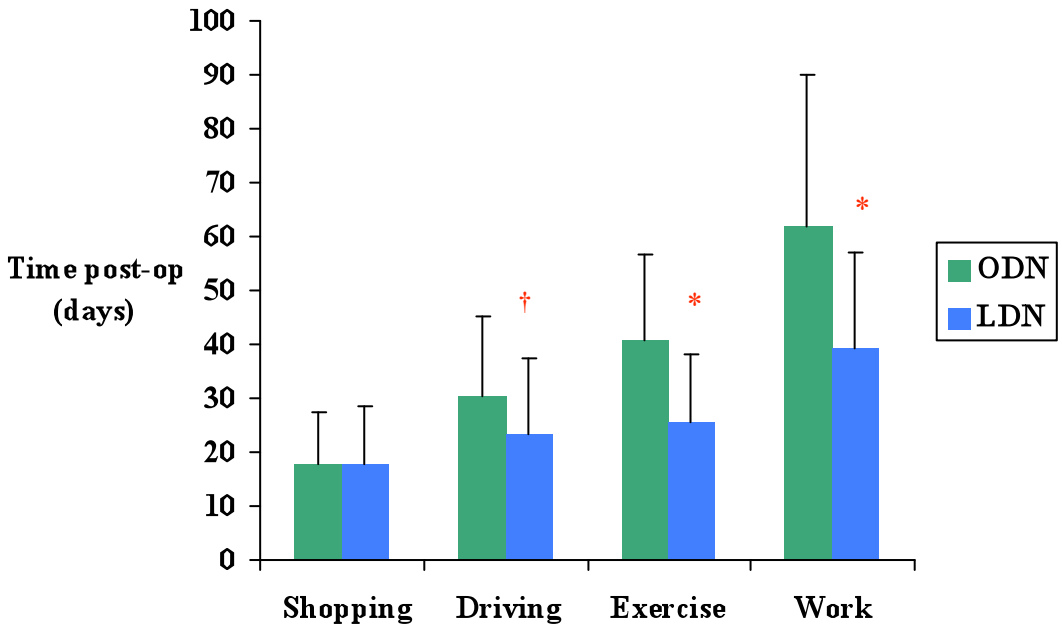
Graph 7 - % time < 95% saturation on day 1
* P<0.01 vs ODN



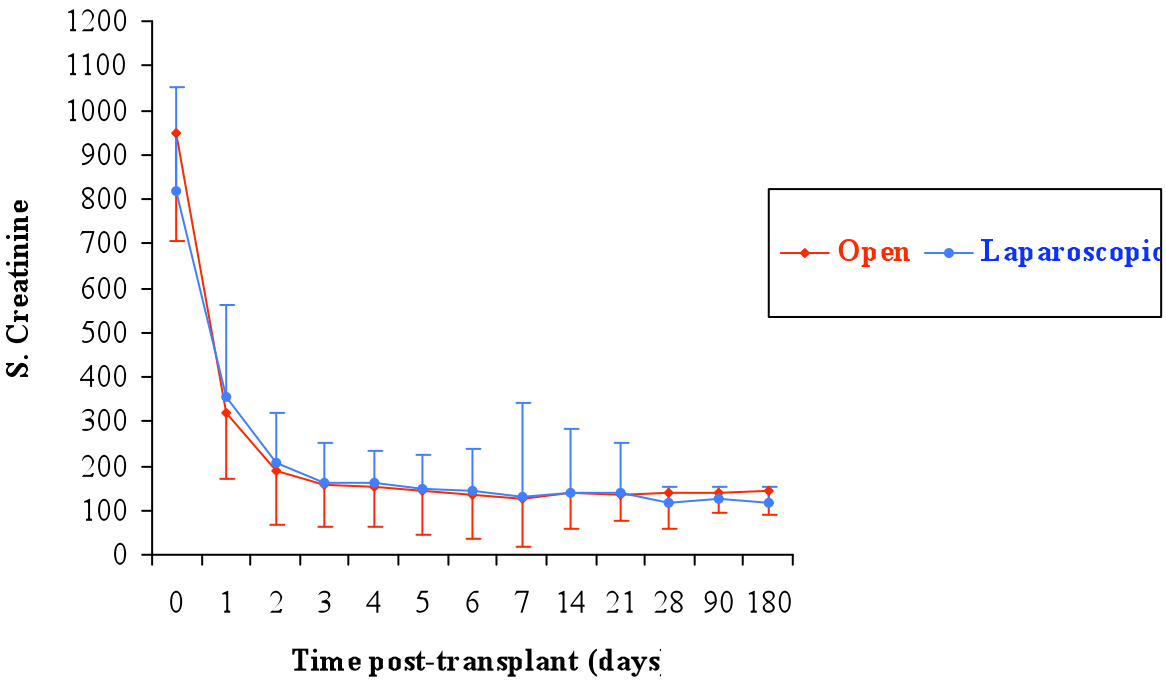
Graph 8 – Desaturation index, 3rd post-op day*P<0.01 vs ODN



Graph 9 – Early postoperative outcome (*P<0.01 vs ODN)



Graph 10 – Recovery rates after donor nephrectomy († P=0.050, *P<0.01)



Graph 11 – Recipient serum creatinine levels

4.4 Discussion

Live organ donation is unique among major surgical procedures, because it exposes an otherwise healthy individual to the risks of major surgery entirely for the benefit of another person. For laparoscopic live donor nephrectomy to become a viable option for procuring kidneys for renal transplantation, several conditions must be met. Most importantly, the laparoscopic donor should suffer no additional or unique morbidity when compared to the open donor. In addition, kidneys harvested using laparoscopic techniques must have graft survival and function rates equivalent to those obtained by 'gold standard' of open nephrectomy using an extraperitoneal flank approach. Finally, the laparoscopic approach should convey some advantage to the patient such as less pain, shorter hospital stay, and earlier return to normal activity.

New laparoscopic surgical approaches have to some extent been technology driven but should not be widely adopted without high-level evidence supporting their safety and efficacy in comparison with conventional surgery[87], and this provided the rationale for the current study. In this randomised controlled trial, laparoscopic live donor nephrectomy was associated with a significant improvement in post operative pain control, better postoperative respiratory function, a reduction in hospital stay, an earlier return to normal activities and improved wound cosmesis. These advantages were achieved without compromise to either donor safety, or to long-term function and survival of the transplanted kidney. These findings concur with the findings of Kok *et al*[39] and Tooher *et al*[41].

The present study had a number of advantages. This is the fifth published randomized controlled trial to compare traditional open and laparoscopic surgery for living donor nephrectomy. The other trials were summarized in the literature review in chapter 2 and this along with the results described in this thesis amounts to level I evidence. As described previously the quality of randomised controlled trials is most commonly judged using the Jadad Scale (Jadad *et al*[106]). If this system is applied to the Leicester trial then a Jadad score of 3 would be achieved (one point each for the study being randomized, use of an appropriate method of randomization and use of a Consort diagram to describe withdrawals and drop-outs). The trial did not reach the maximum Jadad score of 5 as blinding was not involved. Only the trial by Kok *et al*[39] also achieved a Jadad score of 3.

Laparoscopic donor nephrectomy has potential disadvantages. The operation is performed in a closed field with limited access, there is an increase in first warm ischaemic time and the use of a relatively prolonged pneumoperitoneum has been associated with a reduction in renal function due to haemodynamic changes[88]. These factors have led to the concern that laparoscopic surgery may reduce morbidity in the donor but only at the expense of greater morbidity in the recipient. This is the first RCT to present live donor transplant recipient data at a minimum follow-up of four years. There were no differences in renal function or allograft survival for kidneys removed by LDN or ODN at this time point. This demonstrates that any additional early ischaemic injury sustained by kidneys during laparoscopic retrieval does not have adverse consequences for the recipient in the long term.

The Leicester trial was the first to include measurements of respiratory function as an outcome measure in the donors. These were performed as a rigorous assessment of the effects of a prolonged pneumoperitoneum on the donor[89]. At the start of the laparoscopic operation,

carbon dioxide is introduced into the abdomen under pressure in order to create a working space in the peritoneal cavity. The carbon dioxide is held at a pressure of approximately 15 mmHg for the entire duration of the operation, which lasted from 110-240 minutes. The raised intra-abdominal pressure has a number of potential disadvantages. First, it may 'splint' the diaphragm i.e. reduce its normal range of movement. This could decrease ventilation of the lower parts of the lungs and lead to an increase in postoperative respiratory complications (Nadu *et al*[89]). In view of this respiratory function was assessed postoperatively by simple spirometry and by overnight pulse oximetry. These tests showed that some indices of postoperative respiratory were in fact improved in patients undergoing the laparoscopic compared to open operation. Peak flow and forced vital capacity were both improved after the laparoscopic operation and this is probably a reflection of the fact that this operation was less painful than the open operation. The desaturation index was also improved in the laparoscopic group. This is an index of nocturnal episodic hypoxaemia, which may occur due to the use of opiate analgesia, which in turn can cause respiratory depression. This was an unexpected finding but is of great potential importance as there is a relationship in time between episodes of hypoxaemia and the development of myocardial ischaemia[90]. Even though all live donors are carefully assessed for ischaemic heart disease during their preoperative assessments, it is important to identify the surgical technique which best protects the heart during a general anaesthetic. The open operation led to worse postoperative respiratory function and this was associated with a higher rate of chest infections and this is one reason why hospital stay was longer for patients undergoing open surgery. A 15 mmHg pneumoperitoneum exposes the kidney to an unnatural environment and has a theoretically disadvantageous effect on renal function in the donor. This level of pressure could cause ischaemia damage to the kidney and so reduce its function before removal. There was, however, no evidence that renal function in the recipient was adversely affected by

laparoscopic surgery: the rates of delayed graft function, serum creatinine at one and five years and estimated GFR at one and five years were not significantly different between the open and laparoscopic groups. These findings are consistent with a well-designed study, which showed no differences in early renal function between laparoscopic donor nephrectomy operations performed with or without carbon dioxide insufflation[53].
Furthermore, there were no significant differences in urological complication rates after a median follow-up of 74 months and this should assuage some of the previous concerns about higher urological complication rates after laparoscopic nephrectomy[54].

Our trial has a number of limitations. The overall number of patients studied was small but was informed by power calculations. As with other studies of laparoscopic nephrectomy, we did not attempt to blind patients and staff to the surgical procedures being evaluated. While we accept that this would be the ideal situation in which to limit bias in postoperative care[91,] in reality we felt that blinding in this situation would be virtually impossible to achieve. A study of laparoscopic and mini incision cholecystectomy has been conducted in the past with the nursing staff blinded to the treatment group (Majeed *et al*[91]). This involved the surgical wounds being covered up with the same dressings and deliberate slight staining of the dressings using the patient's blood. These patients were only in hospital for 1-2 days and the wounds for both operations were in the same part of the abdomen. The author's study involved wounds in completely different parts of the abdomen and a longer in-patient stay and it was felt that any attempts at blinding the patient and the nursing staff to the type of surgery would have been virtually impossible in this situation.
Our assessments of return to normal activities might be regarded as relying on relatively soft end points. Nonetheless, we believe that patients are highly motivated to return to activities such as driving and that the data provided a reasonable objective measure of recovery. It is

however accepted that variables such as the time taken to return to work are affected by many different factors. The study design included the fact that a letter was sent to the general practitioner of every donor to ask that the GP should not influence the donor's decision about fitness for work. There were no apparent conflicts with this aspect of the study and this should have tightened the meaning of this end-point to some degree.

Unequal randomisation was used in our trial with a 2:1 ratio favouring the laparoscopic group. We felt that this method of randomisation would improve recruitment to the trial at a time when there was increasing publicity about laparoscopic techniques. The modest use of statistical power associated with a 2:1 randomisation was countered by increasing the sample size. This type of randomization reduces the statistical power of the trial. This appeared to be effective as trial recruitment was good with only 10 out 94 invited patients refusing to take part. Unfortunately, three patients randomized to the open nephrectomy group immediately refused that treatment option after the randomization envelope was opened. They stated that they were hoping to be allocated to the laparoscopic arm and in line with their wishes they underwent laparoscopic operations. These patients were not excluded from further study but were analysed as members of the open treatment group on the so-called 'intention to treat' basis. This is important in avoiding a biasing of the results. If these patients happened by chance to be more difficult to treat because of obesity or difficult kidney anatomy then analysing them in the laparoscopic group would bias against this procedure. The correct approach in this situation is to analyse them according to the initially intended treatment rather than the actual treatment received. In this way, intention to treat analysis provides information about the potential effects of treatment policy rather than the potential effects of the specific treatment. The application of intention to treat reduces Type 1 errors (false positive errors which show a difference between treatments when in reality there is no difference).

Live donation is a unique surgical situation as it exposes a completely healthy person to the risks of major surgery entirely for the benefit of another individual. Donor safety should be the first consideration in any live donor transplant programme and donor complication rates must be critically analysed. Intra- and post-operative donor complication rates were carefully recorded in this study and we found a higher incidence of complication rates per donor after ODN. The range and incidence of complications in the LDN group was consistent with the findings of other studies[39,42-43,51,83-85,92].

Nonetheless, it is the incidence of potentially life threatening complications that is more important than overall rates. Bleeding and bowel injury, especially if these are not recognised at the time of surgery, are both potentially fatal and there was one case of significant arterial haemorrhage in our laparoscopic series. Oyen *et al* reported two similar episodes of intra-operative haemorrhage, along with two bowel perforations in a series of 63 laparoscopic operations[43] and concluded that conventional open donor nephrectomy is superior to laparoscopic donor nephrectomy with regards to donor safety. As their complication rate was higher in donors with higher body mass index these authors believe that the laparoscopic approach should be reserved for thinner patients. There continues to be debate over the best way to control the renal artery and a number of donor deaths have been attributed to late clip displacement[93]. Our case of bleeding might have been avoided by securing the renal artery with a stapler-cutter rather than simple metal clips.

Protagonists of the hand assisted laparoscopic donor nephrectomy argue that this approach is safer as the presence of a hand inside the abdomen allows for immediate control of serious arterial haemorrhage[42.43]. This assertion remains unproven as there are no trials comparing transperitoneal LDN with and without hand assistance and furthermore, there is no

comprehensive published data relating to avoidance of 'near-misses' using the hand assist technique. Wadstom *et al* has developed a technique combining hand assistance with a retroperitoneal approach, arguing that this has the advantages of being able to control sudden haemorrhage but also might protect against bowel injury by avoiding breaching the peritoneal cavity[94]. Clearly, the peritonem is a thin layer and it must remain a possibility that a diathermy injury to the bowel could still occur during this approach.

The introduction of laparoscopic donor nephrectomy has stimulated the surgical community to improve techniques of open nephrectomy. Recent advances in this area include the use of smaller incisions[95] and a mini-incision muscle splitting anterior flank approach[96]. The relative safety and efficacy of these newer open techniques will need to be compared to laparoscopic methods by appropriately designed randomised controlled trials. Laparoscopic donor nephrectomy removes some of the disincentives to live kidney donation and should be introduced more widely. The operation is a technical challenge that requires a high-level of laparoscopic expertise and this is still limiting its dissemination. The development of specialised training programmes remains both an opportunity and a challenge for the surgical transplant community. There are now three national fellowships for laproscopic transplant nephrectomy from Royal College of Surgeons and British Transplant Society.

In conclusion, the results of this study support two out of the three hypotheses that were stated in chapter three:

- Laparoscopic live donor nephrectomy leads to less postoperative pain, an improved recovery back to normal activities and better cosmetic results, when compared with traditional open donor nephrectomy
- The benefits of laparoscopic donor nephrectomy over traditional surgery are achieved without greater morbidity in the kidney transplant recipient.

Finally, as the studies presented here were in the context of a well conducted randomised controlled trial, the level of support for these hypotheses should be regarded as strong.

CHAPTER FIVE: COMPARISON OF TECHNIQUES 0F VASCULAR CONTROL IN LAPAROSCOPIC DONOR NEPHRECTOMY

5.1 Introduction

In the United Kingdom, the waiting list for cadaveric transplants continues to increase. However, the potential to expand the number of cadaver kidneys is limited. The potential to increase the number of living donor kidneys is much greater. Laparoscopic donor nephrectomy (LDN) has been developed in an attempt to increase the frequency of kidney donation by reducing the disincentives to donation[45]. The first successful LDN was performed by Ratner *et al* in 1995[29]. Preventing complications for living kidney donors must be paramount in addressing end-stage renal failure through living kidney donation. Major haemorrhage from technical failure, albeit an infrequent occurance can cause significant, yet preventable morbidity or death. Open and laparoscopic approaches to living kidney donation use several vascular control methods, some of which may be more prone to failure and life endangering haemorrhage than others. A crucial step in LDN is to control and ligate the renal pedicle safely, but at the same time obtaining sufficient vessel length to allow transplantation of the kidney. Routinely a linear stapling device or metal clips have been used to obtain vascular control. Herein, our experience is reported using polymer clips (Hem-o-lok®) for control of vessels during LDN.

5.2 Patients and Methods

A consecutive series of 106 patients undergoing transperitoneal LDN were studied prospectively. There was no selection on the basis of body mass index (range 19-41kg/m^2) or because of difficult vascular anatomy, although in general the left kidney was preferred to the right in view of renal vein length. The vascular anatomy of all the donors was assessed preoperatively by spiral CT angiography (CTA).

All LDNS were performed in the modified flank position with a break in the operating table. The access was transperitoneal using 3 to 4 ports (10/12mm) and 30^0 optics; intraperitoneal pressure was maintained at 12 to 15 mmHg. The first six right nephrectomies were excluded from analysis because the renal vein was controlled with a Satinsky clamp placed through a short right upper quadrant incision and then secured with a vascular suture. The next 100 consecutive cases underwent 'pure' laparoscopic nephrectomy. In this series the renal vein was controlled either with a endoscopic linear vascular stapler-cutter (ETS, Ethicon, Endosurgery, Germany; Figure 1) or with 10mm polymer clips (Wecks Closure Systems, Research Triangle Park, NC; Figure 2). The renal artery was secured by one of three different techniques: endoscopic linear vascular stapler-cutter, endoclips (Autosuture, USA; Figure 3) or polymer clips. When positioned on the vessel, the stapling device applies 3 staple lines proximally and distally and the vessel in between is divided. In the case of clips, 2 or more clips (either polymer clips or endoclips) were applied only on the patient side of the vessel. The kidney was then retrieved using an Endocatch system introduced via a suprapubic transverse incision. The length of all renal arteries and veins was measured to the nearest mm on the back table after the kidney had been perfused.

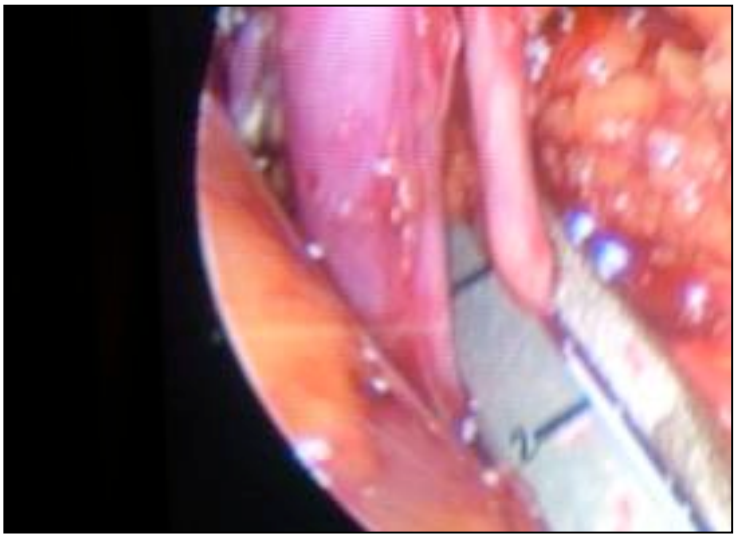


Figure 1 – Endoscopic linear vascular stapler-cutter

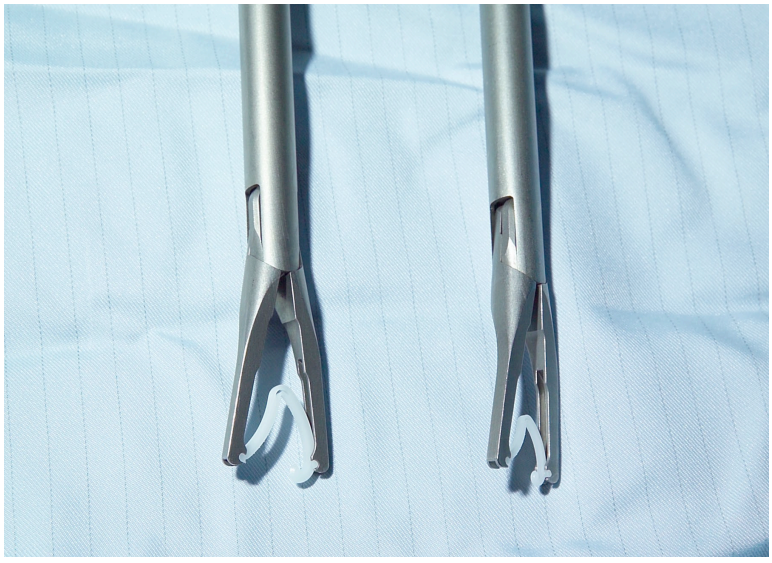


Figure 2 – Hem-o-lok clips for vascular control

Figure 3- Endoclips for vascular control

5.3 Results

One hundred and six live donors underwent LDN (62, women and 44 men). Mean (SD) age was 46 (11) years (range 21-76yr) and body mass index was 25 ± 6 kg/m^2 (range 19-41). Six patients were excluded from the study due to the reasons mentioned in the methods. Of the remaining 100, 19 patients underwent right-sided nephrectomy and 81 underwent left LDN. Three patients in the stapling device group had 2 arteries while in the polymer clip group two patients had 2 arteries and one patient had 3 arteries. In the endoclip group, all patients had single vessels.

Renal vein lengths after stapling (n=76) and application of polymer clips (n=24) were 36 ± 10 versus 37 ± 9 mm respectively (P=0.463; Table 1). There was one episode of stapler malfunction in renal vein division that required the use of a second device.

Renal artery length (mean ± SD) was greater using polymer clips (n=24) compared to stapling (n=56) (34±8 vs 30±7 mm; P=0.030) but there was no difference in arterial length between the endoclip (n=20) and polymer clip groups (34±10 vs 34±8; P=0.850). Renal artery length was greater using endoclips compared to stapling but this was of marginal significance (p=0.0551). In one patient the arterial endoclips were accidentally dislodged during stapling of the renal vein. This led to brisk haemorrhage and immediate conversion to an open operation. The patient required a four-unit blood transfusion but the kidney was retrieved and transplanted successfully.

The mean warm ischemic time (WIT) was longer using polymer clips compared to stapling (296±100 vs 236 ±62 s; p=0.0015). There were no statistical differences between WIT using endoclips (256±100 s) and stapling (p=0.3044) or endoclips and polymer clips (p=0.2044). None of the recipients had delayed graft function.

5.4 Discussion

Laparoscopic donor nephrectomy is technically difficult and considerable care and laparoscopic experience is needed to ensure the safety of the donor and the recipient. Descriptive studies have reported that the morbidity of LDN was less than with open donor nephrectomy (ODN) and that the long term renal graft function of LDN was equivalent to that of ODN[29,97,98]. One of the major concerns of LDN is obtaining a sufficient length of vessels in order to allow uncomplicated transplantation into the recipient.

This is a consecutive series where in the different techniques of ligation were used as they became available in the department. Initially, a stapling device was used for the renal vein and endoclips were used for the artery. However, after the incident of dislodgement of the clips stapling device was used for the renal artery as well. In all the cases, the renal vein was stretched up tight enough to ensure the ligating device goes all the way down to ensure maximal length.

In this study there were no significant differences in renal vein lengths in the stapling device and polymer clip groups. In contrast, Chueh SC *et al*[99] has reported greater renal vein length with polymer clips compared to stapling (approximately 4mm difference). We found that the length of the renal artery was significantly longer in the polymer clip and endoclip groups when compared to the stapling device. The stapling device places three rows of staples on each side of the arterial division point. Removal of the staple line during back-table dissection leads to loss of arterial length. Baldwin *et al*[100] have used polymer clips in hand-assisted LDN (HALDN) and also found that this technique allowed for additional vessel length.

In our series, a malfunction of the stapling device occurred in one patient, while in another case the endoclips were dislodged during stapling of the vein and the surgery had to be

converted to an open procedure. Maartense S *et al*[101] has reported 2 cases of renal artery clip dislodgement during HALDN. Hsu TH *et al*[102] have reported 8 cases (2.3%) of renovascular complications in their series which included 2 cases of failure of stapling device, 4 cases of vessel laceration during stapling and 2 cases of clip dislodgement. We did not see any incidents of slippage nor complications when using polymer clips. These clips have a locking mechanism, which may increase security compared with standard metal clips. Furthermore, there was a saving of approximately £200 per patient. Similar findings have been in other studies[99,100,103] .

The longer WIT in the polymer clips group could also be because we used only one clip applier and this could be avoided by using two appliers to skip the time of re-loading clips by the scrub nurse. However, whilst WIT was significantly longer using polymer clips compared to stapling, this was not reflected in post-transplant allograft function as there were no episodes of delayed graft function in this series.

In a recent news announcement by the manufacturers of the polymer clips used here (Wecks Closure Systems, Research Triangle Park, NC) the use of these clips has not been recommended for renal arterial ligation in laparoscopic live donor nephrectomy. This is because of unpublished reports of the renal arterial clip coming off in two donor cases. However, to the best of our knowledge only one clip was used in these cases therefore, these mishaps could be avoided by using two or more clips.

5.5 Conclusion

In this series, we found that the vascular control of renal pedicle was safe with hem-o-lok polymer ligating clips. This however did not reach any statistical significance as compared to other devices. Hem-o-lok clips also allow for longer vessel length and are more cost effective.

CHAPTER SIX: COMPARISON OF RIGHT AND LEFT LAPAROSCOPIC LIVE DONOR NEPHRECTOMY

6.1 Introduction

Laparoscopic live donor nephrectomy (LDN) was first introduced in 1995[29] with the hope of reducing some of the disincentives to live kidney donation. LDN is the gold standard method in the USA and is fast emerging as such for the procurement of kidneys over open nephrectomy in most centres in the UK. The advantages of LDN have previously been well documented, with shorter hospital stay, better cosmesis, earlier return to work, reduced pain, better respiratory function after surgery, and better overall patient satisfaction [43,83,92].

Since its introduction, the technique for LDN has continued to be refined. Traditionally, surgeons have preferred left LDN because the vein is longer, with right nephrectomy being reserved for cases of complex left-sided anatomy or when the right kidney is smaller. Initial concerns focused on the shorter right renal vein, and the increased complexity of the recipient procedure with a possible need for vein reconstruction[87]. Other authors cited the increased risk of venous thrombosis[104], risk of bleeding from the inferior vena cava (IVC), and liver damage during retraction[105]. The aim of the present study was to compare the anatomy and function of right and left kidneys retrieved by LDN.

6.2 Patients and Methods

This was a prospective study of 130 consecutive transperitoneal LDNs performed between 2004 to 2006. Donors were assessed using a standardized format with spiral CT angiography used for vascular assessment. One hundred and five left and 25 right donor kidneys were procured during the study period. The right kidney was chosen in patients who had complex left sided anatomy or multiple vessels in the left kidney (Table 1). Two different right sided LDN techniques were used. The initial technique involved laparoscopic dissection of the kidney and renal vessels, followed by control of the IVC with a Satinsky clamp introduced through a 6-8cm right upper quadrant incision. The kidney was then removed through the same incision in 6 patients. In the subsequent technique, the IVC was completely mobilised by laparoscopic retrocaval dissection in 19 patients. This allowed the use of a linear stapler-cutter to be placed so that the caval ostium was included with the renal vein. The right kidney was then removed through a short Pfannensteil incision. All left kidneys were procured using the same technique and were removed through a Pfannensteil incision. Anatomical features of retrieved kidneys were recorded prospectively.

6.3 Results (Table 2)

There was no differences in mean donor age (48 vs 47 yrs) or M:F sex ratio (45:60 vs 10:15) for left and right nephrectomy respectively. Left kidneys had statistically significantly longer renal veins than right kidneys (38 ± 9 vs 27 ± 6 mm; $p<0.05$). There were no differences in arterial length between the sides (32 ± 9 vs 31 ± 6 mm, $p=0.83$). Three of the 25 kidneys required renal vein lengthening on the back-table using recipient saphenous vein grafting. The donor operating time was significantly shorter for right-sided LDNs (118 ± 26 vs 175 ± 39 min; $p< 0.05$). Two of the 130 donors (2%) required conversion from LDN to open operation due to intaoperative bleeding; both were left sided donors. The serum creatinine levels for the recipients were similar at 3 months, 131 ± 25 and 134 ± 28 μmol/L for right and left kidneys, respectively. There was no operative mortality and no episodes of delayed graft function, venous thrombosis or liver/splenic injury.

Multiple left arteries	14
Complex venous system	9
Right sided pathology(renal cyst)	1
Other	1

Table 1 – Reasons for procuring right kidney

	Left (n=105)	**Right (n=25)**
WIT (mins)	4.2	3.8
Vein length (mm)	38*	27*
Saphenous vein extension	0	3
Artery length (mm)	32	31
Operating time (min)	175*	118*
Conversion to open	2	0

Table 2 – Results (* Denotes statistical significance, $P<0.05$)

6.4 Discussion

LDN presents a unique surgical challenge, particularly with complex venous or arterial anatomy, making preoperative anatomical assessment of paramount importance. Left LDN remains the side of choice where possible, because the renal vein is longer. The potential technical difficulty of harvesting the right kidney laparoscopically is shortening an already innately shorter renal vein, increasing the complexity of the recipient procedure.

In accordance with the others[58,59] the surgery was faster for right LDN, suggesting that right LDN is technically easier. However, there was a greater need for back-table reconstruction of the right renal vein, requiring saphenous vein harvesting. In our series we found that despite the shorter renal vein, the functional results of right and left kidneys were equivalent, with no evidence that right LDN transfers morbidity from the donor to the recipient. Other studies confirm these equivalent functional results for left and right LDN[58,60].

The initial difficulties with right LDN described by Ratner *et al*[29], have not been confirmed by subsequent authors, probably as a result of modifications and improved techniques. As experience increases, it is likely that LDN will become the standard technique in the UK, with fewer criteria for right LDN.

CHAPTER SEVEN: QUALITY OF LIFE AFTER NEPHRECTOMY FOR LIVE DONOR KIDNEY TRANSPLANTATION

7.1 Introduction

Live donor kidney transplants have many advantages. First, live donor transplants are performed as a planned elective procedure and this allows for the donor and their recipient to be worked up to the point that they are both in an optimum condition at the time of the operations. Second, there is no waiting list for live donor transplantation. Third, live donor transplantation can be performed pre-emptively thus avoiding the need for a period of dialysis with all its disadvantages. Finally and perhaps most importantly, live donor kidneys are taken from healthy individuals with excellent renal function and tend to be of a higher quality than kidneys taken from deceased donors who have usually had significant co-morbidities prior to donation. These differences between live and deceased donor kidneys are reflected in the outcome data, which show improved patients and transplant survival in recipients of live donor kidneys compared to deceased donor kidneys[16,107-109].

The advantages of live donor kidney transplantation come at an important cost: a completely well individual must subject themselves to all of the risks of a major surgical operation without any benefit to their own physical health. Although this act of bravery and altruism is done to help a loved one with a chronic disabling condition, it remains a unique situation in medical practice. The risks of donor nephrectomy are beginning to be well quantified. Of particular importance, the mortality of donor nephrectomy has been studied in the UK by examining national statistics from the NHS Blood and Transplant Service. During the period November 2000 – June 2007, 2509 live donations were performed in the UK and the operative mortality (death within 30 days of surgery) during this time was zero. There was, however, a single death from a myocardial infarction 3 months post-operatively in this series[110]. Kidneys donors are also subjected to all the surgical complications of major

abdominal surgery. These include bleeding, injury to other organs including the spleen, bowel and nerves, wound and chest infections, deep vein thrombosis and pulmonary embolism, wound pain and hernia and adhesions causing bowel obstruction. In addition, blood pressure increases after donation and there is a risk of developing microscopic proteinuria[17].

Much less is known about the effects of live donor nephrectomy on the subsequent quality of life of the donor. This is an interesting area for study as on the one hand donor nephrectomy may adversely affect quality of life due to the recovery required from major surgery but on the other hand there may be important psychological benefits derived from the act of altruism. There are also many factors that could affect quality of life after kidney donation such as the relationship between donor and recipient (parent to child; child to parent; sibling-to-sibling; spouse-to-spouse etc) and the outcome of the kidney transplant in the recipient. In addition, there have been recent improvements in the way that donor nephrectomy is carried out and the newer less invasive operations performed by laparoscopic surgery may have an influence on donor quality of life.

The trials reported by Andersen *et al*[104] and Kok *et al*[39] contained data relating to donor quality of life. Andersen *et al*[104] analysed donor SF-36 scores at baseline and 1, 6 and 12 months post-transplantation. The authors found statistically significant deteriorations from preoperative baseline to one month postoperatively in almost all eight subscales of the SF-36. The only exceptions were 'general health' in the laparoscopic group and 'mental health' in the open group, which did not differ between baseline and one month. In a comparison of laparoscopic and open groups, a significantly greater deterioration in body pain scores between baseline and 1 month was recorded by the open nephrectomy group. However, no significant differences in overall quality of life were found between the laparoscopic and open groups at 1, 6 and 12 months post-donation. In addition, there were no significant differences

between the laparoscopic and open donors when asked about perception of the surgical scars or impact on personal finances. Interestingly, one donor in each group reported that they would not donate again if this were possible.

Donors in the trial reported by Kok *et al*[39] were reviewed in the clinic at three weeks, three months and one year post-donation. They were asked to complete forms relating to body image, fatigue and quality of life at these time-points. Body image was assessed using the body image scale, which consists of an assessment of attitude to bodily image and a cosmetic scale to assess satisfaction with the appearance of the scars. Fatigue was assessed using the multidimensional fatigue inventory and health related quality of life was assessed using the SF-36. For each of the eight SF-36 dimensions a 5 point difference in the raw score (range 0-100) between the laparoscopic and open groups was considered to be statistically significant. The results showed no differences in body image scores for laparoscopic versus open (medians 20 vs 20; p=0.4) and no differences in cosmetic scores (median 20 vs 18 for laparoscopic vs open; p=0.14). Donors undergoing laparoscopic surgery had more motivation and lower physical fatigue scores using the multidimensional fatigue inventory. At the 1 and 12 month time points laparoscopic donors demonstrated higher scores in 2 of the 4 physical health SF-36 dimensions and all 4 of the mental health dimensions. Overall, there was compelling evidence that the laparoscopic operation was associated with improved quality of life.

Quality of life after kidney donation

There is little information in the literature on the quality of life after donating a kidney. This aspect of live donation seems to have been given little attention and there are many questions to be answered. In particular, there are few studies of the effects of the different types of available surgery. Minimally invasive surgical approaches may reduce postoperative pain and speed recovery back to normal activities, and so remove some of the disincentives to kidney donation. The effect of this surgical innovation deserves study, as this may be another way of increasing the kidney transplant rate from live donors.

Methods of evaluating quality of life

Clinicians, families and the patients themselves may have a very different view of the patient's quality of life and the goals of therapy. Quality of life is clearly a rather subjective construct, which varies with the type of patient studied. It is generally conceptualized as a multi-dimensional construct made up of several independent domains including physical health, psychological well-being, social functioning and subjective sense of life satisfaction. Each quality of life domain can be assessed from several different stand-points including the patient and the care-giver. The relatively weighing of the importance of each domain can vary from one observer to another.

A number of instruments are available for the study of quality of life. These include the General Psychological Well-Being Inventory (Dupuy)[111], the Health Perceptions Questionnaire (Ware)[112], the Health Insurance Experiment (Brook et al)[113], the Functioning and Well-Being Profile (FWBP; Stewart and Ware)[114] and various physical and role

functioning measures (Patrick *et al*[115]; Hulka and Cassel[116]; Reynolds *et al*[117]). The FWBP contained 149 items and this was the source instrument for the development of the Short Form-36 instrument.

Some rather more sophisticated quality of life indices are also available, for example the Wisconsin Quality of Life Index. (W-QLI; Diamond and Becker)[118]. This is based on a patient questionnaire, which employs a multi-dimensional measurement tool that reflects the personal priorities and goals of individual mental health patients. This system defines quality of life using nine domains: general life satisfaction, activities and occupations, psychological well being, physical health, social relations/ support, economics, activities of daily living, symptoms and goal attainment. An inventive and attractive aspect of the W-QLI is that it includes other instruments designed to assess quality of life from the perspective of the health care provider and the caregivers. There is another form of the Wisconsin Quality of Life Index, which measures the patient's quality of life from a family member or significant other's point of view. This can also be assessed using a questionnaire designed for the family member. This addresses the level of satisfaction with various aspects of family life. Whilst this type of detailed study was considered for use in the Leicester donor nephrectomy trial, after discussion amongst transplant team members it was felt that this was probably more suited for the study of patient's with chronic mental illness and that the need for health care providers, caregivers and family members or loved ones to complete questionnaires was too complex and labour intensive in an already detailed randomized trial.

The Short Form 36 Instrument for the measurement of quality of life

After a review of the literature and discussion with colleagues, it was decided that a quality of life assessment instrument that examined health related quality of life, with physical and

mental components would be the most relevant and important for the study described in this dissertation. The Short Form-36 questionnaire was chosen as a well-validated quality of life instrument that has been extensively used in other related studies. The SF-36 is relatively easy to use and as it has already been widely used in the field this will allow comparison between the present stud and those already reported in the literature.

The standard form SF-36 was first made available in 1990 (Ware and Sherbourne)[119].

The SF-36 is a short health survey that contains only 36 questions and has multi-purpose usage. It is a generic instrument and as such does not target a particular age group, disease or treatment. The SF-36 yields an eight-scale profile of functional health and well-being summarized by two overall scores of psychometrically based physical and mental health (Turner-Bowker *et al*)[120]. This makes it suitable for use in the study of quality of life after live donor nephrectomy.

As previously stated one important reason that the SF-36 was chosen is that it has been judged as the most widely evaluated generic patient assessed health outcome measure. The SF-36 has been used to evaluate and compare disease specific benchmarks with general population norms in more than 200 conditions and diseases and this has included studies in transplantation (Turner-Bowker *et al*)[120].

Version 2 of the SF-36, which will be used in the present study, was introduced in 1996 (Ware *et al*)[121]. This modification of the original instrument included improvements in instructions and questionnaire items to shorten and simplify the wording and make it more easily understood and less ambiguous. The layout was also improved so that the form was easier to complete and reduced missing responses.

The taxonomy of items and concepts underlying the SF-36 scales has three levels: the items, the eight scales and the two summary scales (physical and mental health). The eight scales are hypothesized to form two higher ordered clusters due to the physical and mental health variance that they have in common. Factor analytical studies confirm that physical and

mental health factors account for 85% of the reliable variance in the general population (Ware *et al*) [122].

Internal consistency and test-retest methods have been used to estimate the reliability of the SF-36. Published statistics suggest that the reliability is very high (0.7-0.8) (Tsai *et al*[123]; McHorney *et al*) [124]. The content validity of the SF-36 has been compared to that of other widely used generic health surveys (Ware *et al*) [121]. Systematic comparisons indicate that the SF-36 includes the most frequently measured health concepts. There are, however, some areas of health not included such as adequacy of sleep, cognitive functioning, sexual functioning, family functioning, eating, recreation/hobbies, communication and symptoms specific to a particular condition.

7.2 Aims

Kidney donation is a complex area of medical practice. Whilst it is established that the mortality and surgical complication rates are low, the psychosocial risks and the effects on quality of life are less well understood. It might be expected that kidney donation would lead to an improvement in self-esteem but our personal experience includes outcomes where family relationships are disrupted with episodes such as depression and even divorce. At the same time, the process of live donor work-up and the operation to remove the donor's kidney have improved over the last decade and these factors may have an influence on quality of life after donation.

There is therefore a need to study the effects of kidney donation on the donor' subsequent quality of life. Such analysis will need to take into account the influence of traditional open and the newer laparoscopic live donor nephrectomy operations on outcome including quality of life. Undoubtedly, the best way to do this is in the setting of a randomized controlled trial of the two different operative techniques.

Hypothesis

The hypothesis is:

Laparoscopic live donor nephrectomy improves quality of life in the donor when compared to traditional open donor nephrectomy patients.

7.3 Patients and Methods

This is a part of the randomised controlled trial described in chapter four. Therefore, the patients were randomised into the two groups of laparoscopic donor nephrectomy and traditional open donor nephrectomy. The randomisation and techniques of the procedure was as previously described.

The primary outcome of this study was - Health related quality of life 6 weeks after kidney donation measured using Short-Form 36 questionnaire. This included physical and mental components of quality of life.

The secondary outcome was – whether or not the donor would make the same decision to donate again if this were possible.

Health Related Quality of Life Assessments

These were made using the English language version 2 short form 36 (SF-36) Health Survey Questionnaire (Ware *et al* 1993[122]; Ware *et al* 2000[121]). The SF-36 includes 1 transition question and 35 questions on quality of life. The transition question asks patients to rate the amount of general health change they have experienced during the past year. The remaining 35 questions are organized into eight sub-scales. The SF-36 is reproduced here in the form used for this study (Table 7.1):

Table 7.1: The Short Form-36 Questionnaire

Short Form 36
Quality of Life Questionnaire

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent……1
Very good……..2
Good……...3
Fair…….4
Poor…….5

2. **Compared to one year ago**, how would you rate your health in general **now**?

(circle one)

Much better than one year ago…….1
Somewhat better now than one year ago…….2
About the same as one year ago……..3
Somewhat worse than one year ago…….4
Much worse than one year ago…….5

3. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(circle on number on each line)

ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking one hundred yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. **During the past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. **During the past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. **During the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(circle one)

Not at all……1
Slightly……2
Moderately……3
Quite a bit……4
Extremely……5

7. How much **bodily** pain have you had during the **past 4 weeks**?

(circle one)

None……1
Very mild……2
Moderate……3
Severe……4
Very severe……5

8. **During the past 4 weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all……1
Slightly……2
Moderately……3
Quite a bit……4
Extremely……5

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time **during the past 4 weeks**.

(circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. **During the past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives etc)?

(circle one)

All of the time……..……1
Most of the time……..2
Some of the time…….3
A little of the time……..4
None of the time…….5

11. How TRUE or FALSE is **<u>each</u>** of the following statements for you?

(circle one number on each line)

	Definitely true	**Mostly true**	**Don't know**	**Mostly false**	**Definitely false**
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Patient Number	**Patient Initials**	**Investigator Number**	**Study Phase** **Screening**
Date of Completion:			

The SF-36 was explained to all participants by the author. The donors then used the SF-36 in a self-administered way, completing answers to all of the 36 questions. The SF-36 was completed to obtain baseline values on the day of admission to hospital, which was the day prior to donor nephrectomy. The postoperative SF-36 was completed at the 6-week follow up clinic. At this clinic, all donors were reviewed by the author . The routine checks at this visit were abdominal examination, blood pressure, stick-testing urinalysis for blood and protein, routine bloods for haemoglobin and renal function tests (blood urea and serum creatinine) and an assessment of wound cosmesis. The appearance of the wounds was graded by the patient using a visual analogue scale. This was followed by repeat measurement of the isotope glomerular filtration rate.

The SF-36 was used to assess the following eight health domains using one multi-item scale:

1. Physical functioning
2. Role limitations caused by physical health problems
3. Bodily pain
4. General Health
5. Vitality
6. Social functioning
7. Role limitations caused by emotional problems
8. Mental health

All data was entered into a web-based scoring system (www.qualitymetric.com). The weighted sums of the questions in each of the eight sections were directly transformed into a 0-100 scale on the assumption that each question carries equal weight and with higher scores indicating better health/ quality of life. The eight scale scores were combined to give two higher order summary measures, a physical component from domains 1-4 and a mental component from domains 5-8. The on-line scoring system used an algorithm to convert the raw values into two summary scores by 'normative comparison' with mean and standard deviation scores from studies of the general population.

7.4 Results

Over the four-year period of the trial a consecutive series of ninety-four eligible patients were invited to take part. After attending the standardised information session and power point presentation, which included details of both the traditional open and the newer laparoscopic procedures, ten patients expressed a strong preference for a particular operative approach (7 laparoscopic and 3 open, figure 1). These 10 patients underwent their operation of choice and as they were not randomised, they were excluded from the study. There were no exclusions for any other reason including obesity or complex renal vascular anatomy. A total of 84 patients were randomised in a ratio of 2: 1 for laparoscopic versus open surgery. This yielded 56 donors in the laparoscopic group and 28 in the open group. Despite the careful explanations given, after randomisation three patients randomised to the open group subsequently declined to undergo open nephrectomy and therefore underwent the laparoscopic operation; in line with the intention to treat principle these three patients were analysed in the open group. Baseline donor demographics are presented in Table 7.2. The LDN and ODN groups were well matched with no statistically significant differences between donor or recipient characteristics in the two study groups.

Table 7.2: Donor baseline demographic details

Characteristic	Laparoscopic group (n=56)	Open group (n=28)	P value
Gender (M:F)	20 : 36	14 : 14	0.243
Age (years)	47 ± 12	45 ± 11	0.248*
BMI (kg/m^2)	26.3 ± 5.0	25.6 ± 3.9	0.529*
Related to donor	40 (71 %)	25 (89 %)	0.096
Unrelated to donor	16 (29 %)	3 (11 %)	0.096
Parental donor	18 (32 %)	11 (39 %)	0.627
Kidney (R:L)	12 : 44	6:22	1.000
Employed	41 (73 %)	18 (64 %)	0.623

Values are mean ± standard deviation

Or raw numbers with percentages in brackets

* Normally distributed therefore statistics using Student's t test

Other values analysed using Mann Whitney U test

Donor intra- and post-operative complications (table 7.3)

Although the complications have been previously described in chapter 4, they are repeated here as a comparison of donor quality of life with the complications sustained as been studied. One laparoscopic operation was converted to an open operation due to intra-operative bleeding from the renal artery stump. In this case, the renal artery was controlled with three metal clips and divided without problems. However, the arterial clips were dislodged when an endovascular stapling device was closed around the renal vein but inadvertently included the arterial stump. This situation was managed by immediate conversion through a transverse muscle cutting incision and suture of the renal artery stump; total blood loss was 2 litres and four units of packed red cells were transfused on-table. The donor recovered well and the kidney was successfully transplanted and demonstrated good initial and long-term function. There was also one intra-operative pneumothorax in the laparoscopic group, caused by a leak of carbon dioxide gas through a previously undiagnosed congenital defect in the left side of the patient's diaphragm. A chest drain was inserted intraoperatively and despite a persistent slow leak of the pneumoperitoneum, the operation was completed without conversion. There were no other intraoperative complications in the laparoscopic or open groups.

Overall, postoperative complication rates per donor were lower in the laparoscopic donor nephrectomy group and in particular, chest infections requiring treatment with antibiotics were not seen as often after this operation. This is consistent with the evidence of better postoperative respiratory function after laparoscopic nephrectomy. One patient undergoing the laparoscopic operation needed a further laparoscopic operation for division of adhesions postoperatively at 8 weeks. Testicular swelling and thigh numbness also occurred more commonly after the laparoscopic procedure but this difference was not statistically significant. Wound problems were more common after open surgery. One donor developed a large incisional hernia, one had a nerve entrapment syndrome that required treatment in the pain

clinic and two donors complained of chronic wound pain for several months after surgery. These problems were not seen at all in the laparoscopic group.

Table 7.3: Donor intraoperative and post operative complications

Complication	Laparoscopic Group (n=56)	Open Group (n=28)	P value
Intraoperative			
Haemorrhage	1	0	0.333
Pneumothorax	1	0	0.333
Conversion to open	1	n/a	n/a
Postoperative			
Wound infection	2	2	0.598
Chest infection	5	8	0.027
Thigh numbness	4	1	0.661
Adhesions requiring surgery	1	0	1.000
Testicular swelling	3	0	0.261
Incisional hernia	0	1	0.333
Chronic wound pain	0	2	0.108
Rectus sheath nerve entrapment	0	1	0.333
Overall complications per donor	**0.3 ± 0.5**	**0.6 ± 0.7**	**0.033***

Statistics using Fisher's exact test; * Values are mean ± standard deviation (t test)

Quality of Life Studies

The overall SF-36 norm adjusted physical and mental component scores are shown in figures 7.1 and 7.2. The physical component score (PCS) fell significantly by 6 weeks post-donation in the laparoscopic group (55.1 ± 6.9 to 46.3 ± 8.9; p=0.001). The PCS also fell significantly in the open nephrectomy group (52.7 ± 8.9 to 44.0 ± 7.9; p=0.008). There were no significant differences in the levels of these decreases between the two different operations. The mental component score (MCS) fell significantly by 6 weeks post-donation in the open group (53.5 ± 7.6 to 45.3 ± 10.1; p=0.0084). In contrast, the MCS did not fall in the laparoscopic group (53.8 ± 6.5 to 51.9 ± 7.2; p=0.2931).

Raw Data Scores for Quality of Life

The raw data for each of the eight SF-36 domain scores in both laparoscopic and open groups are summarised in Table 7.4 and shown in figures 7.3-7.10. These graphs must be interpreted carefully. A fall in any of these scores indicates a worsening of health status for that particular domain. If there is no statistical difference between the pre-donation and the 6-week follow up score for a domain then that shows that there has been recovery back to baseline for that item. If a smaller fall in the norm adjusted score for a domain can be shown for one operation over another, then that is in favour of the operation with the smaller fall.

In the laparoscopic group, three of the physical functioning scores fell from baseline to 6 weeks. Physical functioning fell from 94.8 ± 9.2 to 85.3 ± 17.9 (p=0.001). Role limitations due to physical health problems fell from 93.6 ± 20.4 to 71.0 ± 31.7 (p=0.0059). General health fell from 85.0 ± 17.9 to 81.2 ± 16.8 (p=0.05). In contrast, although the bodily pain score fell numerically after laparoscopic nephrectomy (86.4 ± 19.8 to 81.8 ± 15.9), this fall was not significant statistically (p=0.3294).

In the open group, all four physical functioning scores fell by 6 weeks postoperatively. Physical functioning fell from 93.2 ± 12.2 to 79.7 ± 16.1 (p=0.0005). Role limitations due to

physical health problems fell from 88.9 ±16.0 to 76.3 ± 25.7 (p=0.0215). Bodily pain fell from 87.3 ± 18.3 to 69.0 ± 25.0 (p=0.0322). General health fell from 86.3 ± 15.7 to 72.1 ± 18.1 (p=0.0443).

Considering the mental health scores in the laparoscopic group vitality and social functioning fell but role limitations due to emotional health problems and mental health were not significantly lower at 6 weeks post-donation. Vitality fell from 75.6 ± 17.8 to 60.3 ± 18.5 (p=0.0001). Social functioning fell from 91.8 ± 15.8 to 79.3 ± 21.4 (p=0.0037). Role functioning was 92.7 ± 18.4 vs 87.5 ± 24.7 (P=0.4961). Mental health was 82.5 ± 13.0 vs 79.8 ± 12.9 (p=0.5399).

In the open group vitality, social functioning and role limitations due to emotional health problems all fell postoperatively but the mental health score did not fall significantly. Vitality fell from 74.4 ± 13.5 to 58.9 ± 18.0 (p=0.0327). Social functioning fell from 91.2 ± 16.4 to 83.6 ± 17.5 (p=0.0078). Role limitations due to emotional health problems fell from 92.6 ± 14.3 to 73.3 ± 31.4 (p=0.0234). The mental health scores were 83.5 ± 12.0 vs 71.8 ± 16.6 (p=0.3223).

Table 7.4: Raw Scores for Eight SF-36 Domains

Domain	Laparoscopic		Open	
	Pre-donation	6 weeks	Pre-donation	6 weeks
Physical Component Scores				
PF	94.8 ± 9.2	85.3 ± 17.9	93.2 ± 12.2	79.7 ± 16.1
RP	93.6 ± 20.4	71.0 ± 31.7	88.9 ± 16.0	76.3 ± 25.7
BP	86.4 ± 19.8	81.8 ± 15.9	87.3 ± 18.3	69.0 ± 25.0
GH	85.0 ± 17.9	81.2 ± 16.8	86.3 ± 15.7	72.1 ± 18.1
Mental Component Scores				
VT	75.6 ± 17.8	60.3 ± 18.5	74.4 ± 13.5	58.9 ± 18.0
SF	91.8 ± 15.8	79.3 ± 21.4	91.2 ± 16.4	83.6 ± 17.5
RE	92.7 ± 18.4	87.5 ± 24.7	92.6 ± 14.3	73.3 ± 31.4
MH	82.5 ± 13.0	79.8 ± 12.9	83.5 ± 12.0	71.8 ± 16.6

Values are mean ± standard deviation

Norm adjusted Scoring of Quality of Life

The raw scores were converted into norm adjusted scores using the web-based system (www.qualitymetric.com). This uses a UK based normal population for comparison of the usual levels of the eight domains in a healthy population.

A breakdown of the individual norm adjusted scores for each of the eight SF-36 domains in the laparoscopic and open groups is shown in figures 7.11-7.18. All four physical component domain scores (physical functioning, role limitations due to physical health problems, bodily pain and general health) fell over the 6 week study period in the open operation group. Physical functioning fell from 53.7 ± 5.3 to 48.5 ±6.7 (p=0.0313). Role limitations due to physical health problems fell from 50.4 ± 9.1 to 44.5 ± 12.1 (p=0.01). The bodily pain score fell from 55.4 ± 10.7 to 43.6 ± 15.1 (p=0.0251). General health status fell from 58.3 ± 6.3 to 48.9 ± 9.3 (p=0.0058).

In contrast, although the bodily pain score fell very slightly in the laparoscopic group, this did not reach statistical significance between pre-donation and the 6 week level (55.3 ± 10.1 vs 52.5 ± 6.7; p=0.1296). This shows that bodily pain had improved by 6 weeks in the laparoscopic group compared to the open operation. The other three physical domain scores also fell in the laparoscopic group. Physical functioning fell from 54.9 ±3.8 to 50.8 ± 7.5 (p=0.0012). Role limitations due to physical health problems fell from 53.6 ± 7.2 to 41.7 ± 11.9 (p=0.001). General health status fell from 57.9 ± 5.5 to 53.9 ± 11.5 (p=0.0209).

In the laparoscopic group norm adjusted mental component scores fell for the vitality and social functioning domains. The role limitation due to emotional health problems and mental health scores were not significantly different between the baseline ands 6-week measurements. The vitality score fell from 58.8 ± 8.5 to 51.2 ± 8.6 (p=0.0001). The social functioning score fell from 53.7 ± 6.8 to 47.9 ± 9.3 (p=0.0103). The role limitation due to emotional health problems for the baseline and 6 week values was 53.1 ± 5.7 vs 48.7 ± 11.0 (p=0.1790). The mental health scores were 54.4 ± 7.3 vs 52.5 ± 7.4 (p=0.6431).

In the open group norm adjusted mental component scores fell for vitality, social functioning and role limitations due to emotional health problems. The mental health score was stable over the study period. The vitality score fell from 58.4 ± 6.7 to 49.9 ± 9.3 (p=0.0391). The social functioning score fell from 52.8 ± 8.8 to 41.9 ± 15.9 (p=0.0199). The role limitations due to emotional health problems fell from 52.4 ± 4.9 to 39.2 ± 14.3 (p=0.0234). The norm adjusted mental health score also fell but this was not statistically significant (54.5 ± 7.0 vs 48.5 ± 9.6; p=0.4688).

Table 7.5: Norm Adjusted Scores for Eight SF-36 Domains

Domain	Laparoscopic		Open	
	Pre-donation	6 weeks	Pre-donation	6 weeks
Physical Component Scores				
PF	54.9 ± 3.8	50.8 ± 7.5	53.7 ± 5.3	48.5 ± 6.7
RP	53.6 ± 7.2	41.7 ± 11.9	50.4 ± 9.1	44.5 ± 12.1
BP	55.3 ± 10.1	52.5 ± 6.7	55.4 ± 10.7	43.6 ± 15.1
GH	57.9 ± 5.5	53.9 ± 11.5	58.3 ± 6.3	48.9 ± 9.3
Mental Component Scores				
VT	58.8 ± 8.5	51.2 ± 8.6	58.4 ± 6.7	49.9 ± 9.3
SF	53.7 ± 6.8	47.9 ± 9.3	52.8 ± 8.8	41.9 ± 15.9
RE	53.1 ± 5.7	48.7 ± 11.0	52.4 ± 4.9	39.2 ± 14.3
MH	54.4 ± 7.3	52.5 ±7.4	54.5 ± 7.0	48.5 ± 9.6

Values are mean ± standard deviation

Summary of Quality of life data

The results are summarised in Table 7.6.

Table 7.6: Summary of Quality of Life Data (change between baseline and 6 weeks post-donation)

	Laparoscopic Group (n=56)	Open Group (n=28)
Physical component scores (raw)		
Physical functioning	⇓	⇓
Role limitations (physical)	⇓	⇓
Bodily pain	⇔	⇓
General health	⇓	⇓
Mental component scores (raw)		
Vitality	⇓	⇓
Role limitations (emotional)	⇔	⇓
Social functioning	⇓	⇓
Mental health	⇔	⇔

⇓ Statistically significant fall

⇔ No statistical difference between baseline and 6 weeks

Effect of Complications on Quality of life

Table 7.3 shows the complications suffered by patients in the two study groups. Some patients suffered more than one complication and the total number of patients with complications was 15 in the laparoscopic group and 14 in the open group. A statistical analysis was performed to compare quality of life in complicated and uncomplicated donors in the two study groups. The results are summarised in Tables 7.7 and 7.8.

Table 7.7: Effect of complications on quality of life after laparoscopic donor nephrectomy

Donors with Complications (n=15)		Donors without Complications (n=41)	
Physical Component Scores			
Pre-donation	6 weeks post-donation	Pre-donation	6 weeks post-donation
54.7 ± 7.2	46.8 ± 8.7	55.1 ± 6.9	47.0 ± 10.3
Mental Component Scores			
Pre-donation	6 weeks post-donation	Pre-donation	6 weeks post-donation
54.2 ± 6.4	51.6 ± 10.7	54.9 ± 12.4	51.3 ± 7.6

Values are mean ± standard deviation

Table 7.8: Effect of complications on quality of life after open donor nephrectomy

Donors with Complications (n=14)		Donors without Complications (n=14)	
Physical Component Scores			
Pre-donation	6 weeks post-donation	Pre-donation	6 weeks post-donation
49.4 ± 11.2	45.7 ± 12.0	48.1 ± 11.8	43.4 ± 12.3
Mental Component Scores			
Pre-donation	6 weeks post-donation	Pre-donation	6 weeks post-donation
54.7 ± 7.9	49.9 ± 9.5	53.9 ± 9.5	47.4 ± 8.8

Values are mean ± standard deviation

In the laparoscopic group there were no significant differences in either the physical component scores ($p = 0.9373$) or the mental health scores at the 6 week time-point ($p = 0.8984$). In a similar way, after open nephrectomy there were no significant differences in either the physical component scores ($p = 4806$) or the mental health scores at the 6 week post-donation time point ($p = 0.4920$).

Figure 7.1: SF-36 Overall Physical Component Scores

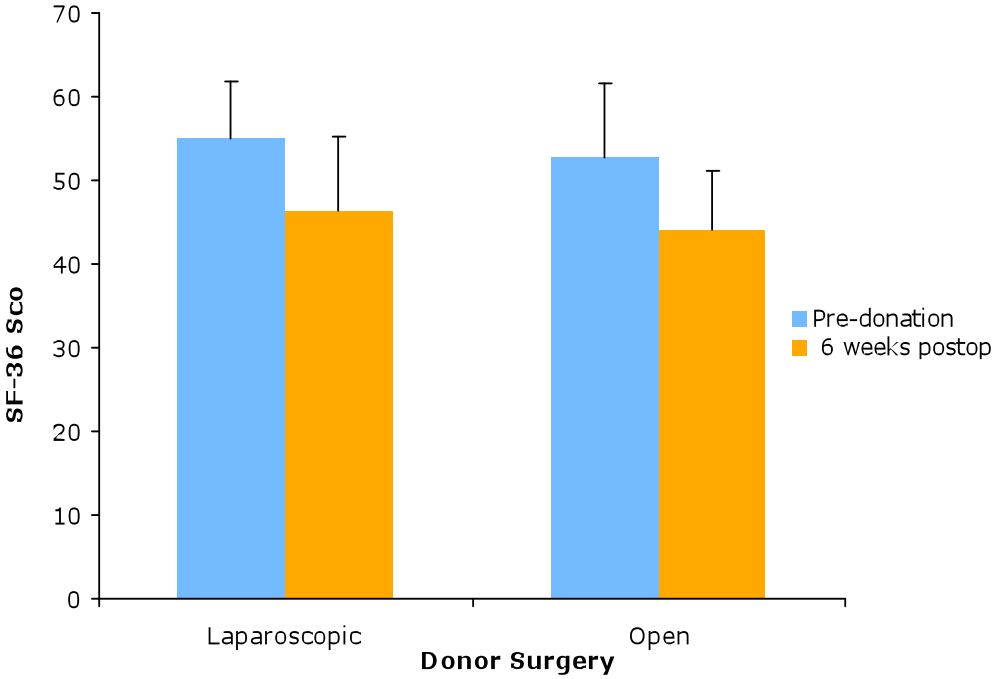


Figure 7.2: SF-36 Overall Mental Component Scores

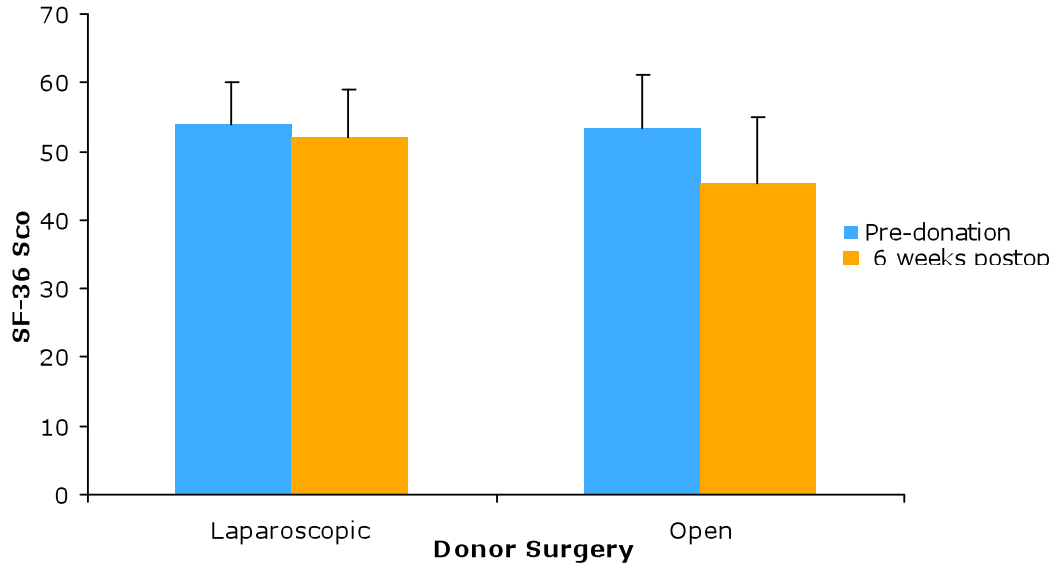


Figure 7.3: SF-36 Raw Scores for Physical Functioning

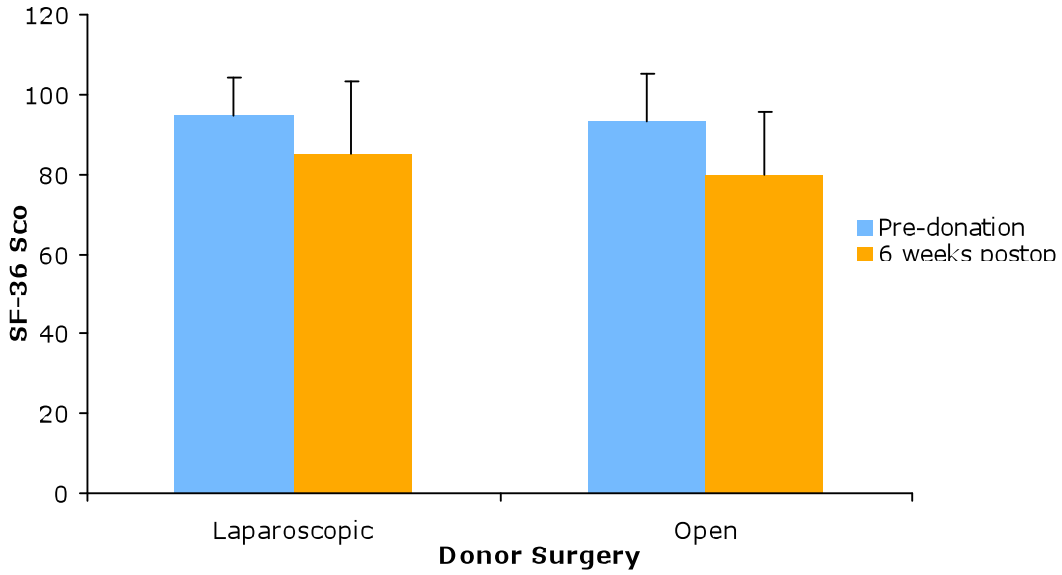


Figure 7.4: SF-36 Raw Scores for Role Limitations caused by Physical Health Problems

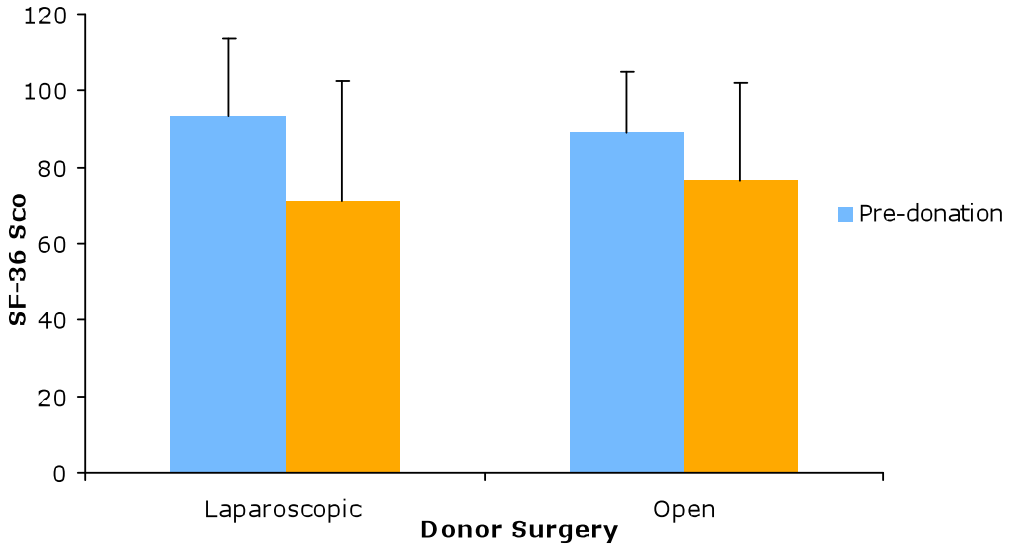


Figure 7.5: SF-36 Raw Scores for Bodily Pain

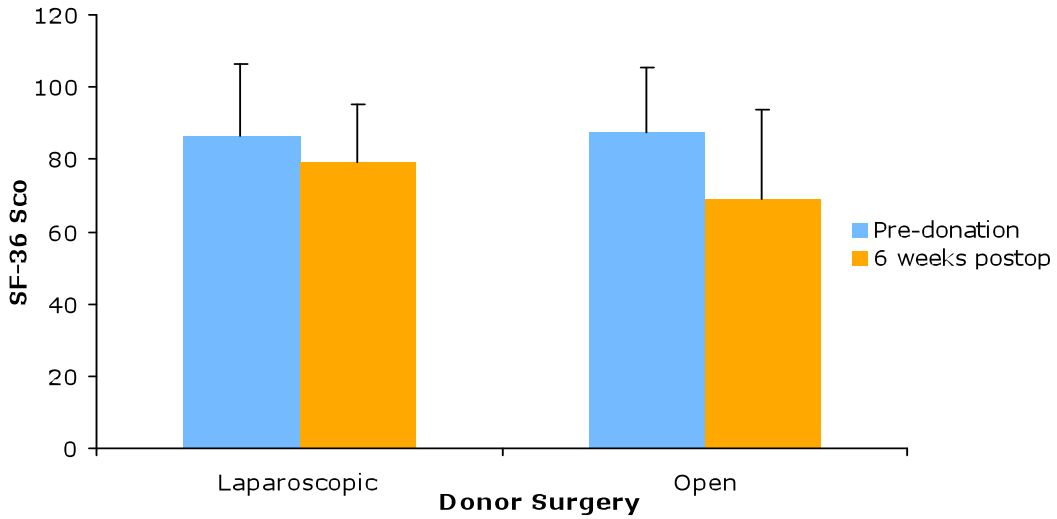


Figure 7.6: SF-36 Raw Scores for General Health

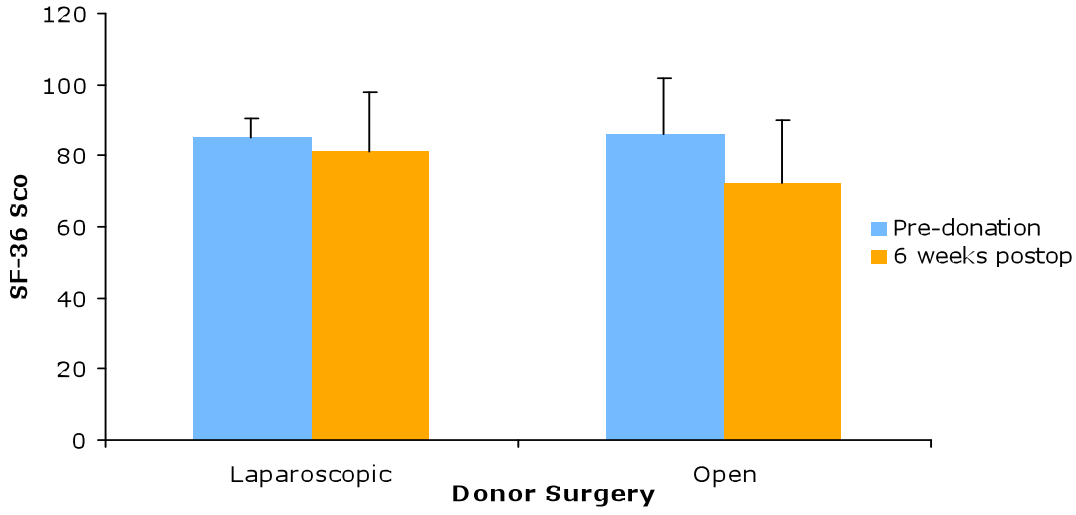


Figure 7.7: SF-36 Raw Scores for Vitality

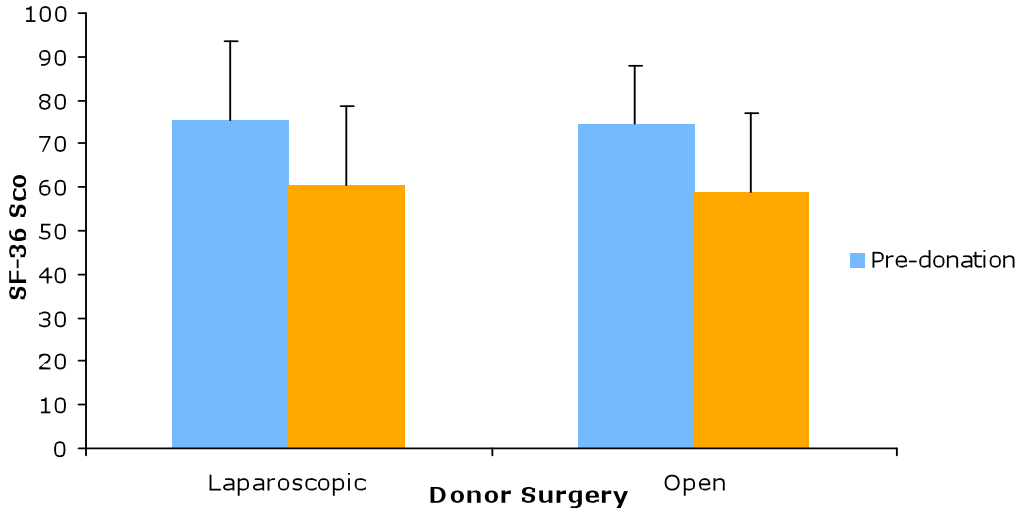


Figure 7.8: SF-36 Raw Scores for Social Functioning

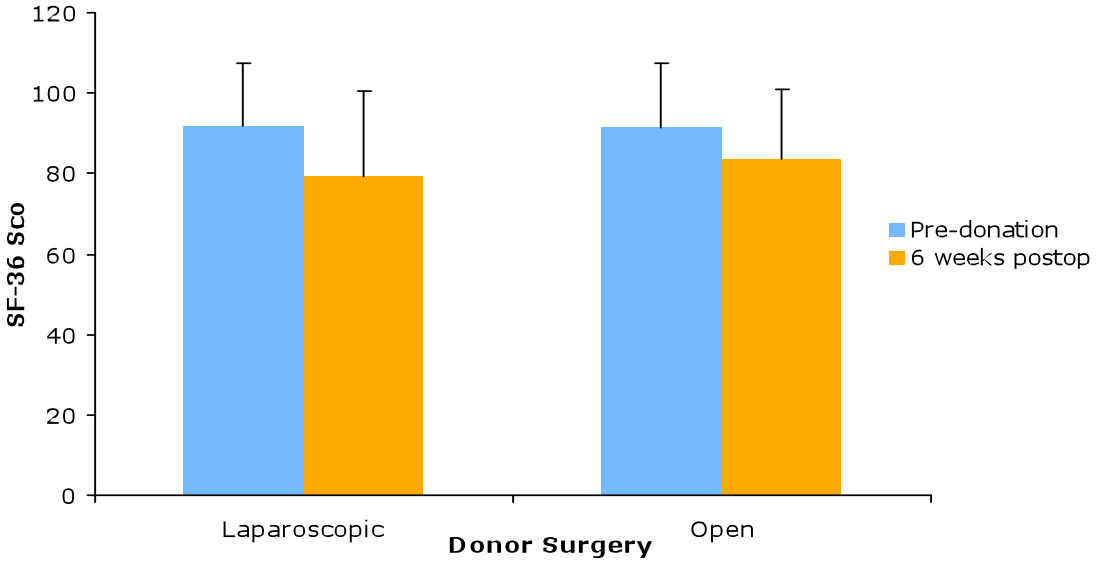


Figure 7.9: SF-36 Raw Scores for Role Limitations caused by Emotional Problems

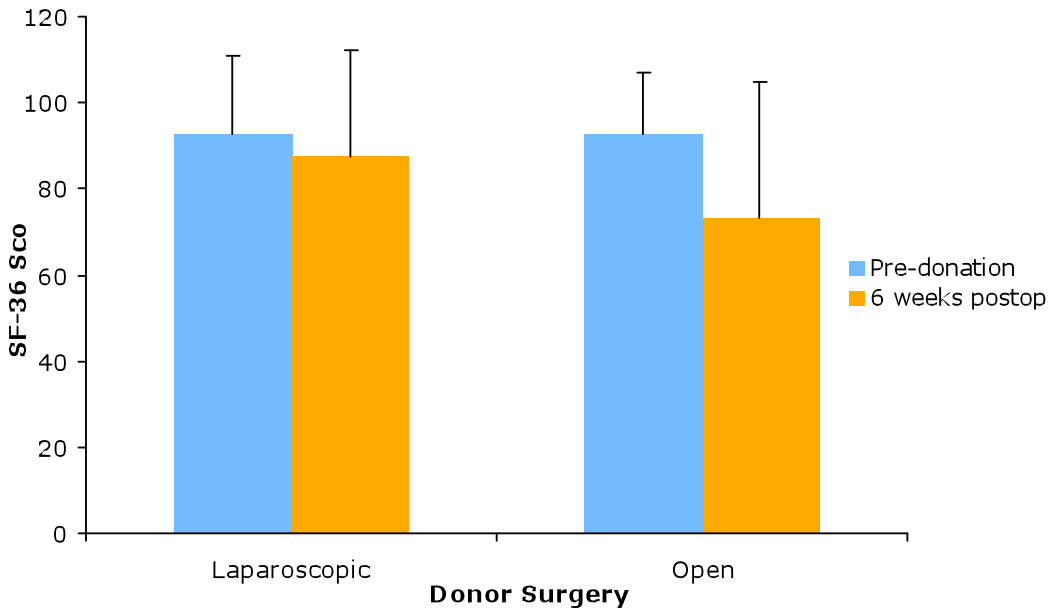


Figure 7.10: SF-36 Raw Scores for Mental Health

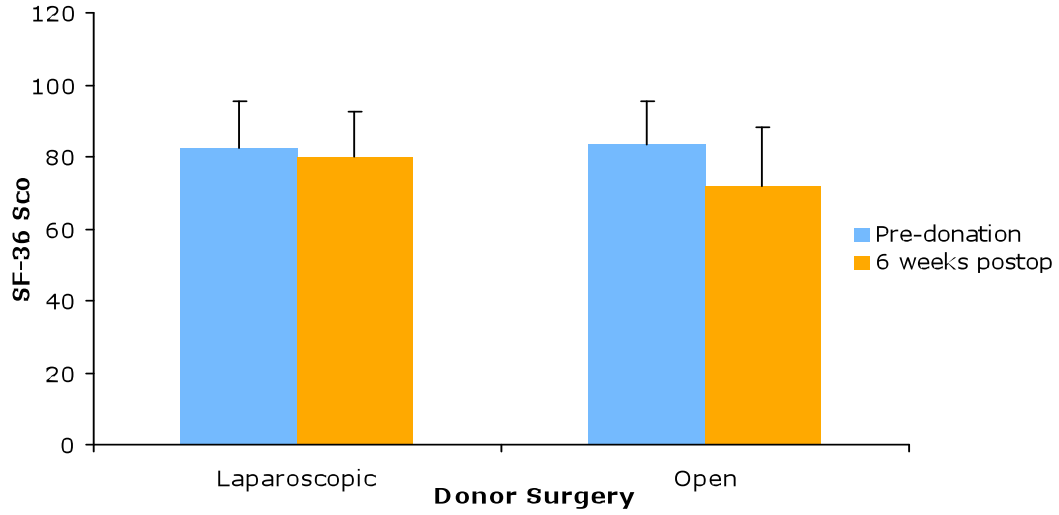


Figure 7.11: SF-36 Normalised Scores for Physical Functioning

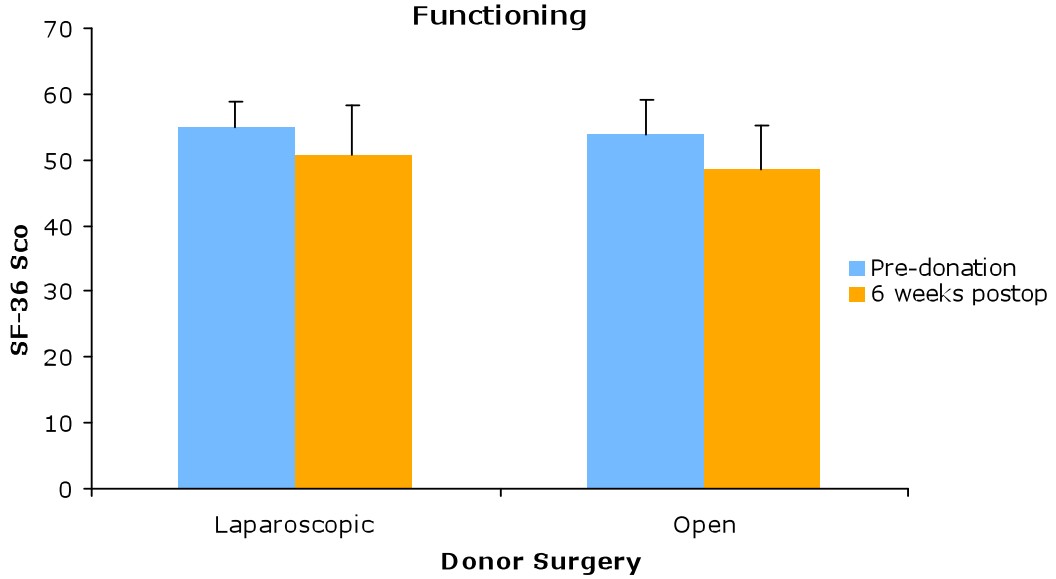


Figure 7.12: SF-36 Normalised Scores for Role Limitations caused by Physical Health Problems

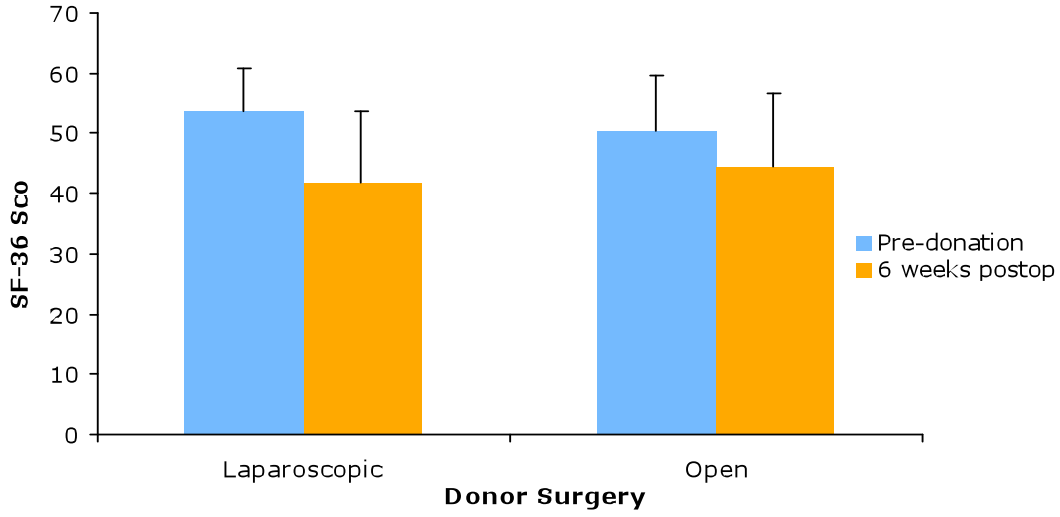


Figure 7.13: SF-36 Normalised Scores for Bodily Pain

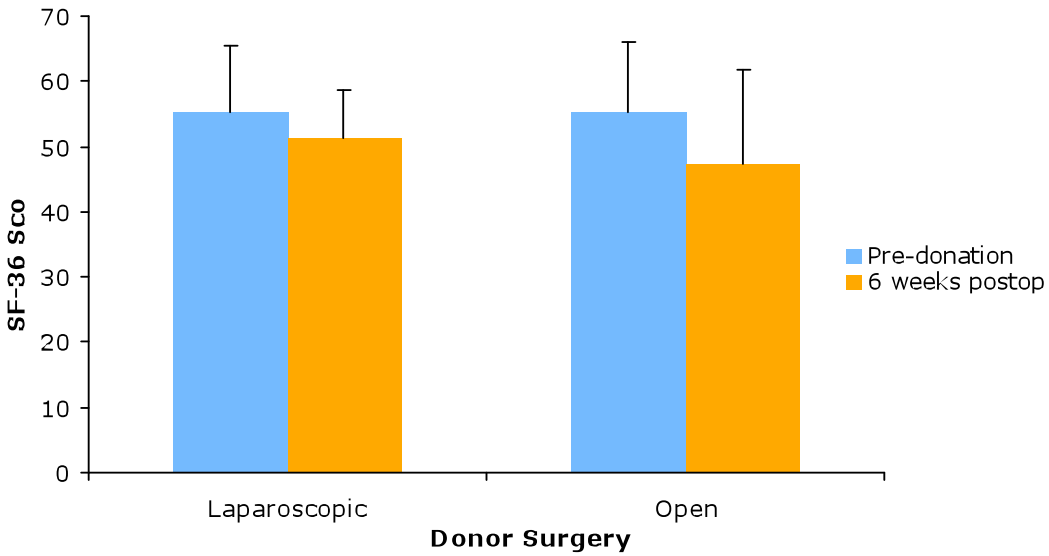


Figure 7.14: SF-36 Normalised Scores for General Health

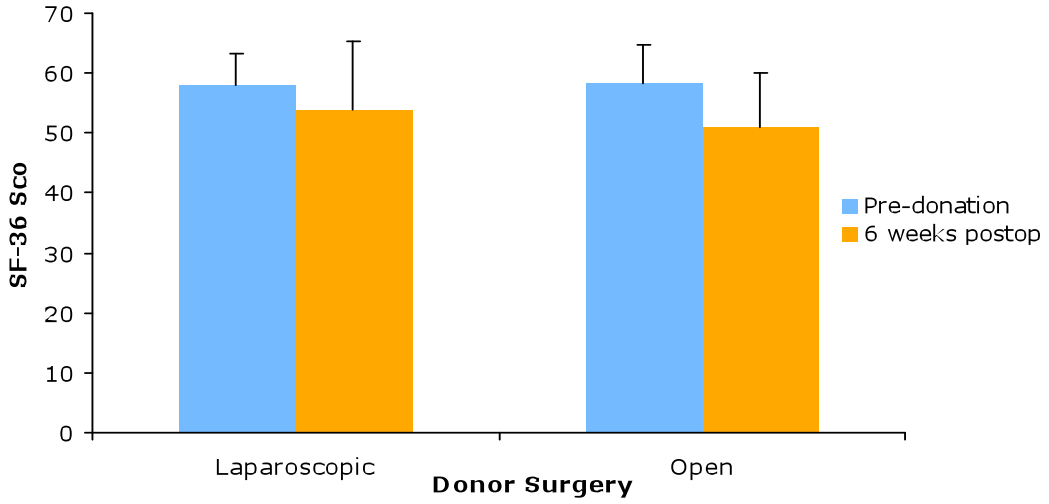


Figure 7.15: SF-36 Normalised Scores for Vitality

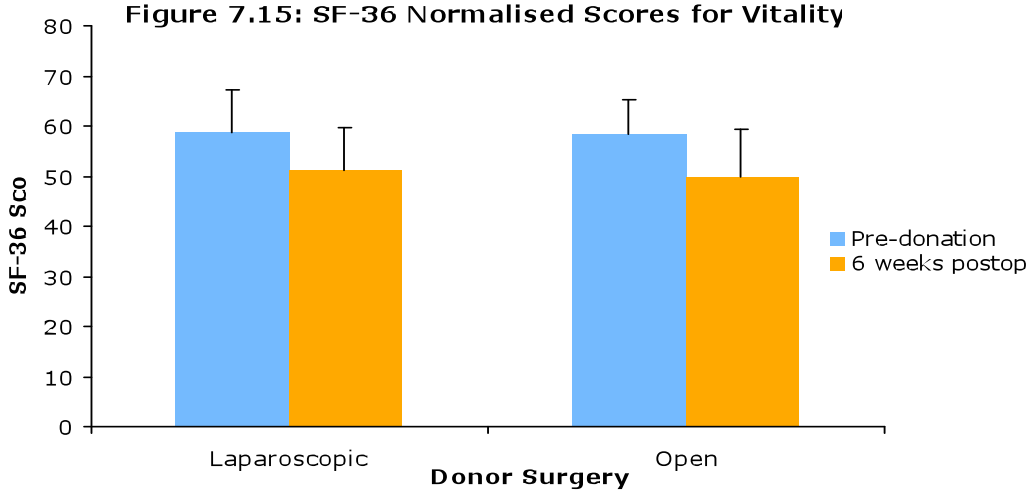


Figure 7.16: SF-36 Normalised Scores for Social Functioning

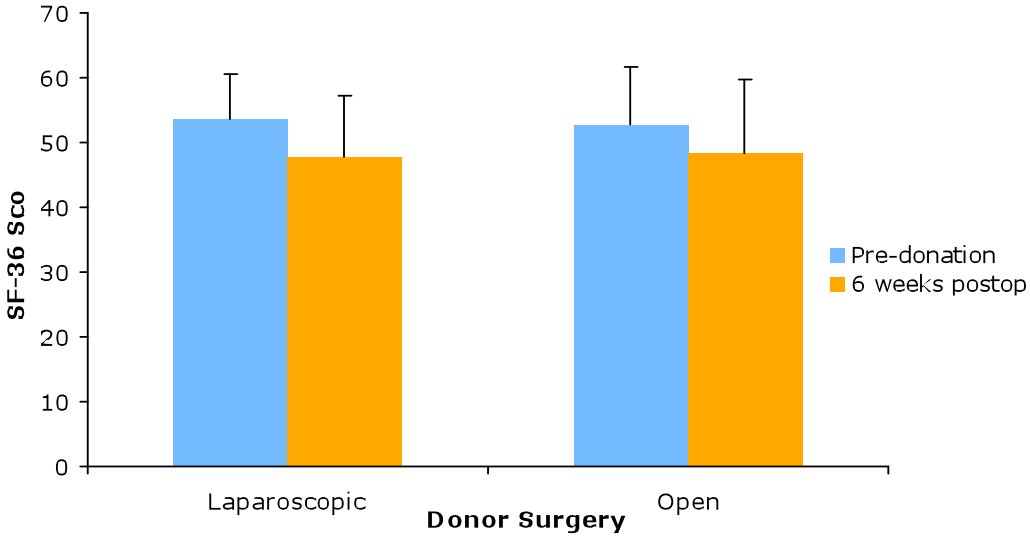


Figure 7.17: SF-36 Raw Scores for Role Limitations caused by Emotional Problems

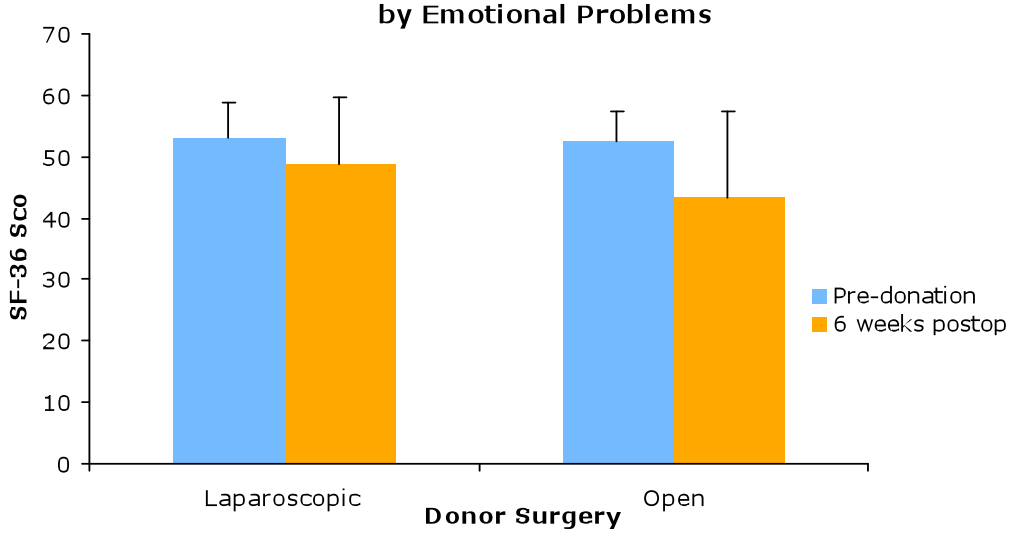
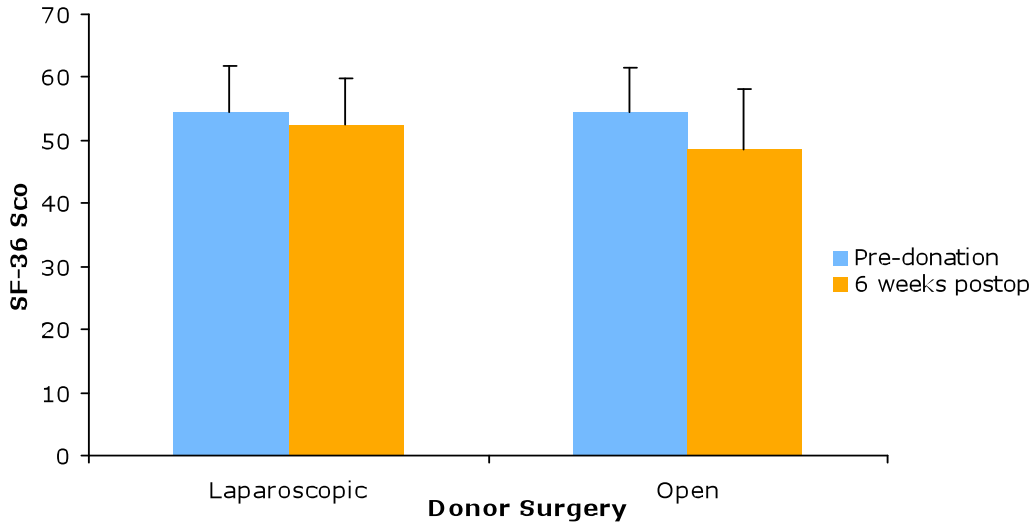


Figure 7.18: SF-36 Normalised Scores for Mental Health



7.5 Discussion

The main finding of this study is that kidney donors undergoing minimal access laparoscopic surgery are advantaged by having an improved mental component score of quality of life when compared to donors who undergo traditional open surgery. Detailed analysis of the eight domain scores from the SF-36 questionnaire shows that the laparoscopic operation reduced bodily pain at 6 weeks post-donation. There was also an improved mental health score in laparoscopic donors.

The most obvious difference between laparoscopic and open operations involves the surgical incisions, which are much shorter in the laparoscopic procedure. The laparoscopic kidney retrieval incision is placed in the suprapubic region of the lower abdomen rather than in the loin during open surgery and this difference in incision site is also an advantage for the laparoscopic group, as lower abdominal incisions are known to be less painful. The surgeons limited the length of the open operation incision as much as possible describing this approach as a 'limited incision nephrectomy'. This was a considerable improvement on the original open operation performed about a decade ago, which involved a very long loin incision and included resection of the twelfth rib in order to access the kidney. Even with a limited approach, the open incision length in this study was an average of 15 cm, which is considerably larger than the 8 cm retrieval incision required for laparoscopic surgery. The open and laparoscopic ('key-hole') approaches lead to very different patient outcomes. Postoperative pain was considerably reduced in the laparoscopic group with significantly lower pain scores measured two different ways and lower postoperative analgesic requirements. The less invasive laparoscopic operation was also associated with improved recovery in other ways. In-patient stay was reduced by an average of 2 days in patients undergoing the laparoscopic operation. Postoperative respiratory function was improved by laparoscopic surgery and these donors resumed oral fluids and diet earlier than those undergoing open surgery. The overall level of postoperative complications was lower in the

laparoscopic group and in particular, there were fewer wound complications and chest infections in the laparoscopic group. Laparoscopic donors also benefited from improved postoperative convalescence with evidence of a quicker return to driving their cars, resuming a normal level of exercise and returning to full-time employment more quickly.

All of these findings show that laparoscopic surgery is less invasive and the reduction in postoperative pain is crucial in leading to the other advantages described. This lower level of postoperative pain and improved recovery is the most likely explanation for the quality of life data obtained. The improved 6-week post-donation mental component score in the laparoscopic donors was due to higher scores in the bodily pain and mental health components of the SF-36 scoring system. Chronic pain leads to a deterioration of mental health and this was why the open donors fared less well in the mental aspects of quality of life. Nevertheless, laparoscopic surgery did not improve the physical components scores of the SF-36 at 6 weeks post-donation when compared to the open group.

The present study has an advantage. Quality of life and donor recovery was studied in the setting of a randomised controlled trial, which provides the highest level of evidence for medical interventions.

The limitation in this study is that donor quality of life was only assessed at the 6 weeks post donation time point. Other studies have followed donors up for a much longer period of time. For example, the study by Andersen *et al*[104] assessed quality of life using the SF-36 at one month, 6 months and 12 months post donation. Review of the literature showed that quality of life always returns to baseline values after a few months and this was the justification for only using an acute outcome (6 weeks) in the study presented in this dissertation.

These findings should be placed into context by comparison with the published literature. The study by Andersen *et al*[104] also used the SF-36 as a quality of life instrument. The Andersen study can be criticized as it only achieves a Jadad[106] score of one, as it does not describe the method of randomization or any details of withdrawn donors. Quality of life was however described at one month post-donation and this should be comparable with the 6 weeks data presented by the author. The findings of the Leicester study are broadly in agreement with the Andersen study, which showed that bodily pain scores fell less in the laparosopic group than the open group and mental health scores did not fall at 6 weeks in either group. However, Andersen also found that the general health score was unchanged in both groups at 6 weeks, whereas this score fell in both groups in the Leicester study. The only other randomized trial to address quality of life using the SF-36 was the study by Kok *et al*[39]. This group found that the bodily pain and role limitations physical domain scores were not significantly different in the laparoscopic and open groups but all other 6 domain scores were lower in the open group. The differences in bodily pain data are difficult to account for but may be due to the fact that Kok[39] *et al* used a muscle splitting rather than muscle cutting loin incision in the open nephrectomy group. Muscle splitting was performed in an attempt to reduce tissue trauma and this may have made their open operation less painful. However, comparison between the Leicester and the Kok[39] findings is difficult as the latter author presented quality of life data only as estimated differences between the groups (laparoscopic nephrectomy score – open nephrectomy score).

Other data relating to kidney donor quality of life is available from non-randomised studies. Isotani *et al*[125] studied quality of life using the SF-36 in 104 donors undergoing open nephrectomy. This was a longer-term study with a mean observation time of 6.95 ± 4.34 years post-donation. The authors found no adverse effects of donor nephrectomy on quality of life when the donors were compared to the general USA population. However, in some domains, including bodily pain and mental health, donors scored slightly higher than the

general population, suggesting that kidney donation affected quality of life in a positive way. Many other studies have suggested that donating a kidney may be associated with psychological benefit for the donors. (Gouge *et al*[126]; Westlie *et al*[127]; Taghavi[128]; Spital and Kokmen[129]; Simmons *et al*[130]; Johnson *et al*[131]).

A secondary end point of the Leicester study was whether or not donors would make the same decision to donate or not. In fact, only one patient, who underwent open donor nephretcomy stated that they would not donate again if this were possible. This patient's surgery was complicated by the development of a large incisional hernia. This was due to flaccid paralysis of the flank muscles due to injury to their nerve supply sustained during the open incision to expose the kidney. The patient suffered prolonged and significant wound pain and it is not surprising that this had an adverse effect on the quality of their life and that they stated that they would not donate again if they had known of this possible outcome.

There were limitations to the quality of life component of the Leicester trial. Only a single instrument, the SF-36, was used to study donor quality of life. Furthermore, subgroup analysis of the outcomes was not performed. For example, it would have been interesting to gauge the effects of complications of the surgery on quality of life. This proved to be impossible as the complication rate was low and this would leave small numbers for analysis in this group. Similarly, attempts to analyse the effect of the success of the recipient transplant on donor quality of life were thwarted as early transplant survival approached 100 percent in both study groups. Another limitation was the lack of a control group from the normal population that was age, gender and race matched for the study groups.

There are many areas of donor quality of life that could build on the findings of this dissertation in future studies. Firstly, longer-term studies would be of interest. Secondly, if larger numbers were studied it would be possible to define the effects of several factors on donor quality of life. These would include the relationship between the donor and the recipient. For example, would quality of life be greater in a parental donor than a sibling

donor? In the present study, it was not possible to compare quality of life in related and unrelated donors as there were only 3 unrelated donors in the open group, leaving too few patients for analysis. A study of the effects of donation in different racial groups would also be fascinating, as would the influence of the outcome of the recipient transplant on quality of life. Again this is rather difficult to study and wasn't attempted in this work because the recipient outcomes are generally very good with excellent renal function and graft survival meaning that there were only a few recipients to study in a 'poor outcome' group. Thirdly, the wider effects of donation should be studied to answer a number of interesting questions: Did the donation cause any family conflicts? Were there other potential donors in the family and how did the process affect them? What effects did the donation have on the donor's subsequent working life and did it cause any financial hardship? There are also more controversial but pertinent questions such as would financial compensation for donation affect quality of life? Finally, some work has already explored quality of life in donor and recipient pairs (Lumsdaine *et al*[132]) and this is a fertile ground for further study.

In summary, this study has demonstrated that laparoscopic surgery has advanced the field of live kidney donation. Laparoscopic surgery has a number of advantages over traditional open operations because it is performed through small incisions. These advantages are reflected in the Short Form-36 data, which shows less bodily pain after laparoscopic surgery and an improvement in the mental component of health related quality of life. Laparoscopic surgery removes some of the disincentives to live kidney donation and should be introduced widely.

In conclusion the results of the studies presented supports the hypotheses presented at the beginning:

Laparoscopic live donor nephrectomy improves quality of life in the donor when compared to traditional open donor nephrectomy patients.

This study provides high-level evidence to show that laparoscopic donor nephrectomy improves the mental component of quality of life.

CHAPTER EIGHT – SUMMARY AND CONCLUSIONS

Summary

This study has shown these two donor procedures to be safe, with rapid recovery time, minimal morbidity and a yield of excellent quality grafts for renal transplantation.

In particular, it has revealed that laparoscopic donor nephrectomy(LDN) is associated with a faster inpatient recovery, less pain and faster outpatient recovery when compared directly to short incision open donor nephrectomy(ODN). These benefits appear to be gained without increased donor morbidity, or a compromise in graft function.
The donor operative time and first warm ischaemic time were significantly longer in the laparoscopic group. ODN wounds were longer than the LDN suprapubic retrieval incision.

Overall postoperative complication rates were lower in the LDN group and, in particular, chest infection requiring treatment with antibiotics was less common after this operation. One LDN operation was converted to an open procedure owing to intraoperative bleeding from the renal artery stump. This patient required blood transfusion, but made an otherwise uneventful recovery. The kidney was successfully transplanted, demonstrating good initial and long-term function. One patient in LDN group had repeat laparoscopy for division of adhesions after 8 weeks. The randomised study from Norway reported a high re-operation rate in both laparoscopic and hand-assisted approaches (8%)[43] , for bleeding (n=2), retained swab, and bowel injury (n=2) in the per-operative period. In addition 2 donors required re-operation for port-site herniation (more than 1 year after donation), another developed chronic abdominal pain. There were fewer complications reported in the Dutch study[39] and none of the donors required re-operation. However, there were three visceral injuries noted during laparoscopic procedures, each of which could potentially have been catastrophic if unnoticed. The remaining intra-operative complications in both groups were haemorrhagic, but none of the

three laparoscopic cases required conversion to open procedure[39]. Testicular swelling and thigh numbness occurred more frequently in LDN group but they were not statistically significant. This complication was not seen in the ODN group and may be secondary to prolonged position in a laterally flexed, 'broken' position intraoperatively.

Donors undergoing LDN used PCAS for a shorter duration of time and required a lower total dose of morphine than donors in open group. Postoperative pain scores were also significantly lower in laparoscopic group. The LDN group resumed oral fluids and diet significantly earlier than the ODN group.

Transplanted kidneys in the two groups had similar features apart from a longer length of ureter being retrieved during the laparoscopic operation. One patient in the ODN group developed an ischaemic stricture of the distal transplant ureter 3 months after the transplant which was treated successfully surgically. This should assuage some of the concerns about higher urological complication rates after laparoscopic nephrectomy[54]. There were no significant differences in 5-year allograft survival after LDN and ODN.

There were significant differences in renal vein length in right-sided kidneys but this did not result in any recipient complications.

Detailed analysis of the eight domain scores from the SF-36 questionnaire shows that the laparoscopic operation reduced bodily pain at 6 weeks post-donation. There was also an improved mental score in laparoscopic donors. The findings in this study are broadly in agreement with the Anderson study[104] , which showed that bodily pain scores fell less in the laparoscopic group than the open group and mental health scores did not fall at 6 weeks in either group. However, Anderson[104] also found that the general heath score was unchanged in both groups at six weeks, whereas this score fell in both groups in the Leicester study.

Comparisons of the hand-assisted and pure laparoscopic techniques have shown comparable donor recovery and graft outcome, but also have demonstrated shorter duration of the operative procedure, and shorter first warm ischaemic time in the hand-assisted group[70,71,72] . It is proposed that the hand-assisted technique may allow faster acquisition of laparoscopic skills, and also afford and element of safety over the pure laparoscopic technique[33] , but randomised trials directly comparing the two techniques, or their learning curves have yet to materialise.

Conclusions

In conclusion, three hypotheses were stated in the beginning in chapter three. The results of the studies presented support all three hypotheses:

Hypothesis 1. Laparoscopic live donor nephrectomy leads to less postoperative pain, shorter in-patient stay, an improved recovery back to normal activities and better cosmetic results, when compared to traditional open donor nephrectomy.

Hypothesis 2. Any benefits of laparoscopic donor nephrectomy over traditional surgery are achieved without greater morbidity in the kidney transplant recipient.

Hypothesis3. Laparoscopic live donor nephrectomy improves quality of life in the donor when compared to traditional open donor nephrectomy patients.

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Appendix

PATIENT CONSENT FORM

A prospective randomised comparison of donor and recipient outcomes following open and laparoscopic live donor nephrectomy

Principle Investigator *Professor M L Nicholson*

This form should be read in conjunction with the Patient Information Leaflet, Version No 2 .

I agree to take part in the above study as described in the Patient Information Sheet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant sections of my medical records, but that all the information will be treated as confidential.

For drug studies if appropriate: At the termination of this trial I understand that there is no guarantee that the drug treatment received during this trial will continue.

I understand medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet on the above study and have had the opportunity to discuss the details with Professor M L Nicholson and ask any questions. The nature and the purpose of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient…….Date……
(Name in BLOCK LETTERS) ……..

I confirm I have explained the nature of the Trial, as described in the Patient Information Sheet, in terms which in my judgement are suited to the understanding of the patient.

Signature of Investigator ……..Date……..
(Name in BLOCK LETTERS)…….

For studies involving children and patients unable to give written consent (e.g. unconscious patients) please refer to the guidelines for consent for these groups.

PATIENT INFORMATION LEAFLET

A prospective randomised comparison of donor and recipient outcomes following open and laparoscopic live donor nephrectomy

Principle Investigator *Professor M L Nicholson*

You may contact *Professor M L Nicholson*

What is the purpose of this study?

The operation to remove a kidney for living donor transplantation (nephrectomy) is performed in Leicester in one of the two ways. The first is an open operation and the second is a laparoscopically assisted operation (keyhole surgery). In the open operation the kidney is removed through a 10-12 cm incision made over the kidney in the region of the flank. In the laparoscopic operation three or four 12 mm stab incisions are made in the abdomen and after the kidney has been separated from the surrounding tissues it is removed through a 8-10 cm cut made low down in the abdomen. Although both of these operations are carried out through relatively small incisions, we are not sure whether the open or the laparoscopic procedures have any advantages over the other. The aim of this study therefore is to compare the outcome of the kidney transplant in the recipient for kidneys removed using these two different techniques. The only scientific way to compare two operations like this is to randomly allocate donors to one operation or the other (on the toss of a coin).

What will be involved if I take part in the study?

If you take part in this study, the work-up for the kidney donation operation and the postoperative management will not differ from that currently used in the Leicester Transplant Unit. Once you have consented to donation you will be randomly allocated to either the open or the laparoscopic procedure and told which operation you are to undergo. Postoperatively we will record the level of any wound discomfort that you have and the amount of painkillers you need. Fluids and diet will be introduced normally on the first and second postoperative days and you will be allowed to go home when you feel well enough, which is usually between the fifth and sixth postoperative day. In the postoperative period we would like to assess how your heart, lungs and kidneys respond to surgery. The function of the lungs will be measured by asking you to blow into an instrument called the spirometer and we will also measure the oxygen saturation in the blood, by a non-invasive probe worn on the finger for the first two or three days after surgery. The response of the heart circulation and the kidneys to surgery will be measured by taking blood and urine samples both during the surgery and on each postoperative day upto fifth day after surgery. As blood is normally taken at these times you will not require any more blood taking procedures but on each occasion an extra 20 ml blood will be taken for various tests. When you are discharged we will give you a diary which will contain a list of events and we would like you to record the date on which each of these occur. The events to be recorded will be as follows: returning to driving, returning to housework, returning to shopping, returning to exercise and returning to full-time

employment. You will be reviewed in the clinic six and twelve weeks after your operation, which is the normal practice for this unit.

Will information obtained in the study be confidential?

Yes. All the features of your progress postoperatively and the outcome of the various tests will be recorded in your medical records and in a special trials folder. The information will then be placed on a computer database for subsequent analysis. Any information collected about you during the study will be held in complete confidence by the doctors on the Transplant Unit. The information on computer will not identify you by name as you will be given a trial number. Only authorized hospital staff will be given the opportunity to see the original medical records or the computerized information about your kidney donation. Finally, your GP will be informed of your participation in this study.

What if I am harmed by the study?

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS, ie compensation is only available if negligence occurs.

What happens if I do not wish to participate in this study or wish to withdraw from this study?

If you do not wish to participate in this study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.