

# **Role of Transverse Abdominis Plane Block in Laparoscopic Donor Nephrectomy**

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**by**

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## ABSTRACT

Post-operative wound pain is a disincentive to potential live kidney donors. The transverse abdominis plane (TAP) block is a technique where the local anaesthetic agent is given to block the afferent nerves of the abdominal wall. The safety and efficacy of this technique is well established for other surgical procedures.

The TAP block technique is shown to be beneficial and reduced the postoperative morphine requirement in lower abdominal surgeries such as hysterectomy, appendectomy, and caesarean section. A similar incision is being used for retrieval of kidney after laparoscopic donor nephrectomy. This technique has never been tested before in laparoscopic donor nephrectomy patients; hence the aim of thesis was to establish the efficacy of TAP block in reducing the pain and assessing its impact on reducing total morphine requirement.

An initial retrospective study showed a potential of TAP block to reduce postoperative pain and cumulative postoperative morphine requirements. Thereafter based on these results, a double blinded randomised placebo controlled trial was setup. The randomised trial has demonstrated that a TAP block with bupivacaine reduced early morphine requirement at 6 hours. But, there was no difference seen in the total postoperative morphine usage.

The visual analogue pain score in TAP block group with bupivacaine was significantly lower on day 1 and 2 after surgery. Further cytokine assay in this randomised study showed no difference in the plasma cytokine levels at 6, 24 and 48 hours after donor nephrectomy.

Hence the TAP block technique appears to be a safe and effective method of postoperative pain in laparoscopic donor nephrectomy patients. The study thus established the contributory role of TAP block in multimodal analgesia. This can be an alternative to post-operative wound infiltration with local anaesthetic agents.

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## PUBLICATIONS AND PRESENTATIONS

### Publications:

- 1) Pain Management in Laparoscopic Donor Nephrectomy- A Review- **Pain Research and Treatment. 2012**-doi:10.1155/2012/201852.
- 2) Randomized clinical trial of transversus abdominis plane block versus placebo control in live-donor nephrectomy. **Transplantation. 2012**; 94(5):520-5.

### Published Abstracts:

- 1) Efficacy of transversus abdominis plane block in laparoscopic live donor nephrectomy – A single centre experience. **International Journal of Surgery; 2012:10(8) S84.**
- 2) Double blinded randomised controlled trial on TAP block in laparoscopic live donor nephrectomy patients. **British Journal of Surgery 2012; 99 (S4): 17–18.**

### Presentations:

- 1) Efficacy of transverse abdominis plane block in laparoscopic live donor nephrectomy- a single centre experience. *Association of Surgeons of Great Britain and Ireland (ASGBI), Liverpool -2012.*
- 2) Double blinded randomised controlled trial on TAP block in laparoscopic live donor nephrectomy patients. *Society of Academic and Research Surgery (SARS), Nottingham- 2012.*

## ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
ADEs	adverse effects
BMI	body mass index
CIT	cold ischemia time
CPSP	chronic post surgical pain
COX	cyclooxygenase
CNS	central nervous system
CXCL	C-X-C-motif ligand
DBD	donation after brain death
DCD	donation after cardiac death
DOP	delta opioid receptor
ESRF	end stage renal failure
FDA	food and drug administration
HALN	hand assisted laparoscopic nephrectomy
HARN	hand assisted retroperitoneal nephrectomy
HLA	human leukocyte antigen
IASP	international association for study of pain
IL	interleukin
KOP	kappa opioid receptor
LA	local anaesthetics
LDN	live donor nephrectomy
LTDN	laparoscopic transperitoneal donor nephrectomy
LLDN	laparoscopic live donor nephrectomy
MAC	membrane attacking complex

MODN	mini open donor nephrectomy
MOP	mu opioid receptor
NHS	national health service
NHSBT	national health service blood and transfusion
NRM	nucleus raphe magnus
NRPG	nucleus reticularis paragigantocellularis
NSAIDS	non-steroidal anti-inflammatory drugs
ODN	open donor nephrectomy
PAG	periaqueductal grey
PCA	patient controlled analgesia
PCAS	patient controlled analgesia system
PG	prostaglandin
PNL	percutaneous nephrolithotomy
PO	per oral
PONV	postoperative nausea and vomiting
QDS	quarter die sumendus
RDN	robotic donor nephrectomy
RADN	robotic assisted donor nephrectomy
TAP	transversus abdominis plane
TNF	tumour necrosis factor

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## ***CHAPTER 1***

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### **Aims and Objectives**

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# **1 Aims:**

The first aim of this thesis was to revisit the history and evolution of transplantation, more specific to renal transplantation models followed by advancement in immunology and immunosuppression; without these new developments, the idea of transplantation itself could still be a dream.

Secondly we reviewed the evolution of different surgical techniques of donor nephrectomy and their place in current transplantation practice. As the laparoscopic donor nephrectomy is well established and widely practiced, the thesis also reviewed the literature on pain management after laparoscopic donor nephrectomy.

Thirdly this thesis examined the role of transversus abdominis plane (TAP) block in patients undergoing laparoscopic donor nephrectomy. Finally we have also assessed the role of TAP block and its effect of cytokines expression in the donor nephrectomy patients.

## ***1.1 Objectives:***

Firstly a literature review was performed to assess spectrum of pain management techniques and their role in laparoscopic donor nephrectomy patients. The search strategy included MEDLINE (PubMed 1966-2015), The Cochrane Central Register of Controlled Trials, EMBASE (1974-2015), the database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) database, and to identify relevant studies, randomised trials, meta-analysis and case series, and all related reference articles in English literature were included and reviewed.

Secondly a retrospective study was set up to assess the effect TAP block on cumulative morphine requirement, pain score, sedation score and postoperative nausea & vomiting score (PONV) in laparoscopic donor nephrectomy patients. The patients who had the TAP block were compared to the historical controls who did not receive TAP block and this study has included consecutive donors in both groups to minimise bias.

Thirdly a randomised placebo controlled trial was performed to assess the role of transversus abdominis plane (TAP) in laparoscopic donor nephrectomy patients. Sample size was estimated on the basis of 24-hour post-operative morphine requirements in a previous series of patients (from pilot data) undergoing laparoscopic donor nephrectomy. For the purposes of sample size calculation, we considered that a clinically important reduction in morphine consumption would be a 50% absolute reduction.

The randomised study also assessed the impact of TAP block and its effect on cytokines expression in a donor nephrectomy setting. Although there is some evidence to support that the cytokine expression/response was significantly high following donor nephrectomy models, the effect of TAP block on neuroendocrine response and cytokine expression is yet to be answered and hence the reason for this investigation.

Finally we summarised our study findings with definitive answers to our questions.

Some of the unanswered questions paved the way for future work as the main aim of this thesis is to assess the role of TAP block in laparoscopic donor nephrectomy patients.

## ***CHAPTER 2***

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### **Introduction: Renal Transplantation and Live Kidney**

#### **Donation**

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## **2 Introduction - Renal transplantation**

### ***2.1 History of early transplantation models:***

The history of renal transplantation starts from 1902; an experimental renal transplantation was performed in an animal model by Emerich Ullmann. Ullmann's autotransplant dog kidney model was anastomosed to neck vessels and did initially produce some urine. This inspired Dacastello who carried out a dog-to-dog kidney transplant at the Vienna institute of experimental pathology in the same year (Dacastello A, 1902).

This was followed by Ullmann's dog to goat renal transplant which also produced a small volume of urine. Neither Ullman nor Dacastello progressed any further with transplant models and further advances depended on advancements in vascular suturing. Later, Mathieu Jaboulay's assistants Carrel, Briau and Villard researched further into techniques of vascular anastomosis. Carrel developed the modern method of vascular anastomosis which eventually led to his Nobel Prize in 1912 (Carrel A, 1902).

Carrel had committed himself more on organ grafting and successfully carried out transplantation in cats and dogs but showed that graft failure sets in after a brief period of function.

### **2.1.1 History of kidney transplantation:**

Mathieu Jaboulay carried out the first human renal transplantation in 1906 (Jaboulay M, 1906). The donors were pig and a goat, transplanting organs to thighs of the recipients. Both the kidneys did work for an hour and then failed. Ernst Unger, who had trained by performing more than one hundred animal transplants, performed a kidney transplant from a still born child's into a baboon. The animal died shortly after operation and a postmortem examination showed that the anastomoses were intact. In the same month, taking advantage of the serological similarities between humans and monkeys, Unger performed a monkey to human renal transplantation. There was no urine production. This eventually led the medical world to think of other potential biochemical barriers. Recurrent failures, an inability to identify the biochemical barrier and the world wars resulted in a loss of interest in transplantation until the 1950s and 60s.

In the early 1950s Dempster and Simonsen revealed that an immunological mechanism was responsible for graft rejection (Simonsen M, 1953; Dempster WJ, 1953) and concluded that it was likely to be due to a humoral mechanism. Further technical lessons learned in the 1950s allowed improved confidence in surgical methods; Murray et al. had performed the first successful renal transplantation between identical twins without immunosuppression in 1954 (Murray JE et al, 1958). From then on, many such transplantations were performed successfully in Boston (Murray JE et al, 1958).

Although sometimes seen now merely as a technical triumph, valuable new findings emerged from this series. Some workers had predicted that, in the short term, the inactivity of the bladder could not be restored, and that in the long term, human kidney grafts would decline in vitality as a result of denervation or ureteric reflux (Hamilton D et al, 2014). Other workers were convinced that a single kidney graft could not restore biochemical normality in an adult, and that the existing changes caused by the chronic renal failure were irreversible (Hamilton D et al, 2014).

All of these gloomy predictions were neutralized by the success of the twin kidney transplants, and the greatest triumph came when one such recipient became pregnant and had a normal infant, delivered cautiously by Caesarean section, with the anxious transplanters in attendance.

### **2.1.2 Immunosuppression and the modern era of kidney transplantation:**

The discovery of the immunological basis of graft rejection has opened a window to the modern era of transplantation (Medawar PB et al, 1948; Billingham RE et al, 1953; Billingham RE et al, 1951). Careful studies by Medawar's group in the early 1950s suggested a modest immunosuppressive effect of cortisone, but when Medwar shortly afterward showed a profound, specific, long lasting graft acceptance via development of immunological tolerance, the weak steroid effect was understandably sidelined and thought to be of no clinical interest (Hamilton D, 2014).

In 1962, Azathioprine had been shown to be an immunosuppression for renal transplant recipients. The immunosuppressive effects of prednisolone and its synergistic effect

with Azathioprine attracted Starzl's group (Starzl TE et al, 1963) who used this combination as a regular immunosuppressive regimen in transplantation.

In the search for better immunosuppression, there was great excitement when laboratory studies by Woodruff and Medawar produced a powerful immunosuppressive antilymphocyte serum, and a production of versions suitable for human use started (Woltenholme GEW, 1967).

Initial studies were favourable, but the whole antilymphocyte serum had an unspectacular role thereafter, added to from 1975 onward by the use of monoclonal antibody versions. Jean Dausset first described an antigen MAC, later known as HL-A2 to be a part of the major histocompatibility complex. Successful clinical application of HLA-DR matching was introduced into clinical practice by Ting and Morris (Ting A, 1978).

In 1980, the fungal metabolite cyclosporine was shown to be useful in preventing organ rejection in kidney transplants by Calne et al. in Cambridge (R Y Calne et al, 1981). Cyclosporine replaced the earlier immunosuppressive regimens and was the dominant agent until the 1990s. Transplantation had grown to a sufficiently large clinical service that it was worth the attention of pharmaceutical companies, and in the 1990s steady production of new agents occurred, including tacrolimus, mycophenolate mofetil, rapamycin, FTY720, brequinar and others (Hamilton D, 2014).

### **2.1.3 Transplant activity in the UK:**

The first live donor renal transplantation, between identical twins, was done in 1960 by Sir Michael Woodruff in Edinburgh. Currently each year in the UK about 2100 renal transplantations are being performed. During the last decade in UK, there has been significant growth in living donor kidney transplantation. The demand for renal transplantation has increased due to the growing prevalence of end stage renal failure (ESRF) and extension of the criteria for accepting patients on to the transplant waiting list. In response to increasing demand for organs, deceased donor programs [donation after circulatory death (DCD) and donation after brain death (DBD)] are being optimised and living kidney donation expanded in several countries to include both related and unrelated donation.

There has been a significant growth in living donor kidney transplantation with 485 transplants in 2005, increasing to 1,114 in 2012-2013 (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM 2013*).

But in spite of this the number of patients on the waiting list is increasing progressively and every year about 3000 new patients are added to the waiting list. Despite the slight drop in the last 5 years, the number of patients registered on the active kidney transplant list at 2014 has risen by 8% since 2005 (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM 2013*).

It is also worth noting that about 6-9% patients on the waiting list either died or were removed. This demand for more organs subsequently improved live donation and now half of kidneys in the UK are coming from a live donors (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM 2013*).

#### **2.1.4 Cost effectiveness of renal transplantation:**

Epidemiological data from the past decade suggest that the global burden of patients with renal failure who receive renal replacement therapy exceeds 1.4 million and that this figure is growing by about 8% a year (Moeller S et al, 2002) (Schieppati A, 2005).

Kidney transplantation is highly cost-effective, particularly in relation to NHS spending, and is the treatment of choice for many patients with end-stage renal failure. The indicative cost of maintaining a patient with end-stage renal failure on renal replacement therapy (dialysis) is £17,500 per patient per year for a patient on peritoneal dialysis and £35,000 per year if the patient is receiving hospital haemodialysis (*Cost-effectiveness of transplantation*-[http://www.organdonation.nhs.uk/newsroom/factsheets/cost\\_effectiveness\\_of\\_transplantation.asp](http://www.organdonation.nhs.uk/newsroom/factsheets/cost_effectiveness_of_transplantation.asp)).

There are over 37,800 patients with end-stage renal failure in the UK. Nearly 21,000 are on dialysis, whilst the remainders have a transplant. Of those on dialysis, 76% are on haemodialysis and 24% on peritoneal dialysis (*Cost-effectiveness of transplantation*-[http://www.organdonation.nhs.uk/newsroom/factsheets/cost\\_effectiveness\\_of\\_transplantation.asp](http://www.organdonation.nhs.uk/newsroom/factsheets/cost_effectiveness_of_transplantation.asp)).

It is also worth noting that 3% of the National Health Service (NHS) budget is spent on kidney failure services in the UK. The indicative cost of a kidney transplant [including induction therapy but excluding National Health Service Blood and Transplant (NHSBT) cost] is £17,000 per patient per transplant for the first year. Thereafter the immunosuppression after renal transplantation costs only £5,000 per patient per year which leads to a cost benefit in the second and subsequent years of £25,800 per year (Cost-effectiveness of transplantation [http://www.organdonation.nhs.uk/newsroom/factsheets/cost\\_effectiveness\\_of\\_transplantation.asp](http://www.organdonation.nhs.uk/newsroom/factsheets/cost_effectiveness_of_transplantation.asp)).

Hence the cost benefit of renal transplantation compared to dialysis over a period of ten years (the median transplant survival time) is £241,000 or £24,100 per year for each year that the patient has a functioning transplanted kidney.

## ***2.2 Why live kidney donation:***

Since 1960 live donor renal transplantation in the UK has grown steadily; initially it was performed in identical twins to avoid an immunological barrier. With advancements in transplant immunology this has reached a fast pace in the 1990s. In 2004, live donor renal transplantation accounted for 25% of total renal transplantation; this has increased further in 2009 to 37% and in 2013-14 it is 52% of all renal transplants (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM 2013*).

In live donors who are close relatives there can be an excellent tissue-type match and this is an added bonus for the recipient. In contrast, unrelated donors, such as spouses, are unlikely to be well matched to their recipient. However, in all but the perfectly

matched situation, the success rates of these transplants are equal to those of related donors (Santori G et al, 2012).

Living kidney donation also allows the transplant operation to be planned at a time that is convenient for the recipient. Another advantage is the reduced cold ischemia time (CIT); every additional hour of CIT affects the graft and patient survival (Debout A et al, 2015).

Living donation provides a better patient and allograft survival when compared with deceased-donor transplantation, especially when the live donor transplant is performed before the onset of dialysis (Meier-Kriesche HU, 2002; Mange KC et al, 2001).

There are several possible reasons why the outcome of live donor renal transplantation is superior to deceased donor transplantation. Live donor kidneys are, by virtue of the rigorous pre-donation assessment and selection procedure, from healthy individuals with good renal function. They are not exposed to major cardiovascular instability, sepsis, or nephrotoxic agents that may occur during the period of hospitalization preceding diagnosis of brain death (or cardiac deaths in the case of non-heart beating donors). Nor are they subjected to detrimental systemic effects of brain death itself and finally kidneys from live donor experience only a short period of ischemia before implantation (Roodnat JI et al, 2003) (Bos EM et al, 2007).

In the past, only family and close friends were allowed donate their kidney because this could lead to an exploitative or coercive relationship between recipient and donor. But since 2006, altruistic non-directed kidney donation has been legalized and there has been significant rise in this type of kidney donation (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM* 2013).

There were 118 altruistic non-directed kidney transplants performed in 2012-13, which is about 10% of total live donations in the UK (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM 2013*).

### **2.2.1 Advantages of live donation:**

Live donor renal transplantation is clearly superior to deceased donor transplantation. The advantages in live donation includes shorter waiting time, less cold ischemic time and greater chance of better HLA mismatch. As live donors are in good health, the organs were perfect and functionally better than from a deceased donor. Because of these factors, usually less immunosuppression is required and with better graft function (Rettowski O et al, 2007).

UK transplant follow up data showed that live donor renal transplants have one-year graft survival of 90-95% compared with 80-90% in organs from deceased donors. This difference in graft survival increases more at five and ten years after transplantation. Other than these, the donor enjoys an immense satisfaction after donating their kidney as a life gift, which improves not only the quality of life in recipients but also increases their life expectancy.

Although there are advantages in live donation, it needs the donor to undergo a major surgical operation entirely to benefit another individual. In the early days after open nephrectomy donors experienced a prolonged hospitalisation and of course postoperative pain as well. This has caused loss of wages and cosmetic issues with a long scar. These are obvious disincentives to potential donors who have to think carefully before making their final decision.

### **2.2.2 Live Donor Nephrectomy (LDN):**

Since the first renal transplantation, the live donor nephrectomy was carried out by an open technique. This was usually performed through a flank incision with rib-resection (Marchioro et al, 1964) or by a supracostal approach (Barry and Hodges et al, 1974) or by an anterior extraperitoneal incision (Jones et al, 1999). The technique had not changed much until the arrival of minimally invasive surgery in the 1990s.

Types of minimally invasive donor nephrectomy are:

1. Mini Open Donor Nephrectomy (MODN)
2. Laparoscopic Transperitoneal Donor Nephrectomy (LTDN)
3. Hand Assisted Laparoscopic Nephrectomy (HALN)
4. Hand Assisted Retroperitoneal Nephrectomy (HARN)
5. Robotic Donor Nephrectomy (RDN)

### **2.2.3 The technique of open donor nephrectomy:**

After induction of general anaesthesia, skin preparation and draping is done from inferior rib margin to the superior iliac spine. The technique was most commonly performed through a loin incision with the patient positioned fully lateral and a break on the table.

Alternatively, an oblique incision can be performed inferior to the 12<sup>th</sup> rib with the separation or division of oblique and transverse musculature. A segmental resection of the inferior rib can be done to improve the access to the upper pole of the kidney (Barth R, 2014).

A combination of diathermy and manual dissection are usually performed around the Gerota's fascia to permit retractor position; this is followed by a gentle anteromedial sweep of peritoneum to create a plane towards the renal vessels (Barth R, 2014).

Retroperitoneal dissection is continued around the kidney and inferiorly to identify and isolate the ureter and gonadal vessels. Normally the ureter is traced down until the iliac vessels are encountered in order to ensure an adequate length. Complete mobilization of the kidney is performed and the artery and vein are isolated proximal to the insertion of the aorta and inferior vena cava. The adrenal gland can be separated from the parenchyma of the kidney lateral to medial and the adrenal vein on the left side can be divided between the clips or ligatures. The lumbar vein posterior to the renal vein is divided to maximize the length of the renal vein (Barth R, 2014).

After complete isolation of the vascular pedicle, division of the renal vessels and ureter proceeds. The ureter and the gonadal vessels are divided; the renal artery is divided after ligation or using vascular staples. Finally the renal vein can be divided in a similar

technique. After securing good haemostasis, the abdominal wall closure is performed layer by layer with preference for absorbable suture material.

#### **2.2.4 Mini Open Donor Nephrectomy (MODN):**

Conventional open living donor nephrectomy is associated with disincentives including long hospital stay, prolonged postoperative pain, cosmetic problems and slow convalescence (Kok NF et al, 2006).

Mini open donor nephrectomy usually requires a similar position to a conventional open donor nephrectomy. But this is being done through a small incision with no rib resection (Kessaris N, 2010) and avoidance of muscle tissue destruction particularly latissimus dorsi muscle. Here, tissue retraction is achieved by using 2.5 cm hand held wound retractors and the surgeon's index and the middle finger. The lead surgeon also uses a headlight and magnifying loupes (Kessaris N, 2010).

Gerota's fascia is then opened, followed by dissection between the perinephric fat and the kidney. Dissection continues in the same way as the open procedure but incorporates a linear articulated stapling device (ETS – FLEX, Ethicon Endo-Surgery, Inc, Cincinnati, OH) for dividing the ureter, artery and vein (Kessaris N, 2010).

A meta-analysis has shown that operative and warm ischemia times were significantly shorter for the MODN compared to fully laparoscopic donor nephrectomy (Antcliffe D et al, 2009).

Nonetheless, analgesic requirements were greater for the MODN procedure. There were no significant differences in blood loss, hospital stay, donor complications or ureteric complications (Antcliffe D et al, 2009).

However further detailed long term cost analysis study has shown that the cost-effectiveness is better with laparoscopic live donor nephrectomy (LLDN) compare the MODN (Kok NF et al, 2007). More importantly, the LLDN rewards both employer and employee because total productivity losses are lower. The donor's experience was also found to be better in LLDN as well as the quality of life (QOL) (Kok NF et al, 2007).

### **2.2.5 Hand Assisted Laparoscopic Nephrectomy (HALN):**

Hand-assisted laparoscopic donor nephrectomy (HALN) was originally described in 2001(Tokuda N et al, 2001). Hand-assisted laparoscopy nephrectomy (HALN) combines the safety of hand-guided surgery with the benefits of endoscopic techniques and retroperitoneal access (Dols LF et al, 2014).

A pneumoperitoneum is created to insufflate the abdomen, increasing the working space. A laparoscope is introduced to provide magnified visualization of the operative field, and laparoscopic instruments are utilized to perform the surgery.

The only difference between standard laparoscopy and HALN is that the surgeons are also able to introduce their hand into the operative field (Stifelman MD et al, 2001).

Surgery is performed with the assistance of a hand port device placed either a left upper abdominal transverse incision or supraumbilical midline incision. Two further laparoscopic ports are inserted in ipsilateral iliac fossa. It is necessary to use a relatively

high pressure (15 mm of Hg) to create enough space for the operative field (Graetz KP et al, 2010). Two further laparoscopic ports are inserted in the left iliac fossa. The surgical techniques are otherwise similar to full laparoscopic donor nephrectomy. The operative hand, via the hand port wound, retrieves the kidney.

Proponents of HALN have justified that the use of this technique provides good hand retraction while allowing rapid control of intraoperative bleeding by direct pressure if needed (Graetz KP et al, 2010).

### **2.2.6 Hand Assisted Retroperitoneal Nephrectomy (HARN):**

Hand Assisted Retroperitoneal Nephrectomy is performed with the donor placed in lateral decubitus position as in HALN. Balloon dilatation or digital creation of the retroperitoneal space is performed to create a working space (Dols LF et al, 2014). Three or more trocars are introduced, and the retroperitoneum is insufflated with carbon dioxide at a pressure of 12 mmHg.

But the remaining steps are as mentioned in open nephrectomy. This approach has been used more commonly for right donor nephrectomy procedures but is practiced by very few centres (Graetz KP et al, 2010). The advantages are related to the avoidance of the peritoneal cavity, hence minimizing the potential for intraoperative viscus injury and postoperative adhesions.

A recent randomised trial of HARN versus transperitoneal laparoscopic donor nephrectomy demonstrated that HARN could be a valuable alternative to the laparoscopic approach for left-sided donor nephrectomy. Though HARN resulted in significantly shorter skin-to-skin time, and shorter warm ischemia, the length of

hospital stay and postoperative complications were not significantly different (Dols LF et al, 2014).

### **2.2.7 Robotic Donor Nephrectomy (RDN):**

The use of the da Vinci surgical system to assist in donor nephrectomy was first reported in 2002 (Horgan S et al, 2002). Robotic-assisted donor nephrectomy (RADN) can be performed as either a ‘pure’ laparoscopic procedure (Hubert J et al, 2007) or with hand-assistance (Gorodner V et al, 2006).

Robotic assistance provides additional freedom of movement of instruments, three-dimensional vision and elimination of tremor (Hubert J et al, 2007). The great potential for robotic approaches to overcome limitations of single port surgery may allow for wider application of both techniques; however, current instrumentation does not allow articulation or use of energy devices (Barth R, 2014).

Robotic approaches are usually performed with multiple laparoscopic ports and require bedside assistance ports for use of energy devices, staplers, and eventually extraction. While the feasibility of the robotic assisted laparoscopic nephrectomy has been demonstrated, it is not clear that there are significant advantages over the total laparoscopic nephrectomy and HALN and there is an associated increase in cost (Boger M et al, 2010).

A recent study of robotic versus laparoscopic donor nephrectomy has shown that the blood loss, operative time, warm ischemia time and recipient estimated glomerular filtration rates were similar. In this study, robotic-assistance did not improve the outcomes associated with LDN (Liu XS et al, 2012).

To date, no high quality evidence is available to compare robotic assisted laparoscopic nephrectomy with other widely practiced techniques for live donor nephrectomy.

### ***2.3 Laparoscopic Transperitoneal Donor Nephrectomy (LTDN):***

As donor nephrectomy is being carried out to benefit another individual, clearly there are only disincentives to the donor. By going through an open operation, prolonged hospitalisation and a large scar all discouraged potential donors for a long time (Nicholson ML et al, 2010). This has stimulated the surgeons to come out with alternative approaches for donor nephrectomy.

Laparoscopic nephrectomy was first performed for neoplasm in 1990 (Clayman RV et al, 1991) and subsequently this technique was applied to live donor nephrectomy. The first laparoscopic live donor nephrectomy was performed at the Johns Hopkins Bay View Medical Center at Baltimore in the USA (Ratner LE et al, 1995).

The donor was discharged on the first postoperative day and returned to work 2 weeks later. This technique has revolutionised donor nephrectomy and also removed many of the disincentives of open donor operation. Improved cosmesis and faster recovery times are the main advantages to the donor patient. Hospital stays have been reduced by several days, with discharge being possible as early as the second postoperative day (Ratner LE et al, 1995). Meta-analysis of laparoscopic versus open donor nephrectomy showed that although the open technique may be associated with shorter operative time and warm ischaemic time, the laparoscopic technique shortens hospital stay and allows early return to work, without compromising allograft function in the recipient (Wilson CH et al, 2011).

In the United States, almost all living donor nephrectomies are performed by a laparoscopic approach. The minority of cases are performed via an open technique this has continued to decrease over the last 5 years with less than 5% of donated kidneys removed by open operation (Rockville MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, 2011).

In the United Kingdom, living donor kidney transplants have increased by 4% to 1114 in 2013-2014, representing 34% of the total kidney transplant programme (Available at: [http://www.organdonation.nhs.uk/statistics/downloads/united\\_kingdom\\_april13.pdf](http://www.organdonation.nhs.uk/statistics/downloads/united_kingdom_april13.pdf)).

More importantly, the number of non-directed altruistic living kidney donations has increased to comprise 10% of live donor procedures. This clearly reflects the positive perception of the public towards live kidney donation and this could not have been possible without the development of laparoscopic donor nephrectomy (Schweitzer EJ et al, 2000).

### **2.3.1 The technique of laparoscopic donor nephrectomy:**

The operation is performed under general anaesthetic using a transperitoneal approach to the kidney. The donor is placed in a modified lateral decubitus position with a slight break in the table. A pneumoperitoneum is established by using a Veress needle and in general four laparoscopic ports are used. The laparoscope is introduced through a 12-mm infra-umbilical port and two further 12 mm ports, in the epigastrium and the left iliac fossa, are used for the main dissecting instruments. One or two 5mm port can be placed in the mid axillary line or in an appropriate location in order to introduce an instrument for retraction of the colon or spleen (see figure 2.2).

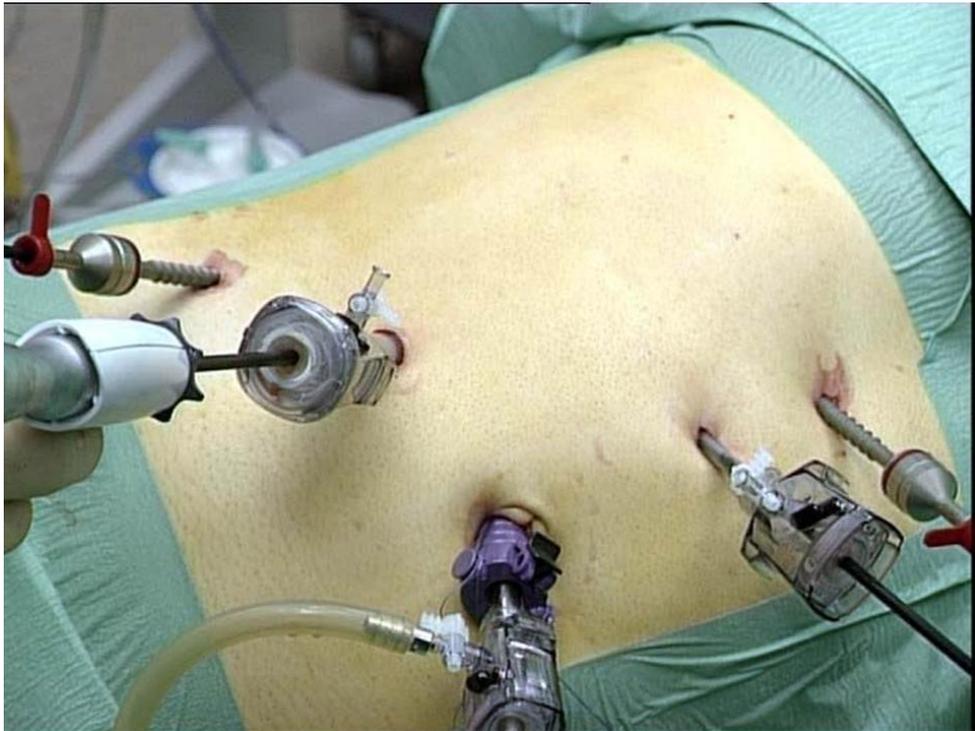
The operation begins with mobilization of the colon by incising the lateral peritoneal reflection (white line of Toldt) from the splenic flexure to the pelvic inlet. The kidney is then identified by opening the overlying Gerota's fascia. The renal vein is dissected to display its adrenal and gonadal tributaries, which are divided between metal clips. The renal artery is then gently dissected free to demonstrate its origin from the aorta.

The ureter is mobilised with a generous amount of meso-ureteric tissue down to the level of the pelvic inlet. The ureter is clipped and divided at this point and then the remaining lateral, posterior and superior fascial attachments of the kidney are divided to leave the kidney attached only by its vascular pedicle.

At this stage a 5–6 cm kidney retrieval incision is made either in the midline below the umbilicus or transversely just above the pubis. A purse string suture is placed in the peritoneum, which is then incised to allow the introduction of a plastic kidney retrieval bag without loss of the pneumoperitoneum.

The renal artery and vein are divided with an endovascular stapler. The kidney is then placed in the retrieval bag and removed through the midline or Pfannenstiel incision.

**2.4**            ***Figure 2.1: Port sites in right laparoscopic donor nephrectomy***



**A 12-mm infra-umbilical port (camera), two further 12 mm ports (main instruments) in the epigastrium and the left iliac fossa; one or two 5mm port at mid axillary line or in an appropriate location to retract colon/spleen.**

### **2.4.1 Benefits of laparoscopic donor nephrectomy:**

When the laparoscopic technique of donor nephrectomy was introduced, it was associated with long operation times but this has been addressed with increasing experience. Initial report of laparoscopic donor nephrectomy had showed rapid convalescence, less postoperative pain, shorter inpatient stay and quicker return to normal activities (Ratner LE et al, 1995).

The advantages of laparoscopic surgery come from minimizing the trauma of access in to the abdomen. By avoiding a long incision through the muscles, many post-operative problems are eliminated and pain is markedly reduced. This enables the donor to breathe and cough better and a previous study from our centre demonstrated improved respiratory function and decreased donor related complications (Nicholson ML et al, 2010).

Meta-analysis of 44 studies showed an overall complication rate of 13.7% for fully laparoscopic and HALN combined, compared with 16.4% for the open nephrectomy group (Fehrman-Ekholm I et al, 1997).

Although LDN was associated with prolonged first warm ischemia time in early studies, this has not increased the risk of delayed graft function and recipient complication rates (Nicholson ML et al, 2010).

This was possibly because of the effect of the learning curve on early cases of this technique. Later it was shown that with experience operation time was reduced (Nanidis TG et al, 2008; Muthu C et al, 2003) and so were the warm ischemic time (Berends FJ et al, 2002) and blood loss (Rawlins MC et al, 2002).

Complication rates were also lower in the LDN group compared with open donor nephrectomy (ODN) (Nanidis TG et al, 2008). The incidence of prolonged wound pain was significantly higher after ODN compared to LDN.

Results from several meta-analyses (Antcliffe D et al, 2009; Nanidis TG et al, 2008) compared the open versus laparoscopic donor nephrectomy and clearly showed that laparoscopic technique is associated with short hospital stay, less analgesic requirement, good aesthetic results and early return to work. A Randomised clinical study in our centre has also confirmed these findings without increasing complication rate in the laparoscopic group (Nicholson ML et al, 2010).

#### **2.4.2 Disadvantages of laparoscopic technique:**

While this technique offered benefits, it does have disadvantages too. Learning these deceptive skills takes a steep, long learning curve before mastery of minimally invasive techniques is attained. In support of this complications have been reported to occur in the first 30 cases, with none occurring in the next 50 cases in a single centre experience (Leventhal JR et al, 2000).

Su et al. have also reported 5 cases of bowel injuries (4 small bowel and 1 large bowel) during laparoscopic donor nephrectomy (Su LM et al, 2004).

There are rare incidences of internal hernia or hernia through the port sites and adhesion formation (Øyen O et al, 2005).

Vascular injuries involving lumbar vessels, the renal artery, the aorta and adrenal arteries, along with retroperitoneal haematomata have all been reported during the laparoscopic donor nephrectomy (Leventhal JR et al, 2004).

## **2.5 Conclusion:**

The arrival of laparoscopic donor nephrectomy has encouraged live kidney donation and significantly increased the number of donor nephrectomies in recent years. The recent trends in live kidney donation, suggests continued growth in the coming years (*Organ Donation and Transplantation Activity Data: UNITED KINGDOM 2013*).

***CHAPTER 3***

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**Review of Literature on Pain Management after Laparoscopic  
Donor Nephrectomy**

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### **3 Introduction:**

Donor nephrectomy is a procedure carried out to benefit another individual but it carries with it a number of important potential disincentives for the donor. Subjecting a patient to an open operation leads to increased hospital inpatient stay and a much more painful larger scar, thus open surgery not only discourages the potential donors but it may also lead to increased morbidity in the longterm. This has stimulated surgeons to come up with an alternative, thus the birth of laparoscopic donor nephrectomy.

The first laparoscopic live donor nephrectomy (LLDN) was performed by Dr Louis Kavoussi and Dr Lloyd Ratner at the Johns Hopkins Bay View Medical Center, Baltimore, USA in February 1995 (Ratner LE et al, 1995).

The donor was discharged on the first postoperative day and returned to work 2 weeks later. This technique thus revolutionized donor nephrectomy and also removed the added disincentives of open operation.

The first laparoscopic donor nephrectomy in the UK was carried out in our centre by Professor Michael Nicholson and Mr Peter Veitch in 1998. LLDN is now the preferred method and gold standard operation for kidney donation. Although LLDN is associated with a longer operation time, it has reduced morphine requirement, hospital stay and postoperative complications with an earlier return to work. Randomized controlled trials and systematic reviews confirmed that LLDN is a safe technique; it has also shown to be associated with reduced morbidity following the operation (Nicholson ML et al, 2010; Greco F et al, 2010; Wilson CH et al, 2011).

Post-operative recovery is largely determined by the consequences of post-operative pain and the concomitant need for opioids. Therefore, adequate assessment and management of post-operative pain is an important clue to the optimisation of recovery after laparoscopic donor nephrectomy. (Ergün M et al, 2014).

### ***3.1 Pain after LLDN:***

Postoperative pain is a common problem. In open LDN, the subcostal wound is often long (10–12 cm in length), making breathing and coughing extremely painful. But pain following LLDN is multifactorial. Pain after laparoscopic surgery can be divided into three components: incisional or superficial wound pain, deep intra-abdominal pain and referred shoulder pain. In addition, urinary catheter discomfort adds up and contributes to the total pain experience (Bisgaard T et al, 2001; Alexander JI et al, 1997; Steinhauser MM et al, 2003; Ekstein P et al, 2006).

Superficial wound pain is mainly nociceptive, although evidence exists that a neuropathic component is also involved. Considering that after every surgical intervention there is a certain degree of nerve injury, there are neuropathic pain features within the post-operative pain itself (Ceyhan D, 2010).

The second component of post-operative pain is deep intra-abdominal pain. In laparoscopic surgery, mechanical stimuli such as bowel handling, stretch of the abdominal wall and compression of organs would be the main cause of deep intra-abdominal pain. The deep intra-abdominal pain component consists of both visceral and parietal stimuli. Visceral stimuli are transmitted through autonomic nerve bundles often leading to a sensation of pain that is described as diffuse and dull, whereas

parietal stimuli are sent directly through local spinal nerves resulting in a more severe and localised pain sensation (Ergün M et al, 2014).

The last component of pain after laparoscopic surgery is referred pain, which is often attributed to a direct effect of carbon dioxide and/or mechanical stretch of the muscle fibers within the diaphragm during the pneumoperitoneum phase (Sarli L et al, 2000).

Several studies have confirmed that laparoscopic and hand assisted nephrectomies produce less pain when compared with an open operation ( Dillenburg W et al, 2006; Bachmann A et al, 2006; Andersen MH et al, 2006; Perry KT et al, 2003).

Nonetheless, some patients undergoing laparoscopic live donor nephrectomy still suffer significant post-operative pain, to the point where they require parenteral opioids. Based on the assumption that minimally invasive approaches are less traumatic, some units avoid opioids and neuraxial techniques. Nevertheless, laparoscopic nephrectomy can cause severe neuropathic pain possibly by nerve lesions caused by trocars (Oefelein MG, 2003).

The aim of this chapter is to create an evidence based document reviewing the current literature with a view to address the best possible pain relief methods for laparoscopic donor nephrectomy patients.

### **3.1.1 Postoperative pain and its implications:**

Pain has a wide spectrum of effects on the body. An inadequately controlled postoperative pain may have harmful physiologic and psychological consequences which potentially increases morbidity and mortality (Joshi GP et al, 2005; Liu SS et al, 1995).

Inadequate postsurgical pain control may also lead to delayed hospital discharge, unanticipated readmissions, delayed convalescence, and increased health care costs (Pavlin DJ et al, 2002).

Risks associated with pain management include opiate overdose, medication adverse effects, and required administration by nursing staff. Non-narcotic pain medications may decrease patient morbidity, expedite discharge, and help contain cost (Knight MK et al, 2002).

All these factors are especially important for elective operations, such as laparoscopic donor nephrectomy, which are often performed on healthy individuals who desire an uncomplicated recovery and a short convalescence.

Studies have confirmed that inadequately treated postoperative pain may lead to chronic pain which is often misdiagnosed and neglected (Williams M, 2003; Nikolajsen L et al, 2004).

The significance of this association has been confirmed in other studies on healthy patients undergoing Caesarean section (Nikolajsen L et al, 2004) and in patients after inguinal hernia repair (Bay-Nielsen M et al, 2001).

The International Association for Study of Pain (IASP) defines chronic post surgical pain (CPSP) as pain lasting more than 6 months after non-tumour cause and more 3 months in cases of malignancy (Merskey H, 1994; Dillenburg W et al, 2006).

It was reported that 20% of patients reported CPSP 6 months after nephrectomy. Similarly high incidences of CPSP have been shown after open donor nephrectomy in other studies (Owen M et al, 2010; Chatterjee S et al, 2004). In our centre, we have reported 5% chronic pain in patients undergoing LLDN (Waller JR et al, 2002).

Chronic persistent pain after surgery can be caused by many factors but most notably the severity of postoperative pain and psychologic vulnerability. Patients with a higher severity of postoperative pain (particularly movement evoked pain - dynamic pain) are more likely to have chronic pain (Katz J et al, 1996; Tasmuth T et al, 1997; Callesen B et al, 1999), (Bisgaard T et al, 2001; Aasvang E, 2005; Poleshuck EL et al, 2006; Gerbershagen HJ et al, 2009). Hence an adequate dynamic pain relief protocol may reduce the development of chronic pain after surgery.

Multimodal analgesic methods have been shown to control the dynamic pain. Opioids are potent analgesics but unfortunately they are mostly inadequate to treat such dynamic pain (Kehlet H, 1994; Wilder-Smith CH et al, 1999).

The local anaesthetic methods, NSAIDs,  $\alpha_2$  agonists and NMDA receptor antagonists may be important for controlling the dynamic type of pain and also in preventing central sensitization (Bisgaard T et al, 2001; Aasvang E, 2005; Poleshuck EL et al, 2006; Gerbershagen HJ et al, 2009).

### **3.2 Multimodal approach in LLDN:**

#### **3.2.1 Non-steroidal anti-inflammatory drugs (NSAIDS):**

NSAIDs and acetaminophen (paracetamol) are commonly used in the management of moderate to severe pain alone or in combination with opioids (Moller PL et al, 2005). Paracetamol is an inhibitor of the synthesis of prostaglandins (PGs) and has some effects similar to those of the selective cyclooxygenase-2 (COX-2) inhibitors, *in vivo* (Graham GG, 2005).

NSAID-mediated inhibition of cyclooxygenases inhibits vasodilatory prostanoid production, thus reducing the diameter of the afferent arteriole and contributing to a decrease in the glomerular filtration rate (Brenner B.M., 2007).

Patients with underlying volume depletion, which is common in the postoperative setting, are at risk for this phenomenon. Non-steroidal anti-inflammatory drugs (NSAIDS) are generally avoided because of their potential nephrotoxicity and other adverse effects. NSAIDS are found to have little effect on the surgical stress response and organ dysfunction (Kehlet H., 1997; Kehlet H, 1998).

NSAIDs are also associated with increased risk of a range of adverse effects (ADEs), including peptic ulcers, gastritis, bleeding, renal dysfunction, bronchospasm, hypertension, and pedal oedema (Dahl JB, 1991; White PF et al, 2002).

Although NSAIDs as a class are associated with an increased risk of cardiovascular events, this risk is primarily attributable to higher doses and/or long-term use and may not affect patients without established cardiovascular disease who are receiving NSAIDs for short-term analgesia (Graham DJ et al, 2005) (Young D., 2005).

Nevertheless, prescribing information for all NSAIDs includes a black box warning about potential increased risk of cardiovascular and GI adverse events and they should be avoided in patients with established cardiovascular disease (Golembiewski J, 2015).

Important ADEs associated with paracetamol include hepatotoxicity and skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Patients with underlying risk factors for acetaminophen-associated hepatotoxicity, such as liver steatosis, obesity, starvation, malnutrition, concomitant use of antiepileptic drugs, and alcohol use, should avoid the use of acetaminophen for postsurgical pain (Forget P et al, 2009).

Concerns about hepatotoxicity associated with paracetamol use have prompted the US Food and Drug Administration (FDA) to limit amounts of paracetamol in prescription drug products (eg, combinations of paracetamol and opioids) to less than 325 mg (*Questions and Answers about Oral Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit.*2011).

The intravenous formulation of acetaminophen, approved for use in the United States since 2010, was found to be an effective analgesic for management of postsurgical pain with a favorable safety profile (Pasero C, 2012) (Jahr JS, 2010).

But on the other hand, it has been shown that NSAIDs provide moderate postoperative analgesia and thereby an opioid sparing effect in about 20-30% (Chatterjee S et al, 2004).

Hence they can reduce the incidence of opioid related ADEs like nausea, vomiting, respiratory depression, ileus and bladder disturbances. If NSAIDs are used for less than 5 days with adequate hydration, they can provide a potential alternative to opioids.

A recent prospective, double-blind, randomized, placebo-controlled trial of a continuous infusion of ketorolac on LDN/ percutaneous nephrolithotomy (PNL) has shown that the patients receiving ketorolac infusion had a numerical, but not statistically significant, decrease in mean pain score compared with that in patients receiving placebo (1.1 vs. 0.6 points, respectively;  $P=0.10$ ) (Grimsby GM et al, 2012).

No statistically significant differences were found between the treatment and placebo groups in time to oral intake of fluids, flatus, or change from preoperative to postoperative weight either overall or by LDN. A statistically significant improvement was noted in time to ambulation in the Ketorolac LDN group (11 vs 13.5 hours;  $P=0.04$ ). In another study, Freedland et al. used Ketorolac in LLDN patients and noted no differences in renal function (Freedland SJ et al, 2002).

Patients who underwent surgery after introduction of Ketorolac-based analgesia had a significantly shorter postoperative stay. But Ketorolac has been associated with serious side effects including gastrointestinal bleeding, postsurgical bleeding, and impairment of renal function, particularly when used for more than 5 days (Gillis JC, 1997; Strom BL et al, 1996; Feldman HI et al, 1997).

This suggests that transplant units should consider the wide use of NSAIDS in donor nephrectomy patients.

### **3.2.2 Opioids:**

Morphine is commonly considered to be the archetypal opioid analgesic and the agent to which all other painkillers are compared (Pathan H, 2012).

There is evidence to suggest that as long ago as 3000 BC the opium poppy, *Papaver somniferum*, was cultivated for its active ingredients. However, it was not until morphine was isolated from opium in 1806 by Sertürner that modern opioid pharmacology was truly born (Pathan H, 2012).

In 1847 the chemical formula for morphine was deduced and this, coupled with the invention of the hypodermic needle in 1853, led to the more precise and widespread clinical use of morphine (Blakemore PR, 2002) (Charlton JE, 2005).

Within the central nervous system, activation of mu opioid (MOP) receptors in the midbrain is thought to be a major mechanism of opioid-induced analgesia (Pathan H, 2012).

Here, MOP agonists act by indirectly stimulating descending inhibitory pathways which act upon the periaqueductal grey matter (PAG) and nucleus reticularis paragigantocellularis (NRPG) with the net effect of an activation of descending inhibitory neurons. This leads to greater neuronal traffic through the nucleus raphe magnus (NRM), increasing stimulation of 5-hydroxytryptamine and enkephalin-containing neurons which connect directly with the substantia gelatinosa of the dorsal horn. This in turn results in a reduction of nociceptive transmission from the periphery to the thalamus (Pathan H, 2012).

All opioids used in clinical practice today exert their action, at least in part, at the MOP receptor, with some having additional activity at one or more further opioid receptors or receptors distinct from the opioid family (Pathan H, 2012).

Of those drugs used in clinical practice, morphine, though generally considered to be the archetypal MOP agonist to which all other analgesics are compared, also displays some degree of activity at additional receptors, acting as an agonist at MOP receptors, but also having activity at both DOP (delta) and KOP (kappa) receptors (Pathan H, 2012).

In clinical practice, morphine is frequently administered via oral or intravenous routes, although subcutaneous, transdermal, sublingual, intramuscular, epidural, intrathecal and intra-articular routes are also commonly utilised depending upon the clinical setting (Pathan H, 2012).

### **3.2.2.1 Opioids analgesia as patient controlled analgesia:**

The use of morphine in the postoperative period is a standard practice in United Kingdom. Morphine can be given either as an intramuscular/intravenous bolus or

through a patient controlled analgesia system (PCAS). Although PCAS systems are widely used, we do not know the best way of morphine administration.

Some studies found PCAS as the preferred method (Chang AM et al, 2004) but others could not replicate similar results (Rosen DM et al, 1998; Gorevski E et al, 2011).

Patient satisfaction was found to be more with the use of PCAS (Ballantyne JC et al, 1993) with less nursing time (Boulanger A et al, 1993).

A recent literature review found that patients receiving intramuscular morphine were found to have higher rates of inadequate analgesia exposure/experience (Dolin S. J et al, 2002). PCAS does not appear to provide optimal dynamic pain relief after major surgery (Dolin S. J et al, 2002).

Meta-analysis (Ballantyne JC et al, 1993) and randomised control trials (Boulanger A et al, 1993) (Chan VW et al, 1995; Egbert AM et al, 1990; Gust R et al, 1999) have also shown that postoperative morbidity is not reduced by PCAS compared to intermittent morphine opioids. These findings are consistent with the lack of effect on PCAS on surgical stress response and organ dysfunction (Kehlet H., 1997; Kehlet H, 1998).

In addition, high incidences of postoperative nausea/vomiting (PONV), respiratory depression and sedation are noted in morphine use when compared to epidural analgesia (Dolin S. J et al, 2002).

Hence the use of opioids is far from being the ideal postoperative analgesic of choice following major surgery like LLDN.

### **3.2.3 Epidural analgesia:**

Epidural analgesia is a well-established technique for managing postoperative pain and this has been in use for decades. Although epidural analgesia is invasive, labour-intensive, and expensive, the costs and potential risks have been justified because of the assumed benefits (Rawal N., 2012).

Some studies have shown a shorter length of hospital stay when the technique is a component of fast-track rehabilitation routines after major abdominal surgery (Kehlet H, 2008; Park WY et al, 2001) thus adding cost-effectiveness to its list of advantages.

Usually this technique is used as a substitute for PCAS in LLDN patients. Epidural opioids and local anaesthetics infiltrations are known to provide more effective dynamic pain relief (Kehlet H, 2001). But it is also worthwhile noting that epidural opioids are less effective on the stress response (Kehlet H, 2001).

Epidural anaesthesia can also block sympathetic responses and may reduce cardiac morbidity (Liu SS et al, 1995). Epidural analgesia is found to be associated with a lower incidence of PONV, sedation and postoperative bowel dysfunction when compared with opioids (Dolin S. J et al, 2002).

But epidural analgesia has its own problems including urinary retention and risk of infection at the catheter site. Urinary retention is a common problem and 23% patients undergoing an epidural needed a urinary catheterization (Dolin SJ, 2005).

Although it is one of the best modalities of analgesia, its efficacy in major abdominal procedures is somewhat smaller because of the insufficient afferent neural blockade (Kehlet H, 2001).

A retrospective series using a cohort of open donor nephrectomies has showed that thoracic epidural analgesia is better than a lumbar (Suarez-Sanchez L et al, 2006). Though epidural analgesia provides good pain relief, it is associated with a high incidence of complications including nausea (47%), vomiting (22%), hypotension (11%), lower extremity motor blockade (8%), pruritus (5.5%), and somnolence (5%) (Suarez-Sanchez L et al, 2006). Although epidural analgesia provides good pain relief, a thorough literature review cannot confirm a single study in LLDN patients.

### **3.2.4 Neuroaxial techniques:**

Blockade of afferent neural stimulus by local anaesthetic agents is very effective in reducing the classical catabolic responses to surgery (Dolin S. J et al, 2002; Ashcraft EE et al, 2001; Kehlet H., 1993). Thus the unusual increase of cortisol, catecholamines and glucose concentration can be prevented, insulin resistance reduced and glucose and nitrogen economy improved (Dolin S. J et al, 2002; Ashcraft EE et al, 2001; Kehlet H., 1993).

There are also unfavourable changes in the coagulation and fibrinolytic systems, which are modified in favour of less thrombosis formation. In contrast, most changes in immune function and markers of inflammation remain unaltered by a neural block and concomitant hormonal inhibition (Dolin S. J et al, 2002; Ashcraft EE et al, 2001; Kehlet H., 1993).

It is also worth noting that pain relief by other techniques such as epidural analgesia, systemic opioids or NSAIDS are less effective than a normal block with local anaesthetic ( Ashcraft EE et al, 2001; Kehlet H., 1993).Opioids are effective at the transmission stage, whereas pre-emptive local anaesthetic and peripheral nerve blockade take effect by preventing conduction of the nociceptive stimulus as well as preventing central sensitization (Katz J et al, 1996) (Yndgaard S et al, 1994).

The sub-fascial administration of local anaesthetic has been shown to be much more effective than subcutaneous injection in reducing the pain (Yndgaard S et al, 1994).

Sub-fascial administration of bupivacaine (0.5%) at the trocar and incision sites not only reduced pain, but they also shortened hospital stay in patients undergoing a laparoscopic donor nephrectomy (Ashcraft EE et al, 2001).

### **3.2.5 Continuous infusion of local anesthetic agents:**

We know that local anaesthetic agents can provide a number of benefits without any systemic adverse effects. The trend towards increased use of multimodal analgesia has led to increased use of local anaesthetics in the management of postsurgical pain. Local anaesthetics represent important therapeutic options for incorporation into multimodal analgesic approaches to postsurgical pain management because their mechanism of action involves suppression of pain neurotransmission at its origin (Beydoun A, 2003) (Thomas JM, 1999).

Local anaesthetics have a well-characterized safety profile that includes the risk of CNS and cardiovascular toxicity and other adverse events such as motor weakness, peripheral nerve irritation, and chondrolysis (White PF., 2002) (Neal JM et al, 2010).

The rate and extent of systemic absorption of local anaesthetics vary widely when administered peripherally, depending on the dose and vascularity at the administration site (Heavner JE., 2007).

Numerous approaches for extending the duration of action of local anaesthetics have been developed, including alteration of molecular structures, combining of local anaesthetic compounds with different pharmacodynamic profiles, and the addition of drugs such as epinephrine or clonidine (Lipfert P et al, 1987) (C.J. McCartney et al, 2007) (B.G. Covino, 1998).

One of the most popular approaches for prolonging the duration of analgesia in the postsurgical setting was to use a continuous infusion of local anaesthetics via an elastomeric pump (Ilfeld BM, 2005). Potential drawbacks of delivery via continuous infusion devices include expense, lack of staff education/knowledge of how to use the devices, the cumbersome nature of the pump apparatus, inadvertent dislodgment of the catheter, unpredictable or inaccurate delivery rate, and technical failure (Ilfeld BM, 2005) (Dowling R et al, 2003) (Pepin JL et al, 2011) (Birrer KL et al, 2011).

Recently Biglarnia and colleagues showed the benefit of a continuous infusion of ropivacaine (0.5%) as a tool for postoperative pain relief (Biglarnia AR et al, 2011). But in this study, the donor nephrectomy was done through a hand-assisted retroperitoneoscopic technique (HARS). Two catheters were placed, one in the retroperitoneal space and another in the rectus sheath followed by continuous infusion of ropivacaine into both these spaces. This technique has dramatically reduced pain scoring and cumulative consumption of morphine equivalent.

Panaro et al. have shown that continuous infusion of ropivacaine is a good pain relief technique following laparoscopic donor nephrectomy (Panaro F et al, 2011).

In this study, a retroperitoneal approach was used during the donor nephrectomy. Two catheters were used; one in between parietal peritoneum and muscle layers and the second catheter was placed on subcutaneous tissue. This study also showed a reduction in the pain score, morphine consumption and hospital stay compared to the counterpart controls.

Unfortunately a similar technique has not been used in transperitoneal LLDN patients. The use of similar technique in the transperitoneal approach would be difficult due to a large peritoneal cavity; leaving the catheter in the peritoneal cavity for a long period also carries the risk of introducing infection and migration.

### **3.2.6 Long acting local anesthetics agents:**

The long acting local anaesthetic agents do play an important role in postoperative pain relief. The prospect of long acting local anaesthetic agents that last for a prolonged period is ideal and attractive but still under evaluation. But preemptive port-site infiltration can reduce central sensitization, facilitates recovery by enabling earlier ambulation and may reduce the postoperative analgesics requirement (Vloka JD et al, 1997; Song D et al, 2000; Li S et al, 2000). However, it is most effective for superficial procedures and analgesia lasts for only 6–8 h.

Simple administration of local anaesthetic after cholecystectomy also reduces right upper quadrant and shoulder pain (Michaloliakou C et al, 2000). Although preincisional infiltration has been shown to reduce postoperative pain after cholecystectomy, (Bisgaard et al, 1999; Fong SY et al, 2001; Hasaniya NW et al, 2001) other investigators reported better pain relief when local anesthetic was infiltrated at the end of surgery (Sarac AM et al, 1996).

Hence the use of local anesthetic infiltration at the trocar site is still controversial (Moiniche S et al, 2000).

The pain from suprapubic Pfannenstiel incision during LLDN could be relieved by local anaesthetic wound infiltration. Recent studies showed local anaesthetic infiltration before and/or after abdominal hysterectomy did not reduce the intensity of postoperative pain and analgesic requirements (Hariharan S et al, 2009; Klein JR et al, 2000).

But another randomized study proved the benefit of preemptive administration of lidocaine as an efficient mode to reduce pain in the first eight hours after hysterectomy (Lowenstein L et al, 2008).

To date, no study has been done in the LLDN setting to assess the effect of long acting local anaesthetic agents for postoperative pain relief.

### **3.2.7 Liposomal bupivacaine prolonged-release formulation in the surgical setting**

Liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals Inc, Parsippany, NJ) is an extended-release formulation of bupivacaine designed to allow drug diffusion to occur for up to 72 hours following a single administration at the end of surgery. It is a multivesicular liposomal formulation of bupivacaine approved by the FDA in 2011. This is indicated for single-dose administration of up to a total of 266 mg into the surgical site to produce postsurgical analgesia; it can be diluted up to 0.89 mg/mL (ie, 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection, if needed for coverage over larger surgical areas. Liposome bupivacaine contains approximately 3% extra-liposomal bupivacaine, allowing for a fast onset of analgesia.

Its pharmacokinetics are characterized by a bimodal release profile with an initial peak serum concentration approximately 1 hour after administration, followed by a later peak that occurs within 12 to 36 hours of administration (Hu D et al, 2013).

In a prospective sequential-cohort study, liposomal bupivacaine has been shown to reduce opioid consumption, lower hospital costs, and shorten length of stay when compared with a standard opioid-based analgesic regimen for postsurgical pain in patients undergoing open colectomy (Cohen SM., 2012).

The efficacy and safety profile of single-dose administration of liposome bupivacaine at the surgical site were evaluated in 10 randomized, double-blind, controlled phase 2 and phase 3 studies in patients undergoing inguinal hernia repair, total knee

arthroplasty, hemorrhoidectomy, breast augmentation, and bunionectomy (Bergese SD et al, 2012).

In a pooled analysis across these studies, in which 823 patients received liposomal bupivacaine (545 received liposomal bupivacaine doses  $\leq$ 266 mg, the highest FDA-approved dose), the drug was found to provide postsurgical analgesia for up to 72 hours and to extend the median time to first postsurgical use of opioid analgesics compared with bupivacaine and placebo (Bergese SD et al, 2012).

A recent prospective randomized controlled trial of liposomal bupivacaine versus 0.25% bupivacaine in laparoscopic, robotic urologic surgery showed no significant difference in median total opioid use in the postoperative period (Knight RB et al, 2015).

Furthermore, pain scores, length of hospital stay, and time to first opioid use did not differ between groups. Subgroup analysis of laparoscopic renal surgery revealed no difference between liposomal bupivacaine and 0.25% plain bupivacaine.

### **3.2.8 Other methods:**

Acetazolamide can decrease the formation of H<sup>+</sup> ions and thereby retard peritoneal acidification which is probably responsible for visceral and referred pain (Ives HIE., 2004). Woehlck et al (Woehlck HJ et al, 2003), have shown that the intravenous use of acetazolamide reduces referred pain following laparoscopic cholecystectomy.

Singh R et al. reported the beneficial use of acetazolamide as a part of multimodal analgesic approach in laparoscopic live donor nephrectomy. In this randomised double-blind controlled trial, nasogastric administration of acetazolamide in combination with

bupivacaine (0.5%) installation into the renal fossa and (0.25%) infiltration at the port and retrieval wounds was shown to be effective (Singh R et al, 2009). The patients who received this multimodal therapy experienced less shoulder tip pain, had lower pain scores at 12 hrs, lower total analgesic requirements and less nausea compared to controls. A limitation of the study was that it was not powered to detect drug-related side effects. It was, the first documented study to test acetazolamide role in multimodal analgesia and this strategy requires further research.

### ***3.3 Transversus abdominis plane (TAP) block:***

Since the arrival of the TAP block technique in 2001, (Rafi AN, 2001) it has been widely used for postoperative pain relief. Previous randomised controlled trials have shown that TAP blocks can reduce post-operative pain and morphine requirement after abdominal surgery for large bowel resection (McDonnell JG et al, 2007) and Caesarean section (McDonnell JG et al, 2008).

The latter study is particularly relevant as caesarean section is performed through a suprapubic Pfannenstiel incision, which is similar to the approach used for retrieving kidneys that have been dissected laparoscopically.

A preemptive TAP block can potentially reduce metabolic responses during surgery and also avoid central sensitization. The principle behind pre-emptive TAP blocking is that local anaesthetic is injected into the neuro-fascial plane where it may act on the afferent sensory nerves of the lower 6 thoracic and upper lumbar nerves as they course through the plane before they pierce the musculature to innervate the abdominal wall.

This plane is poorly vascularized and it has been suggested that a prolonged analgesic effect can be observed in TAP blocking, due to slow drug clearance (McDonnell JG et al, 2007; McDonnell JG et al 2008).

### **3.3.1 TAP block technique:**

With the patient in the supine position, a 22 gauge 50mm blunted regional anaesthesia needle is introduced laterally and posterior to the mid-axillary line between the iliac crest and the inferior extent of the rib cage. An ultrasound probe is placed transverse to the long axis of the abdomen and the needle introduced perpendicular to the linear array beam of ultrasound.

The presence of fascial extensions of the abdominal wall muscles can also be used to correctly place the needle tip using the loss of resistance technique. The needle is held perpendicular to the coronal plane and advanced until resistance is encountered and a first “pop” sensation is felt. This indicates that the needle has entered the plane between the external and internal oblique layers. The needle is then further advanced until a second “pop” sensation is encountered, indicating that the needle tip has traversed the fascial extensions of the internal oblique and is thus within the transversus abdominis plane.

### ***3.4 Conclusion:***

The journey of finding the ideal method for pain relief in LLDN patients is yet far from over. The arrival of new techniques and multimodal approaches appears to be safe and potentially effective in providing postoperative analgesia. It is important that the donors get the best possible postoperative pain relief which could shorten hospital stay and minimally impact on their day to day lives. The TAP block technique has not been tested in LLDN patients thus warrants a randomised control trial. As such, the aim of this thesis is to investigate the role of transverse abdominis plane block in laparoscopic live donor nephrectomy patients.

***CHAPTER 4***

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**Retrospective Study on Transversus Abdominis Plane Block in  
Laparoscopic Live Donor Nephrectomy.**

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## 4 Introduction

Laparoscopic live donor nephrectomy (LLDN) is gaining popularity and has a number of advantages over open surgery including a significant reduction in post-operative pain and early recovery. Nonetheless, the suprapubic incision used for kidney retrieval during LLDN still causes significant pain in some patients, to the point where they require parenteral opiates. Dynamic pain relief may be a powerful technique in modifying the major surgical stress response; it is a pre-requisite to an early post-operative recovery and reduction in post-operative morbidity (Tasmuth T et al, 1997) (Katz J et al, 1996).

Different stages in the pain pathway are susceptible to various analgesic techniques. Opiates are effective at the transmission stage, whereas pre-emptive local anaesthetic and peripheral nerve blockade take effect by preventing conduction of the nociceptive stimulus as well as preventing central sensitisation (Coderre TJ et al 1990).

Despite the analgesic efficacy exerted by morphine at the mu ( $\mu$ ) opioid receptor, troublesome opiate side effects, including respiratory depression, nausea, vomiting, and sedation justify an exploration of alternative methods of pain relief (Calvey TN, 1997).

Regional anaesthetic techniques are thought to produce a substantial reduction in the surgical stress response whilst possessing the benefit of an opioid sparing effect (Tverskoy M et al, 1990) (Kehlet H, 1998).

The transversus abdominis plane (TAP) block has been shown to have good efficacy in other studies (McDonnell JG et al, 2007; McDonnell JG et al, 2008). There is, however, a paucity of published data relating to the use of TAP blocks in laparoscopic live donor nephrectomy.

The aim of this pilot study was to examine the effects of TAP blocks on post-operative pain, morphine consumption and the morphine side effect profile following laparoscopic live donor nephrectomy.

#### ***4.1 Study population and methods:***

A consecutive series of 50 patients receiving TAP block prior to LLDN were compared to a historical control group of 50 patients who had no TAP block. Patients in both groups were offered post-operative morphine delivered by a patient controlled analgesia system (PCAS). The parameters of age, body mass index (BMI), gender, side of the kidney were comparable within the study population (Table 4.1).

Data were recorded in an Excel spread sheet (Microsoft, Redmond, Washington – United States) and GraphPad InStat version 3.06 (GraphPad Software, Inc, San Diego, California, USA). Descriptive statistics for continuous variables were recorded as mean  $\pm$  SD or median (range) according to whether or not they were normally distributed. Normality testing was performed using the Kolmogorov-Smirnov test. Comparison between groups was performed with unpaired *t*-test with Welch correction for parametric variables and the Mann-Whitney test for non parametric variables. Categorical variables were analysed using the Chi-squared test. Statistical significance was defined as  $P < 0.05$ .

**4.2 Table 4.1: Demography of the study population (Values are mean  $\pm$  SD )**

<b>Parameter</b>	<b>No TAP Block (n = 50)</b>	<b>TAP Block (n = 50)</b>	<b>P Value</b>
Age (years)	47 $\pm$ 13	47 $\pm$ 10	P = 0.67
BMI (kg/m <sup>2</sup> )	26 $\pm$ 4	25 $\pm$ 3	P = 0.26
Gender (M:F)	21:29	22:28	P = 0.58
Kidney (R:L)	8:42	8:42	P = 1.21

**4.3 Results:**

The 100 consecutive patients studied here underwent laparoscopic live donor nephrectomy between January 2008 and December 2009. The demographics and clinical characteristics of patients in the TAP block and control (No TAP) groups are shown in Table 4.1. Both groups within the study were well matched without any significant differences.

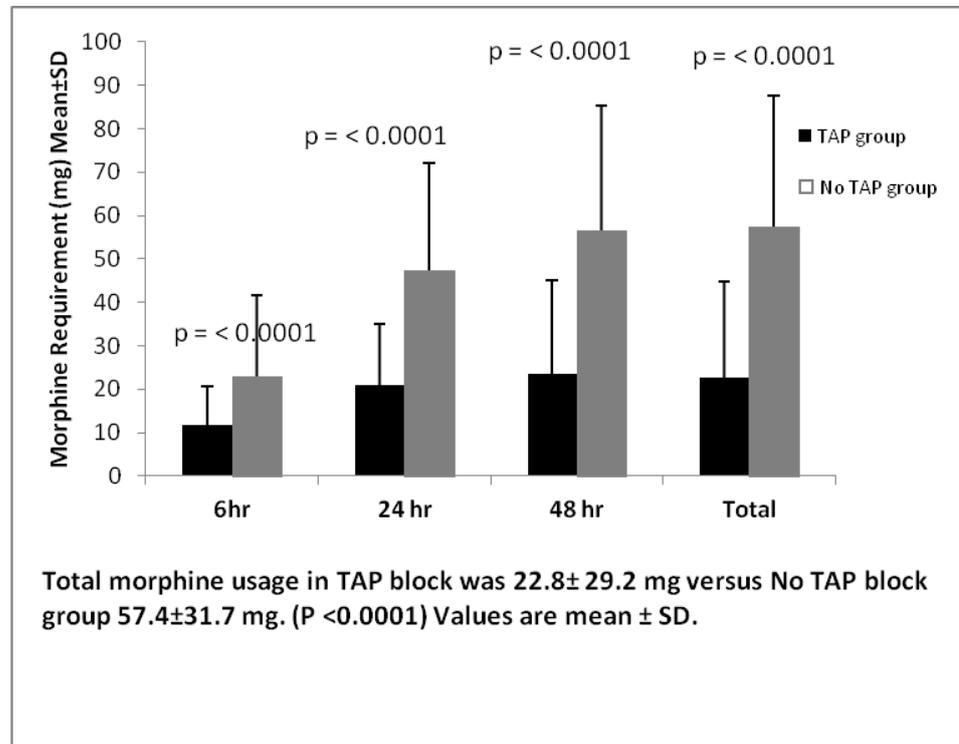
**4.4 Table 4.2: Patient Controlled Analgesia Scoring (PCAS)**

<b>Grade</b>	<b>Pain</b>	<b>PONV</b>	<b>Sedation</b>
0	No pain at rest or movement	No PONV	None- alert
1	No pain at rest, slight at movement	No N&V at rest N&V on slight movement	Mild, awake but drowsy
2	Intermittent pain at rest, moderate on movement	Intermittent N&V at rest, moderate on movement	Moderate, asleep but rousable
3	Continuous pain at rest and severe on movement	Continuous N&V at rest	Severe, unrousable

Post-operative morphine requirement at 6, 24, 48 hours and the cumulative dose of morphine are shown in figure 4.1. Overall, the patients in the TAP group required significantly less post-operative morphine  $22.8 \pm 29.2$  mg versus  $57.4 \pm 31.7$  mg;  $P < 0.0001$  (figure 4.1). The differences in cumulative morphine doses between the two groups were significant at all time points up to 48 hours post-operatively.

Post-operative sedation scores were significantly higher in the control group at 6, 24, 48 hrs after operation.

**4.5 Figure 4.1: Cumulative usage of morphine between TAP and No TAP group**

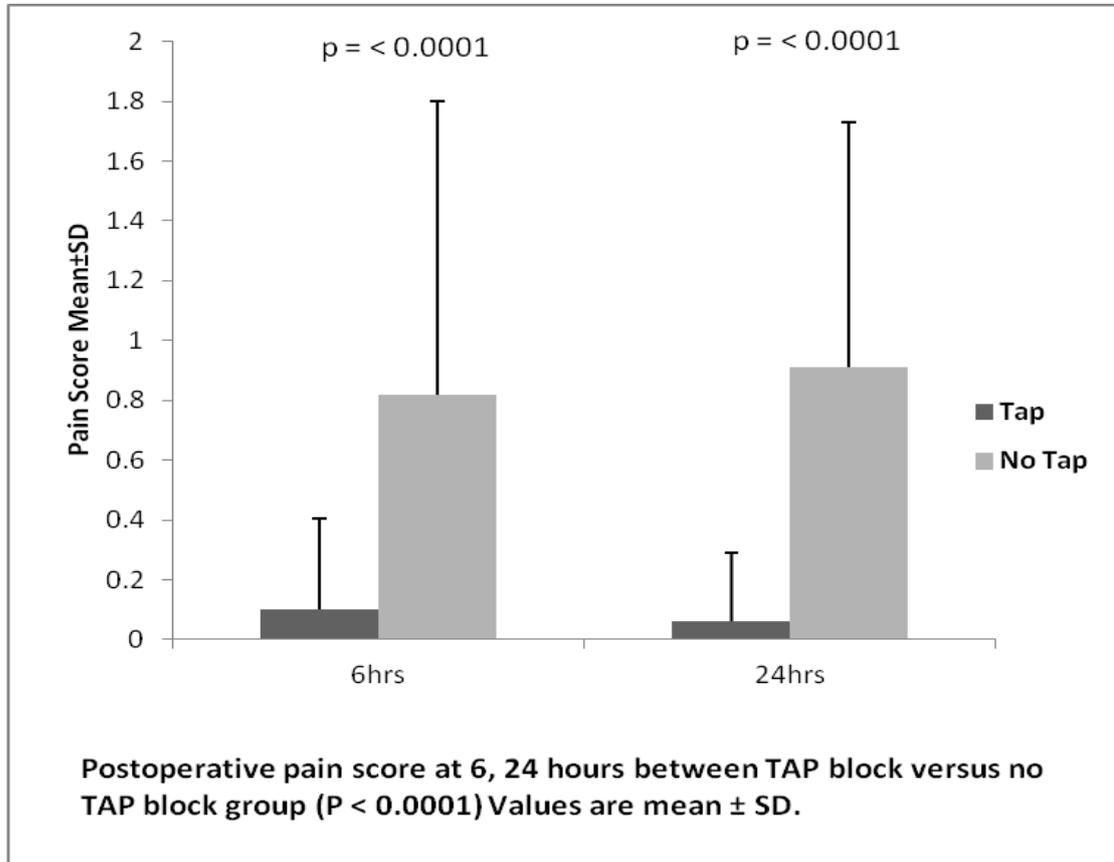


A further analysis showed lower oral analgesic usage in TAP group (paracetamol  $13.35\pm 3.6$  grams versus  $17\pm 4.8$  grams;  $P < 0.0002$ ) and (tramadol  $353\pm 283$ mg versus  $820\pm 521$ mg;  $P < 0.0001$ ) compared with No TAP group. Similar results were noted for anti-emetics (Cyclizine  $60\pm 82.1$ mg versus  $159\pm 212$  mg;  $P < 0.0017$ ) and ondansetran  $3.2\pm 3.8$ mg versus  $5.5\pm 5.5$ mg;  $P < 0.035$ ) requirements as well.

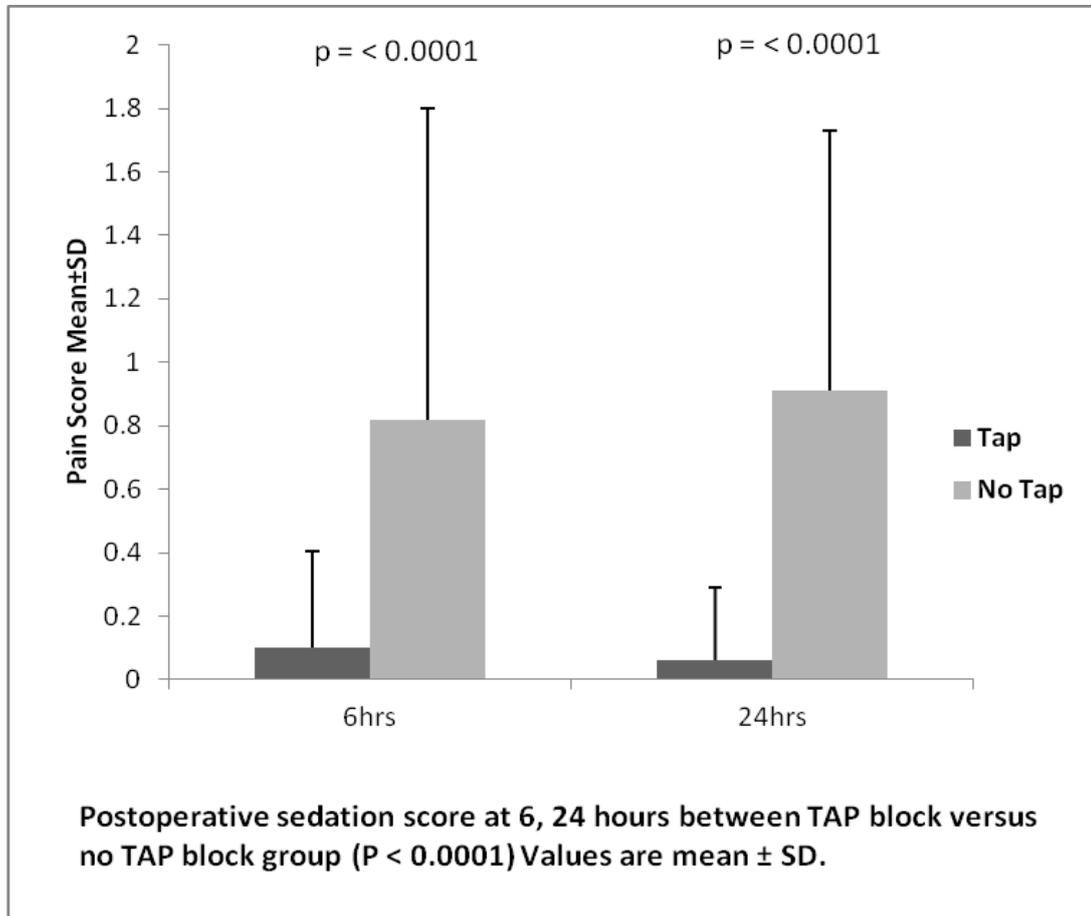
Few patients in either group recorded continuous pain at rest and severe pain on movement at any post-operative time point but grade 1 and 2 post-operative pain were recorded more in patients in the control (No TAP) group, compared to TAP patients (table 4.3, figure 4.2). Post-operative sedation scores were significantly higher in the control group at 6, 24, 48 hrs after operation (table 4.3, figure 4.3). No difference was noted in PONV scoring between TAP and No TAP group and this might be related to adequate use of anti-emetics in both arms.



**4.7 Figure 4.2: Pain scores between TAP and No TAP group**



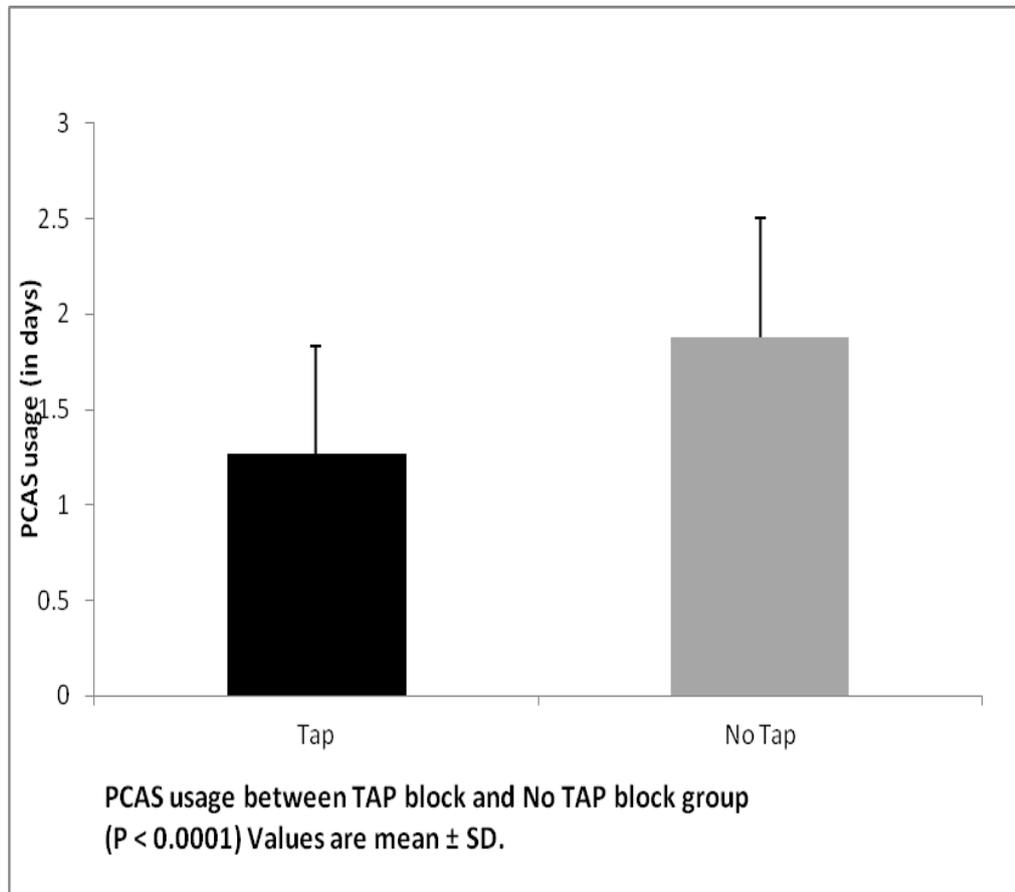
**4.8 Figure 4.3: Postoperative sedation score**



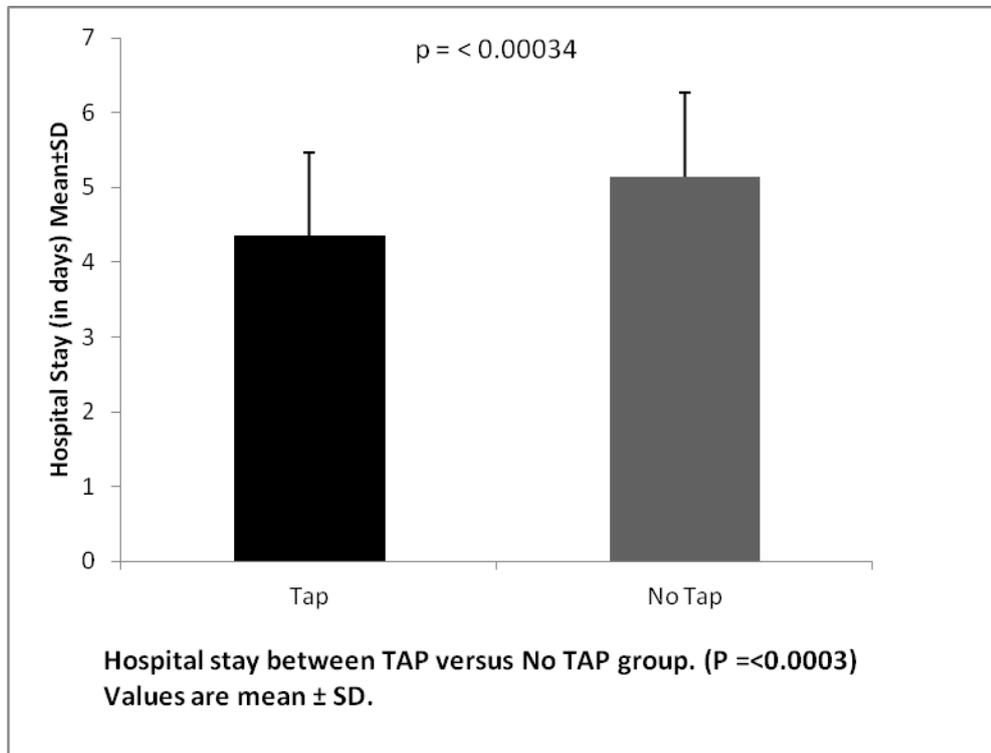
The TAP block group discontinued their PCAS significantly quicker than patients in the control group  $1.3 \pm 0.6$  days versus  $1.9 \pm 0.7$  days;  $P < 0.0001$  (figure 4.4). Similarly, there was a significant difference in the length of hospital stay between the TAP and control group  $4.3 \pm 1.1$  versus  $5.1 \pm 1.1$  days;  $P < 0.0034$ . (Figure 4.5)

There were no episodes of bleeding, bruising or other adverse events in the TAP block group.

**4.9 Figure 4.4: PCAS usage**



**4.10 Figure 4.5: Hospital stay**



#### ***4.11 Discussion:***

This study shows that pre-operative TAP blocks significantly reduced post-operative pain and morphine requirements in patients undergoing laparoscopic live donor nephrectomy. The median post-operative morphine dose in the TAP block was 22.8 mg compared to 57 mg in controls, demonstrating a significant effect. The low morphine requirement in the TAP group was associated with a reduction in postoperative sedation.

In the non-TAP block group, PCAS morphine requirements increased steeply 12-hour postoperatively, presumably due to the effects of local anaesthetic wound infiltration wearing off at this time point. However, this effect was not seen in the TAP block group, where good analgesia was recorded up to 48 hours postoperatively. This prolonged action of TAP blocking has previously been described in patients following Caesarean section and found to be effective up to 36 hours (McDonnell JG et al 2008).

The principle behind pre-emptive TAP blocking is that local anaesthetic agent is injected into the neuro-fascial plane where it may act on the afferent sensory nerves of the lower 6 thoracic and upper lumbar nerves as they course through the plane before they pierce the musculature to innervate the abdominal wall. This plane is poorly vascularised and it has been suggested that the prolonged analgesic effect observed in TAP blocking is due to slow drug clearance (McDonnell JG et al 2008).

The pathophysiological basis of postoperative abdominal wound pain is related to the input of afferent neuronal activity, enhancing sensitisation of the dorsal column to nociception both during and after surgery as the inflammatory process continues at the site of injury (Nicholson ML et al 2010).

Surgical stress is also thought to be due to a combination of endocrine and metabolic responses, which are differentially affected by various pain relieving techniques. Minimally invasive surgery helps to reduce the inflammatory response and morbidity (Andersen MH et al, 2006) (Bachmann A et al, 2006; Perry KT et al, 2003) (Jackobs S et al, 2005).

However opiates have minimal effects on the endocrine and metabolic responses in contrast to regional anaesthetic techniques, which lead to a substantial reduction in surgical stress (Kehlet H, 1998).

Thus opiates should be used sparingly post-operatively as this class of drugs only suppresses intra-operative responses but is much less effective in post-operative responses (Kehlet H, 1998).

In addition, clinically relevant tolerance can occur within hours of intra-operative opioid administration (Guignard B et al, 2000), thus reducing their post-operative efficacy and perpetuating a dose-dependent increase in opioid related side effects (Marret E et al, 2005) (Roberts GW et al, 2005; Zhao SZ et al, 2004), (Wheeler M et al, 2005) (Dolin SJ, 2005).

Pre-emptive analgesia is believed to prevent the establishment of peripheral and central neural sensitisation that is caused by the surgical incision and the subsequent inflammatory injury (Zhao SZ et al, 2004). This prevents the consequent amplification and continuation of pain. Pre-emptive analgesia also allows a reduction in intra-operative opioid requirements. Furthermore, the peak effects of pre-emptive analgesia occur prior to emergence from anaesthesia thus reducing post-operative opioid requirements.

This is the first study of the effects of TAP blocks after laparoscopic live donor nephrectomy. The pilot study was large enough to provide a relatively robust evaluation of the technique and although the study was performed retrospectively, extensive data was available from standardised forms used to record PCAS outcomes. Although the potential benefits of regional anaesthetic techniques are well known, these have tended to be under-utilised. The present study has shown that when the correct anatomical area is targeted with local anaesthetic then efficacious and long-lasting analgesia is possible.

The sensory level achieved by TAP blocks in this study was not formally tested since the patients were under anaesthesia at the time of administration. One of the main targets of the TAP block is the ilioinguinal nerve.

However, its path is known to be subject to considerable variability (Jamieson RW et al, 1952). The point at which the ilioinguinal nerve penetrates through the transversus abdominis muscle to run in the neurovascular plane varies from 20-60% of the distance along the iliac crest from the anterior to the posterior superior iliac spines (Jamieson RW et al, 1952).

The area covered by TAP blocking in patients undergoing laparoscopic nephrectomy is likely to include the suprapubic retrieval incision and perhaps the lower two ports sites but the upper two port sites are unlikely to have been reached by the block. When dye was injected into the transversus abdominis plane, it had been shown to spread cephalad to the T10 dermatome in only 50% of cases (Tran TM et al, 2009).

A recent study has shown that continuous local infusion of ropivacaine administration after donor nephrectomy provides effective postoperative pain relief and reduces the need for opioid treatment (Biglarnia AR et al, 2011).

Similar results were found also in patients undergoing colorectal surgery (Beaussier M et al, 2007).

#### ***4.12 Conclusion***

This retrospective analysis suggests that the use of TAP blocks in laparoscopic donor nephrectomy is effective and provides potential long lasting analgesia. The evidence generated from this pilot retrospective analysis supported the need for a randomised controlled trial.

**CHAPTER 5**

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**A Randomised Clinical Trial of TAP Block in Laparoscopic Live Donor Nephrectomy**

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# **5 Randomised clinical trial of transversus abdominal plane block versus placebo control in laparoscopic live donor nephrectomy**

## ***5.1 Introduction***

Laparoscopic surgery has many advantages over open techniques including reduced analgesic requirements and faster patient recovery (Nanidis TG et al, 2008) (Nicholson ML et al, 2010; Ratner LE et al, 2000; Wilson CH et al, 2005). It is now a preferred and popular method of surgery for live donor nephrectomy throughout the UK. Nonetheless, donors still suffer pain following surgery, resulting in a need for parenteral opiates. The side effects of opiates are numerous and include nausea, vomiting, pruritus and respiratory depression.

The sensory nerve supply to the anterior abdominal wall is largely derived from the anterior divisions of the lower thoracic nerves. Studies have shown that the introduction of a local anaesthetic agent into the anatomical plane between the internal oblique and transversus abdominis muscle on either side of the incision site can block the sensory nerves that supply the lower abdominal wall from a level of T10 – L1(Tran TM et al, 2009). This technique is known as a TAP block and can be used to complement the oral and parental analgesia regimen, targeting the somatic component of pain after surgery.

## **5.2 Recent studies:**

TAP blocks have been successfully used in reducing post-operative pain and the overall requirement for morphine after abdominal surgeries such as hysterectomy (Carney J et al, 2008), appendicectomy (Niraj G et al, 2009) and Caesarean section (Belavy D et al, 2009).

Nonetheless, several recent studies in patients undergoing Caesarean section, which employs a similar incision to the one used for kidney retrieval during laparoscopic donor nephrectomy (Costello JF et al, 2009) have found no benefit in the administration of a TAP block. This questions the suitability of the technique for all types of lower abdominal surgery.

The aim of this study was to determine the safety and efficacy of TAP block in patients undergoing LLDN in a single centre, double-blind, randomised placebo controlled trial.

## **5.3 The trial:**

A consecutive series of 51 patients were invited to take part in the trial (see CONSORT diagram 5.3.2). One patient declined to participate. A total of 50 patients were randomised, 25 underwent the TAP block with 0.375% bupivacaine or 25 TAP block with 0.9% Saline (placebo control). In the bupivacaine group one lady had their donor nephrectomy operation cancelled as she had not stopped taking the oral contraceptive pill. Two patients in the control group had their operations cancelled due to ill health.

A further patient was excluded from the placebo arm due to the trial drug not being available. In three cases (2 bupivacaine, 1 Control group) it was unknown which drug was administered due to an error in dispensing by the Pharmacy Department. These

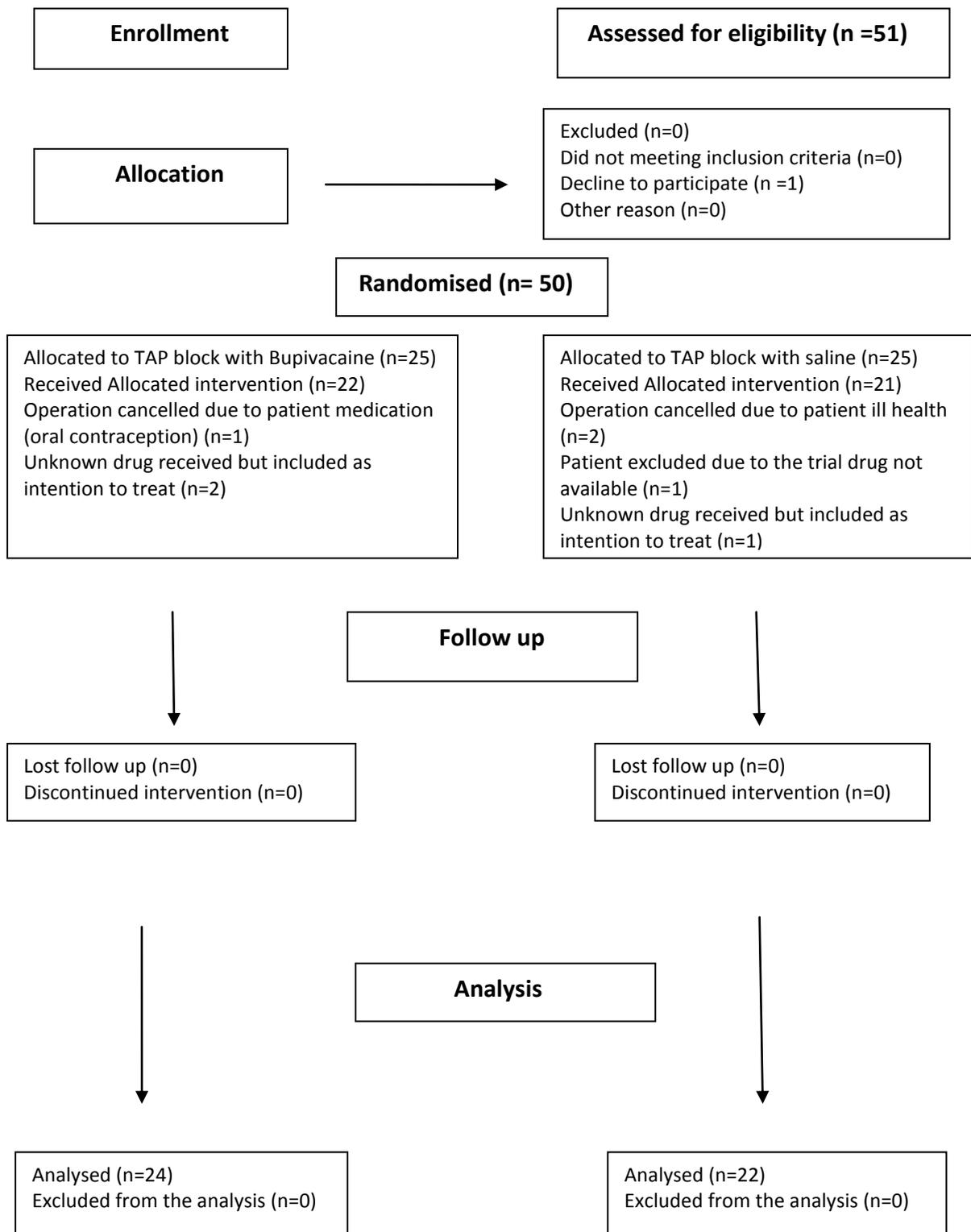
three patients were analysed in their respective groups on an intention to treat basis. Thus a total of 24 patients receiving bupivacaine and 22 in the control group were analysed in the study (Figure 5.3.2).

### **5.3.1 Methods**

Local ethics committee and R&D approval were obtained before the start of the trial and the study was registered (Clinical trial registration is SRCTN14709684). A computer-generated sequence of random numbers was used to create a sealed envelope system for a consecutive series of 50 patients randomised in a 1:1 ratio to either TAP blocking with bupivacaine or the saline placebo (control). There was no significant difference in the demography between two groups. We assume that there will be no difference on cumulative morphine use and other parameters between the placebo and bupivacaine group (null hypothesis). Written consent was obtained the day before surgery.

The trial pharmacist opened the randomization envelope and labelled the assigned pre-filled syringes (bupivacaine 0.375% or normal saline 0.9% sodium chloride) with the trial number and a patient name/number. These syringes were delivered to the consultant anaesthetist who was blinded to the treatment group. All members of the nursing, medical and surgical team apart from the trial administrator/coordinator and the pharmacist were also blinded to the treatment allocation.

### 5.3.2 CONSORT Diagram



### 5.3.3 Table 5.1 Demography

	<b>Bupivacaine</b>	<b>Control</b>	<b>p value</b>
Male: Female	10:14	9:13	1.00
Age (years)	52 (10)	47 (9)	0.19
Weight (Kg)	79.8 (21.5)	74.3 (13.7)	0.31
Body mass index, kg/m <sup>2</sup>	26.2 (4.4)	25.6 (3.0)	0.55
Length of operation (min)	186.4 (32.1)	190.5 (13.4)	0.32
Side of operation (R:L)	2:22	3:20	0.32
Values are mean (SD) or ratios using raw numbers			

**Both groups were comparable in terms of gender, age, weight, BMI and length of operation time.**

### **5.3.4 Anaesthetic protocol**

All general anaesthetics were performed by a member of the consultant anaesthetic staff using a standardised technique. In brief, anaesthesia was induced with propofol 2.5-3 mg/kg and Fentanyl 1-2µg/kg and maintained with isoflurane and 50% oxygen in air. Muscle relaxation was achieved with atracurium 1 mg/kg. Intravenous fluids were administered to maintain the systolic blood pressure above 100 mmHg.

### **5.4 TAP block procedure**

All TAP blocks were performed by a consultant anaesthetist experienced in anaesthetising donor nephrectomy patients. All TAP block needles were inserted under ultrasound control. After skin preparation with antiseptic, a blunt regional anaesthesia needle (22 gauge) was introduced through the skin just cephalad to the anterior superior iliac spine of the pelvis. The needle was introduced until resistance was encountered, indicating that the needle tip was at the external oblique muscle. Gentle advancement of the needle resulted in a 'pop' sensation as the needle entered the plane between the external and internal oblique fascial layers. Further gentle advancement of the needle resulted in a second 'pop', indicating that the needle tip entered the transversus abdominis fascial plane. These manoeuvres were performed under direct ultrasound control which allowed careful delineation of the three lateral muscle layers and ensured that the anaesthesia needle was in the correct plane. After careful aspiration to exclude vascular puncture, 20ml of solution (either 0.375% Bupivacaine or 0.9% saline) was injected through the needle into the TAP plane. The same procedure was then repeated on the contralateral side, again using 20ml of test solution.

## ***5.5 Surgical technique***

All operations were performed by the transplant surgical team using a standardised technique. In brief, four laparoscopic ports were used, two 12 mm ports placed near to the umbilicus and in an iliac fossa and two 5mm ports placed in the epigastrium and flank. The ureter and renal vessels were dissected and then all of the lateral and posterior attachments of the kidney divided until the kidney was free on its vascular pedicle. A 6cm suprapubic retrieval incision was made through a transverse skin incision with division of the abdominal muscles in the midline. An Endocatch II (Covidien, Mansfield, MA, USA) retrieval system was introduced through this retrieval incision. The ureter and renal vessels were secured with clips or staples and then divided. The kidney was captured in the Endocatch bag and removed through the suprapubic retrieval incision. The lengths of wound incisions were recorded.

## ***5.6 Peri-operative protocol***

As prophylaxis against venous thromboembolism all donors wore TED stockings and subcutaneous dalteparin 5000 IU administered once per day until fully mobile. Donors were allowed to begin mobilisation on the first post-operative day and were allowed to start eating and drinking at their own discretion.

### **5.6.1 Post-operative Care**

All patients received post-operative pain relief using a patient controlled analgesia system (PCAS) delivering 1mg boluses of morphine with a 5-minute lock-out period. Opiate analgesia was discontinued at the discretion of the patient and then replaced by oral analgesia with tramadol (50-100mg PO up to QDS) and paracetamol (1g PO up to QDS).

## **5.7 Outcome measures**

### **5.7.1 Primary end points:**

The primary endpoint was the total post-operative morphine requirement. Post-operative analgesic use was recorded by the nursing staff and pain team using the standard PCAS form.

Daily post-operative pain levels were recorded using visual analogue (a continuous scale comprised of a horizontal 10 centimetres (100 mm) in length used to document the pain at the time points and verbal response scales as follows.

0 - no pain at rest or movement

1 - no pain at rest, slight at movement

2 - intermittent pain at rest, moderate on movement

3 - continuous pain at rest and severe on movement.

### **5.7.2 Secondary end points:**

1. Daily post-operative nausea and vomiting (PONV) was recorded by using visual analogue and verbal response scales. (0 - No nausea and vomiting at rest or movement; 1- no nausea and vomiting at rest, slight at movement; 2 -

Intermittent nausea and vomiting at rest, moderate on movement; 3 - continuous nausea and vomiting at rest and severe on movement).

2. Daily post-operative sedation was recorded and scored as following: (0 - None, patient is alert; 1- Mild, awake but drowsy; 2 - Moderate, asleep but rousable; 3 - Severe, unrousable).
3. Adverse events caused by the TAP block procedure were also recorded prospectively. This includes evidence of inflammation or infection, viscus damage at the administration sites or adverse effects of the local anaesthetic agent or saline.
4. Duration of post-operative stay: Patients were encouraged to make their own decision about fitness for discharge from hospital. This decision was not influenced by the views of the medical and nursing team, except in the event of complications.
5. Timed up & go: Patients were timed as they rise from a chair, walk 3 meters, turn, walk back and sit. This was measured before surgery and on post-operative days 1 and 3.
6. Grip strength: A hydraulic Hand Dynamometer was used to measuring grip strength (Kg)

The scores of 3 successive trials using the right and left hand was measure before surgery and on each post-operative day until day 7 or at discharge, whichever was sooner.

7. Estimation of inflammatory cytokines (IL-1, IL-6, IL-8 and TNF $\alpha$ ): Blood samples were taken a day before surgery and post operatively at 6, 24 and 48 hours in addition to routine daily blood samples. These blood samples were centrifuged immediately and the plasma was stored at -80°C until the completion of clinical trial for further analysis.

### ***5.8 Statistical analysis:***

Sample size was estimated on the basis of 24-hour post-operative morphine requirements in a previous series of patients undergoing LLDN. This pilot data showed that the normal 24-hour morphine requirement was  $37 \pm 11$ mg (mean  $\pm$  standard deviation). For the purposes of sample size calculation, we considered that a clinically important reduction in morphine consumption would be a 50% absolute reduction. Using this data, it was calculated that 20 patients per group will be required for an experimental design incorporating two equal sized groups using  $\alpha=0.05$  and  $\beta=0.1$ , thus giving a power of 90%. To minimise any effect of data loss, 25 patients per group were recruited into the study.

The data was collected prospectively and stored on a dedicated departmental computerised database. Comparisons of outcome were made on an intention-to-treat basis. Data are presented as mean (S.D.). Continuous variables were compared using

the unpaired t test with Welch's correction and Categorical variables were analysed using the Chi-squared test.

Statistical analysis was performed using InStat and Prism 5 software (GraphPad Software, San Diego, California, USA).  $P < 0.05$  was considered statistically significant.

### **5.9 Results:**

Patients receiving the TAP block with bupivacaine required less morphine up to 6 hours after surgery compared to the control group ( $12.4 \pm 8.4$  vs  $21.2 \pm 14.0$ mg;  $P = 0.015$ ). However, there was no significant difference in the total amount of morphine used ( $45.6 \pm 31.4$  vs  $52.7 \pm 28.8$ mg;  $P = 0.771$ ) with patients remaining on PCAS for an average of 2 days in both groups.

The visual analogue pain score was significantly lower in those receiving the TAP block with bupivacaine on day 1 and 2 after surgery ( $P = 0.003$  and  $0.031$  respectively; Table 5.2). A higher number of patients in the control group had pain at rest and slight at movement, and intermittent pain at rest and moderate at movement on day 1 after surgery ( $P < 0.05$ ; Table 5.3). Patients in the control group felt more alert on day 2 after surgery compared to those that received bupivacaine ( $P = 0.049$ ; Table 5.3). No significant difference was found between the groups in the nausea & vomiting scores ( $P > 0.05$ ; Table 5.3).

### 5.9.1 Table 5.2 - Visual analogue Score

The visual analogue scale comprised of a horizontal 10 centimetres in length used to document the pain at the time points. This methodology of scoring the pain is well established and being widely used in the clinical research.

Day	Bupivacaine	Control	p value
1	19(15)	37(20)	0.03
2	11(10)	19(13)	0.031
3	13(18)	14(13)	0.523

**Table 5.2 showed a significantly low pain score in bupivacaine group compared to controls in day 1 and 2. The values showed above are in mean  $\pm$  SD.**

Patients receiving the TAP block with bupivacaine required less tramadol  $156.5 \pm 185.4$  vs  $471.4 \pm 372.2$ mg ( $P = 0.001$ ) and ondansetran  $3.7 \pm 4.2$  vs  $7.1 \pm 4.6$ mg compared to the control group during their hospital stay. There were no differences in the amount of paracetamol, codeine or cyclizine required in either of the groups ( $P > 0.05$ ). The average length of post operative stay was  $3.7 \pm 1.8$  vs  $3.1 \pm 1.1$  days in the bupivacaine and control groups ( $P = 0.242$ ).

### 5.9.2 Table 5.3 -Verbal response scores for pain, sedation and nausea & vomiting

	Day 1		Day 2		Day 3	
	<u>Bupivacaine</u>	<u>Control</u>	<u>Bupivacaine</u>	<u>Control</u>	<u>Bupivacaine</u>	<u>Control</u>
Verbal response pain scale <sup>a</sup>						
0	2	0	3	5	6	5
1	17*	9	11	11	9	8
2	4	11**	9	5	4	1
3	0	2	0	0	0	0
Sedation score <sup>b</sup>						
0	13	12	13	18 <sup>©</sup>	17	11
1	8	8	8	3	2	3
2	2	2	2	0	0	0
3	0	0	0	0	0	0
Nausea and vomiting score <sup>c</sup>						
0	13	13	15	15	18	12
1	5	4	5	4	0	1
2	3	5	2	2	1	1
3	2	0	0	0	0	0
<p><sup>a</sup> Verbal Response Pain Scale, (0 no pain at rest or movement; 1 no pain at rest, slight on movement; 2 intermittent pain at rest, moderate on movement; 3 continuous pain at rest and severe on movement).</p> <p><sup>a</sup> Sedation Score, (0 none, patient is alert; 1 mild, awake but drowsy; 2 moderate, asleep but rousable; 3 Severe, unrousable).</p> <p><sup>b</sup> Nausea &amp; Vomiting Score (0 no nausea and vomiting at rest or on movement; 1 no nausea and vomiting at rest, slight on movement; 2 intermittent nausea and vomiting at rest, moderate on movement; 3 continuous nausea and vomiting at rest and severe on movement) in patients receiving a TAP block with either Bupivacaine or saline control on days 1, 2 and 3 after laparoscopic donor nephrectomy.</p> <p><sup>c</sup>*P=0.003, **P=0.031 and <sup>©</sup>P=0.049.</p>						

### **5.10 Timed up & go**

Pre assessment levels of the timed up & go were similar in both groups (bupivacaine  $7.3 \pm 1.0$  vs control  $7.5 \pm 1.2$  seconds;  $P = 0.524$ , Table 5.4). On day 1 post surgery the time taken to complete the task was significantly longer in both groups (bupivacaine  $17.6 \pm 6.3$  vs control  $19.1 \pm 8.5$  seconds;  $P < 0.0001$ ). 7 out of 24 patients receiving bupivacaine and 8 out of 22 in the control group felt unable to perform the assessment on day 1 ( $P = 0.837$ ). On day 3, patients in both groups performed the task quicker compared to day 1 but the time was significantly prolonged compared to the pre operative duration (bupivacaine  $11.4 \pm 4.8$  vs control  $11.4 \pm 4.0$  seconds;  $P = 0.002$ ,  $0.003$ ). One patient in the bupivacaine group was unable to complete the assessment on day 3. However, all patients in the control group were able to perform the task.

#### **5.10.1 Table 5.4 - Time up & go assessments:**

	<b>Bupivacaine</b>	<b>Control</b>
Preop	7.5 seconds	7.3 seconds
Day 1	17.6 seconds	19.1 seconds
Day 3	11.4 seconds	11.5 seconds

Although the time up & go is a validated technique on assessing the mobility in postoperative scenario, there is a possibility for bias due to the connected intravenous line and postoperative complications.

## 5.11 Grip Strength

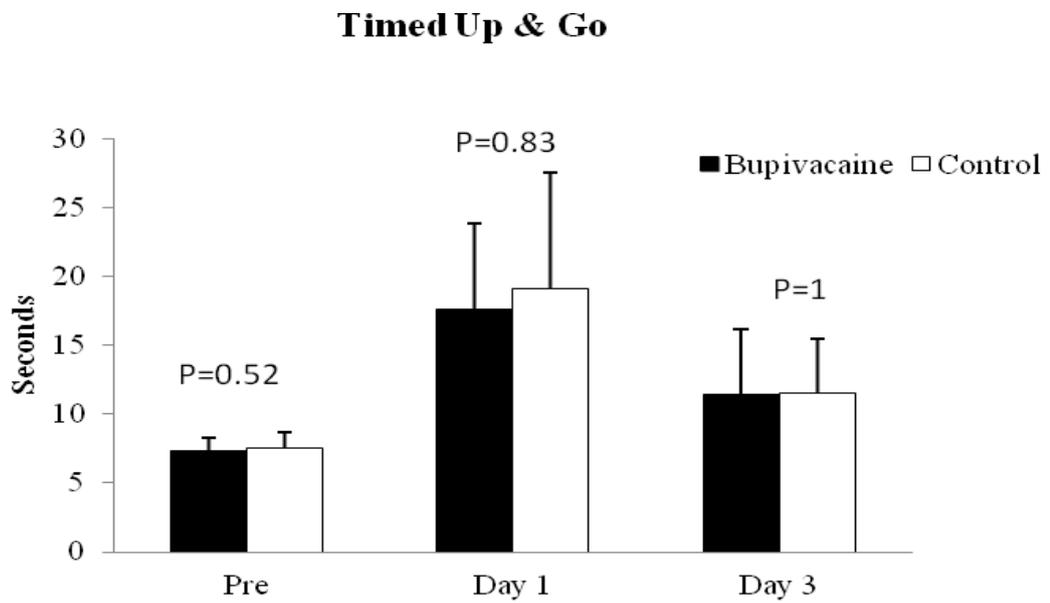
The pre operative grip strength assessed using the dominant hand was similar between groups (bupivacaine  $81.5 \pm 28.2$  vs control  $74.8 \pm 27.5$  Kg;  $P = 0.417$ , Table 5.5). Levels fell significantly in both groups on day 1 after surgery and to a numerically lower level in the control group compared to those receiving bupivacaine (bupivacaine  $76.4 \pm 27.1$  vs control  $61.2 \pm 25.4$  Kg;  $P = 0.058$ ). Levels recovered on day 3 post surgery and were comparable to pre operative levels in both groups (bupivacaine  $74.6 \pm 30.0$  vs control  $67.9 \pm 19.1$  Kg;  $P > 0.05$ ). All patients were able to perform the assessment on the scheduled days.

### 5.11.1 Table 5.5: Grip Strength Assessment

	Bupivacaine	Control
Preop	81.5 Kg	74.8 Kg
Day 1	76.4 Kg	61.2 Kg
Day 3	74.6 Kg	67.9 Kg

Though grip strength assessment is a standardised technique on assessing the postoperative recovery of muscle function, any condition which interferes with the hand movement could bias the values. A simple condition like thrombophlebitis or presence of cannula in forearm/hand could potentially interfere with grip strength testing and hence it is the limitation of this test.

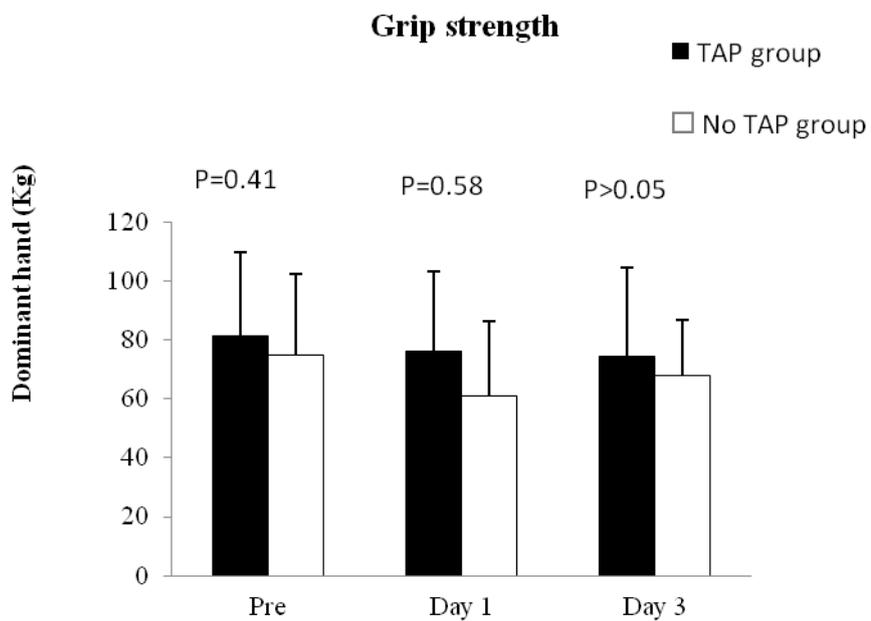
5.11.2 Figure 5.1: Time up & go



**Time Up & go and Grip Strength Assessment between TAP block and control (P=NS) .**

**Timed up & go: Patients were timed as they rise from a chair, walk 3 meters, turn, walk back and sit. This was measured before surgery and on post-operative days 1 and 3.**

### 5.11.3 Grip strength scoring



**Grip strength:** A hydraulic Hand Dynamometer was used to measuring grip strength (Kg).

The scores of 3 successive trials using the right and left hand will be measure before surgery and on each post-operative day until day 7 or at discharge, whichever is sooner.

## ***5.12 Discussion***

This randomised double-blind placebo controlled trial in patients undergoing laparoscopic nephrectomy demonstrated that TAP blocks using bupivacaine reduced early morphine requirements. Interestingly, there was no difference in the total amount of morphine required but patients reported less post-operative pain and required less oral analgesics during their hospital stay.

There is a growing body of evidence in favour of TAP blocks in reducing post-operative pain for various types of surgery (Carney J et al, 2008; Niraj G et al, 2009; Conaghan P et al, 2010; Sandeman DJ et al, 2011).

Nonetheless, the results are inconsistent. A randomised controlled trial by McDonnell et al. found that TAP blocks reduced morphine requirements by more than 70% for up to 36 hours after Caesarean section (McDonnell JG et al, 2008). Patients also had lower visual analogue pain scores for 48 hours after surgery.

In another study of Caesarean section, Belavy et al. also found that TAP blocks reduced post-operative analgesic requirements however, the results were less pronounced with no differences in the post-operative pain scores (Belavy D et al, 2009).

In contrast, Costello et al. found that TAP blocks did not have any beneficial effect after Caesarean sections (Costello JF et al, 2009).

However, TAP blocks were used in conjunction with long acting intrathecal opioids, which are extremely effective and likely to reduce the need for morphine after surgery (Factor D, 2010) (McMorrow RC et al, 2011).

The posterior TAP block procedure used in this study involved a single injection of local anaesthetic which may have potential disadvantages. Bupivacaine has a relatively short duration of action, lasting 6 to 8 hours and its effectiveness can be dependent on the type of surgery (Charlton S et al, 2010).

The results from this trial showed that patients receiving a TAP block with bupivacaine required 42% less morphine in the first 6 hours after surgery compared to patients receiving the placebo control. Thereafter, morphine requirements were similar. Nonetheless, the duration of action using this technique is unknown and the poor vascularisation in this region may prolong the effect, which may also be dependent on the amount and concentration of local anaesthetic agent used.

Higher concentrations have been used (McDonnell JG et al, 2008), however there is a risk of toxicity, as the local anaesthetic may spill over into the adjacent muscle resulting in high systemic concentrations and therefore some caution must be taken (Kato N et al, 2009).

Bupivacaine TAP blocks showed no advantage for patients in terms of nausea and vomiting scores, post-operative recovery or in the length of hospital stay. Surprisingly, sedation scores were lower in the control group with more patients feeling more alert on post-operative day 2 compared to the patients receiving a TAP block with

bupivacaine. Nonetheless, and perhaps most importantly, patients receiving a bupivacaine TAP block had lower visual analogue pain scores for 2 days after surgery and experienced less pain at rest and on movement. Furthermore, patients required less tramadol and anti-emetics during their hospital stay. Although, there was no reduction in the total morphine requirement, the perceived reduction in pain is an important outcome and likely to be of benefit. Pain is influenced by many factors and studies have shown that a higher use of PCA can be influenced by anxiety and the anticipation of pain (Logan DE, 2005) (Crombez G et al, 1996).

Pre-emptive analgesia is an effective and standard way of targeting post-operative pain. A recent study in patients undergoing a hysterectomy found that TAP blocks administered before surgery reduced pain and analgesic requirements compared to TAP blocks placed at the end of the surgery (Amr YM, 2011).

A potential disadvantage of pre-emptive TAP blocks is that some of their post-operative effect may be lost if surgery is prolonged. The effects of TAP blocks can be prolonged by continuous infusion of the local anaesthetic agent via an implanted TAP catheter and this may be more beneficial.

A recent study demonstrated that patients undergoing open donor nephrectomy with a flank incision required significantly less morphine and had lower pain scores up to 48 hours after surgery when local anaesthetic was continually infused through catheters placed in the transversus abdominis plane for 48 hours after surgery (Harish R., 2009).

Continuous administration of local anaesthetic has also been beneficial in kidney transplant recipients (Philip A., 2010).

Nonetheless, more evidence is needed to establish the efficacy of this approach. There have also been reports of using an intra-abdominal approach administering the TAP blocks under direct vision during surgery (Owen DJ et al, 2011). This has been described as a more simple method that improves accuracy and reduces the risk of damaging the viscera.

The numbers of patients included in this study were informed by a realistic power calculation. Furthermore, it must be taken into consideration that although the TAP blocks were administered under ultrasound guidance by an experienced consultant anaesthetist, in some cases they may not have been effective. Pin-prick sensation can be used to assess sensory blockage and the effectiveness of the TAP block. However, this was avoided in the present trial as blinding could not have been maintained. Complications are also possible, including infection or haematoma at the administration site, nerve damage, transient femoral palsy and even the potential to damage underlying organs (Jankovic ZB et al, 2009). Nonetheless, there were no complications associated with the TAP block procedure in this present study.

### ***5.13 Cytokines:***

Cytokines are proteins produced by haematopoietic and non-haematopoietic cells which play a role in innate and adaptive immune responses (Longo D et al, 2012). They are produced from activated leucocytes, fibroblasts and endothelial cells as an early

response to tissue injury and have a major role in mediating immunity and inflammation (Longo D et al, 2012) (Sheeran P, 1997). Cytokines act on surface receptors on many different target cells and their effects are produced ultimately by influencing protein synthesis within these cells (Desborough JP., 2000).

Cytokines have a major role in the inflammatory response to surgery and trauma. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some of the systemic changes which occur (Desborough JP., 2000). They can act in an autocrine manner, affecting the behavior of the cell that releases the cytokine, or in a paracrine manner, affecting the behavior of adjacent cells. Some cytokines can also act in an endocrine manner, affecting the behavior of distant cells, although this depends on their ability to enter the circulation and on their half-life.

After major surgery, the main cytokines released are interleukin-1 (IL-1), tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-6. The initial reaction is the release of IL-1 and TNF  $\alpha$  from activated macrophages and monocytes in the damaged tissues. This stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response (Sheeran P, 1997).

Cytokines and growth factors may have multiple functions that can initiate and influence the wound healing process (Bennett NT, 1993).

Previous studies have shown that the inflammatory cytokines are released following donor nephrectomy though their significance is still debatable (Yap S et al, 2012).

### **5.13.1 Interaction between the immune system and the neuroendocrine system:**

The cytokines IL-1 and IL-6 can stimulate secretion of ACTH from isolated pituitary cells *in vitro*. In patients after surgery, cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol (Desborough JP., 2000).

A negative feedback system exists, so that glucocorticoids inhibit cytokine production. The cortisol response to surgery is sufficient to depress IL-6 concentrations (Jameson P et al, 1997).

### **5.13.2 Hypothesis for cytokines estimation:**

In a mouse model, nephrectomy resulted in early onset of inflammation, apoptosis, and tissue damage in hepatocytes with increased tumour necrosis factor-(TNF) and interleukin (IL-6) (Golab F et al, 2009). Bilateral nephrectomy in animal models has shown an increased TNF-and IL-6 levels, which lead to uncontrolled systemic inflammation, neutrophil infiltration, and impaired vascular permeability resulting in pulmonary oedema (Klein CL et al, 2008).

Patients who underwent donor nephrectomy demonstrated increased serum IL-6 and serum TNF which was possibly secondary to acute deterioration in renal function (Yap S et al, 2012).

Although Yap S et al, showed significantly high levels of cytokines and other inflammatory markers following laparoscopic donor nephrectomy the significance of this elevation whether merely due to significant tissue trauma or due to nephrectomy is not established yet.

Secondly there is also evidence available to support that pain relief techniques does interfere with expression of cytokines and this could potentially be blocked (Stefano GB et al, 1994, Xu YJ et al, 2014). Hence in our study we reassess the cytokine expression following laparoscopic donor nephrectomy and also evaluate the role of TAP block on blocking the cytokine expression in 24, 48 hrs after surgery. The cytokine expression can be spuriously low or high by the use of isoflurane, sevoflurane and dexamethasone and potentially this could bias the values.

### **5.13.3 Cytokines assay:**

Venous blood samples were taken preoperatively then at 6, 24 and 48 hours postoperatively to measure levels of inflammatory cytokines. After collection samples were centrifuged at 1000g, 4°C for 15 minutes and the plasma stored at -80°C until analysed. The Aushon Search Light® Human Cytokine Array 2 (Aushon Biosystems, Billerica, MA. USA) a multiplex sandwich enzyme-linked immunosorbent assay (ELISA) was used to measure levels of interleukin -1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor alpha (TNF $\alpha$ ).

Samples and standards were diluted 2 fold and added to the pre coated plate in duplicate. Unbound proteins were washed away and a biotinylated detecting antibody added to bind to a second site on the target proteins. After washing the excess detecting

antibody, streptavidin-horseradish peroxidase (SA-HRP) was added to produce a luminescent signal which was detected by a cooled CCD camera.

#### **5.13.4 Interleukin-1 Beta (IL-1 $\beta$ ):**

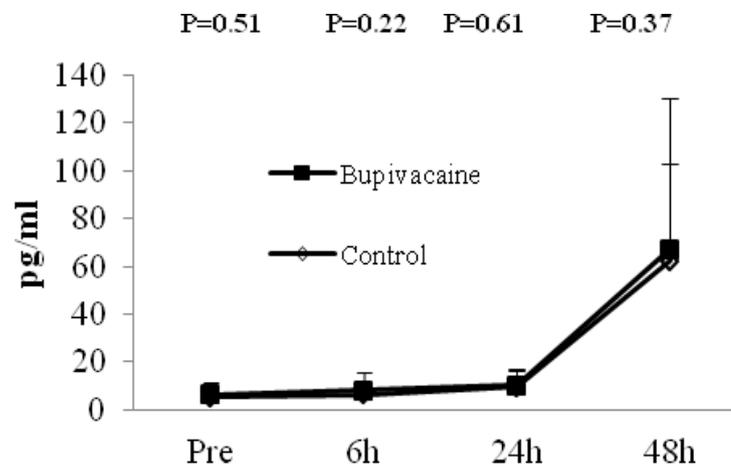
Interleukin-1 (IL-1) is the prototypic pro-inflammatory cytokine. There are two forms of IL-1, IL-1alpha and IL-1beta and their biological activities are indistinguishable (Dinarello CA., 1997). Although IL-1 can upregulate host defences and function as an immunoadjuvant, IL-1 is a highly inflammatory cytokine (Dinarello CA., 1997).

When IL-1 gains access to the circulation, it acts like a hormone and induces a broad spectrum of systemic changes in neurological, metabolic, hematologic, and endocrinologic systems. Usually an early and short-lived IL-1 beta response to major surgery was reported followed by surge of other cytokines (Baigrie RJ et al, 1992). Recent study has shown that a longer operative time is associated with significantly high level of IL-1 (Beyza Özçınar et al, 2014).

#### **5.13.5 Results of IL-1 $\beta$ assay:**

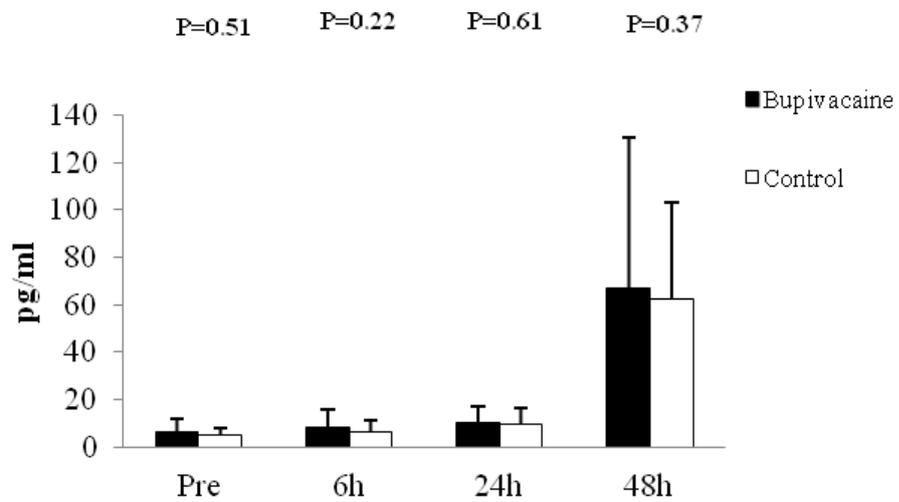
IL-1  $\beta$  was detected in patients in both groups throughout the study period. In the bupivacaine group preop, postop at 6<sup>th</sup> hours, 24 hours, and 48 hours serum levels were 6.51, 8.16, 10.1 and 67.16 picograms/ml respectively. Similarly serum levels of IL-1 in the control group were 5.3, 6.43, 9.45 and 62.38 picograms/ml at preop, 6, 24 and 48 hours respectively. Hence there was no difference between the bupivacaine and control groups at any time point (P=NS; figure 5.2, 5.3). More importantly, in contrast to previous evidence serum IL-1 levels were significantly higher only at 48 hours, not as documented as an early surge following a surgical stimulus (Baigrie RJ et al, 1992).

**Figure 5.2: Results of IL-1  $\beta$  Assay between Bupivacaine and Control**



Estimation of serum IL-1  $\beta$  level at Preop, 6, 24 and 48 hours following laparoscopic donor nephrectomy. Serum level of Interleukin-1 was comparable between the group at all time points and no obvious difference was noted (P =NS). Values are Mean  $\pm$  SD.

**Figure 5.3: Results of IL-1  $\beta$  Assay between Bupivacaine and Control**



Estimation of serum IL-1  $\beta$  level at Preop, 6, 24 and 48 hours following laparoscopic donor nephrectomy. Serum level of Interleukin-1 was comparable between the group at all time points and no obvious difference was noted (P =NS). Values are Mean  $\pm$  SD

### **5.13.6 Interleukin-6 (IL-6):**

IL-6 is a polypeptide with a molecular weight of 21.5-30 kDa (Bauer J, 1991). The concentrations of circulating cytokines are normally low and may be undetectable. The molecular weight heterogeneity of IL-6 results from post-translational modifications such as N- and O-glycosylation and phosphorylation (Bauer J, 1991).

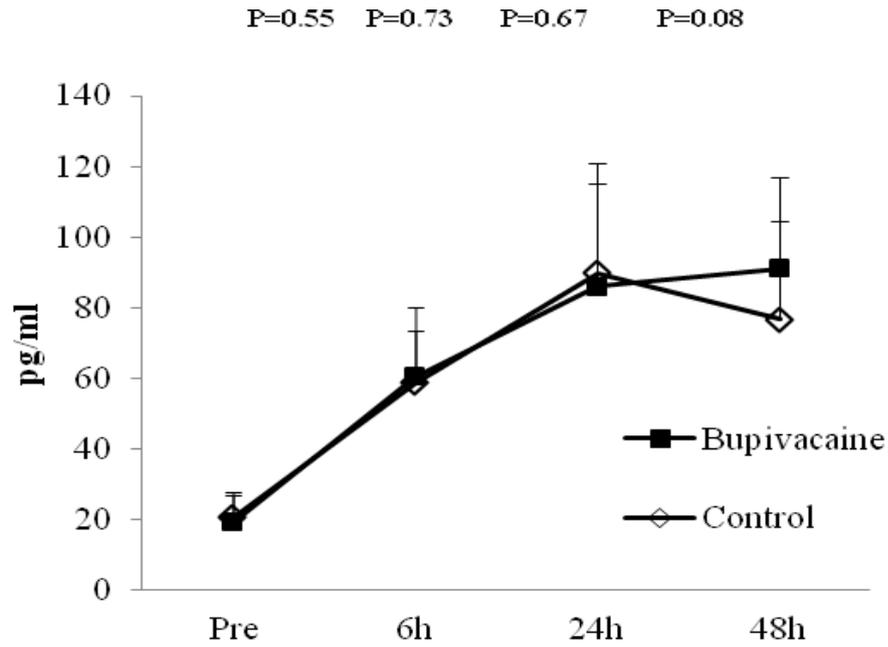
Within 30–60 min after the start of surgery, IL-6 concentration increases, the change in concentration becoming significant after 2–4 h. Cytokine production reflects the degree of tissue trauma, so cytokine release is lowest with the least invasive and traumatic procedures, for example, laparoscopic surgery (Desborough JP., 2000).

The largest increases in IL-6 occur after major procedures such as joint replacement, major vascular and colorectal surgery. After these operations, cytokine concentrations are maximal at about 24 h and remain elevated for 48–72 h postoperatively.

### **5.13.7 Results of IL-6 Assay:**

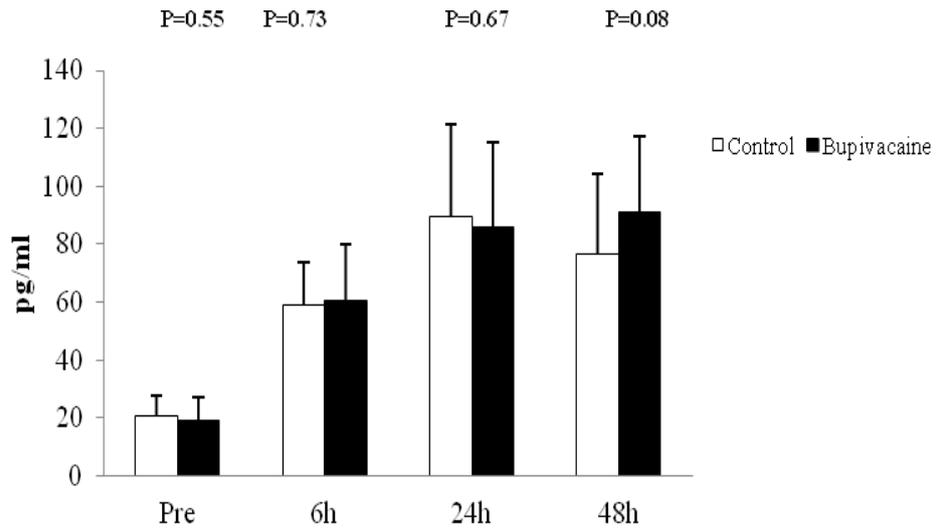
IL-6 was detected amongst all patients in both groups throughout the study period. In the bupivacaine group preop, postop at 6th hours, 24 hours, and 48 hours serum levels were 19.3, 60.5, 85.9 and 91.2 picograms/ml respectively. Similarly serum levels of IL-6 in the control group were 20.6, 58.7, 89.8 and 76.7 picograms/ml at preop, 6, 24 and 48 hours respectively (figure 5.4 and 5.5). Hence there was no difference between the bupivacaine and control groups at any time point (P=NS).

**Figure 5.4: Results of IL-6 Assay between Bupivacaine and Control**



In the bupivacaine group preop, postop at 6th hours, 24 hours, and 48 hours serum levels were 19.3, 60.5, 85.9 and 91.2 picograms/ml respectively. Similarly serum levels of IL-6 in the control group were 20.6, 58.7, 89.8 and 76.7 picograms/ml at preop, 6, 24 and 48 hours respectively. Values are Mean  $\pm$  SD.

**Figure 5.5: Results of IL-6 assay between Bupivacaine and Control**



In the bupivacaine group preop, postop at 6th hours, 24 hours, and 48 hours serum IL-6 levels were 19.3, 60.5, 85.9 and 91.2 picograms/ml respectively. Similarly serum levels of IL-6 in the control group were 20.6, 58.7, 89.8 and 76.7 picograms/ml at preop, 6, 24 and 48 hours respectively. Values are Mean  $\pm$  SD.

### **5.13.8 Interleukin-8 (IL-8):**

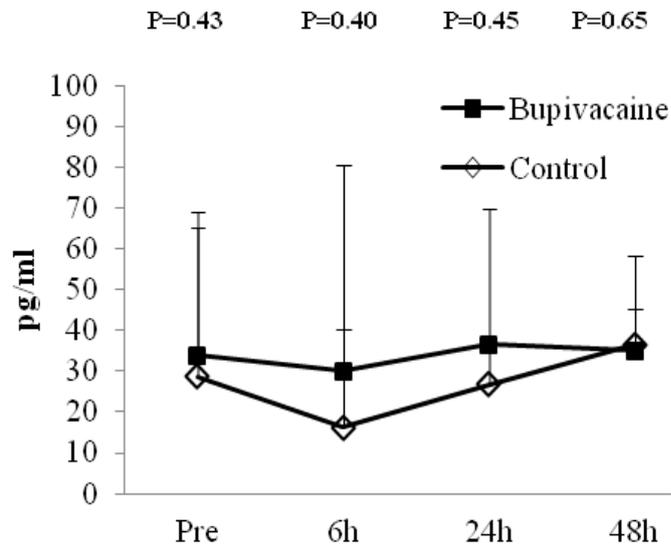
Interleukin-8 (IL-8), also known as CXCL-8, a member of the CXC chemokine family that was originally classified as a potent neutrophil chemoattractant, has been shown to regulate biological processes through interactions with relative receptors (Roebuck KA., 1999).

In leukocytes, IL-8 has been shown to stimulate the activation of G proteins and several downstream serine/threonine kinases that are responsible for chemotaxis, degranulation, and production of superoxide anions by phagocytes (Jones SA et al, 1996, Kupper RW et al, 1992). IL-8 is generated as a precursor of 99 amino acids and is secreted after cleavage of a signal sequence of 20 residues (Baggionlini, 1992). N-terminal extracellular processing of the mature form yields several biologically active variants. The predominant variant consists of 72 amino acids and has a molecular weight of 8,383kDa (Baggionlini, 1992).

### **5.13.9 Results of IL-8 Assay**

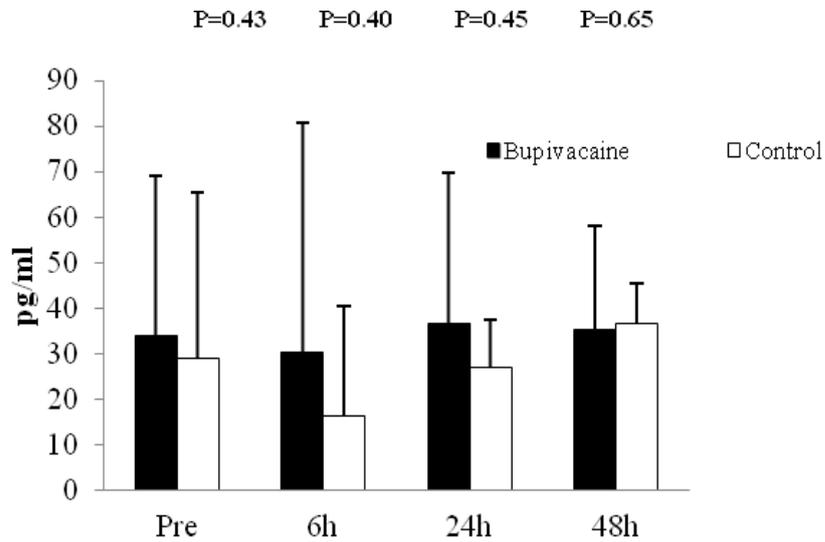
IL-8 was detected in all patients in both groups throughout the study period. In the control group preop, postop at 6 hours, 24 hours, and 48 hours serum levels were 28.7, 16.3, 26.8 and 36.5 picograms/ml respectively. Similarly serum levels of IL-8 in the bupivacaine group were 33.9, 30.1, 36.5 and 35 picograms per ml at preop, 6, 24 and 48 hours respectively. Hence there was no difference between the control group and the bupivacaine group at any time point (figure 5.6 and 5.7) (P=NS). This analysis did not show any significant increase in serum IL-8 level in the postoperative period when compared with preop levels.

**Figure 5.6: Results of IL-8 assay between Bupivacaine and Control**



In the control group preop, postop at 6 hours, 24 hours, and 48 hours serum IL-8 levels were 28.7, 16.3, 26.8 and 36.5 picograms/ml respectively. Similarly serum levels of IL-8 in the bupivacaine group were 33.9, 30.1, 36.5 and 35 picograms per ml at preop, 6, 24 and 48 hours respectively. Values are Mean  $\pm$  SD.

**Figure 5.7: Results of IL-8 assay between Bupivacaine and Control**



In the control group preop, postop at 6 hours, 24 hours, and 48 hours serum IL-8 levels were 28.7, 16.3, 26.8 and 36.5 picograms/ml respectively. Similarly serum levels of IL-8 in the bupivacaine group were 33.9, 30.1, 36.5 and 35 picograms per ml at preop, 6, 24 and 48 hours respectively. Values are Mean  $\pm$  SD.

### **5.13.10 Tumour Necrosis Factor (TNF $\alpha$ ):**

TNF $\alpha$  is a cytokine with effects that include a contribution to initiating and orchestrating the complex events involved in inflammation and immune response (Sethi G et al 2008). TNF-alpha is the prototypic member of a gene superfamily that regulates essential biologic functions such as immune response, cell proliferation, survival, differentiation and apoptosis (Bagul A., 2012; Esposito E, 2009).

When microorganisms activate proinflammatory signals, TNF $\alpha$  is produced by macrophages, dendritic cells, B cells, and T cells; as well as by other types of somatic cells such as endothelial cells, mast cells, neuronal tissue cells, and tumour cells (Vassalli P., 1992) (Sethi G et al 2008).

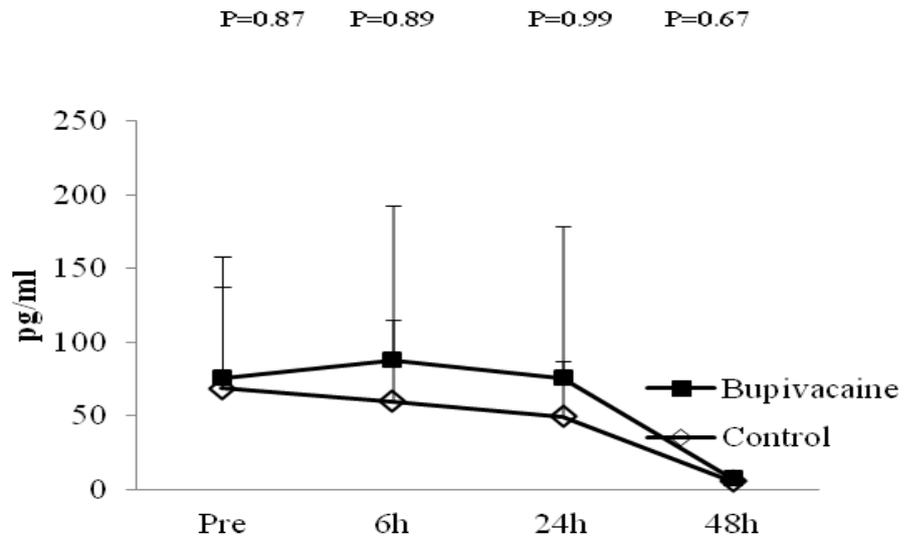
TNF-alpha is a transmembrane protein with a molecular mass of 26 kDa that was originally found to be expressed in macrophages and has now been found to be expressed by a wide variety of cells (Sethi G et al, 2008).

The pro-inflammatory effects of TNF-alpha are primarily due to its ability to activate NF-kappaB. Almost all cell types, when exposed to TNF-alpha, activate NF-kappaB, leading to the expression of inflammatory genes (Sethi G et al, 2008). Over 400 genes have been identified that are regulated by NF-kappaB activation (Sethi G et al, 2008).

### **5.13.11 Result of TNF $\alpha$ Assay :**

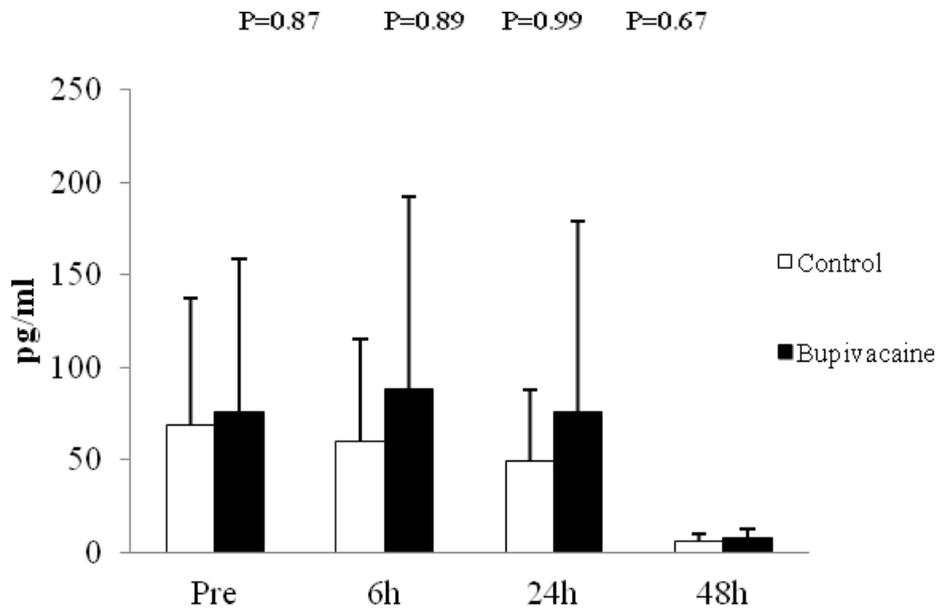
TNF $\alpha$  was detected in all patients in both groups throughout the study period. In the control group preop, postop at 6th hours, 24 hours, and 48 hours serum levels were 68.9, 59.7, 49.3 and 5.7 picograms/ml respectively. Similarly serum levels of TNF $\alpha$  in Bupivacaine group were 75.5, 88, 75.8 and 7.4 picograms/ml at preop, 6, 24 and 48 hours respectively (figure 5.8 and 5.9).. Hence, there was no difference between the control group and the bupivacaine group at any time point. (P=NS). This analysis did not show any significant increase in serum TNF $\alpha$  levels in the postoperative period when compared with preop levels. In fact, there was a high titre of TNF $\alpha$  noted preop which has progressively fallen over time following donor nephrectomy. These results seem puzzling, although previous studies have reported similar findings in patients following major surgery (Høgevold HE et al, 2000) (Shimada M et al, 1993).

**Figure 5.8: Results of TNF $\alpha$  assay between Bupivacaine and Control**



In the control group preop, postop at 6th hours, 24 hours, and 48 hours serum TNF $\alpha$  levels were 68.9, 59.7, 49.3 and 5.7 picograms/ml respectively. Similarly serum levels of TNF $\alpha$  in Bupivacaine group were 75.5, 88, 75.8 and 7.4 picograms/ml at preop, 6, 24 and 48 hours respectively. Values are Mean  $\pm$  SD.

**Figure 5.9: Results of TNF $\alpha$  assay between Bupivacaine and Control**



In the control group preop, postop at 6th hours, 24 hours, and 48 hours serum TNF $\alpha$  levels were 68.9, 59.7, 49.3 and 5.7 picograms/ml respectively. Similarly serum levels of TNF $\alpha$  in Bupivacaine group were 75.5, 88, 75.8 and 7.4 picograms/ml at preop, 6, 24 and 48 hours respectively. Values are Mean  $\pm$  SD.

### ***5.14 Conclusion:***

In conclusion, the addition of a pre-emptive bupivacaine based TAP block in laparoscopic live donor nephrectomy is of benefit in reducing post-operative pain and early post-operative morphine requirements. But TAP block did not show any significant effect on cytokine response following laparoscopic donor nephrectomy. Future studies should aim to extend the effects the TAP blocks by investigating the use of TAP catheters to provide continual infusions to optimise the delivery of local anaesthetic and prolong the effect.

## ***CHAPTER 6***

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### **Discussion - Summary and Future Work**

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## 6 Summary of key findings

This work, to the best of my knowledge, is the first investigation to assess the role of transversus abdominis plane block in laparoscopic donor nephrectomy patients. The initial retrospective study showed the effect of TAP on reducing the cumulative use of morphine when compared to the control group. More importantly, the oral analgesic requirement was also significantly reduced in the TAP group; paracetamol  $13.35 \pm 3.6$  grams vs  $17 \pm 4.8$  grams ( $P < 0.0002$ ) and tramadol  $353 \pm 283$  mg versus  $820 \pm 521$  mg ( $P < 0.0001$ ) compared with control group. Similar results were noted for anti-emetics (cyclizine  $60 \pm 82.1$  mg versus  $159 \pm 212$  mg;  $P < 0.0017$  and ondansetran  $3.2 \pm 3.8$  mg versus  $5.5 \pm 5.5$  mg;  $P < 0.035$ ) requirements as well.

The retrospective study showed that TAP block group discontinued their PCAS significantly earlier than patients in the control group ( $1.3 \pm 0.6$  days versus  $1.9 \pm 0.7$  days;  $P < 0.0001$ ). Similarly, there was a significant difference noted in the length of hospital stay between the TAP and control group ( $4.3 \pm 1.1$  versus  $5.1 \pm 1.1$  days;  $P < 0.0034$ ).

Similar results have been shown in other studies where TAP blocks were successful in reducing post-operative pain and the overall morphine requirement after abdominal surgeries such as hysterectomy (Carney J et al, 2008), appendicectomy (Niraj G et al, 2009) and Caesarean section (Belavy et al, 2009). Results from this retrospective study and the above study findings formed the back-bone to perform a randomised placebo controlled clinical trial.

The randomised clinical trial of TAP block in laparoscopic donor nephrectomy patients has given interesting and supporting results. The study has demonstrated that a TAP block with bupivacaine reduced early morphine requirement at 6 hours with no difference in cumulative morphine usage. More importantly, the bupivacaine group had significantly less post-operative pain and required less oral analgesics during their hospital stay. The visual analogue pain score in the TAP block group with bupivacaine was significantly lower on day 1 and 2 after surgery ( $P = 0.003$ ;  $0.031$ ). A significantly higher number of patients in the control group had pain at rest and on movement, and intermittent pain at rest and moderate at movement on day 1 after surgery ( $P < 0.05$ ).

Recent studies on patients undergoing caesarean section (Costello JF et al 2008) and laparoscopic hysterectomy (Calle GA et al, 2014) demonstrated that patients did not benefit from the administration of a TAP block and therefore this raises questions about the suitability of this technique for all types lower abdominal surgery. The results from our study are supported by a recent study (Waits SA et al, 2015) showing overall reduction of narcotic by 50% through similar pain scores.

## ***6.1 Cytokines after donor nephrectomy:***

The initial cytokine reaction is the release of IL-1 and TNF  $\alpha$  from activated macrophages and monocytes after tissue damage including surgery. This stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response (Sheeran P et al, 1997).

Cytokine analysis has revealed valuable and important findings from our study. A recent study of laparoscopic donor nephrectomy has shown that cytokines levels including interleukin-1 (IL-1), tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-6 and IL-18 (markers of acute kidney injury) were high after nephrectomy (Yap S et al, 2012).

Our study has shown a significantly rise in IL-6 level 6 hours after donor nephrectomy and this continued to be high at 48 hours. Similar results were reported in another study where the IL-6 level was raised significantly 1 hour after nephrectomy and was persistently high a few days after donor nephrectomy (Kielstein JT et al, 2011).

Interestingly, IL-8 and TNF- $\alpha$  levels fell significantly compared with preoperative levels. But in comparison with the previous studies, our sample size is significantly larger and hence the results are likely to be more reliable. This signifies the need for further investigation on IL-8 and TNF- $\alpha$  in donor nephrectomy patients.

Finally, a more enigmatic twist was observed in terms of an IL-1 $\beta$  level raised at 48 hours after donor nephrectomy. IL-1 $\beta$  is known to be an initial cytokine in response to

the inflammatory stimulus, but our result does not support this view. Hence further research is also required to address whether the cytokine response is atypical in this setting.

## ***6.2 Strengths and weaknesses.***

The strengths of this thesis are the retrospective analysis results which helped to set up a successful double blinded randomised placebo controlled trial. The randomised study has given robust and high quality evidence on TAP block in laparoscopic donor nephrectomy patients. Though reduced pain scores and lower oral tramadol doses were noted in the TAP group, cumulative morphine usages between the groups were not different. As we have utilised a lateral approach for TAP block in our patients, the role of an alternative posterior TAP block approach in laparoscopic donor nephrectomy remains to be answered. There is a growing body of evidence to support the hypothesis that the posterior approach could result in better pain relief.

Furthermore cytokine assays up to 48 hours after donor nephrectomy were similar between the TAP block and control groups. Although this may appear as a negative result, further research is needed to focus on the cytokine response following donor nephrectomy. To date, this randomised study is the only study with a large sample size that can be extrapolated as robust evidence on cytokine responses in after donor nephrectomy. In the randomised study, we have analysed cytokine samples up to 48 hours; perhaps further delayed samples may have been beneficial in assessing the cytokine response following donor a nephrectomy. But, one could argue that this means unnecessary donor visit to hospital and potential inconvenience.

### **6.3 Future work:**

For the reasons discussed above, it was essential to confirm the role of TAP block in the setting of laparoscopic live donor nephrectomy. This thesis includes a literature review on pain relief methods, a retrospective pilot study and finally a double blinded randomised placebo controlled trial of TAP block in laparoscopic donor nephrectomy patients. Though it may appear that role of TAP block in donor nephrectomy patients has been established here, the role of the posterior technique of TAP blocking in similar settings is still unknown.

Secondly, in our study we have used the TAP block after general anaesthesia was established; If the TAP block was administered before anaesthesia, the effectiveness of TAP blocks could have been evaluated further.

Thirdly, the role of continuous infusion of local anaesthetics in transversus abdominis plane needs further investigation as this provides constant availability of drug, which in principle could offer a better postoperative pain relief.

Fourthly, the liposomal bupivacaine prolonged-release formulation as a part of multimodal analgesia in laparoscopic donor nephrectomy patients has never been tested before; this area needs early attention and further evaluation.

Finally a cytokine assay in donor nephrectomy with delayed blood samples up to 10 days following operation could shed a light on their role and cytokine response after the donor surgery. To date, there are only conflicting findings available in this setting; hence it is hard to establish a reasonable conclusion.

## **6.4 Conclusion**

The research presented here has established that the TAP block is a useful and beneficial method of analgesia in patients undergoing laparoscopic donor nephrectomy. The study has demonstrated that a TAP block with bupivacaine reduced early morphine requirement at 6 hours. The visual analogue pain score in the TAP block group with bupivacaine was significantly lower on day 1 and 2 after surgery. There was also a reduced oral tramadol usage in the bupivacaine group. But the total usage of morphine has not been reduced by the use of TAP blocks. As a part of multimodal analgesia, TAP blocks could play an important role in conjunction with PCAS in postoperative pain management after laparoscopic donor nephrectomy.

In contrast to the expected result, preoperative local anaesthetic administration did not reduce the cytokine response. The physiological response to surgery can be very complex and clearly the TAP block has not been found to be interfering with this mechanism.

Despite the improvements in the postoperative analgesic modalities in laparoscopic donor nephrectomy patients, the ideal method of analgesia remains to be established.

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Appendix 1 Research Protocol - A randomized controlled trial of transversus abdominis plane  
block after laparoscopic live donor nephrectomy

## Summary

Laparoscopic (Keyhole) live donor nephrectomy is now a well established operation in the UK.

The laparoscopic technique reduces post operative pain and analgesic requirements compared to the traditional open technique. Nonetheless, some patients still suffer significant post operative pain to the point where they require parenteral opiates. A local anaesthetic agent can be used to block the sensory nerves in the abdominal wall at the incision site. This procedure is called a transversus abdominis plane (TAP) block. Previous randomized controlled trials have shown that TAP blocking can reduce post-operative pain after abdominal surgery for large bowel resection and after caesarean section. The aim of this study is to determine the safety and efficacy of TAP blocking in patients undergoing laparoscopic live donor nephrectomy.

This study is a randomized placebo controlled double-blind trial. Eligible patients will be identified, written informed consent will be obtained and patients will be randomized in a 1:1 ratio into one of two groups. Group 1: TAP block performed by injecting local anaesthetic into the transversus abdominis plane pre-operatively, after induction of anaesthesia. Group 2: An equal amount of saline will be injected into the transversus abdominis plane pre-operatively, after induction of anaesthesia.

The primary end points will be the amount of post-operative pain relief that the patients requires and the level of pain that the patient experiences. Secondary end points include post-operative nausea, vomiting and sedation, duration of post-operative stay, time to the introduction of free oral fluids and first solid food. Other secondary measures also include the inflammatory response to surgery and recovery of the patient assessed by the 'Timed Up & Go' and grip strength test. Any adverse events caused by the TAP block

procedure will be recorded and reported. Patients will be required to remain in the trial for 7 days or until they are discharged from hospital, whichever is sooner.

## Introduction

Laparoscopic live donor nephrectomy (LDN) is now a well-established operation in the UK.

Leicester was the first transplant unit in the UK to perform laparoscopic live donor nephrectomy and the Unit has now completed more than 260 of these operations. We have also performed a randomised controlled trial comparing laparoscopic donor nephrectomy with minimal incision open donor nephrectomy and have demonstrated that the laparoscopic operation removes some of the disincentives to donation including a reduction in post-operative pain and analgesic requirements. Nonetheless, some patients undergoing laparoscopic live donor nephrectomy still suffer significant post-operative pain, to the point where they require parenteral opiates. A substantial component of the post-operative pain in these patients is derived from the suprapubic kidney retrieval incision. Opiates are an effective analgesic however they do have side effects, including respiratory depression, nausea, vomiting, sedation and pruritis. Therefore alternative methods of pain relief should be explored 1.

During live donor nephrectomy, the peritoneum is accessed through the suprapubic approach by dividing the linea alba in the midline and separating the rectus abdominis muscles. The muscular wall of the abdomen in this region is innervated by afferent nerves that course through the more lateral oblique muscles of the abdomen. These lateral muscles are in three layers: the external oblique, the internal oblique and the transversus abdominis. The afferent nerves run in the plane between the internal oblique and the transversus abdominis muscle and this is known as the transversus abdominis neurofascial plane. It is possible to block the sensory nerves supplying the lower abdominal wall by introducing

local anaesthetics into this plane. This is known as the transversus abdominis plane (TAP) block. Previous randomised controlled trials have shown that TAP blocking can reduce post-operative pain after abdominal surgery for large bowel resection 2 and after caesarean section 3. The latter study is particularly relevant as caesarean section is performed through a suprapubic Pfannenstiel incision, which is similar to the approach used for retrieving kidneys that have been dissected laparoscopically. The aim of this study is to determine the safety and efficacy of TAP blocking in patients undergoing laparoscopic live donor nephrectomy.

### Hypothesis

The hypothesis to be tested in this study is that the use of a transversus abdominis plane (TAP) block will reduce post-operative pain and analgesic requirements in patients undergoing laparoscopic live donor nephrectomy.

### Inclusion Criteria

Patients will be eligible for the trial if ALL of the following criteria are met:

Age  $\geq$  18

American Society of Anaesthesiology (ASA) grade 1 or 2

Individuals who have completed the full work-up for laparoscopic donor nephrectomy, including an assessment by the Human Tissue Authority

Written, signed informed consent to the trial

### Exclusion Criteria

Patients will NOT be eligible for the trial if ANY of the following criteria apply:

A history of relevant drug allergy

Patients receiving medical therapies considered to result in tolerance to opioids

Any condition which, in the opinion of the investigator, makes the patient unsuitable for entry into the study

#### Study Monitoring

The results will be prospectively reviewed at regular intervals to assess patient safety and any requirement to modify the protocol. Any adverse events will be recorded by a qualified clinician and assessed accordingly.

#### Methods

This study is a randomised placebo controlled double-blind trial to study the safety and efficacy of TAP blocking in patients undergoing laparoscopic live donor nephrectomy.

All patients meeting the inclusion criteria will be given a patient information sheet and the trial explained to them during a pre-assessment appointment approximately 1 – 2 weeks before surgery. Written informed consent will be obtained on admission of the patient the day before surgery. Each patient will be randomly assigned in a 1:1 ratio to one of two treatments groups as follows:

The Trial Administrator/coordinator will use a computer-generated sequence of random numbers to create a sealed envelope system for a consecutive series of 50 patients randomised in a 1:1 ratio to either TAP blocking with Bupivacaine local anaesthetic or the saline placebo control group. Pharmacy will open the randomization envelopes, supply

the drugs and label the syringes with the trial number and code. These syringes will be delivered to the Consultant Anaesthetist who will be blinded to the treatment group. All members of the nursing, medical and surgical team will also be blinded to the treatment allocation apart from the trial administrator/coordinator and the Pharmacy trial staff.

#### Group One – TAP blocking

TAP blocks will be performed by injecting Bupivacaine local anaesthetic into the transversus abdominis plane pre-operatively, after the induction of anaesthesia.

#### Group Two – Placebo Control Group

Donors in this group will have an equal volume of normal saline injected into the transversus abdominis plane pre-operatively, after the induction of anaesthesia.

#### General Anaesthesia

All general anaesthetics will be performed by a member of the consultant anaesthetic staff using a standardised technique as follows:

Anaesthesia will be induced with propofol 2.5-3 mg/kg and fentanyl 1-2µg/kg and maintained with isoflurane and 50% oxygen in air. Muscle relaxation will be achieved with atracurium 1 mg/kg. Intravenous fluids will be administered to maintain the CVP in the range 8-10 mmHg and systolic blood pressure above 100 mmHg.

## Technique for TAP Block

All TAP blocks will be performed by Consultant Anaesthetists who are experienced in anaesthetising donor nephrectomy patients. All TAP block needles will be placed under ultrasound control using an ultrasound machine. After skin preparation with antiseptic a blunt regional anaesthesia needle (22 gauge) will be introduced through the skin just cephalad to the anterior superior iliac spine of the pelvis. The needle will be introduced until resistance is encountered, indicating that the needle tip is at the external oblique muscle. Gentle advancement of the needle will result in a 'pop' sensation as the needle enters the plane between the external and internal oblique fascial layers. Further gentle advancement of the needle will result in a second 'pop', indicating that the needle tip has entered the transversus abdominis fascial plane. These manoeuvres will be performed under direct ultrasound control which will allow careful delineation of the three lateral muscle layers and ensure that the anaesthesia needle is in the correct plane. After careful aspiration to exclude vascular puncture, 20ml of solution (either 0.375% Bupivacaine or 0.9% saline) will be injected through the needle into the TAP plane. The same procedure will then be repeated on the contralateral side, again using 20ml of test solution.

## Laparoscopic Donor Nephrectomy

All operations will be performed by consultant transplant surgical staff using a standardised technique. In brief, four laparoscopic ports will be used, two 12mm ports placed near to the umbilicus and in an iliac fossa and two 5mm ports placed in the epigastrium and flank. The ureter and renal vessels will be dissected and then all of the lateral and posterior attachments of the kidney will be divided until the kidney is free on its vascular pedicle. A 6cm suprapubic retrieval incision will be performed through a transverse skin incision with division of the abdominal muscles in the midline. An Endocatch II® (Covidien, Mansfield,

MA, USA) retrieval system will be introduced through this retrieval incision. The ureter and renal vessels will be secured with clips or staples and then divided. The kidney will be captured in the Endocatch bag and removed through the suprapubic retrieval incision. The length of wound incisions shall be recorded.

#### Post-operative Analgesia

All patients will receive post-operative pain relief using a patient controlled analgesia system (PCAS) delivering 1mg boluses of morphine with a 5-minute lock-out period. The hospital's pain control team, who are independent of the transplant surgical team, will manage the PCAS in all cases. Opiate analgesia will be discontinued as the discretion of the patient and then replaced by oral analgesia with Tramadol (50-100mg po up to qds) or Paracetamol (1g po up to qds).

#### Peri-operative Protocol

As prophylaxis against venous thromboembolism all donors will wear TED stockings and be administered subcutaneous Dalteparin 2500iu once per day until fully mobile. Donors will be allowed to begin mobilisation on the first post-operative day and will be allowed to start eating and drinking at their own discretion. Donors will make their own decision about fitness for discharge from hospital. These decisions will not be affected by the views of the medical and nursing team, except in the event of complications.

#### Patient Assessment & Outcomes

The trial has been designed to test the safety and efficacy of TAP blocking in patients undergoing laparoscopic live donor nephrectomy.

Primary End Points (Assessment of post-operative and analgesic requirement)

Total post-operative morphine requirement. Post-operative analgesic use will be recorded by the nursing staff and pain team using the standard PCAS form. This will include the total dose of morphine used in mg

Daily post-operative pain levels recorded using visual analogue and verbal response scales. [100mm line with 'no pain at all' written at the left hand (zero) end and 'worst pain imaginable' written at the right hand (100) end]. [0 No pain at rest or movement; 1 no pain at rest, slight at movement; 2 Intermittent pain at rest, moderate on movement; 3 continuous pain at rest and severe on movement).

Total duration of PCAS use. Post-operative analgesic use will be recorded by the nursing staff and pain team using the standard PCAS form. This will include the duration of PCAS use in hours.

## Secondary End Points (Recovery from surgery)

Daily post-operative nausea and vomiting recorded using visual analogue and verbal response scales. (0 No nausea and vomiting at rest or movement; 1 no nausea and vomiting at rest, slight at movement; 2 Intermittent nausea and vomiting at rest, moderate on movement; 3 continuous nausea and vomiting at rest and severe on movement).

Daily post-operative sedation recorded and scored as following: (0 None, patient is alert; 1 Mild, awake but drowsy; 2 Moderate, asleep but rousable; 3 Severe, unrousable).

Adverse events caused by the TAP block procedure. These will include evidence of inflammation or infection at the administration sites or adverse effects of the local anaesthetic agent or saline.

Duration of post-operative stay. Patients will make their own decision about fitness for discharge from hospital. This decision will not be affected by the views of the medical and nursing team, except in the event of complications.

Time to the introduction of free oral fluids and the first solid food. Patients will make their own decision about the intake of fluids and solids. This decision will not be affected by the views of the medical and nursing team, except in the event of complications.

Timed up & go. Patients are timed as they rise from a chair, walk 3 metres, turn, walk back and sit. This will be measured before surgery and on post-operative days 1 and 3.

Grip strength. A hydraulic Hand Dynamometer is used to measuring grip strength (Kg)

The scores of 3 successive trials using the right and left hand will be measure before surgery and on each post-operative day until day 7 or at discharge, whichever is sooner.

Inflammation, cytokines (IL-1, IL-6 and TNF $\alpha$ ). A blood sample will be taken pre operatively and post operatively at 6, 24 and 48 hours in addition to routine daily blood samples. The blood will be centrifuged and the plasma stored at -80°C until analysed.

#### Information & Consent

Patients will be given a patient information sheet explaining the trial and written consent will be obtained by a member of the surgical team.

#### Data Collection and Analysis

The Trial Administrator/coordinator will collect and record all data prospectively, entering this onto a computerised database that has been specifically designed for this study. Data will be presented as mean  $\pm$  SD and statistical analysis performed using InStat<sup>®</sup> software for MacIntosh (Graphpad, San Diego, USA, [www.Graphpad.com](http://www.Graphpad.com)). Normality testing of data will be performed using the Kolmogorov-Smirnov test. Continuous variables will be compared using the students' T-test or the Mann-Whitney U-test as appropriate.

Categorical variables will be compared using Fisher's exact test.  $P < 0.05$  will be considered statistically significant.

#### Power Calculation

Sample size has been estimated on the basis of 24-hour post-operative morphine requirements in a previous series of patients undergoing laparoscopic live donor nephrectomy. This pilot data showed that the normal 24-hour morphine requirement was  $37 \pm 11$  mg (mean  $\pm$  standard deviation). For the purposes of sample size calculation, we considered that a clinically important reduction in morphine consumption would be a 50% absolute reduction. Using this data, we calculate that 20 patients per group will be required for an experimental design incorporating two equal sized groups using  $\alpha = 0.05$  and  $\beta = 0.1$ , thus giving a power of 90%. To minimise any effect of data loss, we will recruit 25 patients per group into the study.

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## Appendix 2 - PATIENT INFORMATION SHEET

You are being invited to take part in a research study.

Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

### About the study

Laparoscopic (Keyhole) live donor nephrectomy is now a well established operation in the UK and Leicester was the first unit in the UK to perform this operation and has now carried out more than 270 of these procedures. The laparoscopic technique reduces post-operative pain and the need for pain relieving medication (analgesics) compared to the

traditional open operation to remove kidneys, which was performed through quite a large incision. Nonetheless, some patients still require a reasonable amount of pain relieving medication, including intravenous injections of morphine after laparoscopic nephrectomy. We wish to study methods of decreasing the amount of post-operative pain even further. We would like to investigate the use of a local anaesthetic technique called the transversus abdominis plane (TAP) block. This is a method of anaesthetising or numbing the nerve endings in the abdominal wall at the site of the operation incisions. It involves injecting a local anaesthetic agent into this region after the patient has gone to sleep under general anaesthetic and before the surgery begins. Previous studies have shown that this technique can reduce pain after operations such as caesarean section but there are no studies, so far, in patients undergoing kidney donation.

In this study, patients will be randomly allocated to have either the TAP block, with local anaesthetic, or a similar procedure with an inert salt solution that does not contain any anaesthetic (the control group). The study will be a so-called 'blinded' one in which the patient, the surgeon and the anaesthetist are unaware whether local anaesthetic has been used or not in a particular patient. However, this information will be known by an independent Trial administrator/coordinator, who will only release the information if there are any problems or at the end of the trial when the results need to be analysed. This is the most accurate and impartial way to assess whether the TAP block can reduce post-operative pain.

Outcomes of the study will be judged primarily on the amount of pain relief that you require and the level of pain you experience after surgery. Your recovery will also be assessed and any nausea, vomiting and drowsiness recorded. The duration of your hospital stay and

time to the introduction of free oral fluids and first solid food will also be recorded. A blood sample will also be taken to assess the effects of surgery.

Each participant will remain in the study for the duration of their hospital stay only. Patients will be recruited over a period of 2 years.

Why have I been chosen?

Every patient over 18 years that has completed the full work-up for laparoscopic donor nephrectomy and is eligible will be approached for the trial. A total of 50 patients, 25 in each group will be required for the study.

Do I have to take part?

No - It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. You are still free to withdraw at anytime and without giving a reason. A decision to withdraw at anytime, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We need to establish if the TAP block can reduce the amount of pain after live nephrectomy. Whether you receive TAP anaesthetic or are in the saline control group, will be decided by chance using a sequence of random numbers generated by a computer. Therefore, you will have a one in two chance of receiving either the TAP block with anaesthetic or the same procedure with a simple saline solution. This is called a randomisation procedure and is rather like deciding which treatment you get by tossing a coin. We know that this sort of trial is the best way to determine how well a particular treatment works as it removes biases that may be there if you or your doctors know that you have received a

particular treatment. Neither yourself, nor the surgeon nor the anaesthetist will be told which treatment you have received and so this will have no influence on your subsequent treatment and recovery. The TAP block procedure is performed after you have gone to sleep under general anaesthetic. The anaesthetist uses a very fine needle to inject 20ml of solution into both side of the abdominal wall, just above the groin. These injections are performed using an ultrasound scanner to guide the needle tip into the correct muscle layer of the abdominal wall.

If you decide to take part you will only be participating during your hospital stay.

The following procedures will take place to assess the outcome of the TAP block

- a. After surgery you will receive pain relief through a self-administering system. This is called a patient controlled analgesia system (PCAS). In brief, an intravenous morphine drip is attached to you and you can administer a small dose of morphine to yourself by pressing a button. The system is computerised so that it is impossible for you to overdose yourself. In this way, the button can be pressed successfully only once every 5 minutes, so that this limits the amount of drug you receive. We know that this is a very good method of treating post-operative pain and this is our current best practice. The TAP block, with or without anaesthetic, is being given as an addition to this standard treatment.
- b. The discomfort/pain that you feel will also be assessed daily after surgery by asking you to score the level of pain that you feel.
- c. The amount of nausea, vomiting or drowsiness after surgery will also be assessed daily.

- d. You will be asked to perform a handgrip before, then once daily after your surgery to assess your recovery. This test will only take a minute or two to complete.
- e. Your ability to rise from a chair, walk a few metres, turn, then sit down again will be timed before your operation, and on day 1 and 3 after surgery.
- f. You will have routine blood samples taken before your operation then daily until you leave hospital as part of normal practice. In addition, a small amount of blood will be taken to analysis the effects of surgery.
- g. The time that you stay in hospital and time until you start eating and drinking will be recorded.

What do I have to do?

You will experience no additional restrictions from entering into this trial other than the normal limitations after a surgery.

What is the drug or procedure that is being tested?

We are testing the use of the TAP block local anaesthetic injections in the abdomen. The local anaesthetic agent being used is called Bupivacaine (Marcaine). This is a drug which has been used as a local anaesthetic for many years and has a very good safety record. In the control group of patients, the TAP block will be performed without anaesthetic, simply injecting a salt solution, which should not cause any harm as it has the same composition as salts already present in your body.

What are the alternatives for diagnosis or treatment?

Our current practice is to give pain relief after kidney donation using a patient controlled analgesia system. This delivers small doses of intravenous morphine and the system is controlled by the patient themselves. We know that this system is very good at treating post-operative pain and discomfort after kidney donation. This system will be given to all patients in the trial, whether they receive a TAP block containing anaesthetics or a TAP block consisting of an inert salt solution. In this way, all patients should be comfortable but we will be able to determine whether the addition of some local anaesthetic in a TAP block improves post-operative relief even more than the morphine system alone.

What are the side effects of any treatment received when taking part?

Both Bupivacaine anaesthetic and normal saline are routinely used in clinical practice and should cause no adverse effects. The TAP block procedure will be performed by a Consultant Anaesthetist who is experienced in the technique and giving anaesthetics for kidney donation. As the TAP block involves injections into the skin, it is possible that this will cause a small amount of bruising in the region but this is likely to be very minor. Local anaesthetics do have some adverse effects if they are injected directly into blood vessels. In the unlikely event of this happening, it is possible that there could be effects on the heart and on the nervous system. Precautions are taken to prevent injection of anaesthetics into blood vessels and the injections will also be performed using ultrasound guidance which, again, makes the procedure safer.

What are the possible disadvantages and risks of taking part?

The short term follow up allows an assessment to be made of your recovery from surgery in order to establish whether TAP reduces post-operative pain. There will be no long term risks from taking part in this study and there will be no additional affects on your lifestyle.

What are the possible benefits of taking part?

You will receive an appropriate level of pain relief after surgery according to your needs. You will not know what treatment you have received, however if you are in the treatment group you may need less pain relief which may speed your recovery. This study will help to determine if the TAP block procedure is beneficial to patients undergoing laparoscopic live donor nephrectomy.

What if new information becomes available?

Once you have undergone the surgery you will be treated in the normal post operative way. The additional outcome measures that we ask of you as part of this trial will not interfere with post operative care that you need.

What happens when the research study stops?

Your care will not be affected by the research study stopping. At the end of the study, the treatment groups will be 'unblinded'. At this point, we will be able to know which patients were treated with local anaesthetic and which patients were treated with the inert salt solution. The levels of pain and the requirement for pain relieving medication will be analysed in the two groups to see if TAP blocking with local anaesthetic decreased overall pain levels after the operation.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have

grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Your GP will be notified of your participation in the trial.

What will happen to the results of the research study?

You will not be told which group you are in after you give consent to participate in the trial.

The results of the trial will be analysed and written up as a research paper to be published in a medical journal. The results may also be presented to national and internal meetings of transplant surgeons as an educational activity. A copy of the results can be obtained by contacting a member of the surgical team. You will not be identified in any report or publication.

Who is organising and funding the research?

The funding for the trial will be provided by the Renal and Urology Department, University Hospitals of Leicester NHS trust and sponsored by The University of Leicester. No members of the surgical or research team will receive any additional payment for including you in this study.

Who has reviewed the study?

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informal decision.

Contact for further information

If you require any further information you can contact Professor Michael Nicholson, Ward 17  
Leicester General Hospital.

Thank you for taking the time to read this patient information sheet and agreeing to take part  
in the study.

This information sheet and a copy of the consent form are to be kept for your information.