

## ORIGINAL ARTICLE

# A randomized clinical trial of living donor nephrectomy: a plea for a differentiated appraisal of mini-open muscle splitting incision and hand-assisted laparoscopic donor nephrectomy

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## Keywords

kidney transplantation, laparoscopic surgery, living donors, nephrectomy.

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## Conflicts of Interest

The authors declare no conflict of interest.

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## Summary

A randomized controlled trial was designed to compare various outcome variables of the retroperitoneal mini-open muscle splitting incision (MSI) technique and the transperitoneal hand-assisted laparoscopic technique (HAL) in performing living donor nephrectomies. Fifty living kidney donors were randomized to MSI or HAL. Primary endpoint was pain experience scored on a visual analogue scale (VAS). After MSI living donors indicated lower median (range) VAS scores at rest than HAL living donors on postoperative day 2.5 [10 (0–44) vs. 15 (0–70),  $P = 0.043$ ] and day 3 [7 (0–28) vs. 10 (0–91),  $P = 0.023$ ] and lower VAS scores while coughing on postoperative day 3 [20 (0–73) vs. 42 (6–86),  $P = 0.001$ ], day 7 [8 (0–66) vs. 33 (3–76),  $P < 0.001$ ] and day 14 [2 (0–17) vs. 12 (0–51),  $P = 0.009$ ]. The MSI technique also resulted in reduced morphine requirement, better scores on three domains of the RAND-36, reduced costs and reduced CRP and IL-6 levels. The HAL technique was superior in operating time and postoperative decrease of hemoglobin level. The MSI technique is superior to the HAL technique in performing living donor nephrectomies with regard to postoperative pain experience. This study reopens the discussion of the way to go in performing the living donor nephrectomy.

## Introduction

Persistent shortage of kidney donation from deceased donors and superior results in living donor kidney transplantation have increased the incentive for living kidney donation in The Netherlands. The evolution of the surgical technique from a large lumbotomy to less invasive operations has reduced discomfort and enhanced recovery of living donors following donor nephrectomy. In the past years, two different operative strategies have been developed and refined. This study focuses on advantages

and disadvantages of both strategies in a randomized fashion.

Comparison of the mini-open technique with conventional classic open donor nephrectomy has decreased the need for opioids and promoted a faster recovery [1,2]. In 1995 laparoscopic donor nephrectomy [3] was introduced. This technique also compared favourably to classic open surgery [4–6]. The presumably less difficult and faster hand-assisted variant of the full laparoscopic donor nephrectomy was introduced in 1998 by Wolf [7] and further popularised living kidney donation. Compared to

the classic open technique the hand-assisted laparoscopic technique resulted in a quicker and less painful recovery as well [8]. Two randomized studies have compared mini-open to the full laparoscopic technique [9,10]. Both demonstrated increased pain experience after the mini-open technique. Despite this, the mini-open technique has advantages due to its retroperitoneal approach. It does not open spaces to gain access to the kidney and large mesothelial surfaces are not exposed to surgical manipulation and pressurized CO<sub>2</sub> gas. Furthermore, absence of a pneumoperitoneum precludes significant hemodynamic and respiratory side effects [11,12] during the operation which minimises surgical trauma and enhances recovery.

For these practical reasons we challenged previous reports and have performed a randomized controlled trial comparing the mini-open muscle splitting incision (MSI) and hand-assisted laparoscopic (HAL) living donor nephrectomy. In this study, we tested the hypothesis that the mini-open technique was not inferior to the hand-assisted operation as regards to pain. In addition, we also investigated the magnitude of surgical injury and repair using surrogate serum markers in both techniques.

## Materials and methods

### Study design, endpoints and sample size

This single centre randomized controlled trial compared two different types of operation in performing a living donor nephrectomy. The two types of operations were the MSI and the HAL technique. Postoperative pain was chosen as the primary end point of this study. A non-inferiority design was chosen as we had demonstrated decreased hospital cost in an unpublished retrospective pilot study using the MSI technique. In case the present study would be able to show clinical non-inferiority and confirm cost reduction of MSI compared to HAL technique, this would lead to the conclusion that the MSI technique should be the technique of choice.

Postoperative pain was scored both in rest and during provocation by coughing using the visual analogue scale [13] (VAS) from 0 (no pain) to 100 (most excruciating pain). Secondary endpoints of this study included serum C-reactive protein (CRP) and interleukin 6 (IL-6) as acute phase proteins. Other secondary endpoints were several intra-operative variables (operating time, decrease in hemoglobin), peri-operative complications categorized by the proposed living donor nephrectomy complication classification scheme [14], Quality of Life (QOL) assessment using the validated Dutch RAND-36 up to 1 year after donation [15], total morphine use by means of patient controlled analgesia (PCA), postoperative use of oral analgesics in the outpatient setting, time interval

until return to work, and short term (8 weeks) outcome of renal function in the donor (baseline GFR measured by isotope clearance studies [16]) and the recipient (serum creatinine up to 3 months postoperative). Donors were followed up till 1 year after the operation and checked for hernia and scar healing.

The RAND-36 format included eight dimensions and one change of general health status in the past year. Questionnaires were filled in on four occasions: preoperative, 2 weeks, 4 weeks, 8 weeks and 1 year after donor nephrectomy. Scores for each domain range from 0 to 100 with high scores indicating a good performance.

The cost-effectiveness of MSI versus HAL was assessed by comparing the difference in cost of both procedures with the difference in outcome in terms of pain scores. For cost-effectiveness from the hospital perspective only direct medical costs were included. For an expanded evaluation, costs of absence from work were calculated using the friction cost method. Bootstrap resampling ( $n = 5000$ ) was performed to assess uncertainty regarding cost-effectiveness.

In addition to CRP and IL-6 levels at different time points after the operation, also area-under-the-curves (AUC's) of these variables were calculated for a time integrated summary score using the trapezium rule [17].

At the time of design of this study only one report could be used as reference material [18] for SD of pain VAS scores in this setting. Reports did show that a VAS difference of 16 is clinically relevant [19,20]. The sample size was calculated using a free power and sample size software program [21]. The calculation was based on *t*-test data analyses for independent variables. The non-inferiority design of the study necessitated a one-sided statistical test. Using a power of 0.8, a one sided alpha of 0.05 (=an alpha of 0.1 in two-sided tests), a clinical relevant difference of 16, an SD of 20 and a 1:1 ratio of the control to the experimental group a sample size of 20 in each group was calculated. As we estimated to have a combined drop-out and missing value percentage of 20% the sample size was set at 50 living donors in the two arms of this controlled randomized study.

### Randomisation, blinding and patients criteria

The study was approved by the institutional review board and conducted in accordance with the principles of the 2000 Declaration of Helsinki. The trial was registered at clinicaltrials.gov (NCT00258986). A block randomisation plan was retrieved online at <http://www.randomization.com>. The operating team was informed of the allocated technique the day before surgery. Patients, researchers and nursing personnel were blinded for the randomization. All patients received immediate postoperative coverage of the abdomen with bandages until discharge. Inclusion and

exclusion criteria are listed in Table 1. Both left- and right-sided donor nephrectomies were included.

### Statistical analyses

Statistical analyses were made on an intention-to-treat protocol. Mann–Whitney *U* tests and exactly calculated likelihood ratios were used for continuous and categorical variables, respectively. Continuous data are given as median (minimum–maximum) values unless stated otherwise. The primary endpoint (VAS score) was analysed by means of the *T*-test (in case the Kolmogorov Smirnov test showed a normal distribution) or the Mann-Whitney *U* test if no normal distribution was found. *P* values of less than 0.05 were considered statistically significant. Statistical analyses were performed with the statistical software package SPSS for Windows version 15.0 (©2006, SPSS Inc, Chicago, IL, USA).

### Surgical and anaesthetic protocols

Potential living kidney donors had an extensive preoperative work-up including GFR measurement by nuclear tracers and arterial digital subtraction angiography. The evening before operation, donors were given a drip of 2 l normal saline/24 h. The anaesthetic protocol included the use of Ringer's Lactate (aiming at a diuresis of 1 ml/kg bodyweight/hour), sufentanil, propofol (maintenance TCI-target 2.5) and rocuronium.

The MSI donor nephrectomy was performed using a 10 cm transverse subcostal incision made from the tip of the 10th rib. Oblique muscles were split, avoiding injury to intercostal nerves. A table mounted wound retraction system was installed. The peritoneum was not opened. Ureter and hilar vessels were identified and the kidney was relieved from surrounding fat. Successively, the ureter, artery and vein were ligated and cut. After removal of the kidney the muscles were approximated with interrupted absorbable sutures.

The HAL donor nephrectomy was performed with the patient in right or left tilt without a table break. Ultracision®

(Ethicon Endosurgery, Cincinnati, OH, USA) was used for intra-abdominal dissection. A transverse suprapubic incision of 8 cm was made. The fascia was cut in de midline and the peritoneum opened. The Omniport® hand device (Advanced Surgical Concepts Ltd., Dublin, Ireland) was inserted. Two 12 mm ports were inserted near the umbilicus and the left or right lower abdomen, respectively. Another 5 mm port was inserted in epigastrio. CO<sub>2</sub> insufflation pressure was maintained at 12 mmHg. The kidney was freed from surrounding tissues and ureter and hilar vessels were identified. The ureter and artery were clipped and cut and the vein was stapled and cut (Autosuture EndoGIA Reticulator 30–2.5). After removal of the kidney the port sites of 12 mm were closed at the fascia level by interrupted absorbable sutures. The suprapubic fascia was closed using a running absorbable suture. In both techniques the skin wounds were infiltrated with 30 ml of 0.25% bupivacaine and closed intracutaneously.

Removed kidneys were perfused with UW solution (ViaSpan®, Bristol-Myers Squibb, Park Avenue, NY, USA), bagged and stored on ice (0–5 °C).

All donor nephrectomies in this study were performed by two consultant surgeons out of a group of four. Previous exposure of these surgeons to the two techniques had been at least 20 times of each technique.

Postoperatively, donors started patient controlled analgesia (PCA) for pain relief. Morphine bolus injection was set at 1 mg. Lock out time at the recovery was 5 min and in the ward 10 min. Maximum dosage of morphine in two hours time was 20 mg. Paracetamol 1 g q.i.d. was added on the ward and continued p.r.n. at the time of discharge from the hospital. After discharge donors were advised to resume normal activities as soon as they felt comfortable to do so.

## Results

### Demographics

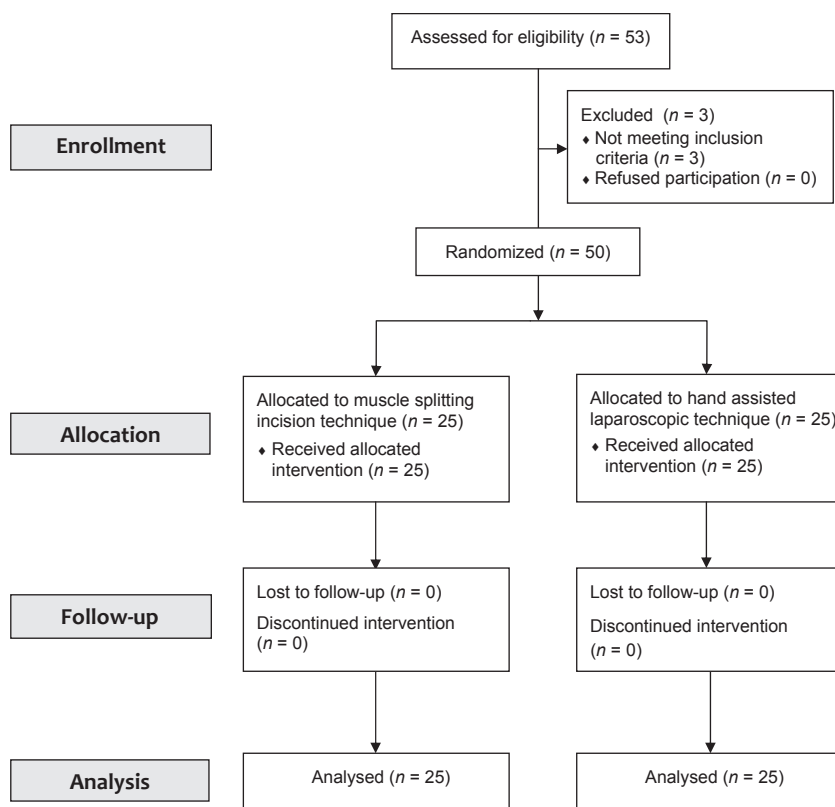
A total of 53 living donor nephrectomies were performed in the trial inclusion period (April 2004–December 2005). The trial flow diagram is shown in Figure 1. Three donors did not participate because of either poor understanding of Dutch language (one) or participation in the Dutch national living donor cross-over programme involving another transplant center (two). In Table 2 the demographic data of the donors and the recipients are listed. In the MSI group no extension to a standard open technique was necessary and in the HAL group no conversion to open surgery occurred.

### Perioperative variables

Table 3 presents the values of continuous perioperative variables. The mean skin to skin operation time was

**Table 1.** Inclusion and exclusion criteria of living kidney donors for participation in the trial.

Inclusion criteria	<ul style="list-style-type: none"> <li>– Accepted as living kidney donor by the local living kidney donor screening protocol</li> <li>– 18 years of age or older</li> <li>– Adequate understanding of the Dutch language</li> <li>– Fit to be operated on by the MSI as well as the HAL technique</li> <li>– Signed informed consent</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>– Previous abdominal surgery</li> <li>– Participation of the Dutch living kidney donor cross-over programme</li> </ul>



**Figure 1** Trial flow diagram.

**Table 2.** Demographic data of living kidney donors operated on according to the muscle splitting incision (MSI) technique or the hand assisted laparoscopic (HAL) technique and their kidney recipients. Categorical data are given as numbers, continuous variables as median values (range).

	MSI	HAL
Donor		
Number of donors	25	25
Male/Female	14/11	10/15
Age in years	52 (23–74)	51 (36–70)
Body mass index	26.0 (20.6–43.7)	25.2 (21.1–31.3)
ASA classification* 1/2	19/6	17/8
Mismatch A and B	2 (0–4)	2 (0–4)
Mismatch DR	1 (0–2)	1 (0–2)
Mismatch total	3 (0–6)	3 (0–6)
Left kidney/right kidney	18/7	22/3
Number of arteries 1/>1	22/3	21/4
Number of veins 1/>1	23/2	24/1
Number of ureters 1/>1	25/0	25/0
Recipient		
Male/female	14/11	16/9
Age in years	33 (15–59)	44 (17–72)
Living related Yes/No	15/10	17/8

\*ASA classification, American Society of Anesthesiologists classification.

36 min longer in the MSI operation (MSI: 242 min, HAL 206 min). The mean time spent in theatre was 26 min longer in the MSI operation (MSI: 311 min, HAL:

285 min). No learning curves, as indicated by decreasing operating times over time, were observed in both MSI and HAL technique (data not shown). As shown in Table 3, the decrease of hemoglobin was more pronounced following MSI indicating more blood loss with the MSI technique.

### Pain

In Table 4 results of the VAS score are shown for 11 different time intervals including the preoperative measurement. Measuring the VAS score was done both at rest and while coughing. At five different measurements (two at rest on days 2 and 3, three while coughing on days 3, 7 and 14) the VAS score is significantly lower in the MSI operated group of patients. The lower pain experience in the MSI group during hospitalization is confirmed by the reduced postoperative morphine consumption depicted in Table 3.

### Inflammatory markers CRP, IL-6

The serum CRP levels were lower after MSI on all postoperative days. On the first and second postoperative day the difference in CRP was statistically significant as well as the area under the curve of CRP (Table 5). Serum levels of IL-6, preceding CRP in the pro-inflammatory cascade, were compared between the two groups as well.

**Table 3.** Peri-operative variables of donors and recipients following live donor nephrectomy using the muscle splitting incision (MSI) technique or the hand assisted laparoscopic (HAL) technique. Categorical data are given as numbers, continuous variables as median values (minimum–maximum).

	MSI	HAL		P	
		N	N		
<b>Donor</b>					
Operating time in minutes	240 (165–312)	25	210 (145–260)	25	0.001
Time spent in theatre in min	310 (230–395)	25	290 (225–330)	25	0.015
Postoperative percentage decrease of Hb	22 (9–34)	25	17 (9–25)	25	0.001
Total amount of morphine consumption in mg	27 (0–81)	25	50 (5–112)	25	0.006
GFR percentage residual function 8 weeks after kidney donation	62 (45–76)	25	64 (53–78)	23	0.521
Hospital admission time in days starting at day of operation	4 (2–13)	25	4 (3–8)	25	0.245
Direct hospital costs in Euro	14.721 (12.402–20.607)	25	16.348 (14.356–18.466)	25	<0.001
Work resumption in days after the operation	53 (18–188)	14	61(21–351)	18	0.730
Costs of absence from work	7.349 (0–19.885)	25	9.294 (0–19.885)	25	0.344
Total costs	20.597 (12.402–40.492)	25	26.398 (14.862–36.388)	25	0.043
Total length of scars in cm	10.0 (9.0–13.0)	24	14.5 (12.5–17.0)	23	<0.001
Number of donors not satisfied with cosmetic result 1 year after surgery	0	17	1	21	NS
<b>Recipient</b>					
1st Warm ischemic time* in min	3 (2–12)	25	4 (2–11)	25	0.130
Cold ischemic time† in min	149 (106–251)	25	151 (89–211)	24	0.212
2nd Warm ischemic time‡ in min	39 (27–146)	25	39 (28–60)	25	0.403
Number of recipients with 1-year graft survival	24	25	25	25	NS

Hb, hemoglobin; GFR, glomerular filtration rate.

\*1st Warm ischemic time, time in minutes between occluding the renal artery and the start of cold flush.

†Cold ischemic time, time in minutes between the start of cold flush and the start of suturing the vascular anastomoses.

‡2nd Warm ischemic time, time in minutes between the start of suturing the vascular anastomoses and reperfusion.

Twelve hours after the surgery the IL-6 level was lower in the MSI group compared to the HAL group (Table 5). The AUC of IL-6 in serum was not significantly different between the MSI and the HAL technique.

### Quality of life

The scores for the eight dimensions of the RAND-36 and the change of general health status, subdivided in the HAL and the MSI group, are shown in Fig. 2. Two weeks after the operation, donors operated with the MSI technique experienced less 'pain', less 'physical limitation' and less 'change' of their general health than HAL operated donors. The interval after the operation to resume work was not different between MSI and HAL nor were any cosmetic dissatisfactions recorded (Table 3).

### Renal function of donor and recipient

Table 3 shows that no differences were found in the percentage residual GFR of donors operated with HAL or MSI technique at 8 weeks postdonation. The kidney function in the recipients in the first 3 months, assessed by creatinine levels in serum, also showed no difference between kidneys from living donors operated by the HAL or the MSI technique at any time point (Fig. 3).

### Complications

Complications are categorized and displayed in Table 6. No mortalities were observed among living kidney donors and recipients. No admissions to an intensive care unit were indicated. If the operating surgeon felt that blood loss exceeded the arbitrary 'normal' amount it was scored as an 'excessive bleeding' complication. No hemodynamic problems or necessity for blood transfusion during the operation were seen on any of these occasions. One transfusion of a unit of red blood cells was given two days postoperatively because of symptomatic anemia (MSI). No readmissions occurred and no incisional hernia was found. No statistical significant differences were observed in the occurrence of major, moderate, minor and total complications in living donors between the MSI and the technique. In the recipients no technical difficulties were encountered that could directly be attributed to the donor operation. One renal artery thrombosed shortly after transplantation requiring a thrombectomy (MSI). The recipient suffered from delayed graft function and was hemodialysed for several weeks. One recipient had recurrence of MPGN in the transplanted kidney that led to the only graft loss in the study within 1 year after the transplantation (HAL). In six recipients, eleven biopsy proven rejection episodes were recorded, that were successfully treated.

**Table 4.** Median (minimum–maximum) visual analogue scale (VAS, range 0–100) scores of living kidney donors at different postoperative time intervals and conditions following muscle splitting incision (MSI) or hand assisted laparoscopic (HAL) living donor nephrectomy.

	MSI		HAL		P
	VAS score	N	VAS score	N	
At rest					
Day -1	0 (0–0)	25	0 (0–0)	25	1.000
Day 0	18 (0–71)	24	18 (0–68)	25	0.659
Day 1.0 (08.00)	30 (0–64)	25	28 (0–55)	25	0.838
Day 1.5 (18.00)	14 (0–56)	23	14 (0–54)	24	0.468
Day 2.0 (08.00)	18 (0–40)	24	21 (0–65)	23	0.254
Day 2.5 (18.00)	10 (0–44)	20	15 (0–70)	20	0.043
Day 3.0 (08.00)	7 (0–28)	16	10 (0–91)	16	0.023
Day 7	2 (0–19)	25	6 (1–65)	24	0.060
Day 14	1 (0–13)	21	2 (0–20)	22	0.328
Day 28	0 (0–5)	24	0 (0–13)	21	0.514
Day 56	0 (0–11)	25	0 (0–16)	23	0.507
Coughing					
Day -1	0 (0–0)	25	0 (0–0)	25	1.000
Day 0	53 (6–89)	24	48 (16–100)	25	0.304
Day 1.0 (08.00)	45 (10–88)	23	61 (17–100)	24	0.077
Day 1.5 (18.00)	37 (15–80)	23	43 (15–90)	22	0.551
Day 2.0 (08.00)	41 (0–71)	23	40 (5–90)	20	0.390
Day 2.5 (18.00)	35 (0–69)	20	40 (9–100)	19	0.238
Day 3.0 (08.00)	20 (0–73)	14	42 (6–86)	16	0.001
Day 7	8 (0–66)	25	33 (3–76)	24	<0.001
Day 14	2 (0–17)	21	12 (0–51)	22	0.009
Day 28	0 (0–8)	24	1 (0–22)	21	0.738
Day 56	0 (0–0)	25	0 (0–18)	23	0.136

**Table 5.** Serum levels and area under the curves (AUC) values of cold reactive protein (CRP) and interleukin 6 (IL-6) in living donors following muscle split incision (MSI) or hand assisted laparoscopic (HAL) nephrectomy. For the AUC cases are excluded listwise in case of one or more missing value. Day 0 (CRP) and T 0 (IL-6) is the time at the start of the operation.

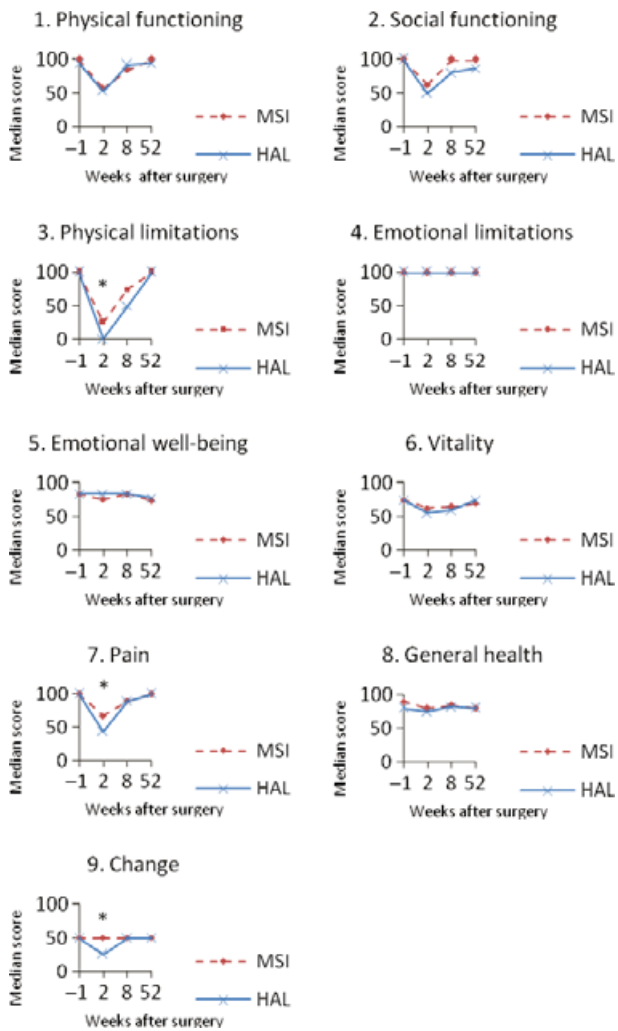
	MSI		HAL		P
		N		N	
Donor					
CRP day 0 (mg/l)	2 (2–20)	25	2 (2–26)	24	0.200
CRP day 1 (mg/l)	32 (10–88)	24	46 (17–186)	25	0.006
CRP day 2 (mg/l)	76 (24–183)	23	112 (41–283)	24	0.024
CRP day 3 (mg/l)	59 (16–174)	21	82 (29–227)	24	0.080
AUC of CRP, censored for patients with missing values	135 (43–310)	20	213 (80–571)	22	0.025
IL-6, T 0 h (pg/ml)	0 (0–12)	23	0 (0–23)	25	0.912
IL-6, T 4 h (pg/ml)	24 (0–59)	23	27 (11–83)	24	0.132
IL-6, T 12 h (pg/ml)	24 (11–52)	22	33 (16–100)	25	0.011
IL-6, T 24 h (pg/ml)	25 (2–74)	23	28 (14–44)	24	0.519
IL-6, T 48 h (pg/ml)	20 (5–50)	24	19 (7–28)	23	0.765
IL-6, T 72 h (pg/ml)	12 (3–22)	22	13 (3–65)	22	0.519
AUC of IL-6, censored for patients with missing values	58 (19–113)	20	72 (32–109)	20	0.099

AUC, area under the curve; CRP, cold reactive protein; IL-6, interleukin 6.

### Costs

Direct hospital cost of the living donors was lower with MSI technique than with HAL technique (Table 3). For

the hospital one MSI operation saved Euro 1.601 compared to one HAL operation, being approximately 10% of the overall hospital cost of a living kidney donor. The difference was predominantly caused by the use of more

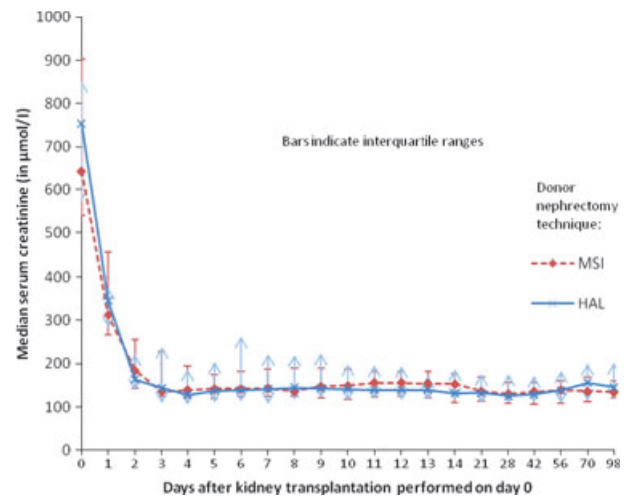


**Figure 2** Median RAND-36 domain scores of living donors before and after live donor nephrectomy using the muscle splitting incision (MSI) technique or the hand assisted laparoscopic (HAL) technique. \* $P < 0.05$ .

expensive disposables amounting to a total of Euro 2.086 for every HAL operation. Cost of absence from work did not differ significantly between HAL and MSI groups. When combined with the direct cost, total costs were still significantly lower for the MSI technique ( $P = 0.03$ ).

**Discussion**

This trial compares two different techniques for living donor nephrectomy: the muscle splitting incision (MSI) technique and the hand-assisted laparoscopic (HAL) technique. As regards to the primary endpoint the MSI technique is superior and associated with less pain than the HAL technique. In addition, a decreased systemic pro-inflammatory response and reduction in hospital cost



**Figure 3** Median (interquartile ranges) posttransplantation creatinine levels in censored recipients (no rejection, no thrombosis, no recurrent disease in the transplanted kidney) of living donated kidneys using the muscle splitting incision (MSI) or hand assisted laparoscopic (HAL) technique.

were found using the minimal open technique. For other secondary endpoints such as operation time and decrease in haemoglobin, the HAL technique was superior.

Many of our findings are not in accordance with previous reports on the same subject that all took the position of a clear advantage of laparoscopic over open technique. Differences are discussed in the following paragraphs.

**Set up**

The study was set up as a single center prospective randomised trial with a non-inferiority design. If the MSI technique for performing the donor nephrectomy would prove to be equal or superior to the HAL technique with respect to clinical outcome, the less expensive MSI operation should be considered the first choice option. The primary end point of clinical outcome in this study was the pain experience measured by means of the VAS score. Several other variables were included as secondary end points. All 50 living donors who fulfilled the inclusion criteria gave consent to participate in the trial. This conspicuous finding supports the unbiased nature of information given to the living donors and contributes to the reliability of the results. Since no conversions or major intra-operative complications occurred the two groups of living donors are homogeneous and very suitable for analyses.

**Techniques**

The retroperitoneal MSI operation was developed in our hospital from a standard open technique. With this

**Table 6.** Categorized numbers of complications of living kidney donation following donor nephrectomy using the muscle splitting incision (MSI) technique or the hand assisted laparoscopic (HAL) technique.

Complications	MSI	HAL
Major		
DVT and pulmonary emboli	1	
Moderate		
Postoperative blood transfusion	1	
Minor		
Lesion small upperpole artery	1	2
Superficial splenic lesion		2
'Excessive bleeding' according to surgeon	3	5
Minor wound infection	2	1
Temporary hypesthesia hand	1	
Temporary ipsilateral orchialgia		2
Urinary tract infection	1	1
Temporary bladder dysfunction	1	2
Total number of donor complications	11*	15*
Donor complications, not related to the donor surgery itself		
Blister (related to the trial)	2	
Recipient complications		
Renal artery thrombosis requiring reoperation; DGF	1	
Postoperative bleeding requiring reoperation	2	
Ureteral stenosis requiring reoperation	1	
Re-MPGN and graft loss (explantation) <1 year		1
Rejection episodes in first year, no graft loss	5	6

DVT, deep venous thrombosis; DGF, delayed graft function necessitating dialysis posttransplantation; MPGN, membranoproliferative glomerulonephritis.

\* $P = NS$ .

technique, great care is taken during dissection of the required structures in natural planes, saving as much as possible of the surrounding structures like nerves and muscles. The transperitoneal HAL technique was adopted from two hospitals that we visited and who have published their technique [8,22].

### Perioperative variables

It was remarkable to find that the MSI technique took 36 min longer of skin to skin operative time than the HAL operation. Antcliffe *et al.* [23] in a 2009 meta-analysis comparing full laparoscopic to mini-incision found that the mini-open technique took less operative time than full laparoscopic techniques. The HAL type of operation in our center takes about the same time or only slightly longer than other centers have published [8,22]. The MSI in our study takes more time compared to published data on mini-open donor nephrectomy [9,10,24–27]. No learning curves were found in this study and a sufficient number of cases of both techniques were performed prior to this study. For this reason we see the

extended operating time in the MSI technique as a reflection of the patient and careful dissection resulting in prolonged operation time.

Blood loss was estimated indirectly through percentage decrease in hemoglobin level. The decrease of hemoglobin was higher in the MSI group indicating more blood loss following this technique compared to the HAL technique. Nanidis [28] has confirmed the higher amount of blood loss during open donor nephrectomy compared to the (hand-assisted) laparoscopic technique in a meta-analysis. In the present study population the amount of blood loss did not seem to be clinically relevant in both treatment arms. Nevertheless, it may be an indication of a technically more demanding operation when the MSI technique is applied.

One may speculate that the increased number of reoperations in the recipients following an MSI donor operation (4 vs. 1) may also support the increased difficulty in the MSI technique. Open key hole surgery may result in less adequate hemostasis and vascular trauma to the kidney resulting in increased reoperations for bleeding, thrombosis and ureteral complications in the recipient. Of course the actual numbers of these complications do not allow irrevocable conclusions.

### Pain

Pain experience is used as one of the major arguments to promote laparoscopic surgery over open surgery. Challenging the superiority of the laparoscopic procedure would only be possible if pain was included as a major outcome in the set up. Furthermore intense postoperative pain is a known risk factor for long term adverse outcome [29]. As postoperative pain score is more intense and clinically more relevant while coughing [30] the assessment of pain by means of VAS was done not only at rest but especially while coughing. In three different outcome variables involving pain the MSI is superior to the HAL: lower VAS scores on day 3 to 14 at coughing and at rest on day 3, less morphine consumption during admission and lower scores on the pain dimension in the RAND-36 quality of life questionnaire 2 weeks after surgery. These findings differ from other studies on the subject as summarized in a recent meta-analysis [23]. Two of these studies are also randomized controlled trials comparing laparoscopic donor nephrectomy to an open mini-incision technique [9,10,31]. In both trials full laparoscopic techniques were superior to mini-open techniques with regard to pain outcome, morphine consumption and a number of quality of life items. When we try to explain the different outcome of our trial, the most obvious difference is that the 'hand-assisted' technique is used versus 'full laparoscopy' in the other two studies.



On the other hand, several other studies have compared hand-assisted and full laparoscopic techniques for donor nephrectomy [32,33] and other indications [34,35]. These trials did not show a difference in outcome of pain and various clinical parameters. A more likely cause for disparity then may be differences between the type of mini-open techniques. The increased operating time using MSI in our trial could confirm such an explanation. Our MSI technique is the ultimate atraumatic mini-open approach and consumes more time. With regard to the reduced pain experience of the MSI technique compared to the HAL technique, it can be hypothesized that the retroperitoneal access to the kidney will result in less pain than the transperitoneal HAL technique due to evasion of many sensory nerve fibers in the (parietal) peritoneum. Thus, a retroperitoneal HAL variant, as described by Wadstrom [36], may overcome this disadvantage.

### Systemic immune response

From a pathophysiologic point of view it was of interest which type of technique evoked the highest acute phase response as an indication of the amount of inflicted surgical trauma. Acute phase proteins CRP and IL-6 in serum were used as markers for the total systemic stress response. These markers have also been used in the past to support advantages of laparoscopic surgery over open surgery [37,38]. Levels of CRP and IL-6 have been used as markers to monitor disease severity and complications [39]. The lower CRP and IL-6 responses to MSI compared to HAL indicate lower severity of inflicted trauma by the MSI technique. We suggest that stimuli during the transperitoneal HAL technique such as pressurized CO<sub>2</sub> gas and manipulation of intra-abdominal contents provoke an increased inflammatory reaction. The suppressive influence of a pneumoperitoneum on hemodynamic and respiratory variables [40] may also contribute to this phenomenon.

### Costs

Hospital costs were Euro 1601 lower for the MSI technique compared to the HAL operation due to expensive disposables used for the laparoscopic procedure. These higher costs of the HAL technique could only partially be compensated by the shorter time spent in theatre. Many reports claim the same tendency of increasing hospital costs following the introduction of the laparoscopic technique [8,41]. When differences in costs associated with absence from work, averaging about Euro 2000, were taken into account, the cost difference further increased favoring the MSI technique.

### Summary and future perspective

This study shows that in our hospital a meticulous retroperitoneal MSI technique causes less pain in patients up to 2 weeks after the operation compared to the transperitoneal HAL technique. MSI induces a lower systemic (pro)inflammatory response and results in less hospital costs. Arguments against MSI are slightly prolonged operating time and a modest increased amount of blood loss. Many of our observations disagree with other studies on this subject. A possible explanation for this controversy may be differences in the mini-open technique. We feel that the approach and results of living donor nephrectomy can still be improved by combining good elements of the MSI and HAL techniques.

### Authorship

HSH: designed the study, wrote the article and as a surgeon was involved in every donor operation. WNN: was the researcher who got informed consent from every eligible donor and collected all clinical donor data. JN: helped in the design of the study and did all the work of the Quality of Life assessment. CK: was one of the other surgeons performing the operations of the donors and recipients according to the study protocol and contributed to the writing of the article. MS, WJvS, and JJHvdH: screened the donors and recipients, informed about the study and supplied all data on renal function and clinical data of recipients. MvW: designed and supervised the anesthetic protocol and patient care, and provided the data on morphine consumption from the PCA. HG: helped in the design of the study, the statistics and in the interpretation of the cost effectiveness part. RJP: was the principal investigator. He contributed in the design, performed operations according to the protocol, contributed to the execution of the study and to the final draft of the article.

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van Vliet, Swades Ramcharam and Taco Buitenhuis collected most of the test VAS scores. Robert Porte was the independent medical doctor for questions about the study by participants.

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