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CHAPTER 5

Fast track hand-assisted laparoscopic donor nephrectomy: a randomized clinical trial

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ABSTRACT
Laparoscopic surgery has improved donor convalescence after kidney donation. In other surgical fields fast track perioperative care has further improved postoperative convalescence. Our aim was to compare fast track with standard care after hand-assisted laparoscopic donor nephrectomy (HALDN) and to investigate if fast track care is advantageous in terms of quality of life and hospital stay.

In a single-center randomized clinical trial 52 kidney donors were randomized to fast track \( (n = 26) \) or standard perioperative care \( (n = 26) \). Primary outcome was postoperative recovery of physical performance one month after surgery measured by the Short Form-36 (SF-36) questionnaire. Secondary outcomes were recovery of physical performance three months after surgery, minor and major complications and postoperative hospital stay.

Baseline characteristics were comparable between both groups. The SF-36 recovery of physical performance score after one month was 73 (standard deviation (SD) \( \pm 2.6 \)) in the standard care group and 75 (SD \( \pm 3.0 \)) in the fast track group \( (P = 0.60) \). No major and two minor complications occurred. Median hospital stay was 4 days (interquartile range (IQR) 3 to 4) for the standard care group, versus 3 days (IQR 3 to 4) for the fast track group \( (P = 0.63) \). Fast track donors had significantly less pain on the first postoperative day \( (P < 0.01) \).

This study did not show a significant benefit of fast track perioperative care on quality of life after HALDN when compared with standard care.

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INTRODUCTION

Laparoscopic surgery improved postoperative recovery, decreased morbidity and postoperative pain and shortened hospital stay when compared with open nephrectomy, without compromising graft function. The introduction of hand-assisted laparoscopic donor nephrectomy (HALDN) further reduced postoperative morbidity and the duration of surgery. In many centers HALDN is the preferred method for donor nephrectomy.

Fast track perioperative care aims to improve and expedite postoperative recovery by optimizing several aspects around surgery such as dietary intake, effective pain management and mobilization, resulting in a faster recovery and shorter hospital stay. Several systematic reviews in gastrointestinal surgery show that the introduction of fast track perioperative care contributes to faster postoperative convalescence. They report a reduction of hospital stay, varying between two to seven days. The mortality and risk of postoperative complications is similar to standard care. The population of kidney donors, however, is not comparable to gastrointestinal surgery patients. Therefore, it is not possible to extrapolate the benefits of fast track care in gastrointestinal patients to kidney donors.

Our aim was to compare fast track perioperative care with standard care in HALDN in a randomized clinical trial. We hypothesize that fast track care results in a quicker convalescence and is advantageous in terms of quality of life and hospital stay.

METHODS

From November 2009 onwards all adult donors were eligible for inclusion in this mono-center randomized clinical trial at the Academic Medical Center, Amsterdam. Exclusion criteria were expected problems with the placement of a thoracic epidural catheter, the inability to give informed consent, use of psychopharmacological medication, chronic use of analgesics, and use of non-steroid anti-inflammatory drugs (NSAIDs) within five days before surgery. Preoperative donor evaluation included blood and urine examination, CT-angiography and renal scintigraphy. Donors were admitted to the surgical ward one day prior to the day of surgery and were discharged when they complied with the following discharge criteria: 1. adequate pain control with oral analgesics, 2. absence of nausea, 3. toleration of solid food, 4. passage of flatus or stools, 5. full mobilization and 6. acceptance of discharge by the donor. If donors preferred to stay in the hospital after meeting the discharge criteria, e.g. to be near the kidney recipient, the date of discharge is defined as the date the donor met the discharge criteria. All patient charts, surgical reports and nursing documentation including mobilization schemes were reviewed retrospectively.
The study was conducted in accordance with the principles of the declaration of Helsinki and according to the CONSORT statement.\textsuperscript{9} The independent medical ethics review board approved the study protocol. The study was registered under NTR2080 (www.trialregister.nl).

**Surgical technique**

HALDN was carried out transperitoneally under general anesthesia.\textsuperscript{10} After open dissection of the distal ureter and gonadal vein through a 7 cm Pfannenstiel incision, the non-dominant operator’s hand was introduced through a handport (Omniport®, Advanced Surgical Concepts, Ireland) and two 10-12 mm trocars were placed. An insufflation pressure of 12 mmHg was used. After full mobilization of the right or left hemicolon and the kidney, the hilar structures were dissected. Transection of the artery and vein was carried out with an endoscopic stapler (Endopath ETS Compact Linear Cutter®, Johnson & Johnson, Belgium). The kidney was extracted through the Pfannenstiel incision and flushed and preserved with cold University of Wisconsin solution (UW). Peroperatively mannitol, furosemide and heparin were administered. All donors received a transurethral bladder catheter after induction of the general anesthesia. One surgeon performed all operations (MMI), with a personal experience of more than 50 left-sided and 50 right-sided HALDN prior to this trial. The surgical technique was similar for fast track and standard care donors. Thoracic epidural catheters were placed by staff anesthesiologists with profound experience of at least 100 placements prior to the study.

**Fast track protocol**

Fast track donors were offered caloric preloading with four portions of 200 ml carbohydrate-loaded (CHL) drinks (preOp®, Nutricia, Dublin, Ireland) on the eve of donor nephrectomy and two portions two hours before surgery. Fast track donors were not allowed to take preoperative sedatives. In the operation room a thoracic epidural catheter was inserted with 8-10 ml bupivacaine 0.25\% and either 20 μg sufentanil or 150 μg fentanyl. The surgical procedure was performed as described above. Postoperatively, a continuous infusion of bupivacaine 0.125\% and fentanyl 2.5-5.0 μg/ml 6-12 ml/hour was administered combined with 1000 mg paracetamol four times a day. At postoperative day (POD) 2 the epidural catheter was removed and 50 mg tramadol was given three times a day in combination with paracetamol until no longer needed. When placement of the epidural catheter failed patient controlled analgesia (PCA) using morphine was given combined with low dose of ketamine until POD 2. The urine catheter was removed at POD 1. A minimum of two hours chair mobilization is required on POD 0 and a minimum of six hours on the following days. Full oral intake had to be 800-1000 ml on POD 0 including two portions of CHL drinks, two liters of oral intake on POD 1 including three portions of CHL drinks and a normal diet on POD 2 including two grams of magnesium oxide. Donors were discharged on POD 3 if they met the discharge criteria.
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Standard care protocol
Standard care donors did not receive CHL drinks. Preoperative sedatives were given before donor nephrectomy. HALDN was performed as described above. Postoperative analgesia was given by PCA using morphine which was continued until POD 2 or until the anesthesiologist deemed unnecessary. When PCA was stopped 50 mg tramadol was given three times a day in combination with paracetamol until no longer needed. The urine catheter was removed at POD 1. On POD 0 the donors received a clear liquid diet and mobilized at will. From POD 1 onwards donors received a preferred diet and mobilized at will. Donors were discharged on POD 3 if they met the discharge criteria.

Primary and secondary outcomes
Primary outcome was postoperative physical functioning one month after surgery measured by the Short Form-36 (SF-36) questionnaire. The SF-36 comprises 36 items which constitute eight dimension scores. The dimension scores are physical functioning, role physical (role limitations due to physical health problems), bodily pain, general health perception, vitality, social functioning, role emotional (role limitations due to emotional problems), and mental health. These eight scores range from 0 to 100. A higher score indicates better health. A difference of 5 points in a particular dimension is considered a minimal clinically and socially relevant change, a 10-point difference is considered moderate clinically and socially relevant, whereas a 20-point difference is considered as significantly clinically and socially relevant. Physical functioning score was the primary outcome because earlier quality of life studies in laparoscopic donor nephrectomy demonstrated this dimension to have the largest postoperative effect.

The Multidimensional Fatigue Inventory-20 (MFI-20) was used to evaluate fatigue and is a 20-item scale that measures fatigue in five dimensions. The Gastro-Intestinal Quality of Life Index (GIQLI) consists of 36 items to assess quality of life of patients with gastro-intestinal disorders. The EuroQol EQ-5D questionnaire was used to assess a generic measure of health status. All questionnaires were scored preoperatively and postoperatively after one and three months. Furthermore, a 0 to 10 visual analogue scale (VAS) measure of pain in rest and exertion was analyzed on POD 1 to 3. Donors were also questioned on the amount of recovered activity at home and at work after one and three months.

Secondary outcomes were recovery of physical performance three months after surgery measured by SF-36, minor complications, major complications and postoperative hospital stay. Major complications were defined as any postoperative complications requiring re-intervention, admission to the intensive care unit or death. Minor complications were defined as all other complications that required a change in management. Hospital stay was counted in days from the day of surgery to the day of discharge including additional hospitalization in case of readmission within 30 days of surgery.
Randomization
Randomization was done by means of an Internet block randomization module after informed consent was obtained at the outpatient department. Regardless of randomization, all donors were admitted to the same surgical ward. The nursing and medical staff working on this ward had been extensively trained to execute both treatment protocols according to good clinical practice. Blinding was not performed.
Statistical analysis and sample size calculation

The primary endpoint was physical functioning measured by the SF-36 questionnaire one month after surgery. A generally used 20-point difference was considered clinically significant.\cite{22,23,24} Considering a standard deviation (SD) of 25 it was calculated that with a power of 80% and a two-sided alpha of 0.05, 26 donors per group were needed. To anticipate for a 20% loss to follow-up, we aimed to include 32 donors per group. With hospital stay as secondary outcome 21 donors per group were needed to detect a one-day reduction of hospital stay. Treatment groups were compared with the $\chi^2$ test for dichotomous outcomes and the Mann-Whitney U test for continuous variables. A two-sided P value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows version 16 (SPSS Inc. Chicago, IL).

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of donors and surgical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard care</strong></td>
</tr>
<tr>
<td>(n = 26)</td>
</tr>
<tr>
<td>Mean age in years (± SD)</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Mean body mass index in kg/m$^2$ (± SD)</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Family related donation</td>
</tr>
<tr>
<td>Left-sided nephrectomy</td>
</tr>
<tr>
<td>Median operating time in minutes (IQR)</td>
</tr>
<tr>
<td>Median blood loss in ml (IQR)</td>
</tr>
</tbody>
</table>

SD = standard deviation, IQR = interquartile range

RESULTS

From November 2009 to October 2012, 124 adult donors at the Academic Medical Center Amsterdam were eligible for inclusion in the study (Figure 1). Sixty-seven donors were excluded of which 46 who refused informed consent, mainly due to reluctance towards epidural anesthesia. Fifty-seven donors were randomized to either standard or fast track perioperative care. Two donors withdrew from the study during follow-up; one moved abroad and one withdrew due to the death of the recipient. In three cases postoperative questionnaires were missing. These donors were considered lost to follow-up and were not included in the analysis. Eventually 52 donors were included in the analysis. Baseline characteristics did not differ significantly between both groups (Table 1). Follow-up was at least three months. The trial ended when sufficient donors had completed the questionnaires after one month. There was no conversion to open nephrectomy in both groups.
The following elements of the post-operative treatment protocol were scored if successfully applied: intake of CHL drinks before and after surgery, omission of preoperative sedatives, thoracic epidural analgesia, postoperative mobilization, day of removal of urinary catheter and first day of normal diet (Table 2). One fast-track donor postoperatively received PCA after failed placement of a thoracic epidural catheter.

Table 2 Protocol compliance

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 26)</th>
<th>Fast track (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHL intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 ml on day before surgery</td>
<td>0</td>
<td>21 (81%)</td>
<td></td>
</tr>
<tr>
<td>400 ml 2 hours before surgery</td>
<td>0</td>
<td>25 (96%)</td>
<td></td>
</tr>
<tr>
<td>600 ml on POD 1</td>
<td>0</td>
<td>22 (85%)</td>
<td></td>
</tr>
<tr>
<td>Omission of preoperative sedatives</td>
<td>5 (19%)</td>
<td>22 (85%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Thoracic epidural analgesia</td>
<td>0</td>
<td>25 (96%)</td>
<td></td>
</tr>
<tr>
<td>Patient controlled analgesia</td>
<td>24 (92%)</td>
<td>1 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative mobilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 2 hours on POD 0</td>
<td>4 (15%)</td>
<td>14 (54%)</td>
<td>0.003</td>
</tr>
<tr>
<td>At least 6 hours on POD 1</td>
<td>8 (31%)</td>
<td>21 (81%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least 6 hours on POD 2</td>
<td>15 (58%)</td>
<td>23 (89%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At least 6 hours on POD 3</td>
<td>19 (73%)</td>
<td>24 (92%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Urinary catheter removed on POD 1</td>
<td>15 (58%)</td>
<td>17 (65%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Normal diet on POD 2</td>
<td>19 (73%)</td>
<td>26 (100%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

CHL = carbohydrate loaded drink, POD = postoperative day

Quality of life
SF-36
Between groups analyses at different time points of the SF-36 survey are given in Figure 2, including mean dimension scores in a healthy Dutch population. Physical functioning one month after surgery was 73% (SD ± 2.6) in the standard care group versus 75% (SD ± 3.0) in the fast track group (P = 0.60). After three months the scores were 89% (SD ± 2.8) versus 93% (SD ± 1.6) respectively (P = 0.16). Compared with the standard care group, fast track donors had higher scores in all dimensions except for general health perception one month after surgery. Three months after donation, fast track donors scored higher in all eight dimensions but these differences were not statistically significant in either dimension. However, a 20-point difference was seen in the role physical dimension after three months, indicating clinical relevance (P = 0.12).
Figure 2 Results as measured by the SF-36 questionnaire (mean ± 2x standard error of the mean) before surgery (n = 52), after 1 month (n = 52) and after 3 months (n = 46). The broken lines represent the mean dimension scores in a healthy Dutch population.
Three months after surgery, the dimensions physical functioning, general health perception, role emotional and mental health had returned to preoperative values. The dimensions role physical, bodily pain, vitality and social functioning were still below preoperative values three months after surgery.

**MFI-20**
Between groups analyses at different time points of the MFI-20 survey could not detect any significant differences (Figure 3). Three months after donation, the fatigue scores did not yet return to preoperative values.

![Figure 3](image-url) Results as measured by the MFI-20 questionnaire (mean ± 2x standard error of the mean) before surgery (n = 52), after 1 month (n = 52) and after 3 months (n = 46).

**GIQLI**
Results of between group analyses at different time points of the GIQLI questionnaire are presented in Figure 4. Donors in the fast track group scored significantly lower in the social wellbeing dimension after surgery (P = 0.04). For all other dimensions, there were no significant differences.

**EuroQol**
Between groups analyses at different time points for the EuroQol questionnaire are presented in Figure 5. Only the usual activities (social) and pain & discomfort dimensions seem to be affected by the surgery. No significant differences were detected between the two groups.
Figure 4 Results as measured by the GIQLI questionnaire (mean) before surgery (n = 52), after 1 month (n = 52) and after 3 months (n = 46). Asterisks indicate a significant difference between both study groups.

Figure 5 Scores as measured by the EuroQol questionnaire before surgery (n = 52), after 1 month (n = 52) and after 3 months (n = 45).
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**Figure 6** Postoperative pain in rest (left) and dynamic pain (right) as measured by the visual analogue score (VAS) for pain (mean ± 2x standard error of the mean) on postoperative day (POD) 1 (n = 52), POD 2 (n = 52) and POD 3 (n = 49). Asterisks indicate a significant difference between both study groups.

Pain VAS scores
The between group analyses at the first 3 postoperative days are shown in Figure 6. Postoperative pain scores were significantly lower in the fast track group on POD 1 in rest and dynamic pain (respectively, P = 0.005 and P = 0.001). However, on POD 3 fast track donors had significantly more pain in rest (P = 0.03).

Secondary outcomes
Postoperative outcomes for donors and recipients are presented in Table 3. Donors in the fast track group had a median hospital stay of 3 days, compared with 4 days in the standard care group. However, this was not statistically significant (P = 0.63). Hospital stay ranged from 2 to 8 days in the standard care group and from 2 to 7 days in the fast track group. Longer hospital stay was mostly due to pain. Two donors in the standard care group postponed discharge due to complications of the acceptor while they already met the discharge criteria. This was the case for four donors in the fast track group. One donor in the standard care group developed an ileus that was conservatively treated with a nasogastric tube for 2 days. One donor in the fast track group developed severe postoperative migraine, prolonging the hospital stay to 7 days.

**DISCUSSION**

This study did not show a significant difference in quality of life between fast track postoperative care and standard care after HALDN. Although fast track donors had a trend towards better scores in several quality of life questionnaires and a shorter postoperative hospital stay, the results were not statistically significant.
<table>
<thead>
<tr>
<th></th>
<th>Standard care (n = 26)</th>
<th>Fast track (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative complications</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Median hospital stay in days (IQR)</td>
<td>4 (3-4)</td>
<td>3 (3-4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Able to work after 1 month</td>
<td>5 (19%)</td>
<td>4 (15%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Able to work after 3 months</td>
<td>14 (54%)</td>
<td>18 (69%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Perception of recovery score (0 to 100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 1 month (mean ± SD)</td>
<td>64 (± 19)</td>
<td>71 (± 21)</td>
<td>0.11</td>
</tr>
<tr>
<td>After 3 months (mean ± SD)</td>
<td>84 (± 18)</td>
<td>89 (± 14)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

IQR = interquartile range, SD = standard deviation

Quality of life after fast track laparoscopic donor nephrectomy has not been described earlier in the literature. Studies in other patients after fast track surgery have not found a clear benefit of fast track care on quality of life.4-7,25 A systematic review on cardiac surgical patients found similar quality of life one month and one year after surgery for fast track and standard care patients.4 A systematic review in liver surgery patients found similar functional recovery for both fast track and standard care patients.7 Several colorectal fast track studies also failed to show an improvement of quality of life after fast track surgery.5,25 Length of hospital stay for both treatment groups was in accordance with postoperative hospital stay in standard care donors in the literature.26 We found no studies on hospital stay in fast track laparoscopic donor nephrectomy. Recart et al. performed a randomized controlled trial between fast track and standard laparoscopic non-donor nephrectomy and found a statistically significant reduction in hospital stay with fast track care from 2.5 days to 1.7 days.27 Furthermore, they report better analgesia in fast track patients with the additional use of local anesthesia at port sites and in the renal fossa. However, patients that undergo nephrectomy for non-donor causes such as renal cancer are not comparable to kidney donors who are relatively healthy and thoroughly screened before donation. The good physical status of kidney donors might be the reason why the fast track program did not show improved convalescence or shorter hospital stay after HALDN in this study. A study by Kuo et al. described laparoscopic donor nephrectomy with a 23-hour hospital stay protocol.28 In this protocol donors were mobilized on the day of surgery and were discharged the following day. This way 36 of 41 donors were discharged within 23 hours after nephrectomy. One donor was readmitted. Pain assessment and management was not described. In our study donors in both study groups had a longer hospital stay compared with the studies by Recart and Kuo.27,28 We hypothesize that this difference in hospital stay is due to differences in pain management.
The use of epidural anesthesia significantly reduced pain on the first postoperative day. When the epidural anesthesia was stopped fast track donors reported significantly more pain than standard care donors. It is hypothesized that this increased experience of pain was due to an increased perception of pain after cessation of the epidural catheter. The complication rate was comparable between both groups.

Limitations of this study were the lack of blinding. The differences in protocol elements could not be blinded, since donors were admitted to the same surgical ward after donation. This might have introduced interference in postoperative care whereas the same medical and nursing staff treated both donor groups. The small sample size could be the reason for non-significant results. However, the number of included donors was the minimum according to the sample size calculations. A larger study might show clinically important differences regarding some of the outcomes we have studied. Fast track donors had a trend towards better scores on almost all questionnaires and median hospital stay was one day shorter. This could indicate a trend towards better recovery for fast track donors.

In conclusion, a multimodal fast track recovery program did not show a significantly enhanced recovery after HALDN when compared with standard perioperative care.

REFERENCES


