Antidiuretic Hormone Release During Laparoscopic Donor Nephrectomy

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**Background:** During laparoscopic procedures, increased intra-abdominal pressure may cause transient renal dysfunction due to impaired renal blood flow and induction of neurohormones. However, the relationship between antidiuretic hormone (ADH) secretion and increased intra-abdominal pressure is poorly understood.

**Hypothesis:** Laparoscopic donor nephrectomy (LDN) is associated with an increase in plasma ADH concentration, which influences renal function in both the donor and transplanted graft.

**Objectives:** To evaluate plasma ADH levels during LDN and to correlate ADH levels with graft function.

**Design and Interventions:** In 30 patients who underwent LDN, plasma ADH levels were collected before insufflation, during surgery, after desufflation, and 24 hours after the procedure. In 6 patients who had open donor nephrectomy, blood samples were obtained as controls. Furthermore, graft function, operative characteristics, and clinical outcome were compared.

**Setting:** University hospital.

**Results:** In the LDN group, mean ADH levels during pneumoperitoneum and 30 minutes postinsufflation were significantly higher compared with preinsufflation values (P<.001). Twenty-four hours after LDN, mean ADH levels had returned to normal values. There were no significant differences in ADH levels in the open donor nephrectomy group. No significant differences in either intraoperative diuresis, blood pressure readings, or postoperative graft function were documented among the 2 groups.

**Conclusions:** In this study, LDN was associated with an increase in plasma ADH that appeared to be related to increased intra-abdominal pressure. We conclude that the increased ADH concentrations during LDN are not associated with clinically significant changes in either the kidney donor or the transplanted graft.

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Laparoscopic surgery requires the use of pneumoperitoneum to create a working space in the abdominal cavity for the safe introduction of trocars and other instruments as well as exposure of the abdominal contents. Intraperitoneal insufflation with carbon dioxide is the most commonly used method to elevate the abdominal wall and suppress the viscera. Clinical and experimental studies have shown that increased intra-abdominal pressure is associated with transient renal dysfunction (oliguria) due to impaired renal blood flow, as a consequence of compression of the renal parenchyma and renal vessels as well as increased systemic resistance.\(^1\)\(^-\)\(^3\) In addition, renal function may be influenced by the release of neurohormones such as catecholamines, endothelin, or antidiuretic hormone (ADH) following increased intra-abdominal pressure.\(^5\) Several studies have reported elevated ADH levels during increased intra-abdominal pressure,\(^5\)\(^-\)\(^8\) although the actual mechanism for this occurrence is poorly understood. The major stimuli of ADH secretion are an increase in plasma osmolality and a decrease in the effective circulatory volume. Increased ADH secretion promotes renal water reabsorption, reducing plasma osmolality and increasing plasma volume.\(^8\) However, the clinical significance of ADH release during pneumoperitoneum is still unclear.

See Invited Critique at end of article

Recently, the laparoscopic approach has been adopted for the procurement of a kidney from a living donor for transplantation purposes.\(^10\) Concern has been raised about the reported incidence of primary dysfunction of transplanted kid-
PATIENTS AND METHODS

PATIENT SELECTION

From November 1999 through December 2000, 38 live donor nephrectomies were performed. Laparoscopic donor nephrectomy, currently the standard approach for this procedure in living donors at our institution, was performed in 32 patients; a conventional open donor nephrectomy (ODN) was performed in 6 patients. The open procedures were performed in patients with severe obesity (n = 4) or multiple renal arteries on both sides (n = 2).

Candidates for donor nephrectomy were thoroughly screened using medical history, physical examination, blood and urine chemistry, immunological studies, and screening for infectious diseases. Informed consent was obtained in all cases. The standard preoperative workup included renography, Seldinger angiography, and selective renal artery angiography in cases of more than one renal artery. Ultrasonography was performed to exclude the presence of kidney deformities. In patients with normal functioning and anatomy of both kidneys, the right kidney was preferred for LDN; on the right side, the gonadal and adrenal veins do not insert into the renal vein, making vascular dissection less time consuming. All LDNs and ODNs were performed by a single transplant surgeon (J.N.M.J.).

Patient data were compared for age, sex, body mass index, and American Society of Anesthesiologists score. In all donors, we documented blood loss, length of operation, mean arterial pressure, and urinary output from time of anesthesia induction until nephrectomy. In recipients, mean serum creatinine levels at 1, 2, 3, 4, 5, 7, 14, and 28 days after transplantation were documented to assess graft function.

OPERATIVE TECHNIQUE

Laparoscopic donor nephrectomy was performed using general endotracheal anesthesia with the patient in the semilateral decubitus position. Details of this procedure have been reported previously. A 30° laparoscope was introduced through a Hasson trocar and placed through a small midline incision, just caudally to the umbilicus. A pneumoperitoneum of less than 12 mm Hg was created, and 4 additional trocars were inserted. The right nephrectomy was conducted as follows: mobilization of the right side of the colon, opening of the renal fascia, and division of the renal fat. The renal vein was dissected up to its entrance into the caval vein and encircled with a rubber vessel loop to enable gentle traction and correct positioning of the stapling device. After 5000 U of heparin were systematically administered, the ureter, renal artery, and renal vein were divided using a linear vascular laparoscopic stapler (Endo-GIA 30; US Surgical, Norwalk, Conn). The left nephrectomy was conducted in a similar fashion: mobilization of the left side of the colon and spleen, dissection of the renal vein up to its point of crossing with the aorta, dissection of the renal artery, ligation of the adrenal and ovarian or spermatic veins with titanium clips, dissection of the ureter, creation of an extraction incision, anticoagulation, division of the ureter, renal artery, and renal vein, and extraction of the kidney. A plastic extraction bag (Endocatch; US Surgical) was used to remove the kidney through the enlarged subumbilical incision. Directly after kidney extraction, hemostasis was restored using protamine sulfate. The kidney was perfused with Eurocollins solution at 4°C and stored on ice awaiting transplantation. After closure of the extraction incision, pneumoperitoneum was reestablished and inspection of the operative field was performed. After assurance of adequate hemostasis, the ports were removed using direct visualization, the abdomen was desufflated, and the incisions were closed. Renal transplantation was commenced following LDN.

HORMONAL MEASUREMENTS

Blood samples were obtained after the induction of anesthesia (T0), 30 minutes after the installation of pneumoperitoneum (T1), and 90 and 150 minutes after the start of insufflation (T2 and T3, respectively). At 30 minutes after abdominal desufflation and extraction of the kidney, another sample was obtained (T4). A final blood sample was obtained 1 day postoperatively (T5). In the 6 ODNs, blood samples (approximately 5 mL of blood at each time point) were obtained at similar times. Samples were obtained in tubes primed with EDTA (K3, 13%; 0.054 mL; 0.34 M/10 mL) for the measurement of ADH. Samples were immediately placed on ice and centrifuged for 10 minutes at 4°C (3000 rpm), and aliquots were stored at −20°C until analysis. Antidiuretic hormone was analyzed by radiommunoassay using a commercial kit (Bühlmann Laboratories, Basel, Switzerland).

STATISTICAL ANALYSIS

Statistical analysis was performed with the supervision of a statistician (E.W.S.) using SPSS 9.0 statistical software (SPSS Inc, Chicago, Ill). Patients undergoing ODN and LDN were compared using nonparametric analysis of variance (Mann-Whitney U test). The Wilcoxon rank sum test was used for within-group comparisons. Percentile values (P5, P25, P50, P75, and P95) were calculated for selected patients at T0 to illustrate the variability and distribution of ADH values during donor nephrectomy. Correlations were determined between urinary output, plasma ADH concentrations, and blood pressure readings. Data are summarized as mean ±SEM. P < .05 was considered statistically significant.

RESULTS

Patient characteristics and intraoperative data for kidney donors are presented in Table 1. There was a significant difference in body mass index between the 2 groups: 25.6 (range, 19-32) for LDN and 32.6 (range, 29-37) for ODN (P < .001). The 2 groups were similar.
Table 1. Patient Characteristics and Operative Data in Kidney Donors*

<table>
<thead>
<tr>
<th></th>
<th>LDN (n = 30)</th>
<th>ODN (n = 6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.6 (25-75)</td>
<td>39.5 (24-55)</td>
<td>.06</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>18:12</td>
<td>3:3</td>
<td>.19</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.8 (19-32)</td>
<td>32.6 (29-37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASA class, I/I</td>
<td>25.5</td>
<td>4.2</td>
<td>.09</td>
</tr>
<tr>
<td>Duration of operation, min</td>
<td>168 (90-270)</td>
<td>145 (120-175)</td>
<td>.19</td>
</tr>
<tr>
<td>Estimated blood loss, mL</td>
<td>313 (50-1000)</td>
<td>480 (130-1200)</td>
<td>.60</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>83 (63-110)</td>
<td>79 (73-85)</td>
<td>.81</td>
</tr>
<tr>
<td>IV fluid hydration, mL/kg per hour</td>
<td>21.4 (12.5-42.4)</td>
<td>19.5 (13.8-26.9)</td>
<td>.58</td>
</tr>
<tr>
<td>Urinary output until nephrectomy, mL/kg per hour</td>
<td>1.8 (0.5-4.6)</td>
<td>2.0 (0.3-3.5)</td>
<td>.79</td>
</tr>
</tbody>
</table>

*Data are presented as mean (range) unless otherwise indicated; LDN indicates laparoscopic donor nephrectomy; ODN, open donor nephrectomy; ASA, American Society of Anesthesiologists; and IV, intravenous.

Figure 1. A, Plasma antidiuretic hormone (ADH) levels in patients having laparoscopic donor nephrectomy (LDN). T0 indicates preinsufflation; T1, T2, and T3 indicate 30, 90, and 150 minutes after the start of insufflation, respectively; T4, 30 minutes after desufflation; and T5, 24 hours after the procedure. Data are presented as mean ± SEM. Asterisks indicate P < .05 compared with T0. B, Plasma ADH levels in patients having open donor nephrectomy (ODN). T0 indicates before skin incision; T1, 30 minutes after skin incision; T2, 90 minutes after skin incision; T3, 30 minutes after kidney extraction; and T4, 24 hours after the procedure. Data are presented as mean ± SEM. No value was measured at T3 because of the shorter operating time for ODN. Normal values for plasma ADH concentrations range between 0.20 and 4.7 pg/mL (0.19-4.35 pmol/L). To convert ADH values to SI units (picomoles per liter), multiply by 0.926.

Figure 2. Percentile values (P5, P25, P50, P75, and P95) of antidiuretic hormone (ADH) levels during laparoscopic donor nephrectomy (LDN) were calculated at T0 (preinsufflation) to illustrate the large variability in plasma ADH concentration during the laparoscopic procedures. The logarithmic scale demonstrates that during pneumoperitoneum, there is a relative increase in ADH concentration compared with T0, which is similar in all percentiles. In addition, it shows that during almost the entire length of the operation, the median value (P50) of plasma ADH is still within the normal range (0.20-4.7 pg/mL [0.19-4.35 pmol/L]). To convert ADH values to SI units (picomoles per liter), multiply by 0.926.

Regarding all other characteristics. Two patients in the LDN group required conversion to flank laparotomy after vascular injuries to either the lumbar or renal vein. Data from these patients were excluded from analysis. The mean operative time from skin incision to closure was similar for both groups (168 minutes vs 145 minutes). Intraoperatively, there were no significant differences regarding estimated blood loss, mean arterial pressure, intravenous volume administration, or urinary output.

Figure 1A shows plasma ADH levels during LDN. After insufflation (T1), ADH levels were significantly increased compared with preinsufflation levels (T0) (P < .001). During laparoscopic dissection, ADH levels remained significantly increased (T2 and T3) (P < .001 and P = .003, respectively). Thirty minutes after kidney extraction and subsequent desufflation (T4), ADH levels were still significantly higher (P < .001). Twenty-four hours after the procedure (T5), plasma ADH levels decreased to control values but were still significantly higher compared with T0 (P = .003). Figure 1B shows the plasma ADH concentrations during ODN. There were no significant increases in ADH levels during or after donor nephrectomy.

In Figure 2, percentile values (P5, P25, P50, P75, and P95) of ADH levels during LDN (T0, T1, T2, T3, and T4) are presented. This figure illustrates the large variability in plasma ADH concentration during the laparoscopic procedures and shows that the relative increase in ADH concentration is similar in all percentiles. During almost the entire duration of the operation, the median value (P50) of the plasma ADH concentration was still within the normal range (0.20-4.7 pg/mL [0.19-4.35 pmol/L]). In 53% of patients (16/30) who had LDN, the increase in plasma ADH levels during pneumoperitoneum was still within this range (data not shown).
A-C shows the results of the regression analysis that was performed to investigate if urinary output was influenced by either ADH or blood pressure. During pneumoperitoneum, no significant correlation was found between an increase in mean ADH concentration and intraoperative urinary production (R = 0.24; P = .18). To convert ADH values to SI units (picomoles per liter), multiply by 0.926. B, Correlation between mean arterial pressure and intraoperative urinary production. Blood pressure did not affect intraoperative urinary production in either LDN or ODN (R = 0.11; P = .52). C, Correlation between the relative increase in ADH concentration (calculated as T2/T0 × 100%) and intraoperative urinary production during LDN and ODN. In all patients, the increase in ADH concentration did not correlate with a reduction in intraoperative urinary production (R = 0.25; P = .23).

In all cases, transplantation was successful. Graft function, reflected by mean serum creatinine levels in recipients, was not significantly different at any point following the laparoscopic or open procedure (Table 2).

Laparoscopic donor nephrectomy reduces donor morbidity in terms of decreased postoperative pain and shorter convalescence. As in most laparoscopic procedures, LDN is usually performed using intraperitoneal insufflation with carbon dioxide to facilitate the required working space. However, the effects of performing a renal allograft in the altered physiologic environment of pneumoperitoneum are not fully understood. Although transient renal dysfunction during a prolonged period of increased intraabdominal pressure has been well documented, various mechanisms such as renal vessel compression, renal parenchymal compression, and systemic hormonal effects have been described to explain these changes.1-3 In a previous study comparing 89 LDNs with 83 ODNs, we found that intraoperative urinary output was significantly lower during the laparoscopic procedure, a finding that may be caused by insufficient intraoperative hydration of the donor.13 However, it has been suggested that increased plasma ADH levels contribute to oliguria due to pneumoperitoneum.15 Therefore, the objectives of our study were to prospectively evaluate plasma ADH levels in recipients during laparoscopic and open donor nephrectomy.

**Table 2. Recipient Graft Function**

<table>
<thead>
<tr>
<th></th>
<th>LDN</th>
<th>ODN</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Mean serum creatinine, µmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>843 ± 152</td>
<td>594 ± 108</td>
<td>.16</td>
</tr>
<tr>
<td>POD1</td>
<td>399 ± 37.5</td>
<td>258 ± 66.9</td>
<td>.19</td>
</tr>
<tr>
<td>POD2</td>
<td>176 ± 15.5</td>
<td>162 ± 49.9</td>
<td>.63</td>
</tr>
<tr>
<td>POD3</td>
<td>139 ± 11.6</td>
<td>168 ± 39.3</td>
<td>.60</td>
</tr>
<tr>
<td>POD4</td>
<td>147 ± 12.2</td>
<td>169 ± 32.7</td>
<td>.51</td>
</tr>
<tr>
<td>POD5</td>
<td>146 ± 10.7</td>
<td>130 ± 19.9</td>
<td>.77</td>
</tr>
<tr>
<td>1 wk</td>
<td>142 ± 9.4</td>
<td>112 ± 13.8</td>
<td>.23</td>
</tr>
<tr>
<td>2 wk</td>
<td>125 ± 7.7</td>
<td>122 ± 11.6</td>
<td>.81</td>
</tr>
<tr>
<td>4 wk</td>
<td>127 ± 7.7</td>
<td>130 ± 12.8</td>
<td>.71</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. LDN indicates laparoscopic donor nephrectomy; ODN, open donor nephrectomy; and POD, postoperative day.*
levels during LDN and to correlate ADH levels with graft function.

This study shows that ADH levels may increase during LDN. After the start of insufflation with carbon dioxide, mean ADH levels were significantly higher compared with preinsufflation values. During laparoscopic kidney procurement, ADH levels remained significantly elevated, even until 30 minutes after abdominal desufflation. Twenty-four hours after LDN, mean ADH levels had returned to normal but were still significantly higher compared with preinsufflation values. In patients who had ODN, ADH levels did not significantly change. Therefore, the cause of the increase in intra-abdominal pressure appears to be the increased intra-abdominal pressure, not the induction of general anesthesia or the mere act of surgery.

An increase in ADH in response to elevated intra-abdominal pressure has been demonstrated both in animal studies and clinical studies. Melville et al reported a 45-fold increase in ADH levels at an intra-abdominal pressure of 45 mm Hg compared with values before the induction of pneumoperitoneum. The mechanism of this massive release of ADH may be explained by reduced cardiac filling pressure due to the impairment of venous return, as was recently suggested by Odeberg et al. In other studies, no stimulatory effect of increased intra-abdominal pressure on ADH secretion was found, indicating that the ADH response due to pneumoperitoneum is still a matter of controversy.

In our study, the increase in mean plasma ADH levels during pneumoperitoneum was only 2- or 3-fold compared with normal values. At our institution, maximal insufflation pressure during LDN does not exceed 12 mm Hg, which suggests that vasopressor substances may be activated at pressures higher than those currently used for clinical pneumoperitoneum. Because there was a large variability in plasma ADH concentrations during LDN, we calculated percentiles to illustrate the distribution in ADH levels. In more than 50% of patients who had LDN, plasma ADH concentrations increased during pneumoperitoneum but were still within the normal range. In theory, it is possible that a 2-fold increase in plasma ADH level in one patient is consistent with that in a patient in whom the plasma ADH level did not increase following insufflation. Therefore, we calculated the relative increase in plasma ADH concentration during LDN to correlate this data with intraoperative urine production. Comparison of patients with an increased ADH response and their ADH-unchanged counterparts did not reveal a single clinically significant difference.

Furthermore, intraoperative blood pressure readings and urinary production were comparable in both groups, and the kidney graft functioned equally well afterward. Therefore, the clinical significance of the increase in ADH observed during LDN appears limited.

In summary, LDN was associated with an increase in plasma ADH, which appears to be related to increased intra-abdominal pressure. However, the increased ADH levels during LDN were not associated with clinically significant changes in either the kidney donor or the transplanted graft.

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REFERENCES

Laparoscopic donor nephrectomy has supplanted ODN as the procedure of choice in suitable patients. Hospitalization is shorter, pain management is easier, and return to work comes faster.¹ Historically, open donors have had good long-term renal function.² Because LDN is in its infancy, long-term results are not available, but the assumption based on the ODN data is that the results will be comparable.³

Laparoscopic donor nephrectomy is radically different from ODN. Pneumoperitoneum alters the donor’s physiology significantly⁴,⁵; therefore, the effect on the kidney could be profound. Hazebroek and colleagues seek to address one physiologic perturbation: the liberation of ADH in response to pneumoperitoneum.

Because ADH release follows the stimulation of extrarenal baroreceptors, ADH release in LDN is probably not due to pneumoperitoneum. The release of this hormone may be a secondary response of endothelin 1 (ET-1), which is produced and released from vascular endothelial cells as well as the posterior pituitary gland. Endothelin 1 may play a role in modulating ADH release⁶ and has been implicated in the physiologic response of a decreased glomerular filtration rate and urine volume following pneumoperitoneum.

Ambrose et al⁷ found a significant decrease in glomerular filtration rate (87%) and a 79% decrease in urine volume compared with controls in rats that underwent pneumoperitoneum. PreproET-1 messenger RNA levels and the ET-1 peptide were localized within the kidney. The reverse transcription polymerase chain reaction showed a significant increase in the expression of preproET-1 messenger RNA in the laparoscopic group, along with an enhanced expression of the ET-1 peptide in the renal vascular endothelium and proximal tubular cells. The renal juxtaglomerular apparatus, an intrarenal baroreceptor, may also be stimulated by pneumoperitoneum to activate the renin-angiotensin system.

Although Hazebroek and colleagues did not find an adverse response in the LDN grafts to elevated ADH levels, further studies are needed to elucidate the effects of pneumoperitoneum and their consequences on the donated kidney.

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