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INSTITUTO NACIONAL DE CIENCIAS MEDICAS Y NUTRICION "SALVADOR ZUBIRAN"

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LAPAROSCOPIC VERSUS OPEN ADRENALECTOMY IN CUSHING'S SYNDROME AND DISEASE

Trabajo de Investigación que para obtener el título de Especialista en Cirugía General presenta: **Dr. Eric Acosta Ponce de León.**

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INSTITUTO NACIONAL DE CIENCIAS
MEDICAS Y NUTRICION
"SALVADOR ZUBIRAN"
22 NOV 2000
DIRECCION DE CIRUGIA

Laparoscopic versus open adrenalectomy in Cushing's syndrome and disease

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Background. *Adrenalectomy in Cushing's syndrome and disease involves particular risks and complications. The aim of the study was to compare the open posterior and the flank laparoscopic approaches in this group of patients.*

Methods. *Forty patients who underwent unilateral or bilateral adrenalectomy for hypercortisolism between 1991 and 1999 were studied. Patients were divided as follows: adenoma—5 laparoscopic and 8 open; hyperplasia—17 laparoscopic and 12 open. Demographics, surgical details, outcome, and complications were comparatively analyzed.*

Results. *Patients undergoing laparoscopic or open adrenalectomy were comparable in terms of age, sex distribution, body mass index, respiratory status, and anesthetic risk. Operative time was longer in the laparoscopic group. One patient in the laparoscopic group died of upper gastrointestinal tract bleeding on postoperative day 17. Two patients in the open group and one in the laparoscopic group experienced postoperative complications. Cure of the disease occurred in all patients. Mild abdominal wall pain developed in one patient in each group. No abdominal wall weakness was identified in either group.*

Conclusions. *Cure rate and operative and long-term morbidity were similar for laparoscopic and open adrenalectomies in this series. However, it is important to emphasize that late complications in our patients who underwent the posterior open procedure were rather infrequent. (Surgery 1999;126:1111-6.)*

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ADRENALECTOMY IS THE TREATMENT OF CHOICE for adrenocortical adenomas and carcinomas, primary bilateral cortical hyperplasia, persistent or recurrent disease after pituitary surgery, and occult or unidentifiable ectopic ACTH-secreting tumors.[1] Traditionally, the most common surgical approach for unilateral or bilateral adrenalectomy in patients with hypercortisolism has been the posterior approach. However, with rapid improvements in technology and better surgical skills, laparoscopic adrenalectomy has become a common procedure for most benign functioning and nonfunctioning adrenal masses as well as for those with hyperplasia.[2-7]

Comparisons of laparoscopic adrenalectomy and the open technique have generally documented advantages of minimally invasive procedures in terms of decreased hospital stay, reduced convalescence, and greater patient satisfaction.[3-5] However, patients with Cushing's disease and syndrome are a particular group. They have higher rates of surgical morbidity and mortality because of decreased wound healing and increased risk of postoperative infections, deep venous thrombosis, and pulmonary embolism.[8-11] In addition, the excessive fatty tissue that these patients have makes the operation more difficult and may compromise the completeness of gland resection.

The aim of the study was to comparatively analyze two cohorts of patients with either Cushing's syndrome or Cushing's disease who underwent open or laparoscopic adrenalectomy, with emphasis on the analysis of long-term results and complications.

PATIENTS AND METHODS

From a total of 78 patients who underwent adrenalectomy at the service of endocrine surgery of our Institution from August 1991 to March 1999, a group of 40 patients was selected for the study. This group represents all of the patients with a preoperative diagnosis of Cushing's adenoma or hyperplasia.

Presented at the 20th Annual Meeting of the American Association of Endocrine Surgeons, New Haven, Conn, May 2-4, 1999.

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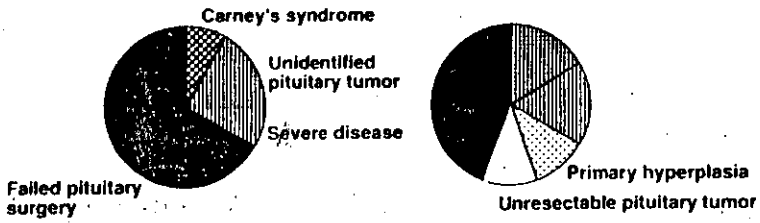

Figure. Indications for surgery in patients undergoing open bilateral adrenalectomy (*left pie ch*
laproscopic bilateral adrenalectomy (*right pie chart*).

Table I. Demographics of patients undergoing unilateral adrenalectomy

	Open (n = 6)	*Laparoscopic (n = 5)*
Age* (y)	27 (17-35)	32 (21-54)
Female (n)	6	5
Body mass index* (kg/m^2)	30 (17-41)	32 (25-35)
Vital capacity* (%)	97 (77-102)	94 (81-112)
FEV-1* (%)	90 (77-110)	103 (87-116)
ASA score II/III (%)	83/17	100/0
Preoperative block (n)	3	4

*Values are median (range).

FEV-1, Forced expiratory volume in one second.

Diagnosis. Confirmation of hypercortisolism was based on basal serum levels of cortisol, urinary free cortisol excretion, and the low-dose dexamethasone suppression test. Differential diagnosis between pituitary and adrenal hypercortisolism was established by serum ACTH and the high-dose dexamethasone suppression test. CT and MRI were used as localizing studies.

Surgical technique. All open posterior adrenalectomies were performed between 1991 and 1994. Patients were placed in the prone position with hyperflexion, and a hockey stick incision was made 6 to 8 cm from the spinous processes. The muscular layers were incised, and the twelfth rib was excised with careful identification and preservation of the twelfth intercostal nerve. Adrenal glands were dissected, starting from the upper pole. The main arterial branches and the adrenal vein were divided between clips. All bilateral procedures were performed, gland by gland, by the same surgical team.

Laparoscopic adrenalectomy was introduced in our hospital in 1994. In all patients, the transabdominal flank approach was used. Patients were placed in the lateral decubitus position with the operative side facing upward. Carbon dioxide insufflation was initiated directly in the subcostal area with the Veress needle. Three 10-mm trocars were used for the left and 4 for the right adrenal gland. The posterolateral ligaments of the spleen were incised, and the spleen was mobilized medially to expose the left adrenal gland. To expose the right gland, the triangular ligament of the right lobe of the liver was incised and
retracted in the cephalad direction
coagulation or the harmonic scalp
most of the dissection, and the ma
was divided between clips in both
were extracted in a sterile plastic ba
inal pressure was maintained at 15
and the tidal carbon dioxide was
tored and kept below 45 mm Hg.

Perioperative management. As so
nosis was confirmed and the
cation established, Ketoconazole, 6
Aminoglutetimide, 500 mg/day, was ad
period of 4 to 6 weeks to reduce the d
of cortisol overproduction.

High-dose glucocorticoid covera
used during and immediately after t
cedure. Our standard glucocortico
for surgery was one dose of 100 mg
at the beginning and a second dos
the operation. This dose was contin
a day during postoperative day 1 an
50 mg three times a day for 1 to 2
diet was tolerated. The patient's cl
guided the dosage of corticoid re
determined the time to initiate or
Typically, patients were dismissed fr
on a regimen of prednisone, 5 mg
or its equivalent of hydrocortisone
sone, 0.05 mg to 0.1 mg per day.
later, the dose of prednisone was d
7.5 mg or its equivalent of hydroco

Intraoperative features and in-hospital outcome of patients undergoing unilateral adrenalectomy

	Open (n = 6)	*Laparoscopic (n = 5)*	*P*
time* (hr)	2.5 (1.5-3)	3.5 (2-4)	NS
sfusions (n)	0	0	NS
e* (cm)	2 (1.3-3.5)	2 (1-4.7)	NS
right/left (n)	3/3	2/3	NS
tay* (days)	4 (3-5)	3 (3-6)	NS

median (range).

. Demographics of patients undergoing bilateral adrenalectomy

	Open (n = 12)	*Laparoscopic (n = 17)*	*P*
	32 (22-42)	27 (15-57)	NS
ale (n)	3/9	3/14	NS
s index* (kg/m^2)	25 (20-37)	28 (17-48)	NS
city* (%)	79 (42-108)	90 (64-105)	NS
%)	85 (42-105)	72 (61-114)	NS
e II/III (%)	81/9	64/26	NS
tive block (n)	12	17	NS

median (range).
d expiratory volume in one second.

tients undergoing bilateral adrenalectomy, ment is administered lifelong. In patients with unilateral resection, it was administr 6 to 12 months until the hypothalamic--adrenal axis recovered. Patients were d with respect to stress steroid coverage.

design and analysis. Patients were divided groups according to the extent of adrenalec- follows: *Unilateral adrenalectomy.* Six of the atients with a cortisol-producing adenoma ted with the open posterior approach and 5 roscopy. *Bilateral adrenalectomy.* Twelve of the nts with Cushing's hyperplasia were treated n posterior adrenalectomy and 17 with the opic approach.

al and pathological records of all patients iewed to analyze demography, diagnosis, details, operative time, need for transfu- ospital stay, and short- and long-term com- ns. Patients were interviewed at the latest p. A careful interrogatory and physical ation was performed to look for signs or ns of recurrence, the presence of Nelson ne, and abdominal wall complications relat- e surgical technique, such as chronic pain, ss, hernias, and muscular laxity.

ps were compared with the use of non- ric statistics (ie, the Fisher exact test and oxon rank sum test).

S

teral adrenalectomy. Patients in the open and laparoscopic adrenalectomy groups were comparable in terms of preoperative features. Demographic characteristics of the 11 patients with cortisol-producing adenomas are shown in Table I. All patients underwent a successful adrenalectomy, with no conversions in the laparoscopic group. Laparoscopic resection of a 5-cm right adenoma was accomplished in a patient who was 25 weeks pregnant, with an uneventful recovery. Intraoperative and postoperative details of the total group are presented in Table II. There was no operative mortality or morbidity in either group. In a mean follow-up of 56 and 20 months for the open and the laparoscopic groups, respectively, there were no complications related to the surgical procedure. There was a late death in the laparoscopic group. A 48-year old woman died 1.5 months postoperatively of an adrenal crisis caused by a severe gastrointestinal infection.

Bilateral adrenalectomy. General characteristics of the 29 patients undergoing open or laparoscopic adrenalectomy were highly comparable (Table III). Indications for surgical intervention are shown in the Figure. Nine of the 21 patients with pituitary tumors received radiotherapy before or after adrenalectomy. Intraoperative features and short-term outcome are presented in Table IV. There was one conversion from laparoscopy to open surgery because of inability to find the left gland in a morbidly obese patient. Right adrenalectomy was not attempted laparoscopically after conversion and was performed via the lateral open approach. This patient was excluded from the analysis of long-term

Table IV. Intraoperative features and in-hospital outcome of patients undergoing bilatera

	Open (n = 12)	*Laparoscopic (n = 17)*
Operative time* (hr)	4 (3-7)	6 (4-8)
Blood transfusions (n)	0	0
Gland weight (g)	10 (5-68)	10 (3-19)
Hospital stay* (d)	6 (3-61)	6 (3-17)

*Values are median (range).

Table V. Complications of patients undergoing bilateral adrenalectomy

	Open (n = 12)			*Laparoscopic (n = 17)*	
	Complication	*n*	*%*	*Complication*	*n*
Acute	Wound problems	2	16	Hypoglycemia	1
	Empyema	1	8		
Late	Back pain	1	8	Back pain	1

complications. In the laparoscopic group, there was an operative death not related to the surgical technique. A 33-year-old woman with severe recurrent Cushing's disease had a massive episode of gastrointestinal bleeding 17 days after the operation and died. An autopsy was not performed. In a mean follow-up of 60 and 27 months, respectively, for the open and the laparoscopic groups, two late deaths have been documented. One patient died 3 years postoperatively of sepsis related to a diabetic foot, and one patient had a pulmonary embolism 3 months postoperatively. No cases of clinical recurrence, muscular laxity, or numbness have been identified in either group. One patient in each group experiences episodic mild pain at the periphery of the surgical incision(s). Skin hyperpigmentation developed in a total of 12 patients, four patients in each group experimented chronic fatigue, and a single case of pituitary tumor enlargement has been detected on subsequent CT scans. Short-term and incision-related complications are shown in Table V.

DISCUSSION

Despite the multiple risk factors associated with cortisol overproduction, better understanding of adrenal pathophysiology and improvement in anesthesia, perioperative management, and surgical techniques have dramatically reduced morbidity and mortality rates associated with adrenal surgery in patients with Cushing's syndrome and disease over the years. In 1991, Priestly and colleagues[12] from the Mayo Clinic reported a 20% operative mortality rate in this group of patients. More recent studies from the United States and Europe involving open techniques have shown an operative mortality rate ranging from 0 to 9.6% and an overall morbidity below 15%.[1,8,13,14]

Since the introduction of lapa
ectomy in 1992,[15] many series have
this approach is safe, successful, and
its advantages for the resection of
and nonfunctioning adrenal corti
supported worldwide.[2-7]

The role of laparoscopic ad
been less extensively evaluated i
diseases: adrenal carcinoma, phe
and hypercortisolism. Patients wi
noma have occasionally been tre
cally. However, invasive adrenal ca
ter treated with open surgery
complexity of the operation requ
include en bloc resection of
regional lymph nodes, and adjace

Several reports have addressed
scopic adrenalectomy in the
pheochromocytomas. Although it
strated that it is feasible,[16,17] it has
nized that resection of pheochro
longer, especially when the tumors
is associated with a higher surgica
that it requires extensive laparosco

The third group of patients i
with Cushing's syndrome and dis
treatment for Cushing's disease is
adenomectomy. The success rate f
gical procedure exceeds 75%.[1,8] T
with this operation are more likel
resection of large pituitary tumors
when a small microadenoma cann
during surgery. Thus, depending
characteristics and the experience
team, a variable number of pa
transsphenoidal adenomectomy h
sequently require bilateral adrenal

s a role as initial therapy in patients
ole pituitary tumors, in patients with
ortisolism, and in patients with
production, when the site of the
own, or when it is metastatic or local-

endogenous hypercortisolism have
nly significant truncal obesity and
fat. Laparoscopic identification and
renal glands in this setting may be
ime consuming. Residual function-
ue after open total bilateral adrenal-
n recognized,[19] and it is also widely
all fragments of adrenal tissue may
ience function when transplanted.[20]
completeness of adrenal tissue
e safety of the procedure should be
ted in this group of patients.

tages of laparoscopic procedures
ction in convalescence time. Since
pain and diet tolerance were not
our study, similar results between
e anticipated. We found it valuable
paroscopic adrenalectomy is a safe
is high-risk group, that the conver-
y small, and that wound infection
are not particular problems. We
omplete gland resection can be
either technique since none of our
nical evidence of recurrence.

ative times have consistently been
ies comparing open against laparo-
res.[3-5] Operative times are in part
learning curve, but bilateral laparo-
ectomy entails two separate laparo-
res, and the time is increased by the
tion and prepare the patient after
first gland. The increased operative
her hand, does not seem to have a
act on the patient's recovery.

nospitalization in our patients is
most reported series. Many of our
ferred from outside, and we keep
ed until they are able to travel con-
ces back to their homes.

es in complications related to the
und in this study. A striking finding
nalyzing long-term outcome of pos-
nalectomy is the high percentage of
complaints. Buell and colleagues[14]
of the 21 patients who underwent
peritoneal bilateral adrenalectomy
ning's syndrome experience chronic
h was considered incapacitating in
l[3] found that 18% of the patients
who underwent adrenalectomy through the posterior approach at their institution had persistent dysesthesia and incisional pain several weeks postoperatively, and Thompson et al[4] reported a 54% incidence of incisional complications. In our open adrenalectomies, we have been obsessive in identifying and preserving the twelfth intercostal nerve, which we think has resulted in the fortunate absence of significant abdominal wall problems.

The retroperitoneal laparoscopic approach has been used in a limited number of patients.[6,21] The peritoneal cavity is not entered in this approach, which has the potential advantage of avoiding the disturbances associated with the pneumoperitoneum. The retroperitoneal approach also eliminates the need to reposition the patient between procedures on the two sides, which may reduce the intraoperative time. On the other hand, working space in the retroperitoneum is small, which makes the resection of large tumors less feasible. If bleeding occurs, it may obscure the view of the laparoscope, increasing the risk of conversion. This approach may also be more difficult in patients with Cushing's syndrome and disease who have large amounts of retroperitoneal fat. Takeda and coworkers[21] succeeded in only two of six ptients with Cushing's syndrome in whom the laparoscopic retroperitoneal approach was attempted, converting three to a laparoscopic flank approach and one to an open procedure.

Considering the consistently good results reported by others and ourselves with use of the flank approach, we believe that this should be the standard technique for adrenalectomy in patients with Cushing's syndrome and disease, although more experience with the retroperitoneal approach is needed to define its role. Continuous technologic improvements, such as the laparoscopic probe for intraoperative ultrasonography, may help in the identification of glands immersed in dense fatty tissue, facilitating their removal.

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DISCUSSION

Dr Dimitrios A. Linos (Kifisaia, Greece). The longer the operation time that you presented is just a matter of a learning curve. Secondly, you show the right adrenalectomy in the right lateral decubitus position. For right laparoscopic adrenalectoiny, you do not need that position. It is very easy just to lift the liver, a
where you want to be. So in cases of bila
tomy for Cushing's disease, you can use
tion, go first to the left side with the pat
al position so the bowel is away, then y
the bed, and you are ready to do the rig

Dr Norman W. Thompson (Ann Arbo
with your conclusions. However, I want
something that almost slipped by that I
before. Did you pre-treat all of your pa
conazole, in both your open and laparo

Dr Acosta. Yes, Dr Thompson, that is

Dr Thompson. Can I just comment
know whether all the audience knows t
is going to affect the contralateral no
well, and if you are effectively trying to
ma, you are killing some of the normal
cells. We know that all of these patients
be on replacement therapy and maybe i
are going to recover. Can you tell us h
before you wean your patients off steroi
ation? Do you think it is more prolong
that has been on ketaconazole com
patients in whom it has never been used

Dr Acosta. We don't have that data
from Europe and South America have a
of ketaconazole in preparation for surge
we have not evaluated their usefulness i
we feel that it improves tissue fragil
weight, which makes surgery easier,
laparoscopy.

Dr Thompson. I understand your t
and we use it frequently in patients wi
ease and the ectopic ACTH syndrome.
you and the audience that it could inj
eral normal adrenal, and you may n
these patients off steroids if used in pati
adenomas.

Dr W. Barry Inabnet (New York, NY
around the adrenal gland in Cushi
make identification of a Cushing adre
ficult and challenging, and I strongly a
laparoscopic ultrasonography. Was t
study and in the one conversion?

Dr Acosta. No, we have not had t
use it. The patient in whom we were u
adrenal was operated before we got
ultrasound

Dr Miguel F. Herrera (Tlalpan, Mex
mention that we use preoperative
mainly for bilateral adrenalectomies.
with adenomas in whom we have use
found any clinical impact on the time
tinue hormone replacement.