PAPER

Laparoscopic vs Open Adrenalectomy for the Treatment of Primary Hyperaldosteronism

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Hypothesis: That the clinical presentations, biochemical profiles, and surgical outcomes of patients treated with laparoscopic vs open adrenalectomy for primary hyperaldosteronism are different.

Design, Settings, Patients, and Interventions: The medical records of 80 patients with primary hyperaldosteronism who underwent open adrenalectomy between 1975 and 1986 or laparoscopic adrenalectomy between 1993 and 1998 at the University of California–San Francisco were reviewed by a single unblinded researcher (W.T.S.).

Main Outcome Measures: Severity of hypertension and hypokalemia at diagnosis, their improvement after adrenalectomy, and operative complications.

Results: Thirty-eight patients underwent open adrenalectomy and 42 patients underwent laparoscopic adrenalectomy. The patients who underwent open adrenalectomy had documented hypertension for a median of 5 years before surgery; all had diastolic blood pressures greater than 100 mm Hg. Laparoscopically treated patients had documented hypertension for a median of 2.5 years preoperatively, and 20 (48%) had diastolic blood pressures greater than 100 mm Hg. The median preoperative serum potassium levels for the open and laparoscopic groups were 2.6 mmol/L and 3.3 mmol/L, respectively; the mean serum aldosterone levels were 1.47 nmol/L and 1.30 nmol/L. Thirty-two (84%) of the 38 patients who underwent open surgery and 41 (98%) of the 42 patients treated laparoscopically had adrenal adenomas. The sensitivity of preoperative computed tomographic scanning for adenomas was 83% for the patients treated with open adrenalectomy and 93% for those treated laparoscopically. There were 4 postoperative complications in the open surgery group and none in the laparoscopic group. Postoperatively, 30 (81%) of 37 patients (excluding 1 patient who died of adrenocortical carcinoma) in the open surgery group and 37 (88%) of 42 patients treated laparoscopically were normotensive. Postoperative values were 3.6 to 5.0 of serum potassium per liter and 3.5 to 4.9 of serum potassium per liter in the open and laparoscopic groups, respectively.

Conclusions: Patients who are treated with laparoscopic adrenalectomy for primary hyperaldosteronism are being referred with less severe hypertension and hypokalemia than patients formerly treated with open adrenalectomy. Patients treated laparoscopically had fewer postoperative complications and were equally likely to improve in blood pressure and hypokalemia. Laparoscopic adrenalectomy has become the treatment of choice for patients with primary hyperaldosteronism because of lower morbidity.

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PRIMARY hyperaldosteronism is an uncommon but surgically correctable disease that affects approximately 1 in every 200 hypertensive patients.[1] First described by Jerome Conn in 1954, primary hyperaldosteronism is characterized by hypertension, hypokalemia, elevated plasma aldosterone, and low plasma renin activity. The most common underlying pathology for this syndrome is an aldosterone-producing adrenal adenoma. Primary hyperaldosteronism can also be caused by bilateral adrenal hyperplasia and other rarer diseases such as primary unilateral adrenal hyperplasia, glucocorticoid-responsive hyperaldosteronism, and adrenocortical carcinoma.

The surgical treatment of choice for primary hyperaldosteronism caused by an aldosterone-secreting adenoma is unilateral adrenalectomy.[2-10] Until recently, this operation required an open surgical procedure, usually through a posterior "Hugh-Young" incision. We have previously reported our experience with open adrenalectomy for the treatment of primary hyperaldosteronism in the 1970s and 1980s.[11] Since that time, however, several technological advancements have been made in the diagnosis and treatment of this condition. Improvements in the sensitivity of

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 80 patients who underwent adrenalectomy for primary hyperaldosteronism at University of California–San Francisco between 1975 and 1998. Open adrenalectomy was performed in 38 patients between 1975 and 1986. Thirty-four patients underwent unilateral open adrenalectomy, while 4 patients underwent bilateral open adrenal exploration with removal of 1 adrenal tumor. The patient profiles and results of operation from these 38 patients have been previously reported.[11] Laparoscopic adrenalectomy was performed in 42 patients between 1993 and 1998; all 42 patients underwent unilateral exploration and adrenalectomy.

Several biochemical and clinical parameters were measured in the preoperative evaluation of patients in this study. Serial blood pressure measurements were obtained, along with preoperative serum potassium levels, plasma aldosterone levels, and plasma renin activity. Plasma aldosterone levels were measured with the patient in the supine and upright positions, whenever possible. We also recorded the duration of documented preoperative hypertension. Preoperative localization of the aldosterone-secreting adenomas was done using CT scanning; 5-mm to 1-cm sections were used in 29 (76%) of the 38 patients treated with open adrenalectomy and 3-mm sections were used in all patients who underwent laparoscopic adrenalectomy. Other methods of localization included selective adrenal vein catheterization to measure the gradient of plasma aldosterone levels, iodocholesterol I 131 adrenal scintigraphy, and NP-59 (^{131}I-6β-iodomethyl-19-norcholesterol) scanning.

We also studied operative approach (posterior or lateral), complication rates, and tumor pathology. Postoperatively, we documented blood pressures and serum potassium levels as indications of cure. The duration of follow-up ranged from 6 months to 6 years for the patients who underwent open adrenalectomy and from 4 months to 3 years for the laparoscopically treated patients.

computed tomographic (CT) scanning have facilitated the imaging of the adrenal glands.[12,13] In addition, the introduction of laparoscopic adrenalectomy has dramatically altered the approach to surgical treatment of patients with primary hyperaldosteronism.

Within the past decade, laparoscopic adrenalectomy has become an increasingly popular surgical treatment for patients with primary hyperaldosteronism, Cushing syndrome, and pheochromocytoma.[4,5,7,9,10] Since 1993 we have performed more than 150 laparoscopic adrenalectomies, including 42 laparoscopic adrenalectomies for primary hyperaldosteronism. Few publications have compared the clinical profiles and outcomes of patients treated with laparoscopic vs open adrenalectomy for primary hyperaldosteronism. We therefore decided to analyze our experience with patients with primary hyperaldosteronism and to determine whether there were differences in demographics, biochemical and clinical presentations, and postoperative outcomes between patients treated with laparoscopic adrenalectomy and those treated with open adrenalectomy.

RESULTS

The 38 patients treated with open adrenalectomy included 6 men and 32 women, with a median age of 35 years. The 42 patients who underwent laparoscopic adrenalectomy included 29 men and 13 women, with a median age of 50 years. There were statistically significant differences in age ($P<.05$, t test) and sex ($P<.05$, χ^2 analysis) between the 2 groups. All patients had documented hypertension on serial blood pressure measurements. The median duration of documented hypertension was 5 years for the patients who underwent open adrenalectomy and 2.5 years for the laparoscopically treated patients. All of the patients treated with open adrenalectomy had a diastolic blood pressure of greater than 100 mm Hg without antihypertensive medications, whereas only 20 (48%) of the 42 patients treated laparoscopically had diastolic blood pressures of greater than 100 mm Hg with no medications.

Preoperative laboratory evaluation included serum potassium levels, plasma renin activity, and plasma aldosterone levels, usually measured with the patient in the supine and upright positions. The median serum potassium level was 2.6 mmol/L in the patients who underwent open adrenalectomy and 3.3 mmol/L in patients treated laparoscopically. There was a statistically significant difference in median serum potassium levels between the 2 groups ($P<.05$, t test). Spironolactone, potassium supplements and, occasionally, amiloride were used to correct preoperative hypokalemia. The mean plasma aldosterone level in patients who underwent open adrenalectomy was 1.47 nmol/L (reference range, <0.86 nmol/L); the mean plasma aldosterone level in laparoscopically treated patients was 1.33 nmol/L. There was no statistical difference in the mean plasma aldosterone levels in the 2 groups. Supine and upright plasma aldosterone levels were measured in 35 patients treated with open adrenalectomy; 34 (97%) exhibited abnormal postural responses (paradoxical decrease or minimal change) in serum aldosterone levels. Abnormal postural responses in plasma aldosterone levels were noted in 14 (93%) of 15 patients who were treated laparoscopically. Plasma renin activity was decreased in all 38 patients who underwent open adrenalectomy and in 39 (93%) of the 42 laparoscopically treated patients.

Preoperative imaging studies differed according to the period during which the operation was performed. The 38 patients treated with open adrenalectomy underwent CT scanning (29 patients), iodocholesterol I 131 adrenal scanning (16 patients), or selective adrenal vein catheterization (11 patients). Iodocholesterol I 131 scanning correctly identified the adenoma in 9 (56%) of 16 patients. Computed tomographic scanning correctly identified the adenoma in 22 (83%) of 29 patients. Selective venous catheterization was conclusive in 9 (82%) of 11 patients and inconclusive in the remaining 2 patients. All of the 42 patients who underwent laparoscopic adrenalectomy were studied with preoperative high-resolution CT scanning using 3-mm sections (as opposed to the 5-mm to 1-cm sections used in the CT scans of the open adrenalectomy patients). Computed tomographic scanning correctly

identified the adenoma in 39 (93%) of these 42 patients. Selective venous catheterization was performed in 2 patients who underwent laparoscopic adrenalectomy; both of these studies correctly localized the adenoma. Scanning with NP-59 was used in 1 patient treated with laparoscopic adrenalectomy and correctly identified the adenoma. Of note, none of the adrenal tumors were identified incidentally ("incidentaloma").

Of the 38 patients who underwent adrenalectomy via the open approach, 34 underwent unilateral exploration and adrenalectomy, while 4 patients underwent bilateral adrenal exploration and resection of one adrenal tumor. These 4 bilateral explorations were performed because of equivocal localizing studies, and all occurred between 1975 and 1977, which were the first years of our experience included in this study. The 42 laparoscopically treated patients all underwent unilateral exploration and adrenalectomy.

Twenty-eight (74%) of the patients treated with open adrenalectomy were operated on through a posterior approach, 6 (16%) underwent lateral exploration, and 4 (10%) underwent exploration bilaterally through an anterior approach. The 42 laparoscopically treated patients included 28 (67%) who underwent lateral transabdominal exploration and 14 (33%) who underwent posterior retroperitoneal exploration.

Of the 38 patients who underwent open exploration, 32 had aldosterone-secreting adenomas, 5 had bilateral adrenal hyperplasia, and 1 had adrenocortical carcinoma. The five patients with bilateral adrenal hyperplasia were all thought to have adenomas prior to operation; 2 had false-positive CT scans (showing adenomas that were not found in the pathologic specimen) and 3 had negative CT scans (showing no abnormalities). Two patients with hyperplasia achieved normalization of blood pressure following unilateral adrenalectomy. The 1 patient with adrenocortical carcinoma exhibited all of the preoperative biochemical and symptomatic criteria for an aldosterone-producing adrenal adenoma. He died of disseminated adrenocortical carcinoma 2 years after surgery.

Forty-one (98%) of the 42 patients who underwent laparoscopic adrenalectomy had histologically confirmed adenomas. The one exception in this group was a patient who had a preoperative CT scan that showed a 2-cm left adrenal adenoma and a possible smaller mass in the right adrenal gland. A laparoscopic unilateral left adrenalectomy was performed with removal of a 2-cm adenoma within a hyperplastic cortex; however, the patient continued to be hypokalemic and hypertensive following operation. In retrospect, we found that this patient had bilateral adrenal hyperplasia and a nonfunctioning left adrenal adenoma that could have been diagnosed if a preoperative selective venous catheterization had been performed based on the CT scan showing possible bilateral abnormalities.

Postoperative complications occurred in 4 (11%) of the 38 patients who underwent open adrenal exploration and adrenalectomy. Two patients developed postoperative hypotension and anemia; they required vigorous fluid replacement but no transfusions. Two other patients developed postoperative persistent acidosis and hyperkalemia due to mineralocorticoid deficiency. As mentioned, 1 patient with adrenocortical carcinoma died 2 years after the adrenalectomy. No postoperative complications occurred in the patients who underwent laparoscopic adrenalectomy; the difference in postoperative complication rates between the 2 groups was statistically significant ($P<.05$, Fisher exact test).

Postoperatively, 30 (81%) of the 37 patients who underwent open adrenalectomy for benign disease became normotensive and no longer required postoperative blood pressure medications. Thirty-seven (88%) of the 42 laparoscopically treated patients became normotensive and did not require medications postoperatively. The postoperative serum potassium levels ranged from 3.6 to 5.0 mmol/L in the open adrenalectomy group and from 3.5 to 4.9 mmol/L in the laparoscopic adrenalectomy group. The differences in postoperative blood pressures and serum potassium values were not statistically significant.

COMMENT

The results of this retrospective review document that laparoscopic adrenalectomy is a safe and effective treatment for primary hyperaldosteronism. Laparoscopically treated patients had fewer postoperative complications and were equally likely to improve in blood pressure and hypokalemia when compared with patients treated with open adrenalectomy. Additional benefits of laparoscopic adrenalectomy that were not addressed in this study include smaller incisions, decreased postoperative pain, and shorter hospitalizations, as reported by others.[4,5,7,9,10] All of these factors have contributed to the increasing popularity of laparoscopic adrenalectomy for the treatment of patients with primary hyperaldosteronism and, in many medical centers (including our own), the laparoscopic technique has replaced open surgery as the treatment of choice for this condition and other benign adrenal gland tumors.

Besides providing information regarding the safety and efficacy of laparoscopic vs open adrenalectomy for primary hyperaldosteronism, this study also allows us to comment on changes that have occurred during the past decade in both the diagnosis and clinical presentation at the time of referral of patients with this disease. All of the patients in this study who underwent laparoscopic adrenalectomy were operated on after 1993, whereas patients who were treated with open adrenalectomy underwent surgery between 1975 and 1986. An important technological advancement during the past decade has been the improvement of CT scanning. All patients treated laparoscopically were studied with high-resolution CT scanning (3-mm sections), with an overall sensitivity of 93%. In contrast, the patients treated with open adrenalectomy underwent CT scanning (5-mm to 1-cm sections) or other imaging studies, including iodocholesterol I 131 adrenal scanning and selective adrenal vein catheterization; the sensitivity of CT scanning in this group was 83%. When used in conjunction with the appropriate laboratory tests, high-resolution CT scanning has helped endocrinologists and surgeons to differentiate more accurately between an adrenal adenoma and bilateral adrenal hyperplasia. This observation is supported by the fact that 32 of 38 patients in the open adrenalectomy group and 41 of 42 laparoscopically treated patients were correctly identified preoperatively as having adrenal adenomas; the differentiation between adenoma and

hyperplasia in patients with primary hyperaldosteronism is crucial because patients with adenomas are almost always responsive to surgery while those with hyperplasia are best managed medically.[1,13,14]

There were statistically significant differences in the demographic and clinical profiles of patients between the laparoscopic and open groups. Patients who underwent laparoscopic adrenalectomy were older and had been hypertensive for a shorter period of time than patients who were treated with open surgery; in addition, there were more men than women in the laparoscopic group (29 men, 13 women), while the opposite was true in the open surgery group (6 men, 32 women). These differences between the 2 groups lead us to believe that we are currently operating on a different population of patients with primary hyperaldosteronism than we were in previous decades. We offer 2 reasons for this change in patient populations. First, improvements in CT scanning have resulted in the earlier detection of aldosterone-secreting adenomas and have therefore facilitated the diagnosis of patients with less severe disease, including patients whose tumors may have been missed in the decades prior to improved CT scanning. Second, it is possible that the introduction of laparoscopic adrenalectomy has altered the referral patterns of primary care physicians and endocrinologists; these physicians may be referring older patients and patients with less severe disease for surgical treatment because they perceive the laparoscopic procedure to be less invasive and therefore having less morbidity for patients.

In conclusion, the improved sensitivity of CT scanning during the laparoscopic era has improved the diagnosis and localization of adrenal adenomas in patients with primary hyperaldosteronism. Patients who underwent laparoscopic adrenalectomy for primary hyperaldosteronism had less severe hypertension and hypokalemia than patients treated with open adrenalectomy. In addition, patients treated laparoscopically suffered fewer postoperative complications and were equally likely to improve in blood pressure and hypokalemia. As reported in other series, laparoscopic adrenalectomy causes less pain than open adrenalectomy and usually requires only an overnight hospital admission. It has therefore become the procedure of choice for the treatment of patients with primary hyperaldosteronism caused by an aldosterone-secreting adenoma.

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DISCUSSION

Richard A. Prinz, MD, Chicago, Ill: I want to compliment the San Francisco group for continuing to unfold the story of the surgical management of primary hyperaldosteronism for us. This problem, when due to a small, benign unilateral adenoma, is ideally suited for laparoscopic management. The hypertension that these patients have can be reversed with minimal morbidity and risk from the operation. The authors have confirmed the safety and efficacy of the laparoscopic approach in comparison with open adrenalectomy. I was struck by the patient demographic differences in their 2 groups.

First, it seems that the 38 open operations were accumulated during an 11-year period from 1975 to 1986. The laparoscopic patients have all been treated in the last 5 to 6 years. I wonder why there is this hiatus in between the 2 groups? Are you reporting all of the patients treated with primary hyperaldosteronism by the surgeons at UCSF? Clearly, you are seeing more patients now. I think you would have access to your referral sources to tell us if these have widened to explain the increased number of patients? Do you think that, much like laparoscopic cholecystectomy, there has been a loosening of indications for this operation in patients with suspected hyperaldosteronism? The gender and age of the 2 groups are significantly different, with the laparoscopic patients being much older and more commonly male. Is this actually the same disease that you are seeing? It is hard to explain such a change in gender and age characteristics. You would think that you would be diagnosing patients at an earlier age today, rather than a later age.

I would like to touch on your preoperative evaluation. Three of your laparoscopic adrenalectomy patients did not have suppressed plasma renin activity. This is supposed to be one of the hallmarks of this disease. I would like to know, what was the outcome in these 3 patients? Was one of these the patient that you noted as having hyperplasia? More importantly, what is your laboratory criteria for diagnosis of primary hyperaldosteronism? Computed tomographic scanning was used throughout the study. More recently with the laparoscopic patients, 3-mm cuts were used to identify the tumor, and you did so in 39 of the 42 laparoscopically treated patients.

I would ask about the use of NP-59 scanning and selective venous catheterization and how you use these studies in your current practice. Keeping in mind that as many as 2% of

patients undergoing CT scanning will have an incidental adrenal nodule identified, do you use these functional localizing studies to rule out an incidental adrenocortical nodule and do you think that the patient who remained hypokalemic and hypertensive after your unilateral laparoscopic adrenalectomy actually had an incidental adrenal cortical adenoma that you initially removed? Both the lateral and posterior retroperitoneal approaches were used in two thirds and one third of the laparoscopically treated patients, respectively. I know a subsequent paper will deal with this issue, but can you comment on the specific advantages of each approach for primary hyperaldosteronism? I would also like to ask you why your follow-up is short for the open adrenalectomy patients. This group offers a unique opportunity for studying the long-term outcome in primary hyperaldosteronism, and I think it would be important for you to share that with us.

Norman Thompson, MD, Ann Arbor, Mich: Mr Shen mentioned that the first patient with an aldosteronoma was operated on at the University of Michigan. I think I am the only person in this room who actually helped to take care of that patient. That was 44 years ago when I was a medical student. She had one of the complications that you mentioned, anemia. However, her anemia was due to the fact that she was in the hospital for 6 months preoperatively and 1 month postoperatively and had blood drawn every day. That was before we had HMOs. Her exploration occurred on December 14, 1954. Jerry Conn was in attendance with William Baum, the urologist who explored her. He was the most junior attending surgeon on the urology service. Reed Nesbitt, who was chief, was not very enthusiastic at that time in this new entity that was proposed by Jerry Conn. The operation proposed was a bilateral adrenalectomy because hyperplasia was the suspected diagnosis. No one had ever described an aldosterone-secreting adenoma before. On exploration, a 4-cm tumor was found in the right adrenal and removed. The first paper on aldosteronism was published 2 months later, almost record time. It was part of Jerry Conn's presidential address to the Society of Clinical Investigation given in October 1954 but included an addendum about this first patient and operation. Looking into the reason for that, the *Journal of Laboratory and Clinical Medicine* was edited by William Robinson, who was chairman of the Department of Internal Medicine at the University of Michigan. With that background, I would like to make a few comments about this particular paper. It is very surprising that you found so many males when in most series 3 of 4 are females. It makes me wonder whether in the era before laparoscopic surgery, males were afraid to be operated on. Could that be the explanation?

The other point is related to early diagnosis. Again, it is hard to understand that patients with a mean age of 50 years compared with those with a mean age of 35 years would suggest earlier diagnosis. There is some discrepancy. You make note that diagnosis of an adenoma was established or suspected by CT scanning. Fortunately, you did point out that CT scanning might detect an incidentaloma rather than an aldosteronoma. I would warn everyone that one can be misled to remove an incidentaloma on the side opposite a small adenoma. Subsequently you could end up with a bilateral adrenalectomy, which would be a real tragedy. We have emphasized the use of NP-59 scintiscanning which, incidentally, was also developed at the University of Michigan. We do that in every patient because we do not want to take out an adrenal that may not have the small adenoma. About 10% of patients have adenomas that are too small to be detected even by either the type of CT you are using or NP-59 scans. In those cases, I think there is a place for selective venous sampling. Dr Clark, tell us what you actually do. Are you taking a risk in not obtaining substantiating localization studies in patients who could have incidentalomas?

Steven DeJong, MD, Maywood, Ill: I have 2 brief questions. Could you give us some information about operative time and pain medication required in your patients as this experience is evolving into the operation of choice or the route of choice for treating patients with surgical hypertension from excess aldosterone production.

Did you use any other technology, such as intra-abdominal laparoscopic ultrasonography, when operating on these patients? Was it helpful? These are relatively small tumors compared with some of the other adrenal tumors that we deal with and some have reported that this technology might be helpful.

Dr Clark: One weakness of our study is that we compared our laparoscopically treated patients with patients who had previously been treated by open adrenalectomy at our medical center and were previously reported by Dr Robert Lim. This difference certainly contributed to the variation in patient profiles in the 2 groups. The short-term follow-up in our open group was because no one has done a long-term outlook study in these patients. During the period we did open adrenalectomies, it was more difficult to make the diagnosis of primary hyperaldosteronism as assays for aldosterone and renin were not as accurate as they are today and localization tests were not as sensitive. Thus, for almost all of our initial (open) group of patients, a referring endocrinologist would send his patients to another endocrinologist at UCSF who specialized in adrenal tumors and hypertension.

Dr Prinz asked if there is a loosening of indications for laparoscopic adrenalectomy similar to that observed for cholecystectomy, and the answer we believe is yes. He also asked why the change in demographics? We are not sure. In the laparoscopic group, 9 operations were done at the VA Medical Center in San Francisco, but this would not completely account for the predominance of men in our laparoscopic group since most endocrine diseases are more common in women. Has the disease changed? I do not think so. We make the diagnosis the same way it was done previously, that is, by documenting an increased aldosterone level in a patient with a low renin level. More postural studies were done in our open group. In patients with an adrenocortical adenoma the aldosterone levels would paradoxically fall or fail to increase with standing whereas in normal patients and in those with hyperplasia, the aldosterone levels usually increased with standing.

Dr Thompson asked a very important question regarding the possibility of an adrenal "incidentaloma" in patients with primary hyperaldosteronism. This is a real possibility since adrenal incidentalomas occur in about 1.5% of the population. For example, a patient with primary hyperaldosteronism could have a coexisting nonfunctioning adrenocortical adenoma. Our one failure in our laparoscopic group might have been prevented if we had done postural studies or adrenal vein catheterization studies for aldosterone and cortical levels preoperatively. I would strongly recommend that such studies be done for any patient when hyperplasia (bilateral disease) is a possibility. Scanning with NP-59 might also be useful in such patients as suggested by Dr Norman Thompson, but we have limited experience with this study.

In this retrospective study, we did not compare duration of hospitalization, postoperative pain, or time taken to return to work. These data have been reported by others and after laparoscopic adrenalectomy, patients can be hospitalized for a shorter time, experience less pain, and return to work sooner. However, after an open Hugh-Young (posterior) approach, most patients could also go home within 24 hours.

Dr DeJong, our duration of operation was initially about 3 hours, but now takes less time. These procedures are done with our surgical residents and most have been directed by Dr Siperstein and Dr Duh. Intraoperative ultrasound is quite useful, especially in some of the heavier patients. Most adrenocortical adenomas that cause primary hyperaldosteronism are small (<2-cm) tumors. Intraoperative ultrasound certainly helps identify these tumors.