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Parathyroid Adenomectomy under Local Anesthesia with Intra-Operative Monitoring of UcAMP and/or 1-84 PTH

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Because 80% of patients with primary hyperparathyroidism have a single adenoma and because most adenomas are now visualized by ultrasonography, we have attempted to remove these suspected single adenomas under local anesthesia with intra-operative monitoring of urinary cAMP (UcAMP) and 1-84 parathyroid hormone (PTH) serum levels. In the last 2 years, 45 patients (mean age 65 years) with primary hyperparathyroidism underwent surgery with local anesthesia when a single adenoma was strongly suspected by ultrasonography. Patients with equivocal or misleading ultrasonography, e.g., those with associated thyroid or multiglandular pathology and those who were non-cooperative, were excluded from this procedure. UcAMP and 1-84 PTH were determined prior to the incision, at the time of removal of the adenoma, and at regular intervals until 120 minutes after the operation. Results were available 45 min to 60 min after sampling for PTH and 60 min to 80 min for UcAMP. Forty-two adenomas were removed through a 2 cm to 3 cm skin incision in a mean time of 25 minutes, with no adverse effect, no morbidity, and minimal discomfort. The 42 patients were normocalcaemic on follow-up. The monitorings always predicted the success of the operation. In the 3 remaining patients, because the monitorings remained elevated at the end of the procedure, the patients underwent classical bilateral neck dissection under general anesthesia. This new approach can be safely accomplished with short operative time and hospital stay. The absence of general anesthesia is reassuring for the patients who are reluctant to undergo general anesthesia. The intra-operative monitoring which predicts the cure of primary hyperparathyroidism with high accuracy allows the surgeon to conclude the operation with confidence.

Primary hyperparathyroidism (PHP) is a frequent disease, being identified more and more often in the course of routine health examinations. Its treatment is surgery, although in asymptomatic forms and in older patients this therapy is debated [1, 2]. The operation is usually performed under general anesthesia and requires a bilateral cervical dissection to identify all of the parathyroid glands [3–5]. Five years ago, we successfully treated an elderly woman under local anesthesia, who had been affected by a symptomatic hyperparathyroidism associated with cardiac disease and respiratory insufficiency. Others authors [6, 8] have also incidentally performed a unilateral neck approach, sometimes even with loco-regional anesthesia [9], and succeeded in curing the hypercalcemia.

We considered the question of limited surgical access under local anaesthesia. In favor of this procedure were the following arguments: first, approximately 85% of patients with PHP have a single enlarged parathyroid gland [10]; second, an experienced radiologist using ultrasonography can find the adenoma in 80% of patients [11]; third, intra-operative measurements of urinary cyclic AMP (UcAMP) [12–15] and intact parathyroid hormone (PTH) [16–20] are efficient methods to monitor the success of the operation. The aim of this study was to evaluate the results of minimal surgical therapy under local anesthesia.

Patients and Methods

Forty-five patients with PHP underwent a unilateral minimal cervical exploration under local anesthesia in our center from July, 1989 to July, 1991. There were 36 female patients and 9 male patients with a mean age of 65 years (range 35 years to 80 years). The diagnosis of PHP was based on an elevated serum calcium concentration (normal < 2.6 mmol/l) associated in the majority of the cases with an elevated concentration of intact PTH. Pre-operative localization studies were performed on all patients, and included 10 mHz real time ultrasonography (n = 45) and thallium-technetium scanning (n = 10).

Indications and Contraindications for Exploration under Local Anesthesia

The primary indication for local anesthesia is the high probability of finding a single adenoma in the neck area when pre-operative localization studies strongly suggest this diagnosis. Excluded from this procedure were: a) patients who had an equivocal or suspicious history of a familial endocrine disorder (multiple endocrine neoplasia); b) patients whose pre-operative radiologic examinations were equivocal, misleading or noncordant; c) patients with associated multinodular goiter or solitary thyroid nodules, although a solitary associated ipsilateral thyroid nodule might not exclude this procedure; and d) patients who suffer from anxiety, deafness, allergy to local

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anesthesia, or who are uncooperative. Consequently during the study period, 67 patients underwent classical bilateral neck dissection under general anesthesia.

Operative Procedure

The patient is sedated with hydroxyzine 100 mg orally, approximately 30 minutes before scheduled surgery. The patient is positioned in the same manner as for thyroid surgery, and operative installation of fields allow, if necessary, immediate general anesthesia with tracheal intubation and cervical skin incision. After infiltrating the subcutaneous tissue and the skin with 10 ml Xylocaine 1% (lidocaine hydrochloride), a 2.5 cm to 3.5 cm unilateral, transverse, or oblique skin incision is made. After infiltrating the platysma and strap muscles with Xylocaine, these structures are incised transversally with electrocoagulation of the small vessels. After division of the unilateral strap muscles, the ipsilateral thyroid lobe is elevated and reclined. Xylocaine is again injected in cellular fatty tissue surrounding the thyroid. After meticulous dissection of the fatty tissue and careful hemostasis, most large adenomas are easily identified because of their yellow or reddish brown color. They are dissected with special care to the recurrent laryngeal nerve because the nerve can sometimes be embedded in the capsule of the adenoma, particularly in superior adenomas. The adenoma is removed after ligation or insertion of a small clip on its pedicle. After removal of the adenoma, we identify the second ipsilateral gland (presumed normal) without insisting or prolonging the operation for this search. Then, the incision is closed and results of the UcAMP and/or 1-84 PTH monitoring are awaited while the patient is brought to the recovery area.

Intra-operative UcAMP and 1-84 PTH Monitoring

Urine was collected prior to the incision, at the removal of the adenoma, and 30 min, 60 min, 90 min, and 120 min after the removal of the adenoma for UcAMP determinations. This measurement is expressed as previously described [5, 13] with a ratio R = UcAMP/urinary creatinine (normal R is < 0.47). UcAMP was measured with a radioimmunoassay modified by our laboratory (Cyclic AMP RIA Kit, Immunotech S.A., Marseille, France) and results were obtained 60 min to 80 min after sampling. All patients had normal renal function (serum creatinine < 100 μmol/l). This monitoring was used in 35 patients.

Serum intact PTH measurement was used with 25 patients, 15 of whom also had measurement of UcAMP. Thus intact PTH was the sole measurement in 10 patients. Sample collections were taken prior to the incision and from 5 min to 90 min after excision of the adenoma. Using our modifications of this assay the results were available 45 min to 60 min later, quicker than the results of cAMP. 1-84 PTH was measured with an IRMA test (Allegro Intact 1-84 PTH, BYK, Evry, France) using our modifications of this assay. The lower limit of detection was 5 ng/ml which was the undetectable assigned value and our reference value calculated on 57 healthy subjects, ranged from 10 ng/ml to 62 ng/ml.

Histopathologic Diagnosis

The histopathologic diagnosis was based on the weight and histologic features of the excised glands (cellular arrangement, adenoma criteria, ocular estimation of the relative amount of fat cells) and the size and appearance of the other ipsilateral gland left *in situ* if it was identified.

Follow-up

The outcome of surgery was evaluated for all patients by several calcium determinations in the post-operative period and 1 month to 12 months later.

Results

The surgical procedure was successful in 42 of the 45 patients with no adverse effect or reaction related to local anesthesia and with a minimal discomfort in few patients. None of these 45 patients suffered a recurrent nerve paralysis. Operative time ranged from 15 min to 55 min (mean 25 min). All 42 patients had an adenoma, 22 adenomas were on the right side and 20 adenomas were on the left side. The average size of the adenoma was 1.5 cm (range 1 cm to 2.4 cm). Sixteen were superior adenomas, 26 were inferior adenomas.

All of these patients were normocalcemic or hypocalcemic in the postoperative period and in follow-up studies ranging from 2 months to 24 months. All of the 42 patients were discharged the day following the operation. In all of these 42 patients, the cure of the PHP was predicted close to the end of the surgical procedure by the monitoring of UcAMP (i.e., R) and/or 1-84 PTH. Thirty-one of 35 patients for whom UcAMP monitoring was used had a high initial value of R. Normalization of R occured 60 min to 90 min after adenomectomy (Fig. 1).

The mean R value in these 31 patients was compared to the R value of the control group which was always < 0.5. As the 4 other patients had a normal R ratio at the beginning of the operation, the method was unable to predict their successful outcome. However those 4 patients were successfully monitored by 1-84 PTH.

The variation of the serum level of 1-84 PTH for the 22 successfully treated patients is indicated in Figure 2. In all but one of these 22 patients, intact PTH was above the normal level prior to the beginning of the operation. The PTH level often rose at the beginning of the operation, and dropped to the normal range from 15 min to 30 min after adenomectomy. The mean value of the 1-84 PTH in these 22 patients was below the normal range 15 min after adenomectomy (Fig. 2).

In the 3 remaining patients R values and 1-84 PTH remained elevated after the removal of the presumably single adenoma. One patient underwent an immediate bilateral neck exploration under general anesthesia and was found to have a chief cell hyperplasia of all 4 glands. A subtotal resection was performed and normalized R and PTH levels (Fig. 3). The second patient refused immediate general anesthesia and large cervicotomy and remained hypercalcaemic after excision of 1 adenoma. Six months later she underwent repeat surgery and a second contralateral adenoma previously unseen by ultrasonography was discovered and treated successfully. The third patient underwent immediate general anesthesia and large cervicotomy. Frozen section examinations of the gland removed under local anesthesia did not demonstrate any abnormalities. Two other parathyroid glands were checked and were normal. The fourth gland was not found and the patient remained hypercal-

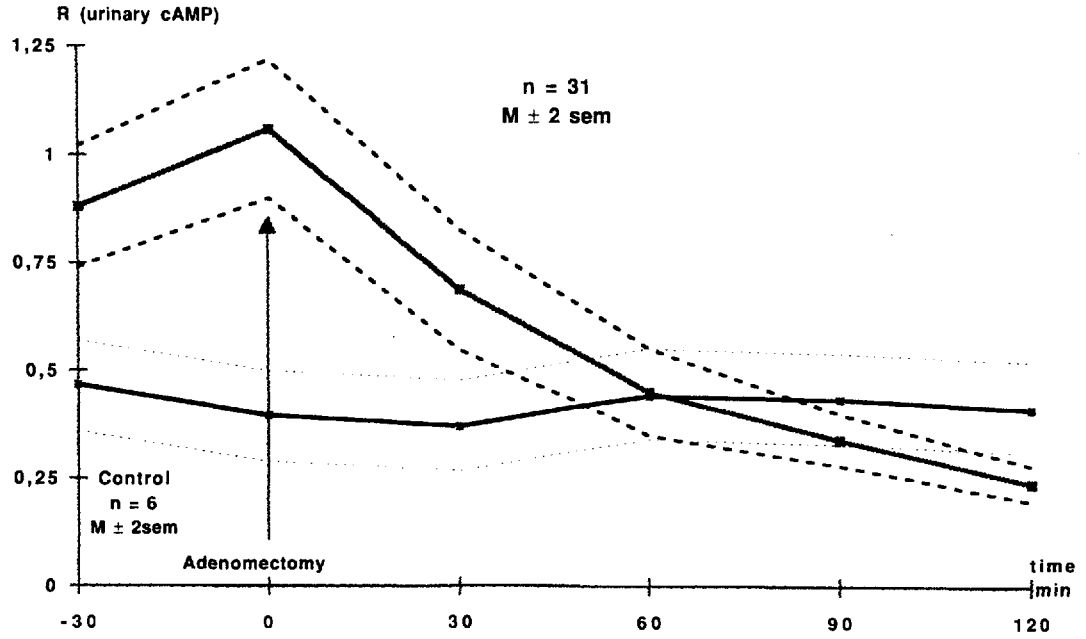

Fig. 1. Intra-operative values of R before and after successful parathyroidectomy. The results are mean ± 2 standard errors of the mean.

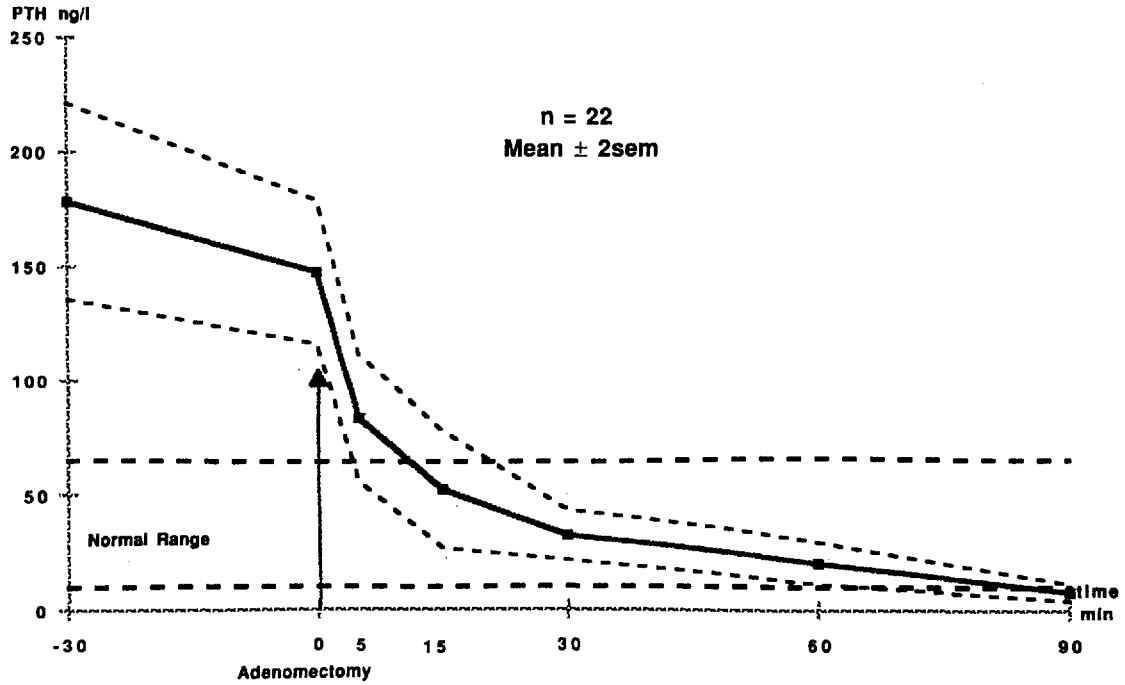

Fig. 2. Intra-operative values of serum 1-84 PTH before and after successful adenomectomy. During dissection of the adenoma, PTH levels peaked. After removal of the adenoma, levels fell to normal value.

cemic on follow-up. In this case it was an error of indication of local surgical access and a failure of large cervicotomy.

Discussion

The incidence of PHP is increasing, particularly in older patients because the serum calcium level is today more routinely determined in health examinations than in the past. Consequently, most patients have asymptomatic disease or nonspecific equivocal symptoms like fatigue and weakness. Because many patients have only vague symptoms and are over 70 years old, sometimes with associated cardiac or pulmonary disease, they or their clinicians [1, 2, 21, 22] are reluctant to use general anesthesia, surgery, and the classical large neck exploration. Consequently, they advocate nonsurgical treatment. Many patients are understandably afraid of surgery and especially of general anesthesia and it may be difficult to convince them to undergo surgery when they are asymptomatic or when

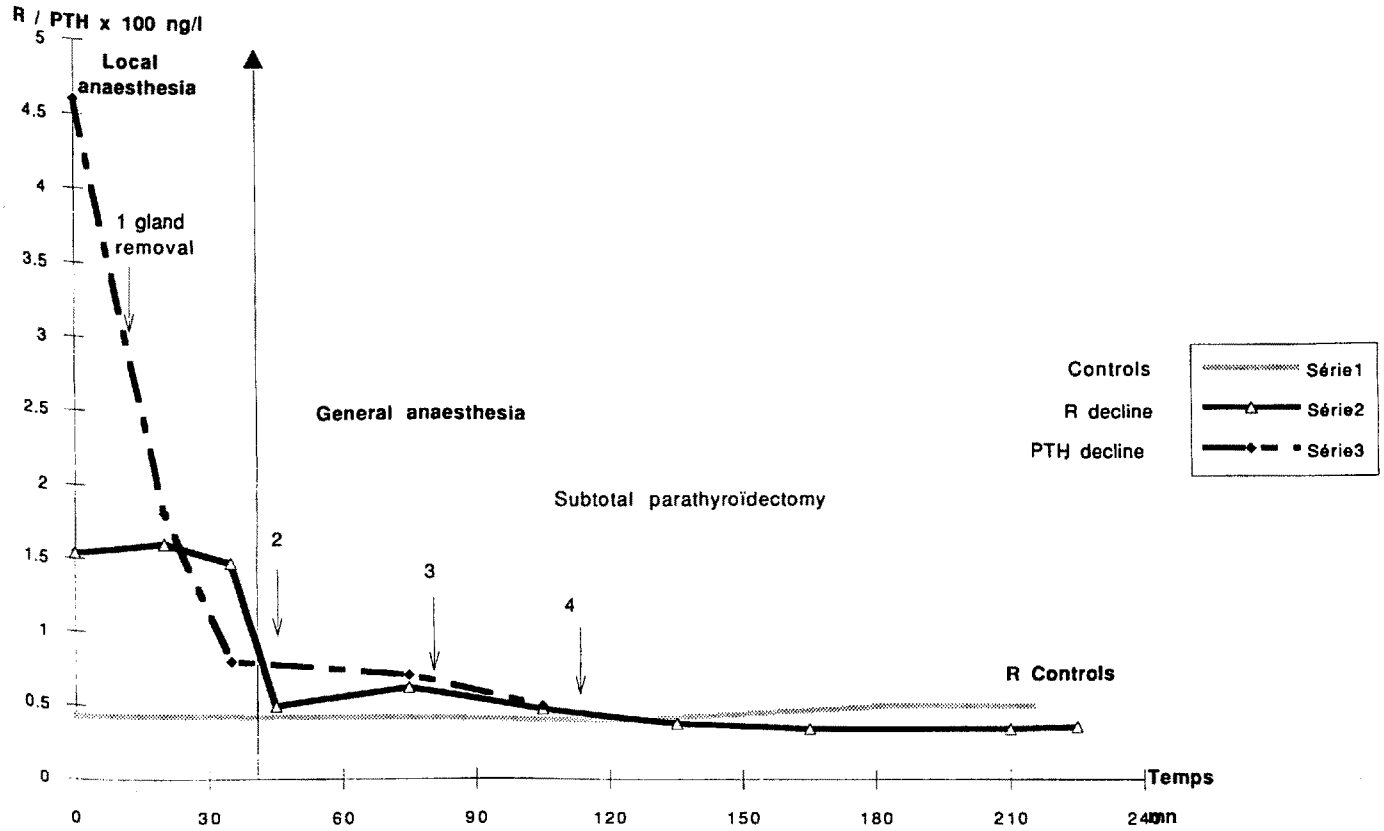

Fig. 3. Example of a patient with parathyroid hyperplasia. After the first gland was removed under local anesthesia, values of R and PTH remained elevated. Values returned to normal after subtotal parathyroidectomy under general anesthesia.

they have mild disease. We have adopted a new approach to the surgical treatment of PHP which involves the removal of a parathyroid adenoma under local anesthesia. We have previously used this method, like others [9] have used locoregional anesthesia, in exceptional cases such as poor-risk patients with major contraindications to general anesthesia. This new policy of minimal approach is supported by the following arguments: First, in about 80% to 90% of patients the PHP is associated with a single adenoma and removal of this sole pathologic gland is sufficient to achieve the cure of the illness. The identification of all parathyroid glands may be questionable and sometimes excessive resection or biopsy from normal glands may be detrimental and may increase recurrent laryngeal nerve morbidity and/or hypoparathyroidism [23]. Moreover, even experienced parathyroid surgeons do not always identify all parathyroid glands in all patients.

Second, today pre-operative localization studies, thallium-technetium scanning, magnetic resonance imaging, or computed tomography scanning are excellent for identifying solitary parathyroid neoplasms that are >1 cm in size. Experienced radiologists identified parathyroid neoplasms in about 75% to 80% of the cases [11, 24–26]. When two tests are used, about 90% of the parathyroid adenomas are identified [25].

Third, intra-operative monitoring of UcAMP [13–15] and/or 1-84 PTH [16–19] predict with high accuracy, after parathyroidectomy, whether all pathologic parathyroid tissue has been removed and whether the operation can be ended. In our experience 1-84 PTH monitoring appears to be an easier procedure (absence of bladder catheter, lower number of samples) and gives faster results. Because of the short half-life of 1-84 PTH, not exceeding a few minutes, serum PTH values return to the normal range within 10 min to 30 min after successful parathyroidectomy [16, 17]. However the monitoring of the 1-84 PTH is questionable on two points. The first is the significance of the 1-84 PTH value, because it is related to the degree of the coefficient of variation which could affect the results in cases where 1-84 PTH values are near the normal range. This is largely dependent on the time of incubation. With a time of incubation of 30 min, this coefficient is about 10% in our laboratory. In this eventuality it is important to consider the drop of intact PTH after adenomectomy and the percentage of variation between the beginning and the end of the operation. The second question is the way of expressing the results. We have chosen to consider the change of the value of 1-84 PTH expressed in nanograms per liter rather than the percentage of the fall between the initial measurement and the lower level after adenomectomy (Fig. 2).

Finally, parathyroid adenomectomy under limited surgical access and local anesthesia resulted in the cure of patient having a single adenoma previously found by ultrasonography in 95% of the cases. The operation is fast, very well tolerated, and without morbidity. The length of hospitalization is reduced, and this procedure could probably be performed as an ambulatory surgery. In the eventuality of no biological normalization of intact PTH, an immediate or delayed complete neck exploration under general anesthesia must be performed. The fact

that very few cases of PHP are difficult surgical challenges is not a good reason to refuse, in the majority of the patients, to perform a procedure simpler than a large cervicotomy. However, the limited surgical approach must be performed by an experienced endocrine surgeon.

Résumé

Puisque 80% des hyperparathyroïdies primaires sont dues à un adénome solitaire, et puisqu'il est actuellement possible de bien visualiser les parathyroïdes par échographie, nous avons essayé d'opérer sous anesthésie locale en dosant la concentration urinaire d'AMPc (UAMPc) et de PTH 1-84 dans le sérum pendant l'intervention. Dans les deux dernières années, 45 patients (âge moyen 65 ans) ayant une hyperparathyroïdie primaire ont été opérés sous anesthésie locale car l'échographie laissait soupçonner l'existence d'un adénome solitaire. Les critères d'exclusion étaient l'absence d'échographie formelle ou typique, la notion de pathologie multiendocrininne gandulaire (dont l'association à une pathologie thyroïdienne) et la mauvaise coopération des patients. Les dosages de l'U AMPc et la PTH 1-84 étaient déterminés avant l'incision, au moment de l'exérèse de l'adénome et à intervalles réguliers jusqu'à 120 minutes après l'opération. Les résultats étaient disponibles en 45 à 60 minutes en ce qui concerne la PTH, et en 60 à 80 minutes pour l'U AMPc. Quarante-deux adénomes ont été enlevés ainsi par une incision de 2–3 cm. La durée de l'intervention était de 25 minutes; il n'y a eu aucun effet secondaire, pas de morbidité et l'inconfort a été minimal. Les 42 patients ont tous été normocalcémiques. Le monitorage a toujours prédit le succès de l'opération. Chez les trois autres patients, les valeurs de calcémie sont restées élevées en fin d'intervention et ces patients ont été opérés sous anesthésie générale avec une dissection cervicale classique. Cette nouvelle approche est compatible avec un temps d'intervention et d'hospitalistaion courts. L'absence d'anesthésie générale présente un attrait certain pour le malade qui y est réticent. Le monitorage peropératoire qui prédit la cure d'hyperparathyroïdie avec une grande précision permet au chirurgien de terminer l'intervention en toute confiance.

Resumen

Teniendo en cuenta que 80% de los casos de hiperparatiroidismo primario se deben a un adenoma único, y puesto que actualmente la mayoría de los adenomas pueden ser visulizados con ultrasonografía, hemos intentado resecar posibles adenomas únicos bajo anestesia local con monitoría intraoperatoria de la AMPc urinaria y de los niveles séricos de PTH 1-84. En los últimos dos años hemos operado 45 pacientes (65 años de edad en promedio) con hiperparatiroidismo primario bajo anestesia local y la demostración ultrasonográfica de un muy posible adenoma único. Se excluyeron de la serie los pacientes con ultrasonografía equívoca, así como los casos asociados con patología tiroidea o enfermedad multiglandular y los pacientes poco cooperadores. Se hizo la determinación de UcAMP (AMP urinaria cíclica) y de 1-84 PTH antes de efectuar la incisión, en el momento de la remoción del adenoma y a intervalos regulares hasta 120 minutos luego de terminada la operación. Los resultados estuvieron disponibles a los 45 a 60 minutos de la toma de la muestra para PTH y a los 60 a 80 minutos para la UcAMP. Se resecaron 42 adenomas a través de una incisión de 2–3 centímetros en un tiempo promedio de 25 minutos, sin efectos adversos, sin morbilidad y con mínima incomodidad para el paciente. Los 42 pacientes aparecieron mormocalcémicos en el seguimiento postoperatorio. La monitoría intraoperatoria predijo regularmente el éxito de la operación. Los tres pacientes restantes, y porque los niveles de las sustancias utilizadas para la monitoría continuaban elevados al final del procedimiento, fueron sometidos a la operación clásica bajo anestesia general, con disección bilateral del cuello. Este novedoso aproche, que puede ser practicado con seguridad, resulta en un tiempo operatorio muy breve y una corta permanencia en el hospital. Evitar la anestesia general resulta satisfactorio para aquellos pacientes que son reacios a aceptar la anestesia general. La monitoría intraoperatoria, que predice la cura del hiperparatiroidismo con un elevado grado de certeza, permite al cirujano completar la operación con la confianza de un buen resultado.

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Invited Commentary

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The surgical principles in hyperparathyroidism have changed over the years since 1925 when Dr. Mandl performed the first successful parathyroidectomy. Initially, the removal of the pathological parathyroid tissue was the prevailing policy but with increasing experience of persistent or recurrent hypercalcemia identification of all 4 glands was advocated. The intraoperative histopathological evaluation of the parathyroid glands was unreliable. The differentiation between the solitary adenoma disease and multiglandular hyperplasia was difficult, as was the differentiation between normal and hyperplastic tissue. A development towards a more exact histopathological diagnosis of parathyroid disease as well as improved methods to pre-operatively localize the affected parathyroid gland has resulted in less extensive parathyroid explorations.

Chapuis and colleagues are to be congratulated on their paper in which they describe parathyroid surgery under locoregional anesthesia. Since 1989 they have systematically applied this technique in their surgical treatment of primary hyperparathyroidism. There are some contraindications, however, such as previous history of familial hyperparathyroidism, misleading or nonconcordant information in pre-operative localization, coexistence of multinodular colloid goiter and patient anxiety, deafness, or allergy to local anesthesia. A certain degreee of co-operation is necessary. Of 125 patients undergoing surgery during the study period, 45 (37%) patients were suitable for surgery under locoregional anesthesia according to the above criteria. Intra-operative monitoring of UcAMP and/or 1-84 PTH was performed in all patients. A sharp drop was observed in all except 3 patients after the removal of the adenoma. The average adenoma size was 1.5 cm, ranging from 1 cm to 2.4 cm. The operative time ranged from 15 min to 55 min. In 1 of the patients with unsuccessful initial surgery, hyperplasia of all 4 glands was the reason for the failure. Only 1 (2%) patient with hyperplasia is a surprisingly low figure. In the second patient a probable double adenoma was the reason for persisting serum calcium elevation and in the third patient the reason for failure was not possible to identify in spite of a complete surgical exploration.

With their elegant technique, the authors reach a 93% success rate, which is acceptable, especially considering the fact that the risk of hypocalcemia is completely eliminated as the contralateral side is never explored. I share their preference of 1-84 PTH to UcAMP. The inspection of the ipsilateral normal parathyroid gland is an important part of the operation and preferably this gland should be removed in order to give the pathologist a chance to exclude nodular hyperplasia.

It is not completely clear whether Chapuis and colleagues advocate intra-operative histopathology. Although the need for this examination is reduced by the monitoring of 1-84 PTH intra-operatively, the histopathological diagnosis of a solitary adenoma is of great help for the management of the patient. The limitation of ultrasound and technetium-thallium scan is no doubt related to the size of the adenoma and the coexistence of thyroid disease. Most likely a greater proportion of their patients would be managed by a unilateral approach if preoperative selective venous sampling from the neck was applied, as this method allows the localization to which side of the neck in parathyroid adenomas down to 200 mg.

This paper of Chapuis and colleagues is an important contribution to the process of simplifying parathyroid surgery. The great advantage of not exploring one side of the neck is the avoidance of postoperative hypocalcemia. Although most cases of postoperative hypocalcemia are transient there are a few which become permanent. There is certainly no greater mishap in parathyroid surgery than reversing a mild hyperparathyroidism into hypoparathyroidism.