Usefulness of combined ultrasonography and scintigraphy in the preoperative assessment of secondary or tertiary hyperparathyroidism

A.R. Oliva, P.A. Lobos, J.M. Moldes, D.H. Liberto

Pediatrics Department, Pediatric General Surgery Unit. Buenos Aires Italian Hospital. Buenos Aires, Argentina.

ABSTRACT

Objective. To determine whether combined ultrasonography and parathyroid scintigraphy improves hyperplastic parathyroid gland detection in the pediatric population for parathyroidectomy planning in patients with secondary or tertiary hyperparathyroidism.

Materials and methods. An observational and analytical retrospective cohort study was carried out. Patients diagnosed with secondary or tertiary hyperparathyroidism from 2011 to 2018 undergoing total or subtotal parathyroidectomy were included – provided there was information available on pathological examination and surgical protocol.

Results. N = 15 patients. A total of 53 parathyroid glands diagnosed with hyperplasia using either of the imaging methods were analyzed. For each method (ultrasonography and scintigraphy) and the combination of both, sensitivity and area under the curve were calculated, using pathological examination result as a reference. Ultrasonography and scintigraphy diagnostic match was 66%.

Discussion and conclusions. The intraoperative difficulty of parathyroid gland identification as well as the anatomical variation that these present is well-known. Ultrasonography detected more glands than scintigraphy when diagnosing parathyroid hyperplasia. The combination of both methods allows patients with a first negative study to be detected.

KEY WORDS: Hyperparathyroidism; Parathyroidectomy; Ultrasonography; Parathyroid scintigraphy.

UTILIDAD DE LA COMBINACIÓN DE ECOGRAFÍA Y GAMMAGRAFÍA EN EVALUACIÓN PREOPERATORIA DE HIPERPARATIROIDISMO SECUNDARIO O TERCIARIO

RESUMEN

Objetivo. Determinar si la combinación de la ecografía y la gammagrafia paratiroidea mejora la capacidad de detección de glándulas paratiroideas hiperplásicas en población pediátrica para la planificación de paratiroidectomía en pacientes con hiperparatiroidismo secundario o terciario.

Material y métodos. Estudio observacional y analítico de una cohorte retrospectiva. Se incluyeron pacientes con hiperparatiroidismo secundario o terciario, entre 2011 y 2018, que fueron operados de paratiroidectomía total o subtotal, en los que haya podido recabarse información de la anatomía patológica y protocolo quirúrgico.

Resultados. N = 15 pacientes. Se analizaron un total de 53 glándulas paratiroides con diagnóstico de hiperplasia en alguno de los métodos por imágenes evaluados. Para cada método (ecografía y gammagrafía) y para la combinación de ambos, se obtuvieron la sensibilidad y área bajo la curva, tomando como referencia el resultado obtenido por anatomía patológica. La concordancia en el diagnóstico de la ecografía y de la gammagrafía fue del 66%.

Discusión y conclusiones. Es bien conocida la dificultad intraquirúrgica que se plantea en cuanto a la localización de las glándulas paratiroides así como la variación anatómica que estas presentan. La ecografía detectó más glándulas que la gammagrafía en el diagnóstico de hiperplasia paratiroidea. La combinación de ambos métodos permite detectar a aquellos pacientes en los cuales un primer estudio resultó negativo.

PALABRAS CLAVE: Hiperparatiroidismo; Paratiroidectomía; Ecografía; Gammagrafía paratiroidea.

INTRODUCTION

Hyperparathyroidism occurs as a result of increased parathyroid gland activity, which causes inadequate parathyroid hormone (PTH) secretion. Secondary hyperparathyroidism originates from a series of metabolic disorders secondary to loss of renal function. This finding is prevalent (70%) in patients with chronic renal insufficiency (CRI)[1] and the main cause of morbidity and mortality in these patients during childhood. On the other hand, tertiary hyperparathyroidism is characterized by the presence of hypercalcemia in response to excessive PTH secretion[2]. It occurs in cases of permanent parathyroid gland hyperfunction, even once the inducing stimulus has disappeared[3].

Corresponding author: Dr. Daniel H. Liberto. Buenos Aires Italian Hospital. Tte. J. Domingo Perón 4190. Zip Code: C1199ABB. Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina.
E-mail address: daniel.liberto@hospitalitaliano.org.ar

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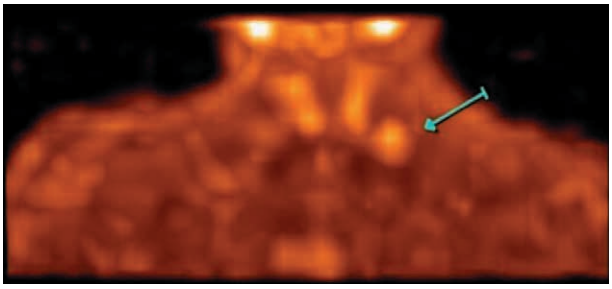

Figure 1. Parathyroid scintigraphy of a 19-year-old patient with tertiary hyperparathyroidism showing an ectopic parathyroid gland (arrow).

Medical treatment occasionally reduces hypercalcemia and prevents side-effects[4]. However, effectiveness is limited, so parathyroid gland surgical resection is the next therapeutic option.

The objective of surgical treatment is to reduce PTH levels, thus preventing hyperparathyroidism complications in patients with terminal CRI. Surgical options include parathyroidectomy of three and a half glands, or total parathyroidectomy with heterotopic self-implantation[5]. Even though cases of total parathyroidectomy without implantation have been reported, this is not indicated in the pediatric population as it is associated with high morbidity and mortality rates.

Regarding the procedure as such, once routine anatomical dissection has been performed, difficulty is often encountered when attempting to find all glands, since they are small in size and may be located at various sites[6], as demonstrated in Figure 1. Therefore, a more accurate dissection is required to identify them all.

Preoperative assessment of hyperparathyroidism patients at our healthcare facility consists of physical examination, cervical ultrasonography, and parathyroid scintigraphy evaluation.

Objective

The objective of this study was to determine whether combined ultrasonography and parathyroid scintigraphy improves hyperplastic parathyroid gland detection in the pediatric population for adequate surgical planning.

MATERIALS AND METHODS

An observational and analytical retrospective cohort study of secondary and tertiary hyperparathyroidism patients treated from 2011 to 2018 was carried out. Patients undergoing partial or total parathyroidectomy, as well as ultrasonography and parathyroid scintigraphy as part of preoperative assessment, were included.

Patients without pathological examination or surgical report data available were excluded.

Preoperative assessment

Standard preoperative assessment of hyperparathyroidism patients was carried out by means of a laboratory study (ionic and total calcium, phosphorus, urea and creatinine, PTH, and vitamin D) and complementary imaging tests (cervical ultrasonography with linear transducer and parathyroid scintigraphy, with intravenous injection of Tc99m-Sestamibi, subsequent early and late readings, and neck and chest SPECT)[7]. Surgery was planned according to the anatomical location suggested by both methods.

Surgical procedure

A cervical transversal incision was carried out. The unilateral thyroid space was approached. The superior and inferior parathyroid glands were identified and resected, while preserving the ipsilateral recurrent nerve. The material resected was divided, and half of the gland was submitted for intraoperative pathological study. The contralateral thyroid space was approached, and the same procedure was repeated.

Following gland resection, ultra-rapid intraoperative PTH levels were measured 0, 5, 10, and 15 minutes following resection using chemiluminescence (Abott immunoassay). A ≥ 80% decrease in PTH levels as compared to baseline following 15 minutes should be observed. A drainage was left in place in the surgical bed.

In this patient series, all surgeries were carried out by the same primary surgeon.

Statistical analysis

Quantitative variables were expressed as median and 25-75 interquartile range (IQR). Qualitative variables were expressed as absolute and relative frequency. Sensitivity and area under the curve (AUC) were estimated with a 95% confidence interval (95% CI) for each imaging method – ultrasonography and scintigraphy – and the combination of both for all glands correctly identified. Deferred pathological examination result was used as the gold standard. Statistical analysis was performed using the STATA 15 software.

Regarding pathological examination, two parameters were analyzed: confirmation of parathyroid tissue in the frozen section study, and presence of parathyroid hyperplasia in the deferred study.

RESULTS

A total of 18 patients with surgical indication of parathyroidectomy, 15 of whom met the inclusion criteria, were included. 11 patients were male. Median age at surgery was 15 years (IQR: 12-18).

Regarding diagnosis leading to surgery, 12/15 (80%) patients had secondary hyperparathyroidism, while 3/15 (20%) had tertiary hyperparathyroidism.

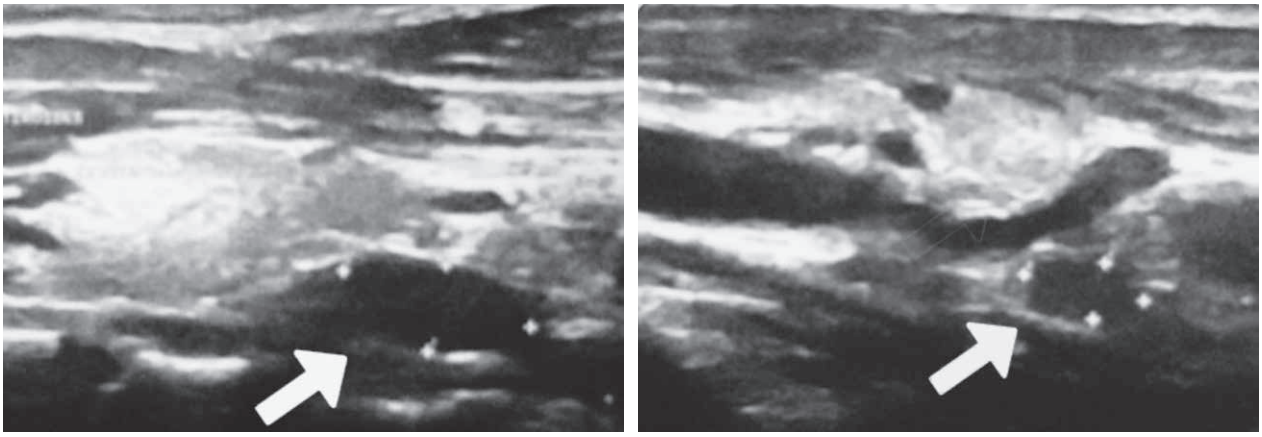

Figure 2. Cervical ultrasonography demonstrating hyperplastic parathyroid glands (arrow).

Table 1. Sensitivity and areas under the curve (AUC) for each imaging test individually and combined.

Diagnostic test	*Sensitivity (%)*	*95% CI*	*AUC*	*95% CI*
Ultrasonography	55	40-69	0.77	0.70-0.84
Scintigraphy	41	26-53	0.69	0.63-0.76
Ultrasonography + Scintigraphy	65	50-77	0.82	0.76-0.89

A total of 53 parathyroid glands diagnosed with hyperplasia using either of the imaging methods – cervical ultrasonography (Fig. 2) or parathyroid scintigraphy with positive result – were analyzed. Median glands assessed per patient were 3 (IQR: 2-4).

Ultrasonography and scintigraphy diagnostic match was 66%. Figure 3 shows the results from both diagnostic studies.

Table 1 features sensitivity and areas under the curve for each imaging study individually and the combination of both as compared to gold standard (Table 1, Fig. 4).

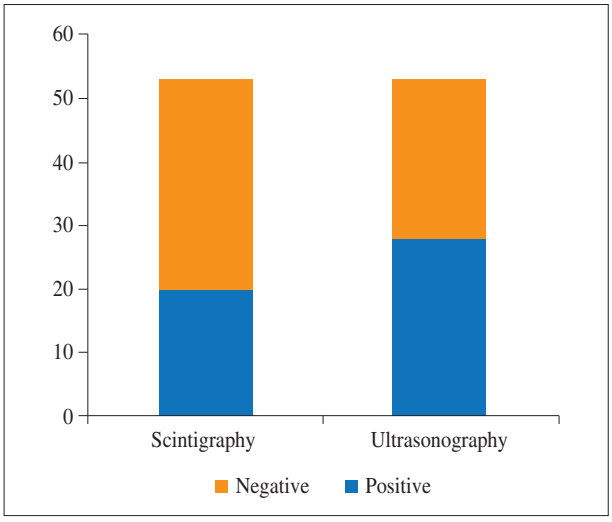

Figure 3. Bar chart featuring ultrasonography and scintigraphy results individually. The number of glands assessed is represented on the ordinate axis.

DISCUSSION AND CONCLUSION

Hyperparathyroidism is a rare pathology in pediatric patients, but it has a great clinical impact and requires surgical treatment in many cases. The glands to be resected have significant anatomical variations, with atypical locations, and are often difficult to find intraoperatively[6,8]. Ectopic locations of superior glands include the upper mediastinum (1-4%) and the intrathyroidal location (< 3%), whereas ectopic locations of inferior glands include the cervical portion of the thymus (26%), the medium third of the thyroid lobe (7%), the anterior mediastinum (4-5%), and the intrathyroidal location (< 3%)[7]. Therefore, preoperative assessment using the adequate methods is key to achieve an optimal intraoperative location and thus:

- Reduce anesthetic exposure times in patients with increased risk as a result of the baseline pathology
- Avoid large, unnecessary dissections increasing the risk of intraoperative and postoperative complications
- Identify ectopic gland locations in order to establish an adequate approach. It should be noted that, as mentioned in the literature, most re-interventions in these patients are caused by the presence of a lost gland in the neck[9].

The cost of diagnostic tests – Sestamibi scintigraphy and ultrasonography – for routine preoperative identifi-

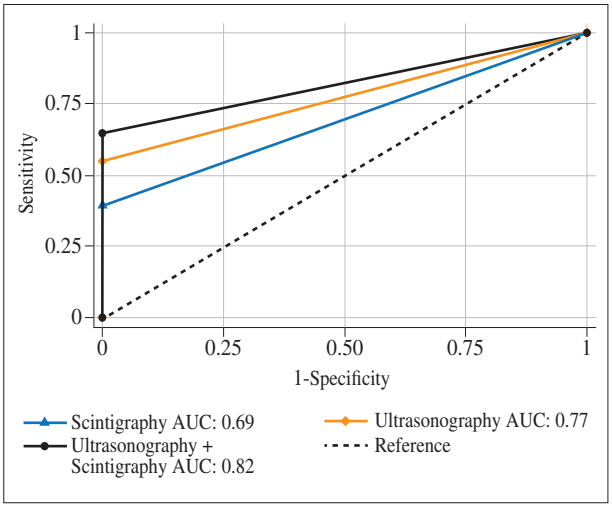

Figure 4. Ultrasonography and parathyroid scintigraphy ROC curves, both individually and combined.

cation in patients with primary hyperparathyroidism has been minimized in the literature when compared with that of re-intervention. There seems to be no reason why the cost-effectiveness analysis should be different in patients with renal or secondary hyperparathyroidism[9].

According to the results, ultrasonography looks superior to scintigraphy in the diagnosis of parathyroid hyperplasia. The combination of both allows patients with a first negative study to be detected.

Compared with scintigraphy alone, the diagnostic yield of both methods combined looks higher. However, in this study, no statistically significant differences were found when comparing confidence intervals, which could be a result of sample size.

This is one of the few studies carried out in a pediatric patient cohort. The study by Périé[9] showed similar findings, with higher sensitivities. This may be explained by the fact it was conducted in adult patients, where parathyroid gland detection is less difficult than in pediatric patients. However, no inferential estimators were described.

This work was based on a secondary database, with the limitations inherent to this type of study. For instance, patients in the sample presented at a private university hospital, which may not be representative of the whole nation, since Argentina's healthcare system is made up of both public and private sectors.

All data were retrieved from electronic, prospective, full clinical history records, which allowed for both inpatient and outpatient follow-up, with data available on all studies and techniques carried out.

The main strength of this study is the fact it was conducted at a reference facility in pediatric surgical pathologies, equipped with highly complex diagnostic technology and staffed by pediatric head and neck surgery specialists.

To sum up, this study establishes a hierarchical organization regarding the preoperative usefulness of ultrasonography and scintigraphy when it comes to identifying hyperplastic parathyroid glands. Future prospective studies with a larger patient cohort will allow this hypothesis to be confirmed.

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