Can intraoperative parathyroid hormone (IOPTH) assay replace combined IOPTH and frozen section in Parathyroidectomy for 1ry hyperparathyroidism: A comparative study?

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ABSTRACT

Introduction: *Primary Hyperparathyroidism (PHPT) is caused by single adenoma in most of the cases and surgery is the only curative management till now. Routine frozen section was and still an important operative step for many surgeons but with the introduction of highly accurate preoperative localization with sestamibi scan and available IOPTH assay, can surgeons skip this step?* ***Objectives:*** *Comparing IOPTH alone versus combined IOPTH and frozen section for detecting successful parathyroidectomy in cases of primary hyperparathyroidism.* ***Patients and methods:*** *Forty patients with primary hyperparathyroidism and indicated for parathyroidectomy were divided into 2 groups, Group A had only IOPTH assay while group B had both IOPTH and frozen section for parathyroid tissue confirmation.* ***Results and conclusion:*** *The 2 groups had similar features regarding demographics. The mean time for receiving FS results was statistically highly significant when compared with IOPTH mean time (P value less than 0.0001). Those results were consistent with those resulting from calculating the total operative time in both groups which were undoubtfully and statistically in favor of IOPTH alone group. IOPTH assay when available could alone guide intraoperative decision-making during parathyroidectomy surgeries.* ***Disclosure:*** *This article is not sponsored by any company, so the authors have no competing interests as defined by Nature Publishing Group, or other interests that might be perceived to influence the results and/or discussion in this article.*
Keywords: *Primary Hyperparathyroidism, intraoperative parathyroid hormone assay, parathyroidectomy, frozen section.*

INTRODUCTION

A single adenoma is the cause of primary hyperparathyroidism in 85% of cases, about 15% is due to hyperplasia or multiple adenomas and rarely is caused by carcinoma [1]. Surgery is the only curative management till now in the form of excision of the diseased parathyroid gland or glands [2].

Normalizing postoperative serum calcium and parathyroid hormone is the primary target of parathyroidectomy while minimizing complications, dissection, operative time and resources [3].

Due to the standardized use and high accuracy of sestamibi scan, preoperative localization of abnormally functioning parathyroid glands permits the wide use of minimally invasive parathyroidectomy with only exposing and removing the affected gland [4].

Intraoperative parathyroid hormone (IOPTH) assay had proved its high efficiency and accuracy for detecting success of parathyroidectomy due its very short half-life (3-5 min.) [5]. Achieving more than 50% fall in the preoperative PTH level 10 minutes after removal of the abnormal parathyroid tissue, indicates successful parathyroidectomy [6].

As a routine, the excised gland is sent for histopathological examination by frozen section to confirm its nature and to exclude malignant gland disease. In fact, in most cases frozen section cannot differentiate normal from abnormal parathyroid gland [7] raising the question, what about omitting this step while relying only on IOPTH as the only intraoperative parameter for successful parathyroidectomy.

Objectives

The aim of the present study is to compare IOPTH alone versus combined IOPTH and frozen

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section for detecting successful parathyroidectomy in cases of primary hyperparathyroidism.

PATIENTS AND METHODS

Forty consecutive patients with primary hyperparathyroidism and indicated for parathyroidectomy were included in this prospective study which was performed at Ain Shams University Hospitals in association with Helwan university hospital during the period of March 2019 and May 2020.

After approval of our department ethical committee and obtaining informed consent about this study, full operation information and postoperative follow-up protocol from all patients, any patient with sporadic 1ry hyperparathyroidism were included in this study while patients with familial or MEN associated hyperparathyroidism, previous neck surgery or suspected malignancy were excluded.

Block randomization of patients into 2 groups on the day of surgery in a 1:1 ratio was done. Group A had only intraoperative parathyroid hormone (IOPTH) assay while group B had both IOPTH and frozen section for parathyroid tissue confirmation.

Routine preoperative investigations were requested for all patients. Laboratory investigations for confirmation of the diagnosis in the form of serum parathyroid hormone, calcium and phosphate were ordered. Accurate preoperative parathyroid localization was performed using neck ultrasound and 99mTc-sestamibi scan. The patients were admitted 24 hours before the operation and pre-excision PTH assay was done on the day of admission.

Surgical procedure:

Targeted (Minimally invasive) unilateral parathyroidectomy was adopted in most cases where focused surgical procedure to identify and remove the only single enlarged abnormal parathyroid gland preoperatively localized by 99mTc-sestamibi scan. Bilateral exploration was needed in cases where suspected double adenoma by preoperative 99mTc-sestamibi scan or failure of intraoperative IOPTH decrease.

Under general anesthesia, 1-2-inch low cervical (Kocher) incision was used. Dissection proceeded down through the platysma muscle to reach the thyroid capsule which was mobilized on the side with the presumed affected parathyroid gland. Identification, dissection and removal of the abnormal gland while maintaining meticulous hemostasis and preserving the recurrent laryngeal nerve was done.

10 minutes after excision of the abnormal parathyroid gland, in both groups, a sample from a peripheral vein for a quick IOPTH was taken. In group B only, the apparently abnormal parathyroid gland was sent for intraoperative histopathological frozen section examination. Closure of the wound was only done after receiving IOPTH results and confirming that a decrease of more than 50% of the preoperative PTH value was achieved (according to Irvin et al. [6]) in group A. While in group B, waiting for additional confirmation of the excised tissue by frozen section to be of parathyroid tissue in addition to IOPTH was done before wound closure.

Postoperative follow up:

In all patients, PTH and serum calcium assay were measured 24 hours after the operation, and the excised parathyroid gland was sent for paraffin section histopathological examination. All patients were discharged in the second postoperative day. Follow up at 1 week, 1 month, 3 months and 6 months' intervals and serum PTH were measured with each visit for recurrence recording.

Statistical Analysis

Two-sample unpaired t-Test for continuous variables and chi-square tests for categorical variables were used for statistical analysis via IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp.). By conventional criteria, the difference was considered to be statistically significant when the two-tailed P value is less than 0.05.

RESULTS

Demographics and patients' related data:

Forty patients were included in this study. As regard the age, sex, preoperative serum PTH and results of preoperative 99mTc-sestamibi scan, there was no statistically significant difference between both groups as shown in **Table 1.**

Table 1: preoperative patients related data. SD: Standard deviation, M: Male, F: Female, PTH: parathyroid hormone, NS: non-significant

Variables	Group A	Group B	P value
Number of patients:	20	20	
Age (mean ± SD):	44.3 ± 10.761	39.15 ± 7.1176	.1485 (NS)
Sex M: F:	2:18	5:15	1 (NS)
Preoperative serum PTH (mean ± SD):	933.9 ± 160.4674	925.25 ± 149.9003	.8602 (NS)
Preoperative no. of patients with parathyroid gland adenoma detected by 99mTc-sestamibi scan:	20 (100%)	20 (100%)	
Single gland disease (no. of patients):	19 (95%)	20 (100%)	.6384 (NS)
Multiple gland disease (no. of patients):	1 (5%)	0 (0%)	.6346 (NS)

Intraoperative data:

All forty patients underwent successful parathyroidectomy. 37 (92.5%) patients had targeted unilateral parathyroidectomy distributed as 19 (95%) patients in group A and 18 (90%) patients in group B. Two (5%) patients had bilateral neck exploration for double parathyroid adenoma (one patient in each group). One patient in group B had hemithyroidectomy due to intrathyroidal parathyroid adenoma.

As regard IOPTH, 38 (95%) patients (20 (100%) in group A and 18 (90%) in group B) had more than 50% lower values in comparison with the preoperative data ten minutes after excision of the abnormal parathyroid glands while in group B two patients did not achieve acceptable more than 50% decrease (25% and 21% respectively) of preoperative PTH.

In the first patient, ipsilateral parathyroid gland exploration was apparently normal so, bilateral exploration was performed and revealed another abnormal parathyroid gland. Excision was done and another blood sample for IOPTH was sent. 81% decrease of the preoperative PTH was confirmed and the operation was terminated successfully.

In the second patient, further ipsilateral exploration of the ipsilateral thyroid lobe revealed suspicious nodule closely related to the site of the previously excised parathyroid gland. The decision was to perform hemithyroidectomy and 88% preoperative PTH level decrease was attained.

To be noted, in the case of preoperatively diagnosed double gland disease, IOPTH sample was only sent after removal of both abnormal glands. The mean time for receiving IOPTH sample results (with the addition of the ten minutes limit before the sample was withdrawn) was 33.25 ± 1.8913 SD. **(Table 2).**

Table 2: IOPTH data. NS: non-significant, No.: Number of patients, SD: Standard deviation, IOPTH: intraoperative parathyroid hormone

Variables	Group A	Group B	Total	P value
% decrease of preoperative PTH (mean ± SD):	73.65 ± 13.484	71.05 ± 20.4874	72.35 ± 17.1697	.6287 (NS)
≥ 50% (No.):	20	18	38	1 (NS)
□ 50% (No.):	0	2	2	
IOPTH results time (mean ± SD):	33.5 ± 1.9868	33 ± 1.8064	33.25 ± 1.8913	0.81 (NS)

Frozen section examination was only performed in Group B patients and the results were summarized in **Table 3**.

Table 3: frozen section results summary. FS: frozen section, No.: number of frozen section samples sent, PTA: Parathyroid gland adenoma, SD: Standard deviation

✚ Frozen section (FS) results:	
1. Parathyroid tissue (No.):	6 (27.2%)
2. Hypercellular parathyroid gland (No.):	9 (40.9%)
3. Parathyroid gland adenoma (PTA) (No.):	5 (22.7%)
4. Fat tissue (No.):	1 (4.5%)
5. Intrathyroidal PTA (No.):	1 (4.5%)
✚ Mean FS results time ± SD:	45.4 ± 4.2723

As mentioned in **Table 3**, most of the samples sent for frozen section (15 samples (68.2%)) were diagnosed as parathyroid tissue or hypercellular parathyroid gland with no confirmation of the type of hypercellularity whether adenoma or hyperplasia. Only 5 samples (22.7%) were confirmed to be adenoma. The case associated with fat tissue result was linked with low % of decrease of the preoperative PTH and after ipsilateral hemithyroidectomy for suspicious nodule, frozen section revealed Intrathyroidal PTA.

The mean time for receiving FS results was 45.4 ± 4.2723 which was statistically highly significant when compared with IOPTH mean time (P value less than 0.0001). Those results were consistent with those resulting from calculating the total operative time in both groups which were undoubtfully and statistically in favor of IOPTH alone group as shown in **Table 4**.

Table 4: Comparing mean time for IOPTH, FS and total operative time. SD: Standard deviation, NS: non-significant, S: significant, FS: frozen section, IOPTH: intraoperative parathyroid hormone.

Variables:	Group A	Group B	P value
Mean IOPTH result time ± SD:	33.5 ± 1.9868	33 ± 1.8064	0.81 (NS)
Mean FS result time ± SD:	0	45.4 ± 4.2723	☐ 0.0001 (S)
Mean Total operative time ± SD:	61.35 ± 6.2431	81.95 ± 11.4684	☐ 0.0001 (S)

Postoperative data and follow up:

Successful parathyroidectomy was confirmed in all patients in both groups when correlated with the normalization of postoperative PTH assay and serum calcium. All patients were discharged on the second postoperative day. No morbidity or mortality was recorded in this study apart from small wound hematoma in one patient which was managed conservatively. Paraffin section histopathological examination revealed single parathyroid adenoma in 37 patients, double gland adenoma in 2 patients and one patient with ectopic intrathyroidal PTA. No cases of hyperplasia or carcinoma were recorded in this study. No cases of recurrence were recorded after following up serum PTH for up to 6 months.
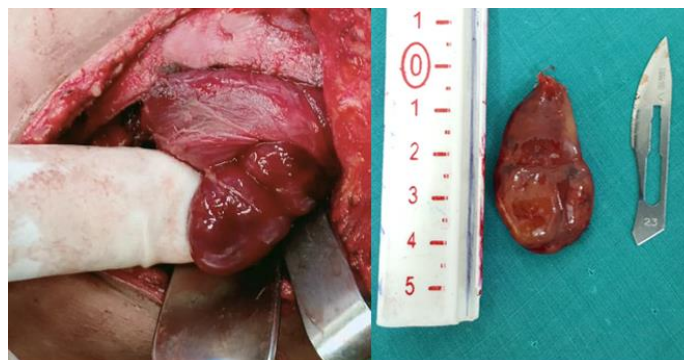
Fig. 1: Intraoperative view of the abnormal parathyroid gland (left) and after its excision (right).
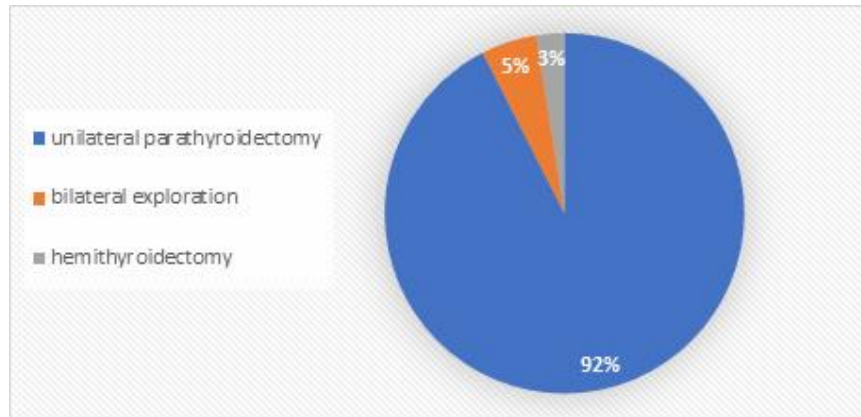
Fig. 2: Types of surgical approaches for pararathyroidectomy in this study.

DISCUSSION

Primary Hyperparathyroidism (PHPT) is one of the commonest endocrine disorder with globally increasing incidence and prevalence [8]. While single parathyroid gland adenoma is the most common cause of PHPT, multiple gland adenoma, hyperplasia and parathyroid carcinoma are very uncommon [9]. These facts were correlated with this study as 38 (95%) patients had single parathyroid gland adenoma including one patient with ectopic intrathyroidal adenoma while only 2 (5%) patients had double gland adenoma with no reported cases of hyperplasia or carcinoma.

From this point of view listed above, minimally invasive or targeted unilateral parathyroidectomy (MIP) became more and more popular [10] (Agarwal G et al.) while the traditional bilateral neck exploration with 4 gland examination was reserved for special situations [11] (Chen H. et al.). In this study, 37 (92.5%) patients, parathyroidectomy was performed via straight forward unilateral approach while 3 (7.5%) patients needed bilateral exploration for double adenoma in 2 patients and for ipsilateral hemithyroidectomy in one patient for better exposure.

This conservative parathyroidectomy approach did reduce risk for postoperative hypocalcemia, recurrent laryngeal nerve injury, operative time and hospital stay [12] (Irvin GL et al.) however it was limited due to the possibility of a multiglandular disease in up to 15% of cases of PHPT [13]. Two important factors had contributed to the possibility of replacing bilateral exploration with MIP.

The first factor is the wide use of sensitive preoperative localization imaging namely technetium 99m sestamibi scan [14] with a reported sensitivity of up to 90% [15] by Riss P et al and Saengsuda Y et al. In this study, sestamibi scan detected single adenoma disease in 39 (97.5%) patients and double gland disease in one patient (2.5%) but intraoperatively another patient was detected intraoperatively to have double adenoma which was not detected preoperatively.

The second factor is the intraoperative PTH assay which was proved that in expert hands the success of unilateral parathyroidectomy with IOPTH assay can reach 98.1% [16]. Due to very short half-life of PTH (about 3 minutes) and exclusive parathyroid gland secretion, IOPTH assay became viable highly accurate guide for surgeons intraoperatively whether to continue neck exploration for abnormal parathyroid gland or to terminate the procedure [17] (Bergenfelz A et al.). The results of the present study agreed with those previous trials as the decision to do unilateral exploration only based on IOPTH assay was made in 38 patients meanwhile it guided the operating surgeon to continue exploring the neck in 2 patients after failure of IOPTH to decrease $\geq$ 50% of its preoperative values. Those data were hardened by the fact that all patients had disease free (clinically and laboratory) postoperative period up to 6 months of follow up.

Due to the above factors, the use of intraoperative FS for parathyroid gland identification became debatable by Mehta NY et al [4] and others. Many surgeons nowadays still rely on FS for confirmation of the excised tissue to be of parathyroid gland despite the fact that FS cannot accurately differentiate adenoma from

hyperplasia [18] as stated by many trials as Iacobone M. et al and Ranchod, M [7]. In this study only 6 patients were identified by FS to have Adenoma while 33 patients were diagnosed to have either normal or hypercellular parathyroid tissue which was not a proper guide for the surgeon to take a proper decision of the next step if IOPTH was not available.

Historically, FS was more superior than IOPTH because of the availability, cost and time factor [19] (Madira W et al). As regard the IOPTH result time, it had been reduced from hours to merely 15-20 minutes while FS still needs up to 30 minutes for results to be available thus reducing the total operative time if IOPTH assay was used alone as described by Udelsman R. et al [20]. In addition, IOPTH assay had MIP to replace traditional bilateral exploration thus much reducing operative time [21] (Nelson CM. et al). The present study results revealed highly statistically significant difference (P value $\square$ 0.0001) between mean total operative time in using IOPTH assay alone (61.35± 6.2431 SD) and with FS examination (81.95 ± 11.4684 SD) and between mean IOPTH (33.25 ± 1.8913 SD) and FS (45.4 ± 4.2723 SD) result time.

This study did not compare cost burden in both groups, but theoretically, decreasing operative time, hospital stay, lower incidence of complications can contribute to lower cost burden on medical facilities [22] (Gurnell EM. Et al).

CONCLUSION

For cases of primary hyperparathyroidism, IOPTH assay is very sensitive and specific marker of successful parathyroidectomy in experienced hands. FS could be omitted in these cases or at least requested for special situations such as unavailable IOPTH, suspicious for malignancy or ectopic gland locations. Otherwise, IOPTH assay could alone guide intraoperative decision-making during parathyroidectomy surgeries.

Limitations
More studies with larger sample size are needed with special consideration of the cost and availability of IOPTH for definitive standardization of the daily surgical practice for parathyroid surgery.

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