

Letter to the Editor

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Use of a modified IDS-ISYS intact PTH assay for intraoperative PTH measurements

<https://doi.org/10.1515/cclm-2020-0412>

Received March 31, 2020; accepted April 30, 2020

Keywords: hyperparathyroidism; IDS-ISYS; intraoperative PTH; parathyroid hormone.

To the Editor,

Primary hyperparathyroidism (PHP), the excretion of abnormal amounts of parathyroid hormone (PTH) relative to serum calcium levels, is most often caused by parathyroid adenoma (80–85% of cases) [1]. When indicated, surgery remains the only curative intervention for PHP [2]. When performed by an experienced surgeon, cure rates are high and may approach 100% [3]. Intraoperative PTH measurements are a cornerstone in the surgical strategy for PHP [4]. Although multiple criteria for success have been defined (reviewed in [4]), fast PTH measurements are required for optimal use. This optimal use may not stem from patient outcome, as this is similar for fast and standard-length PTH assays in patients with monoglandular disease [5], but on reduced time in the operation theatre [6]. Also, one may hypothesise that patients suffering from causes other than monoglandular forms of hyperparathyroidism will benefit from fast turnaround times as the surgeon will be able to act faster to a lack of decrease in PTH.

Typically, decay in PTH is measured and timing is set to 10–20 min after resection. At this moment, only few marketed options are widely available [7]. Abbott's Architect, Siemens Advia Centaur and Beckman's Access intact

PTH assays are available but have relatively long incubation times (time-to-result: 18 min). Also, these machines are commonly found in the core laboratory and thus necessitate sample transport. Shorter incubation times can be achieved using Roche's Elecsys (time-to-result: 9) which is commonly found in the core laboratory and Future Diagnostics' point-of-care IO-PTH package which can be brought up to the patient's bedside (time-to-result: 8 min).

Here, we describe a modified intact PTH measurement protocol with shorter incubation times that can be implemented on IDS's ISYS automated immunoassay platform (IDS, Boldon, UK). The standard incubation times (first, 26 min and s, 10 min) were shortened to 7 min and 3 min, respectively. This protocol was compared to the standard protocol in left-over samples from routine measurements ($n=71$) as well as samples collected during parathyroid surgery ($n=51$) of patients suffering from PHP. Ultimately, measurements of both the non-modified (IVD) and modified (LDT) assays were compared to results from a Future Diagnostics IO-PTH analyser (Future Diagnostics, Wijchen, The Netherlands) as well as a third-generation PTH assay on a Fujirebio Lumipulse G1200 analyser (Fujirebio, Tokyo, Japan).

Measurement variation of the LDT was CV 9.5% (mean 5.5 pM) and CV 6.7% (mean 105.5 pM), in 21 separate runs. This was comparable to the CV% found for other IO-PTH platforms [7]. Measurement uncertainty of the IVD assay was CV 6.7% at 6.5 pM and CV 8.0% at 119.0 pM. Long-term measurement uncertainty of the FD assay was not assessed by retrospective analysis as each kit comes with new controls. From the literature, it was derived that the intra-assay CV% is 23.5% for this platform [7]. Measurement uncertainty of the Lumipulse assay was CV 4.9% (mean 2.1 pM) and CV 6.7% (mean 40.4 pM), in 24 separate runs.

In leftover samples, a small proportional bias was found between IVD and LDT assays ($\beta=97\%$, 95% CI 96–99%, Figure 1A). Also, a small absolute bias ($\alpha=0.3$ pM, 95% CI 0.1–0.4 pM) was found. Both findings were most likely due to the fact that the IVD and LDT assays were

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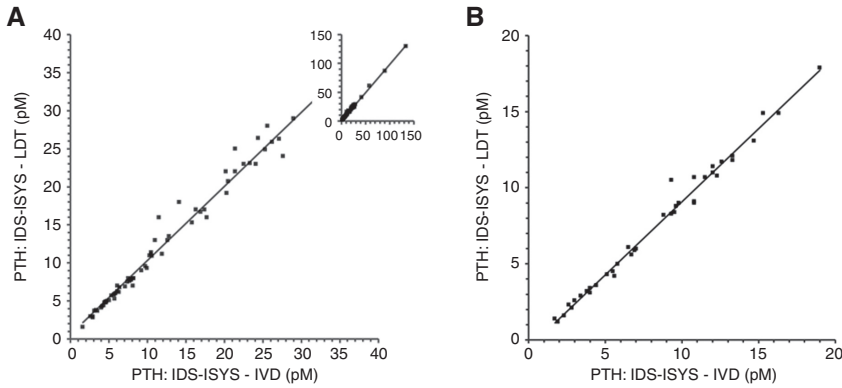


Figure 1: Parathyroid hormone (PTH) measured using IDS-ISYS employing the manufacturer provided protocol (X-axis) vs. an adapted protocol (Y-axis). Adaptation was based in shortening the incubation steps from 26 and 10 min to 7 and 3 min, respectively. (A) PTH measured in left over samples of non-surgical patients. (B) PTH measured in left over samples of patients during parathyroid surgery.

run on different machines, and the magnitude of bias was deemed clinically irrelevant as it fell well within the intermediate precision of the IVD assay. In surgical patient samples, a similar proportional bias was seen ($\beta = 96\%$, 95% CI 92–99%, Figure 1B) in addition to a small absolute bias ($\alpha = -0.5$ pM, 95% CI -0.8 to -0.1 pM). Together, these data show that the IDS-ISYS LDT can be used interchangeably with the IVD assay.

Taking these data, we used the LDT as the standard and compared outcomes, both absolute and relative, to a dedicated IO-PTH platform (FD). When comparing absolute data, a significant proportional bias was seen ($\beta = 271\%$, 95% CI 234–308%, data not shown), which was expected from previous findings by others [8]. Also, we found an absolute bias ($\alpha = 2.5$ pM, -3.3 pM, data not shown). These data prevent the use of the IDS-ISYS LDT and FD assays interchangeably.

Based on these data, we tested whether the LDT would result in similar outcomes in terms of percentage decrease in PTH when compared to the IVD. As expected, when expressed as %decrease of PTH in time, the IVD and LDT produce similar results. The proportional bias was significant ($\beta = 101\%$, 95% CI 100–101%, Figure 2A) but deemed irrelevant given its magnitude. No absolute bias was found ($\alpha = 2\%$, 95% CI 0–3%).

Finally, we used the LDT to predict outcome of the FD assay. Although the absolute results of the assays were different, the results of the LDT and FD assay were similar in terms of %decrease in PTH. No proportional bias was found ($\beta = 105\%$, 95% CI 100–110%, Figure 2B). Also, no absolute bias was found ($\alpha = -2\%$, 95% CI -4% to 0%).

Given the nature of the disease and intervention performed, it is reduction in production of PTH and not reduction in circulating fragment concentration that

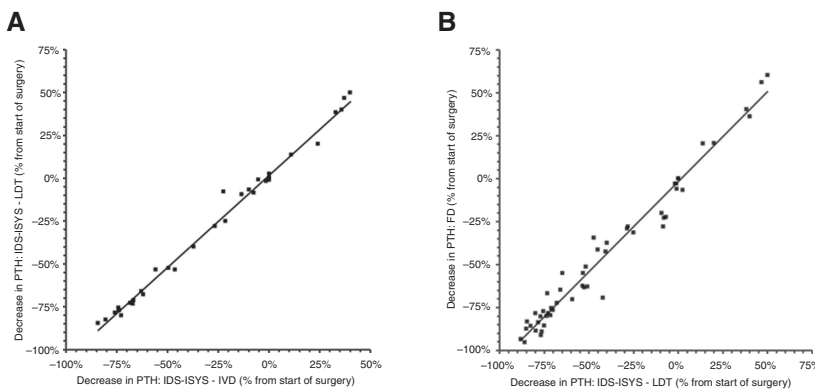


Figure 2: Decrease in parathyroid hormone (PTH) during parathyroid surgery. (A) PTH was measured using IDS-ISYS employing the manufacturer provided protocol (X-axis) vs. an adapted protocol (Y-axis). (B) PTH was measured using IDS-ISYS employing the adapted protocol (X-axis) vs. measurement of PTH on a dedicated intra-operative PTH measurement platform (Future Diagnostics IO-PTH (Y-axis). Adaptation of the IDS-ISYS protocol was based in shortening the incubation steps from 26 and 10 min to 7 and 3 min, respectively.

causes the decrease in PTH concentration. This was confirmed by measuring PTH in all samples using a third-generation PTH assay which specifically measures PTH1-84, the mature hormone released by the parathyroid gland. As hypothesised, the decrease in PTH seen with the third-generation assay was similar to the decrease in the LDT; there was no proportional ($\beta=102\%$, 95% CI 93–110%, data not shown) or absolute bias ($\alpha=-8\%$, 95% CI -11 to 3%, data not shown). We must, however, keep in mind that our study only included patients with PHP. Comparability of results between platforms may differ in patients with reduced kidney function and accompanied impairments of PTH fragments when using second- (but not third-) generation PTH assays [9].

Together, these data show that an incubation time-modified IDS-ISYS intact PTH can be used for intraoperative PTH measurements in patients suffering from PHP. The modified IDS assay had no bias when compared to the IDS IVD assay in samples collected randomly or during parathyroid surgery, and equal measurement uncertainty. Also, estimation of fractional decrease in PTH and thereby clinical interpretation of results during surgery were similar using the LDT when compared to both a dedicated STAT IO-PTH platform.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: Authors state no conflict of interest.

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