Original Article

Prolactin-adjusted ACTH Ratio in Predicting Lateralization of ACTH Source During Simultaneous Bilateral Inferior Petrosal Sinus Sampling in Patients with Cushing's Disease

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Abstract

Introduction: Prolactin-adjusted adrenocorticotropic hormone (ACTH) ratio is used to improve the diagnostic accuracy of bilateral inferior petrosal sinus sampling (BIPSS) for lateralization of pituitary adenoma. **Objective:** To study the use of prolactin for successful catheterization during BIPSS, the role of prolactin-normalized ACTH ratio for confirmation of Cushing's disease (CD) and prolactin-adjusted ACTH ratio in predicting the lateralization. **Patients and Methods:** BIPSS was done in patients with CD; prolactin-adjusted ACTH ratio was compared with intersinus ACTH ratio, magnetic resonance imaging, and intraoperative findings for localization of pituitary adenoma. Histopathology was taken as "gold standard" for the diagnosis of CD. **Results:** Eight patients underwent BIPSS. All the patients underwent transsphenoidal surgery. All these patients had proper venous sampling during BIPSS as determined by inferior petrosal sinus (IPS):Peripheral prolactin ratio of ≥1.8. Prolactin-normalized ACTH ratio of ≥1.3 was achieved in all the eight patients, which was consistent with the diagnosis of CD. Concordance of intersinus ACTH ratio ≥1.4 with the intraoperative findings was found in five of eight (62.5%) patients depicting correct lateralization. Concordance of prolactin-adjusted ACTH ratio with intraoperative findings was found in four of eight (50%) patients. Seven of eight patients had concordance of intersinus ACTH ratio with prolactin-adjusted ACTH ratio. **Conclusion:** Prolactin is a useful marker for successful catheterization, confirming the diagnosis of CD during BIPSS, and prolactin-adjusted ACTH ratio does not add to the accuracy of lateralization of pituitary adenoma compared with intersinus ACTH ratio.

Keywords: Bilateral inferior petrosal sinus sampling, Cushing's disease, human corticotropin releasing hormone

Introduction

Bilateral inferior petrosal sinus sampling (BIPSS) is a gold standard test to distinguish between Cushing's disease (CD) and ectopic adrenocorticotropic hormone (ACTH) syndrome. The diagnostic accuracy of BIPSS in localizing ACTH source is well established, but its ability to lateralize side of corticotropinoma in pituitary is limited. BIPPS demonstrated 100% sensitivity and specificity in earlier studies; however, recent studies have shown that its accuracy is not that high due to false-positive and false-negative results which may be up to 10%.[1-4] Variable venous drainage, catheter misplacement, improper sampling, cyclicity of disease, mild CD, low responsiveness to corticotropin releasing hormone (CRH) stimulation, and patients on medical therapy can lead to lower accuracy of BIPSS.[5] Improved diagnostic accuracy of BIPSS is therefore important to obtain the correct diagnosis for appropriate treatment and to minimize morbidity in these patients. Venous angiography and intermittent fluoroscopy are used to confirm the position of catheters.[6] Growth hormone, thyroid-stimulating hormone, α-subunit of human chorionic gonadotropin, and prolactin have been measured to assess catheter placement during IPSS.[7-11] Prolactin is an abundant pituitary hormone and is

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least affected by cortisol, and so this hormone can be used reliably for success of catheter placement in petrosal sinus, and prolactin-adjusted ACTH ratio is used to improve its diagnostic accuracy in lateralizing adenoma. Some studies have shown improved accuracy of prolactin-adjusted ACTH ratios for tumor localization during BIPSS.[12-14]

Objective

The objective of this study was to determine the role of prolactin-adjusted ACTH ratio in predicting the lateralization of pituitary adenoma during simultaneous BIPSS.

Patients and Methods

Eight patients with CD, biochemically confirmed hypercortisolemia, pituitary adenoma on histopathology, and all the patients who had undergone BIPSS for evaluation of the disease were included in the study. All except one had magnetic resonance imaging (MRI) localization of adenoma. Written informed consent was taken from all the patients/parents for the study. Ethical approval was obtained from the institute's ethics committee.

BIPPS procedure

BIPSS was done in the neuroradiology unit of the institute. Informed consent was taken from all the patients before the procedure. Bilateral IPSs were catheterized using femoral route under local anesthesia. 5-French catheters were used to reach the bilateral petrosal sinuses. Once catheters were placed in the petrosal sinuses, the position was confirmed using fluoroscopic guidance. Catheterization of bilateral IPSs was successful in all the patients. Human CRH (100 μm) was used in seven patients for ACTH stimulation and injected intravenously as bolus through peripheral catheter after mixing it with diluent. Vasopressin was used in one patient as infusion for ACTH stimulation and was given as infusion over 6 min. Simultaneous blood samples were taken from three sites (right IPS, left petrosal sinus, and peripheral vein) at basal and post stimulation (0, 2, 3, 5, 10, and 15 min). The patients were monitored for blood pressure, heart rate, oxygen saturation, or any other complaint given by the patient. Samples were immediately transported to endocrinology laboratory of the institute for processing.

Prediction of successful catheterization, localization, and lateralization of pituitary adenoma during BIPSS

The ratio of IPS: peripheral (P) prolactin was calculated at each point of time to confirm accurate inferior petrosal venous sampling. A value of ≥1.8 was taken as successful IPS catheterization. Prolactin-normalized ACTH ratio was calculated by dividing dominant ACTH IPS: P ratio by the concurrent and ipsilateral IPS: P prolactin. A value of ≥1.3 was considered as diagnostic of CD. Intersinus ACTH ratio of ≥1.4 either at basal or after stimulation was taken for lateralization of pituitary adenoma. Prolactin-adjusted ACTH ratio was calculated as described by Mulligan *et al.*[14] Localization results with these two methods were compared with intraoperative findings and histopathology.

Imaging, transsphenoidal surgery, and histopathology

Dynamic contrast-enhanced (CE) MRI 3 Tesla was done in all the patients. Transsphenoidal surgery was done in patients with CD; intraoperative findings of surgeon were noted. Histopathological findings were considered as gold standard for diagnosis of CD.

Assay

ACTH and prolactin were assessed by electro-chemiluminescence-immuno-assay (ECLIA) (Elecsys 2010; Roche Diagnostics, Germany). Inter- and intra-assay coefficient of variation (CV) were 2.3%–6.4% and 1.4%–2.8% for ACTH and prolactin, respectively.

Statistical methods

For calculating the comparison and concordance for localizing and lateralizing source, simple manual calculations were done case by case.

Results

Eight patients underwent BIPSS; human CRH was used in seven patients for ACTH stimulation, whereas vasopressin was used in one patient, and all the patients underwent transsphenoidal surgery. All these patients had proper venous sampling as determined by IPS: P prolactin ratio of ≥1.8. Prolactin-normalized ACTH ratio of ≥1.3 was achieved in all the eight patients, which was consistent with the diagnosis of Cushing's syndrome.

Taking intersinus ACTH ratio of ≥1.4 during BIPSS, all the patients had lateralization of adenoma. Concordance of this ratio with the intraoperative findings was found in five of eight patients. All the patients showed lateralization of adenoma using prolactin-adjusted ACTH ratio, whereas concordance of this ratio with intraoperative findings was found in four of eight patients. Comparing intersinus ACTH ratio of ≥1.4 with prolactin-adjusted ACTH ratio for lateralization, seven of eight patients had concordance, whereas one patient had discordant result. In the patient with discordant results, MRI as well as intraoperative TSS localization were concordant with intersinus ACTH ratio of ≥1.4. MRI sella localized microadenoma in seven patients, whereas in one patient MRI was normal. Concordance of MRI and lateralization using ACTH ratio of ≥1.4 were seen in five of eight patients. Similarly, concordance of MRI for lateralization using prolactin-adjusted ACTH ratio was seen in four of eight who had concordance with BIPSS.

Concordance of MRI findings with intraoperative localization was found in six out of seven patients, whereas one patient had normal MRI of sella in whom BIPSS correctly lateralized pituitary adenoma.

In this small series of patients, the accuracy of intersinus ACTH ratio of ≥1.4 for lateralization of pituitary microadenoma was found to be better than prolactin-adjusted ACTH ratio. MRI localization correlated well with intraoperative findings in this study. Table 1 shows the sites of localization by intersinus ACTH ratio, prolactin-adjusted ACTH ratio, CEMRI sella, and intraoperative findings of surgeon during surgery.

Discussion

Diagnostic accuracy of BIPSS in lateralizing the pituitary adenoma using intersinus ACTH ratio is limited and comparable to MRI. Prolactin-adjusted ACTH ratio has been used to increase the accuracy of lateralization during BIPSS.[14] In this study, prolactin-normalized, we found prolactin-adjusted ACTH ratio was not better than intersinus ACTH ratio for lateralization of pituitary adenoma.

Hypercortisolemia does not affect prolactin levels, and simultaneous measurement of prolactin during BIPSS has been used as an indicator of successful catheterization, prolactin-normalized ratio for confirmation of CD, and prolactin-adjusted ACTH ratio can be used to increase the diagnostic accuracy of lateralization.[12-17] In our study, successful catheterization was confirmed with prolactin IPS: P ratio, and diagnosis of CD was confirmed with prolactin-normalized ratio. In some studies, a cut-off of 0.8 has been used for confirmation of CD.[12,16,17] We took a cut-off of ≥1.3 for prolactin-normalized ratio as suggested by Mulligan *et al.*, as this ratio has high specificity for confirmation of CD.[15] In this study, successful catheterization was achieved using IPS: P prolactin ratio, and diagnosis of CD was confirmed in all the patients using prolactin-adjusted ACTH ratio.

Initial studies showed higher diagnostic accuracy of intersinus ACTH ratio (≥1.4) for lateralization of pituitary adenoma.[17,18,19] However, several studies have shown that its diagnostic accuracy is between 50% and 70%.[20-24] Although in some studies post-CRH stimulation diagnostic accuracy of this ratio was improved when compared with basal ratio, most of the studies have shown that post stimulation ratios add little to its accuracy.[22-25] It has been shown that its ability to predict side of adenoma is comparable or lower than MRI.[26,27] In our study, all the patients achieved an intersinus ACTH ratio of ≥1.4 pre or post stimulation, but lateralization was correct in 62.5% (five of eight) of the patients, which is similar to other studies. Similarly, concordance with MRI was found in 62.5% (five of eight) of the patients, which is similar to the literature. However, MRI alone could localize adenoma in 87.5% (seven of eight) of the patients, and its accuracy of localization was 85.7% (six of seven).

Prolactin-adjusted ACTH ratio adds to the diagnostic accuracy of lateralization of adenoma during BIPSS. There are few studies in the literature on the use of prolactin-adjusted ACTH ratio during BIPSS for lateralization of pituitary adenoma.[14,17] A study by Mulligan *et al.* showed that prolactin-adjusted ACTH ratio was better than intersinus ACTH ratio, 75% versus 54% for localization of adenoma. The study by Qiao *et al.* showed that using the formula suggested by Mulligan *et al.* for calculation of prolactin-adjusted ACTH ratio, the accuracy for localization of adenoma was improved from 45% to 65% using this ratio. In our study, prolactin-adjusted ACTH ratio did not improve the accuracy of intersinus ratio for localization, 50% versus 62.5, respectively; however, in our series the number of patients was few.

In conclusion, our study showed that prolactin is a useful marker for successful catheterization and confirmation of diagnosis of CD during BIPSS. However, prolactin-adjusted ACTH ratio does not add to the accuracy of lateralization of pituitary adenoma from intersinus ACTH ratio.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Table 1: Lateralization of ACTH source on BIPSS with ACTH ratio and prolactin-adjusted ACTH ratio, MRI, and intraoperative localization of transsphenoid surgery

Age (years)/sex	Drug used during BIPSS	Dose	Lateralization with different modalities					Histopathology
			Intersinus ACTH ratio ≥1.4	Prolactin adjusted ACTH ratio	MRI	Size of tumor (mm)	TSS localization	
26/M	Vasopressin	5 unit	Right	Right	Right	6 × 5	Right	Adenoma
25/F	Human CRH	100 μm	Right	Right	Right	9 × 8	Left	Adenoma
21/F	Human CRH	100 μg	Right	Right	Right	8 × 8 × 6	Right	Adenoma
28/F	Human CRH	100 μg	Right	Left	Right	9 × 7 × 4	Right	Adenoma
25/M	Human CRH	100 μg	Right	Right	Right	5 × 3	Right	Adenoma
16/F	Human CRH	100 μg	Right	Right	Left	4.8 × 4.0	Left	Adenoma
26/F	Human CRH	100 μg	Right	Right	Normal	Normal	Right	Adenoma
25/M	Human CRH	100 μg	Right	Right	Left	6.9 × 0.5	Left	Adenoma

ACTH: Adrenocorticotropic hormone; BIPSS: Bilateral inferior petrosal sinus sampling; MRI: Magnetic resonance imaging; CRH: Corticotropin releasing hormone

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