Preoperative Octreotide Treatment in Newly Diagnosed Acromegalic Patients with Macroadenomas Increases Cure Short-Term Postoperative Rates: A Prospective, Randomized Trial

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Context: Surgery is the primary treatment of acromegaly. However, it often fails to cure the patient. New strategies that improve surgical outcome are needed.

Objective: Our objective was to investigate whether 6-month preoperative treatment with octreotide improves the surgical outcome in newly diagnosed acromegalic patients.

Patients: During a 5-yr period (1999–2004), all newly diagnosed acromegalic patients between 18 and 80 yr of age in Norway were screened and invited to participate in the study. A total of 62 patients was included in the Preoperative Octreotide Treatment of Acromegaly study.

Research Design and Methods: After a baseline evaluation, patients were randomized directly to transsphenoidal surgery (n = 30) or pretreatment with octreotide (n = 32) 20 mg im every 28th day for 6 months before transsphenoidal surgery. Cure was evaluated 3 months postoperatively primarily by IGF-I levels.

Results: According to the IGF-I criteria, 14 of 31 (45%) pretreated patients *vs.* seven of 30 (23%) patients with direct surgery were cured by surgery ($P = 0.11$). In patients with microadenomas (≤10 mm), one of five (20%) pretreated *vs.* three of five (60%) with direct surgery were cured ($P = 0.52$). In patients with macroadenomas, 13 of 26 (50%) pretreated *vs.* four of 25 (16%) with direct surgery were cured ($P = 0.017$).

Conclusions: Six-month preoperative octreotide treatment might improve surgical cure rate in newly diagnosed acromegalic patients with macroadenomas. These results have to be confirmed in future studies. (***J Clin Endocrinol Metab* 93: 2984–2990, 2008**)

In the majority (98%) of cases, acromegaly is caused by a GH-producing pituitary adenoma. Retrospective cohort studies suggest that mortality in acromegaly is at least doubled compared with the general population (1–3). Morbidity and mortality are associated with elevated levels of GH and IGF-I (1, 2, 4). The aim of treatment is to relieve

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Abbreviations: CI, Confidence interval; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; POTA, Preoperative Octreotide Treatment of Acromegaly; SSA, somatostatin analog; ULN, upper limit of normal.

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symptoms, control tumor growth, and ensure biochemical cure.

Neurosurgery is the accepted first-line treatment of acromegaly. Outcome predictors include tumor size, extrasellar extension, dural invasion, pretreatment GH levels, and the experience of the neurosurgeon (5, 6). The best reported cure rates for microadenomas and macroadenomas are 80–90% and 50–60%, respectively (5–7), whereas overall cure rates as low as 18% (39% in microadenomas and 12% in macroadenomas) have been reported (8). It is possible that studies with low cure rates remain unpublished.

Medical treatment of acromegaly with somatostatin analogs (SSAs) can lead to normalized GH and IGF-I levels (9) and relief of symptoms (10). SSA treatment may cause shrinkage of GH-secreting pituitary adenomas (9, 11). Theoretically, this could improve the likelihood of a radical resection, particularly in macroadenomas. Furthermore, it has been suggested that SSA treatment softens the tumor parenchyma and thereby facilitates tumor removal (12, 13). Finally, it has been reported that SSA pretreatment leads to a shortening of postoperative hospital stay (14).

Previous studies addressing preoperative SSA treatment and subsequent surgical cure rates are conflicting, reporting a benefit (12, 14, 15), or no difference between groups (13, 16, 17). Most of these studies were retrospective in design.

Between 1999 and 2004, we included patients in the randomized Preoperative Octreotide Treatment of Acromegaly (POTA) study to investigate whether 6-month pretreatment with the SSA octreotide would improve the surgical cure rate of newly diagnosed acromegalic patients.

Patients and Methods

Study population

In Norway all pituitary surgery is performed by one dedicated neurosurgeon at each of the five university hospitals. All five neurosurgical departments participated in the POTA study. All acromegalic patients in Norway diagnosed between September 1, 1999, and October 31, 2004, were invited to participate in the study. Inclusion criteria were: 1) newly diagnosed, previously untreated patients with GH nadir more than 2.5 μg/liter during a standard 75-g, 2-h oral glucose tolerance test (OGTT); 2) pituitary adenoma verified by a pituitary magnetic resonance imaging (MRI) scan; and 3) age between 18 and 80 yr. Exclusion criteria were: 1) immediate surgery indicated by clinical criteria, 2) pregnancy, 3) contraindications to MRI scan, and 4) patients judged not suitable to participate in the study for other reasons such as personality disorders and alcohol abuse. Power calculations indicated that 31 patients had to be included in each group to have an 80% probability of demonstrating an increase in overall cure rate from 40–75%.

There were 83 consecutive patients with previously undiagnosed acromegaly identified during the inclusion period of 5 yr and 2 months. Of these, 21 were not included due to contraindications, unwillingness to participate, or because the diagnosis of acromegaly was established after surgery. The present study presents data from the 62 (75% of eligible) included in the POTA study.

Written informed consent was obtained from each patient before inclusion, and the declaration of Helsinki was followed throughout the study. The study was approved by the Committee for Medical Research Ethics in each of the five health regions in Norway, and The Norwegian Medicines Agency.

Investigations

The diagnosis of acromegaly was made in each participating center based on a GH nadir more than 2.5 μg/liter during a 2-h, 75-g OGTT, which was performed according to the World Health Organization procedure. Samples for GH measurements were drawn at baseline and every half hour for 2 h. The presence of a pituitary adenoma was confirmed by a pituitary MRI scan (T1-weighted coronal and/or sagittal and/or axial scans, 3–5 mm slice thickness at 1.5 T).

Fasting serum samples for IGF-I analysis were drawn at baseline and 3 months postoperatively, and stored at −70 C until assayed. The samples were analyzed after the last patient had completed the study schedule, as single measurements in one run using an ELISA kit from R&D Systems, Inc. (Minneapolis, MN). The upper limit of normal (ULN) was set as the age-adjusted 95th percentile by regression based on 40 samples run in parallel with a commercial kit from CISbio Intl. (Bagnols-sur-Cèze, France), with given reference interval (18). The intraassay and interassay coefficients of variation were 3.8 and 7.2%, respectively. In two patients, sera from the postoperative evaluation were missing, and the locally measured IGF-I values against local ULN were used instead. GH analyses were performed consecutively by standard laboratory procedures at each of the participating study centers. In Norway GH values are given in mIU/liter. We chose to use a "conservative" conversion factor of 2.0 for conversion between μg/liter and mIU/liter.

MRI scans were examined retrospectively in a blinded fashion by two physicians (J.K.H. and S.L.F.), one being an experienced neuroradiologist. Adenomas measuring 10 mm or less on MRI in the largest dimension were classified as microadenomas, and larger tumors as macroadenomas. No distinction between enclosed, suprasellar, and invasive macroadenomas was made because this was not predefined in the protocol. The longest anterior-posterior, vertical, and transverse diameters were measured, and tumor volume was calculated by the formula height $\times$ width $\times$ length $\times$ 0.5 (19).

Treatment

After a baseline evaluation, patients were randomized separately for each study center in blocks of four directly to transsphenoidal surgery (direct surgery group, n = 30) or to 6-month preoperative treatment with octreotide (pretreatment group, n = 32). Randomization was completely balanced between the two study groups at the three centers that included an equal number of patients. One more patient was randomized to pretreatment with octreotide at each of the two remaining study centers that included an odd number of patients.

To reduce the risk of gastrointestinal adverse effects in the pretreatment group, octreotide was initiated at a dose of 50 μg sc three times a day for the 1st week and 100 μg sc three times a day for the 2nd week. From the 3rd week on, the patients received octreotide LAR (Novartis International AG, Basel, Switzerland) 20 mg im every 28th day for 6 months. They underwent transsphenoidal surgery within 28 d of the last injection. If surgery was delayed, an extra octreotide LAR injection was given before surgery. Therefore, all patients in the pretreatment group underwent surgery with therapeutic levels of the study medication. All patients were operated by standard microneurosurgical technique via the transsphenoidal route. During surgery, the consistency of the adenoma was graded as soft, mixed, or firm, and the neurosurgeon evaluated the operative result as radical *vs.* subtotal resection. Peripostoperative and postoperative surgical complications and duration of postoperative hospital stay were registered. If indicated, octreotide could be administered after the 3-month postoperative evaluation.

Aims of the study

The aim of the study was to investigate whether 6-month treatment with the SSA octreotide before transsphenoidal surgery in newly diagnosed acromegalic patients would improve the outcome, using cure rate at evaluation 3 months postoperatively as the primary endpoint. Secondary endpoints included postoperative hospital stay duration and complication rates.

Definition of cure

Cure was evaluated 3 months postoperatively primarily by fasting IGF-I less than or equal to age-adjusted ULN (20, 21). In addition, a GH nadir less than or equal to 1.0 μg/liter during an OGTT was used.

Statistics

All statistical procedures, except estimation of confidence intervals (CIs), were performed with SPSS version 13.0 (SPSS, Inc., Chicago, IL). CIs were estimated by binominal exact estimations using StataCorp LP, version 9.0 (College Station, TX). Data are presented as absolute numbers or means and SD values. Two-sided Fisher's exact test for categorical variables and two-sided *t* tests for independent samples for continuous variables were used. No adjustments for multiple testing were performed. *P* values less than 0.05 were considered significant.

Results

Baseline data

There were 83 patients with previously undiagnosed acromegaly identified during the inclusion period of 5 yr and 2 months. With 4.5 million inhabitants in Norway, this equals an incidence of acromegaly in Norway of 3.6 cases per million per year.

At baseline there were significantly more males than females ($P = 0.042$) and lower IGF-I levels ($P = 0.004$) in the pretreatment group. However, when evaluating IGF-I as percentage of age-adjusted ULN, this difference lost its significance ($P = 0.056$). Patient age, working status, GH nadir during an OGTT, tumor volume, and ratio between microadenomas and macroadenomas did not differ between groups (Table 1). All the included patients were Caucasians. One male patient with a microadenoma did not undergo surgery because the tumor regressed during pretreatment. He was excluded from analyses of surgical cure rates. None of the patients withdrew from the study or was lost to follow-up during the study period.

MRI scans

By central blinded evaluation of baseline MRI scans, there were 11 microadenomas (≤10 mm in the largest diameter) and 51 macroadenomas. In six patients, at least one of the MRI scans was not available for central evaluation. For these patients the classification of adenoma size and estimation of tumor volume were based on local evaluation of the tumor during the study.

At inclusion there were six adenomas in the direct surgery group with signs of cavernous sinus invasion. In the pretreatment group, there were four adenomas with signs of cavernous sinus invasion both before octreotide treatment and the same number after pretreatment but before surgery.

Primary outcome

IGF-I criteria

Cure, defined solely by IGF-I less than or equal to the ULN 3 months postoperatively, was established in 14 of 31 (45%) pretreated patients *vs.* seven of 30 (23%) direct surgery patients ($P = 0.11$) (Table 2). Subdividing tumors according to initial size, one of five pretreated patients *vs.* three of five direct surgery patients with microadenomas were cured ($P = 0.52$). In patients with macroadenomas, 13 of 26 (50%) pretreated patients *vs.* four of 25 (16%) direct surgery patients were cured ($P = 0.017$).

Cure was also estimated for age-adjusted cutoff levels of IGF-I ranging from 80–120% of the ULN (Table 3). In macroadenomas, pretreatment significantly increased cure rates evaluated by IGF-I at cutoff levels ranging from 95–120% of the ULN ($P = 0.009–0.034$).

None of the six patients with signs of cavernous sinus invasion in the direct surgery group was cured. One of four patients with signs of cavernous sinus invasion after pretreatment with octreotide was cured.

The overall cure rates according to IGF-I levels ranged from 0–62% in the participating study centers, with the smaller ones performing as well as the larger one (Table 2).

Combined criteria

When adding a GH nadir during an OGTT less than or equal to 1.0 μg/liter to the cure criteria, three patients, all with macroadenomas, lost their status of being cured (GH nadirs of 1.8, 2.9, and 3.5 μg/liter). Thus, the overall cure rate in the total study population was reduced to 35% (pretreated) and 23% (direct surgery), respectively ($P = 0.40$). In macroadenomas 38% (10 of 26 pretreated) *vs.* 16% (four of 25 direct surgery) of patients were cured when adding GH nadir during an OGTT to the cure criteria ($P = 0.12$).

TABLE 1. Baseline data according to treatment group

	Pretreatment (n = 32)	Direct surgery (n = 30)	*P* value[a]
Age (yr)	49.9 ± 13.8	45.1 ± 12.3	0.79
No. of males/females	20/12	11/19	0.042[b]
Working status (working/sick leave) (no.)	20/12	16/14	0.47[b]
GH nadir during OGTT (μg/liter)	19.3 ± 19.9	16.7 ± 13.2	0.55
IGF-I (nmol/liter)	92.1 ± 32.0	132.0 ± 60.3	0.004[c]
IGF-I (% of ULN)	326 ± 116	415 ± 222	0.056
Tumor classification (micro/macro) (no.)	6/26	5/25	0.83[b]
Tumor volume (cm^3)	1.66 ± 1.38	1.96 ± 2.60	0.57

Values given as means ± SD values if otherwise not stated.

[a] *P* values given as independent samples *t* tests used if otherwise not stated.

[b] *P* values given as two-sided Pearson χ^2 tests.

[c] This was also significantly different ($P < 0.05$) for both men and women.

TABLE 2. Cure according to IGF-I less than or equal to ULN and GH nadir less than or equal to 2.0 mIU/liter during OGTT 3 months postoperatively

	According to IGF-I					According to IGF-I and GH nadir				
Treatment	No.	Cured	Not cured	*P* value[a]	Cure (95% CI)	No.	Cured	Not cured	*P* value[a]	Cure (95% CI)
All										
Pretreatment	31	14	17		45% (27–64)	31	11	20		35% (19–55)
Direct surgery	30	7	23	0.11	23% (10–42)	30	7	23	0.40	23% (10–42)
Microadenomas										
Pretreatment	5	1	4		20% (1–72)	5	1	4		20% (1–72)
Direct surgery	5	3	2	0.52	60% (5–95)	5	3	2	0.52	60% (5–95)
Macroadenomas										
Pretreatment	26	13	13		50% (30–70)	26	10	16		38% (20–59)
Direct surgery	25	4	21	0.017	16% (5–36)	25	4	21	0.12	16% (5–36)
All										
Center 1										
Pretreatment	15	5	10		33% (12–62)	15	5	10		33% (12–62)
Direct surgery	14	1	13	0.17	8% (2–34)	14	1	13	0.17	8% (2–34)
Centers 2–5										
Pretreatment	16	9	7		56% (30–80)	16	6	10		38% (15–65)
Direct surgery	16	6	10	0.48	38% (15–65)	16	6	10	1.00	38% (15–65)

[a] *P* value given as two-sided Fisher's exact test for difference between treatment groups.

Tumor volume

In the pretreated patients, both initial tumor volume (1.98 ± 1.61 ml *vs.* 1.49 ± 1.13 ml; $P = 0.33$) and tumor volume change during pretreatment (−38 ± 30% *vs.* −31 ± 29%; $P = 0.56$) were equally distributed among cured and noncured patients, respectively. In addition, when performing separate analyses with the macroadenomas, initial tumor volume and percent change during pretreatment were equal (data not shown).

Three months postoperatively tumor volume was 0.51 ± 0.73 ml in pretreated patients and 0.80 ± 1.45 ml in direct surgery patients ($P = 0.34$).

Secondary outcomes

Tumor consistency

In pretreated patients the tumor was classified as firm in eight and mixed in one patient. In direct surgery patients, no firm and five mixed tumors were identified. The rest of the tumors were soft ($P = 0.002$). Data on two pretreated and one direct surgery patient were missing.

Surgical complications

Immediate surgical complications were reported in four patients (two transient liquorrhea, one hematoma, and one tran-

TABLE 3. Cure according to IGF-I less than or equal to ULN 3 months postoperatively

IGF-I as percentage of ULN	Treatment group	All			Microadenomas			Macroadenomas		
		Cured	Not cured	*P* value[a]	Cured	Not cured	*P* value[a]	Cured	Not cured	*P* value[a]
80%	Pretreatment	8	23		0	5		8	18	
	Direct surgery	5	25	0.53	3	2	0.17	2	23	0.075
85%	Pretreatment	9	22		0	5		9	17	
	Direct surgery	7	23	0.77	3	2	0.17	4	21	0.20
90%	Pretreatment	11	20		1	4		10	16	
	Direct surgery	7	23	0.40	3	2	0.52	4	21	0.12
95%	Pretreatment	13	18		1	4		12	14	
	Direct surgery	7	23	0.17	3	2	0.52	4	21	0.034
100%	Pretreatment	14	17		1	4		13	13	
	Direct surgery	7	23	0.11	3	2	0.52	4	21	0.017
105%	Pretreatment	15	16		1	4		14	12	
	Direct surgery	8	22	0.11	3	2	0.52	5	20	0.020
110%	Pretreatment	15	16		1	4		14	12	
	Direct surgery	8	22	0.11	3	2	0.52	5	20	0.020
115%	Pretreatment	16	15		1	4		15	11	
	Direct surgery	8	22	0.067	3	2	0.52	5	20	0.009
120%	Pretreatment	17	14		1	4		16	10	
	Direct surgery	10	20	0.12	3	2	0.52	7	18	0.025

[a] *P* value given as two-sided Fisher's exact test for difference between treatment groups.

sient diabetes insipidus) in the pretreated group *vs.* two patients (one transient liquorrhea, one sinusitis) with direct surgery ($P = 0.67$). During the postoperative period, before the 3-month postoperative evaluation, further complications were seen. Persistent surgical complications were seen in three patients (one anterior pituitary insufficiency, one diabetes insipidus, one minor bitemporal visual field deficit, and one nose complication) in the pretreated group *vs.* four patients (one anterior pituitary insufficiency, one diabetes insipidus, one olfactory nerve dysfunction, and one eye muscle palsy, most probably secondary to progressive cavernous sinus growth) in the group with direct surgery ($P = 0.71$).

Altogether, surgical complication was seen in two of the 21 (10%) cured patients and in nine of 40 (23%) noncured patients ($P = 0.30$). In patients without surgical complications, eight of 39 (21%) adenomas were classified as mixed or solid *vs.* four of 14 (29%) mixed or solid adenomas in patients with surgical complications ($P = 0.54$). Data were missing in eight patients.

The postoperative hospital stay was similar between groups, being 3.7 ± 1.8 d in pretreated patients *vs.* 3.6 ± 1.6 d in direct surgery patients ($P = 0.54$).

Surgical resection evaluation

In all the 21 patients cured by the IGF-I criteria, cure was anticipated by the neurosurgeon. However, surgical cure were also anticipated in 27 of the 37 noncured patients. Noncure was anticipated in three of 29 pretreated patients *vs.* seven of 29 direct surgery patients ($P = 0.16$). Data were missing on three patients.

Discussion

The present prospective, randomized study indicates that pretreatment of newly diagnosed acromegalic patients with octreotide before transsphenoidal surgery leads to an increased surgical cure rate in patients with macroadenomas, whereas no benefit, or even a possible adverse effect, was seen in patients with microadenomas. Our findings are in accordance with some (12, 14, 15) but not all previous reports (13, 16, 17).

In acromegaly, levels of IGF-I as well as mean daytime GH levels and GH nadir during an OGTT can be used as criteria for cure (21). However, IGF-I measurements correlate better than GH levels with clinical disease activity (22); and in patients with very mild disease, IGF-I is elevated, whereas GH secretory parameters are virtually normal (23).

In the present study, only stored fasting serum was available for centralized analyses. Therefore, central quality control was only possible for IGF-I measurements and not for dynamic GH measurements (24). Therefore, and in accordance with the protocol, we primarily used IGF-I as criteria for cure. This decision was also supported by the fact that in the general population, both GH and IGF-I levels decline with increasing age, whereas age-adjusted reference values are available for the latter only (25).

The biochemical criteria for cure based on different commercial assays for GH and IGF-I are presently a matter of debate (24, 26). We set the primary endpoint ULN according to the age-adjusted 95th percentile found by regression in our own laboratory. This might have induced a systematic error with respect to the ULN used. However, interassay variability was thereby reduced to a minimum, thereby optimizing the evaluation of cure at a given level. However, the overall very low cure rate might be influenced by this method but should not affect the difference between the two treatment arms. Moreover, additional analyses of cure rates according to the ULN ranging from 95–120% of the values used in the present study all showed significant benefit in the group of pretreated patients with macroadenomas. This way of presenting IGF-I data is untraditional. Nevertheless, given the present discussion on the IGF-I measurements and reference ranges, we believe this presentation is valuable in underlining that our results are relatively independent of the values for the ULN used.

In the present study, evaluation of cure was performed 3 months postoperatively, which is in accordance with present clinical routine in Norway. This means that the patients were evaluated at least 12 wk, but some as long as 16 wk, after the last injection with octreotide. Pharmacokinetic studies indicate that by that time, levels of octreotide are well below therapeutic levels (27–29). Furthermore, withdrawal and dose extension studies indicate that in the great majority of patients, octreotide effects have disappeared 12 wk after the last injection (30–32). Although this does not quite fit with the present guidelines demanding at least a 4-month delay in evaluation when using a long-acting SSA (33), this essentially excludes the possibility that the observed effect 3 months postoperatively is only representing a "hangover" effect of preoperative octreotide treatment.

Overall, the cure rates observed in the POTA study were 23% in newly diagnosed acromegalic patients treated directly with transsphenoidal surgery, and 45% in patients pretreated for 6 months with octreotide LAR and still being on treatment during the surgical procedure. In patients with macroadenomas, the cure rate tripled from 16% in direct surgery patients to 50% in octreotide-pretreated patients. This effect was evenly distributed between the largest and smaller study centers (data not shown). This is an impressive increase, which is only possible when cure rates in control patients are low. In addition, a low overall cure rate in direct surgery patients (29.7%) was also observed in one previous study indicating the benefit of SSA pretreatment before surgery (14). Thus, one intriguing question is whether the effect of pretreatment with octreotide depends on the low cure rate seen in direct surgery patients in the present study. It should be emphasized that the low cure rate also reflects the strict criteria for cure used. Moreover, in a pragmatic multicenter study like this one, overall cure rates are expected to be lower than results from a center of excellence. A low overall cure rate has recently been presented in the Belgian registry on acromegaly study that also used strict criteria for cure (34).

It is interesting to observe the absolute numbers for patients with microadenomas. The results might indicate an adverse effect of pretreatment. However, there were too few patients with microadenomas in the study to draw firm conclusions ($P = 0.52$). Nevertheless, this is an important clinical question, which should be explored in future studies.

Contrary to previously published observations indicating that treatment with a SSA tends to increase the softness of the adenomas, this prospective randomized study showed a signif-

icant increase in the firmness of the adenomas. Therefore, it is not likely that our findings depend on the open design and the possible awareness by the neurosurgeons of previous data indicating increased softness of the adenomas by SSA treatment (12).

If octreotide treatment increases the firmness of the adenoma, this might affect the surgical outcome negatively. However, we found no indication of an adverse effect of firm tumor consistency on surgical cure in microadenomas or macroadenomas (data not shown). One possible explanation is that SSA induced changes in tumor consistency might assist in the discrimination between the adenoma and surrounding tissue, including normal pituitary tissue, and, thus, facilitate surgical cure. On the other hand, a change in tumor consistency might be more pronounced with more prolonged treatment with SSAs. If so, this might evolve as a relative contraindication for long-term primary octreotide treatment of acromegalic patients that later might be considered for pituitary surgery. Therefore, future studies should also aim to evaluate the optimum duration of preoperative SSA treatment.

In contrast with one previous report (14), pretreatment with octreotide did not affect the duration of hospital stay. However, the standard care of pituitary surgery patients has changed markedly over the last decade, which might have influenced the results. Furthermore, we did not find any difference in surgical complication rates between the study groups.

Preliminary results from our study, based on local classification of tumor size and IGF-I measurements, were presented at the European Congress of Endocrinology in Gothenburg in September 2005. No difference between study groups was reported. The discrepancies between these preliminary results and the final results are due to reclassification of initial tumor size and cure by centralized MRI and IGF-I evaluations. These changes were mainly related to one study center. This emphasizes the importance of central quality evaluation of data and measurements in multicenter studies. This is illustrated by the discrepancy between locally and centrally measured IGF-I levels, which supports our decision to rely primarily on a centrally measured variable (Fig. 1).

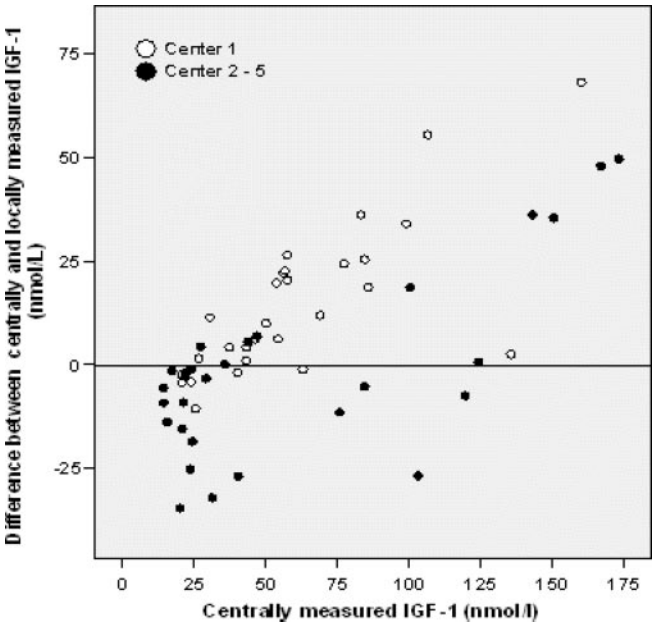

FIG. 1. Bland-Altman plot of locally and centrally measured IGF-I levels 3 months postoperatively.

In conclusion, the POTA study indicates that pretreatment with octreotide before transsphenoidal surgery improves surgical cure rates in patients with GH-secreting pituitary macroadenomas. The effect on microadenomas is inconclusive due to small numbers. Pretreatment does not affect surgical complications or duration of hospital stay. These findings have to be confirmed by future well-designed studies.

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