

Presurgical Octreotide: Treatment in Acromegaly

Achille Stevenaert and Albert Beckers

One hundred seventy-two acromegalics who were operated on using the trans-sphenoidal approach underwent long-term follow-up evaluation. Sixty-four received 100 µg octreotide subcutaneously three times daily: for 3 to 6 weeks before surgery in 14 patients (group 1); and for 3 to 9 months in 41 and for 13 to 39 months in nine (n = 50, group 2). In 18 group 2 patients, the dose was increased stepwise to 500 µg three times daily because of incomplete suppression of growth hormone (GH)/insulin-like growth factor-1 (IGF-1). Tumor shrinkage was seen in 60% within 3 weeks, being nearly maximal by 3 to 4 months. More group 2 patients had greater than 25% tumor shrinkage (14 of 48 v 1 of 14 in group 1). Clinical response was excellent or good in 89%. Decrease in soft-tissue swelling and weight loss, and improved vitality, performance, carbohydrate metabolism, and cardiovascular function, facilitated anesthetic and surgical management; tumor removal was easy in virtually all cases. In all 64 patients, GH levels decreased by ≥50%, and to <2 µg/L in three of 14 patients initially and 25 of 50 patients after more prolonged treatment. IGF-1 levels decreased to normal in seven of 14 group 1 and 31 of 50 group 2 patients. Light and electron microscopy showed that adenomatous tissue exposed to octreotide had lysosomal accumulation, amyloid deposition, mild to moderate perivascular fibrosis, and moderate size reduction in both cytoplasmic and nuclear areas, with virtually no cellular complications. Remission with enclosed adenomas was greater (*P* < .05) than for the 108 patients not treated with octreotide; there was no difference for invasive adenomas. Octreotide use for 3 to 4 months before surgery can be recommended.

Copyright © 1996 by W.B. Saunders Company

SURGICAL MANAGEMENT of acromegaly is directed towards removing the pituitary adenoma to relieve compression on the pituitary gland and surrounding structures and normalize biochemical parameters. Results of trans-sphenoidal surgery have been reported in large series. Preoperative octreotide (a somatostatin analog) may improve surgical outcome. It has been shown to improve clinical symptoms in the majority of acromegalic patients, to decrease plasma growth hormone (GH) levels to 5 µg/L in almost 50% of cases, and to induce varying degrees of tumor shrinkage.¹ Controlled data from large series are lacking; we present data from 172 acromegalic patients.

PATIENTS AND METHODS

The patient series consisted of 172 acromegalics (79 male and 93 female; age range, 15 to 70 years) who were operated on using the trans-sphenoidal approach and underwent long-term follow-up evaluation (range, 0.5 to 24 years; mean, 6.4 years). Presurgical octreotide treatment was given to 64 patients. Therapy was initiated with 100 µg octreotide subcutaneously thrice daily and maintained for 3 to 6 weeks before surgery in 14 patients (group 1); and for 3 to 9 months in 41 and for 13 to 39 months in the remaining nine patients (n = 50, group 2). In 18 group 2 patients, the dose was increased stepwise to 500 µg thrice daily because of incomplete suppression of GH/insulin-like growth factor-1 (IGF-1).

Serum GH and IGF-1 levels were assayed before any treatment, during octreotide therapy, and after surgery. Cure of the disease was defined as GH levels less than 2 µg/L and less than 1 µg/L during an oral glucose tolerance test, and IGF-1 levels within normal limits.

In patients who were given octreotide, pituitary computed tomographic (CT) scans and/or magnetic resonance imaging (MRI) were performed before octreotide treatment, after 3 weeks of treatment in 14 patients, and after periods ranging from 2 to 14 months in 48 patients (two patients had no radiological controls).

RESULTS

The clinical response was excellent or good in 89% of patients. Decrease in soft-tissue swelling and weight loss, increased vitality and performance, amelioration of carbohydrate metabolism, and improved cardiovascular function facilitated anesthetic and surgical management.

In all 64 patients, octreotide administration resulted in a ≥50% reduction of initial GH levels (Fig 1). GH levels decreased to less than 2 µg/L in three of 14 patients during short-term treatment and in 25 of 50 patients during more prolonged treatment. IGF-1 levels decreased to within normal limits in seven of 14 patients and 31 of 50 patients, respectively.

Changes in pituitary size in the 64 patients pretreated with octreotide were seen in 59.7% of cases (Table 1). The higher dose and longer duration of pretreatment in group 2 patients led to an increased incidence of marked (>25%) tumor shrinkage (1 of 14 v 14 of 48 in groups 1 and 2, respectively).

During surgery, the adenomatous tissue was soft in 52 cases, firm in nine, and hard in three. Tumor removal was easy in all cases, except three in which the tumor was hard and three others in which the tumor was divided by fibrous septa. No noticeable changes were observed in the apparently healthy pituitary tissue.

With light and electron microscopy, significant findings in adenomatous tissue exposed to octreotide were lysosomal accumulation, amyloid deposition, mild to moderate perivascular fibrosis, and moderate size reduction in both cytoplasmic and nuclear areas. With the exception of a few cases with hemorrhagic necrosis, no cell necrosis, endothelial

From the Department of Neurosurgery and Endocrinology, University Hospital, Liege, Belgium.

Address reprint requests to Professor Achille Stevenaert, MD, Department of Neurosurgery and Endocrinology, CHU Sart-Tilman, Bat B23, 4031 Angleur, Belgium.

Copyright © 1996 by W.B. Saunders Company
0026-0495/96/4508-1012\$03.00/0

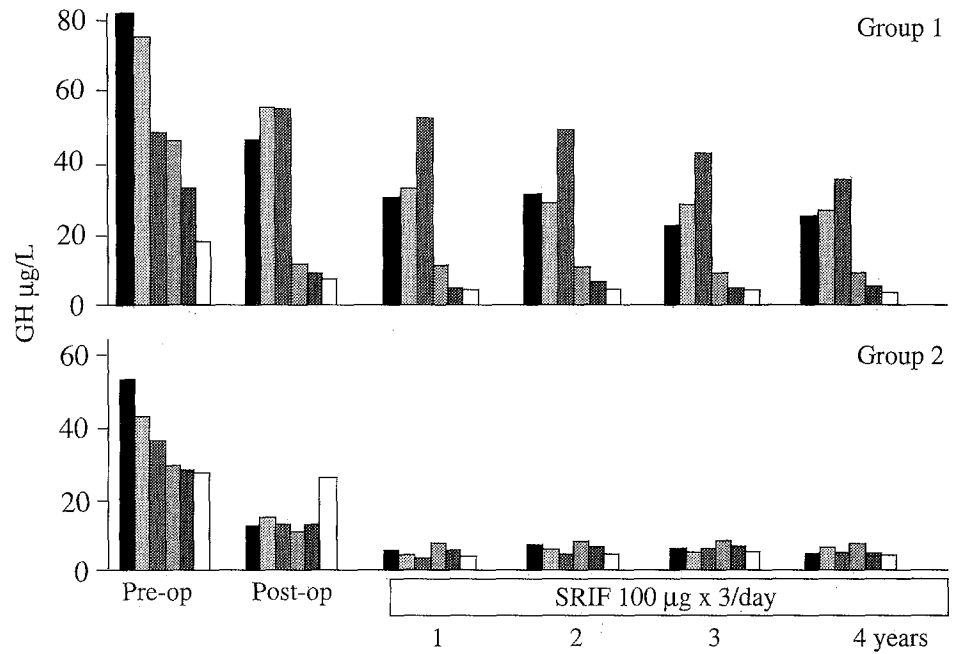


Fig 1. GH levels in acromegalics treated with octreotide before surgery. Group 1 patients pretreated with somatostatin for 3 to 6 weeks; group 2 pretreated for 3 to 39 months.

injury, platelet aggregation, vascular damage, or thrombosis was noted.

Surgical cure rates in the 64 pretreated patients were compared with those of the 108 patients who did not receive octreotide before surgery (Table 2). In the whole series, the remission rate was higher in small- and medium-sized (diameter <15 mm) enclosed adenomas than in large (diameter > 16 mm) enclosed adenomas or invasive adenomas. The incidence of remission in enclosed adenomas was significantly higher ($P < .05$) in pretreated patients than in untreated patients. No difference was seen in invasive adenomas.

DISCUSSION

The suppressive action of octreotide on GH secretion is well established, as is the resulting clinical improvement and pituitary adenoma shrinkage. From a surgical point of view, clinical improvement may facilitate anesthesia management and lower mortality and/or morbidity due to surgical risks, allowing patients to undergo surgery and giving them a chance to be cured. In our series, varying degrees of tumor shrinkage were seen in 60% of cases. Tumor size reduction occurred within the first 3 weeks after octreotide

administration and appeared as nearly maximal after 3 to 4 months of treatment.

The surgical outcome in acromegaly is dependent on the experience of the surgical team, and on the pathological characteristics of the pituitary adenoma, such as adenoma size, tissue consistency, and degree of invasiveness into the pituitary gland and adjacent structures. Tumor shrinkage and softening of adenomatous tissue aided complete removal of the tumor and were probably responsible for better surgical outcome in octreotide-pretreated patients suffering from enclosed adenomas. Recent works^{2,3} have suggested the possibility of improved surgical results in invasive adenomas; however, the series have been too short and the criteria for biochemical cure were not severe enough, so that definitive conclusions could not be drawn. Moreover, since morphological studies⁴ did not show any signs of cytotoxic or vascular effects of octreotide on adenomatous tissue, it is unlikely to be helpful in transforming an invasive adenoma into an enclosed adenoma.

From our experience, we conclude that presurgical octreotide treatment in acromegaly is effective in improving clinical condition, reducing pituitary tumor size, and softening adenomatous tissue. These effects facilitate better anesthesia management and surgical procedures and improve surgical outcome. Octreotide administration for 3 to 4 months before surgery can be recommended.

Table 1. Pituitary Tumor Size Reduction During Octreotide Therapy (measured using serial CT scans and/or MRI)

Tumor Size After Treatment	Group 1 (n = 14)	Group 2 (n = 50)	Total (n = 64)
No measurement	0	2	2
No significant change	7	18	25
Shrinkage < 25%	6	16	22
Shrinkage > 25%	1	14	15

NOTE. Group 1 pretreated for 3 to 6 weeks. Group 2 pretreated for 3 to 39 months.

Table 2. Surgical Remission Rate in 172 Acromegalic Patients

Adenoma Grade	Adenoma Size (mm)	All Cases		Untreated Cases		Pretreated Cases	
		No.	%	No.	%	No.	%
Enclosed	≤ 15	64	84	31	74	33	94
Enclosed	≥ 16	27	67	18	61	9	89
Invasive	—	81	32	59	32	22	32

REFERENCES

1. Vance ML, Harris AG: Long-term treatment of 189 acromegalic patients with the somatostatin analog octreotide. Results of the International Multicenter Acromegaly Study Group. *Arch Intern Med* 151:1573-1578, 1991
2. Barkan AL, Lloyd RV, Chandler WP, et al: Pre-operative treatment of acromegaly with long-acting somatostatin analog SMS 201 995: Shrinkage of invasive pituitary macroadenomas and improved surgical remission rate. *J Clin Endocrinol Metab* 67:1040-1048, 1988
3. Lucas-Morante T, Garcia-Uria J, Estrada J, et al: Treatment of invasive growth hormone pituitary adenomas with long-acting somatostatin analog SMS 201-995 before transsphenoidal surgery. *J Neurosurg* 81:10-14, 1994
4. Beckers A, Kovacs K, Horvath E, et al: Effect of treatment with octreotide on the morphology of growth hormone-secreting pituitary adenomas: study of 24 cases. *Endocr Pathol* 2:123-131, 1991
5. Stevenaert A, Beckers A: Presurgical octreotide treatment in acromegaly. *Acta Endocrinol* 129:18-201, 1993 (suppl 1)
6. Stevenaert A, Harris AG, Kovacs K, et al: Presurgical octreotide treatment in acromegaly. *Metabolism* 41:51-58, 1992 (suppl 2)