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Original article

The dose of somatostatin analogues during pre-surgical treatment is a key factor to achieve surgical remission in acromegaly

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Abstract:

Purpose: To determine whether pre-surgical treatment using long-acting somatostatin analogues (SSAs) may improve surgical outcomes in acromegaly.

Methods: Retrospective study of 48 patients with acromegaly operated by endoscopic transsphenoidal approach and for first time. Surgical remission was evaluated based on the 2010 criteria.

Results: Most patients, 83.3% (n=40), harboured macroadenomas and 31.3% (n=15) invasive pituitary adenomas. Fourteen patients were treated with lanreotide LAR and 6 with octreotide LAR, median monthly doses of 97.5 [range 60-120] and 20 [range 20-30] mg, respectively, for at least 3 months preoperatively. Presurgical variables were comparable between pre-treated and untreatred patients (P>0.05).

Surgical remission was more frequent in those pre-treated with monthly doses ≥90 mg of lanreotide or ≥30 mg of octreotide than in untreated or pre-treated with lower doses (OR=4.64, P=0.025). However, no differences were found between pre-treated and untreated patients when lower doses were included or between those treated for longer than 6 months compared to those untreated or pre-treated for shorter than 6 months. Similarly, no differences were found either in terms of surgical or endocrine complications (OR=0.65, P=0.570)), independently of the doses and the duration of SSA treatment (P>0.05).

Conclusions: The dose of SSAs is a key factor during pre-surgical treatment, since the beneficial effects in surgical remission were observed with monthly doses equal or higher than 90 mg of lanreotide and 30 mg of octreotide, but not with lower doses.

Keywords: acromegaly; somatostatin analogues; presurgical treatment; surgical remission.

1. Introduction

Acromegaly is associated wth a two-fold risk mortality, mainly due to neoplastic disease, but also cardiovascular, respiratory and metabolic complications [1]. However, restoration of normal GH secretion by the different modalities of treatment available improves the prognosis and life expectancy of these patients. At present, transsphenoidal surgery is the first-line therapeutic option in most patients with newly diagnosed acromegaly [2].

However, primary or pre-surgical treatment with somatostatin analogues (SSAs) in patients who are not expected to be cured by surgery could be considered [3,4]. The surgical remission rate is stabilized around 60–75 % in large series from expert centres, but the overall remission rates decreased to 40-60% for macroadenomas and even 10-20% for invasive macroadenomas [5].

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SSAs play an important role in the treatment of GH-secreting pituitary adenomas (PAs) owing to the significant effectiveness in both serum GH reduction and tumor shrinkage [6–8]. However, the question of whether preoperative therapy with SSAs may improve surgical outcome in patients with acromegaly has not been definitively answered [9][10]. Surgical remission and better surgical results have been reported in patients pre-treated with SSAs [11,12], although the effect remains inconsistent. Some studies showed that only macroadenoma and invasive macro- or giant PAs benefited from the pre-treatment with SSAs [13][14], whereas others reported advantage in all acromegalic patients

[15][16]. On the other hand, some studies showed no apparent beneficial effect of SSAs pre-treatment on surgical outcome [17,18]. Due to the absence of consistent evidence, clinical guidelines for acromegaly recommend SSAs pre-treatment only for selected patients and patients with severe pharyngeal thickness, sleep apnoea syndrome, or high-output heart failure [2]. Therefore, the issue of SSAs pre-treatment to improve surgical remission and/or reduce perioperative morbidity is yet to be settled and further studies are necessary to clarify this question.Thus, the aim of our study was to evaluate whether presurgical treatment with SSAs affects surgical outcomes in terms of surgical remission rates and complications in patients with acromegaly. In addition, we analysed different subgroups of GH secreting-PAs and doses and durations of pre-treatment with SSAs to determine whether there are specific presurgical or pre-treatment features associated with a greater chance of a favourable effect of SSAs.

2. Materials and Methods

Patients

Data were collected from a retrospective database of all endonasal endoscopic procedures to pituitary tumors performed at the Hospital Ramón y Cajal and Hospital HM Puerta del Sur between 2008 and 2019. Out of 232 patients with PAs, 56 presented acromegaly. Inclusion criteria were: i) Confirmed acromegaly diagnosis (GH levels >1 ng/mL after oral glucose tolerance test (OGTT) and fasting plasma IGF-1 levels above reference ranges for age and sex [2], ii) operated by the same neurosurgeon (VRB) and iii) by endoscopic endonasal transsphenoidal approach. Exclusion criteria were: i) Previous pituitary surgery and/or radiotherapy, ii) not available information of clinical, hormonal, and radiological tumor characteristics in the pre- and postoperative stage and iii) patients operated by approaches different from transsphenoidal surgery. A total of 48 patients were included in the study (Figure 1).

Because near-maximal tumor shrinkage is usually reached within 3 months from the beginning of the therapy, patients in whom the duration of SSAs therapy was less than 3 months were considered as untreated (one patient received only one dose of lanreotide and another two doses of octreotide before surgery). Twenty patients were treated with long-acting SSA in the preoperative stage and the remaining underwent surgery directly. In most cases, the referring endocrinologist decided whether to initiate therapy with SSAs based on tumor size, invasiveness and/or waiting list (Figure 1). The pituitary tumors register was approved by the local ethical committees of both hospitals.

Assays and Remission Criteria

All anterior pituitary hormones including GH and IGF-1were measured pre- and postoperatively following our protocol [5]. Presurgical measurements were performed at time of diagnosis, before any medical or surgical treatment.

GH and IGF-1 were measured by chemiluminescence assays. Before May 2013 they were measured with IMMULITE 2000; between May 2013 and October 2018 with Isys (IDS Vitro) and after then, by Liaison XL (Diasorin). The intraassay coefficient of variation (CV) was <10% with all methods. The assays were calibrated according to the WHO international standard for GH and IGF-1 with code 98/574 and 02/254, respectively.

We have evaluated surgical remission at least 3 months after surgery (and at least 4 months in those pre-treated with SSA [19]), using the 2010 criteria (random GH <1 ng/mL or GH nadir <0.4 ng/mL, on OGTT, along with a normal age- and sex-matched IGF-1) [20].

Clinical definitions

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Visual evaluation was performed using our protocol [10], and visual involvement was defined as the presence of any degree of visual acuity compromise, from mild visual acuity involvement to severe and from partial to complete field conditions. For the diagnosis of hypopituitarism, we have employed the same definition as we have previously reported in previous studies [21]

Radiological assessment

Magnetic resonance imaging (MRI) studies were performed with 1.5T, GE 450w. MRI, sagittal and coronal T1, T2-weighted and dynamic sequences, with gadolinium contrast being performed preoperatively and before any medical or surgical treatment, and 3-6 months postoperatively. Based on the largest diameter of the adenoma, PAs were categorized into microadenoma (< 10 mm), macroadenoma (≥10 mm), very large (≥ 30mm) and giant PA (≥40 mm). Tumors were considered invasive into the cavernous sinus when they corresponded to Grade 3 or 4 of the classification of Knosp.

Surgical procedure and histological analysis

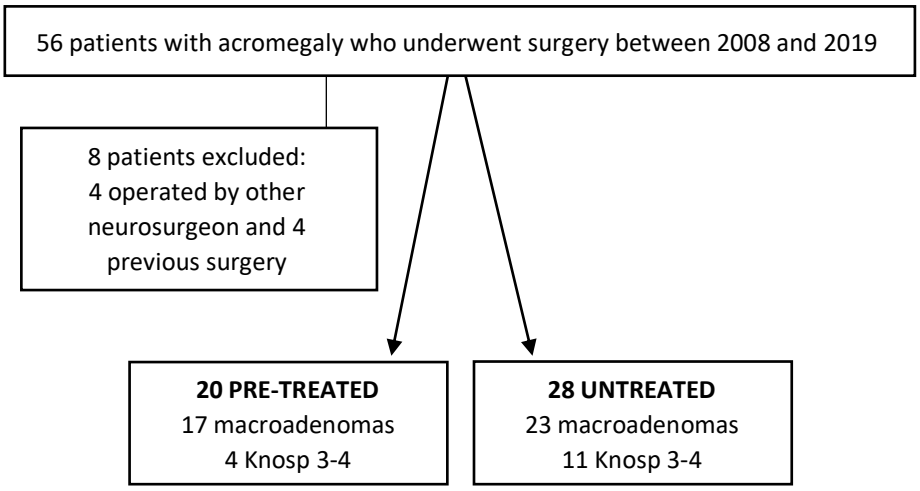
Surgeries were performed by an experienced endoscopic pituitary surgeon (VRB) with more than 300 endoscopic pituitary surgeries performed and an average of 35 pituitary surgeries/year during the last ten years. A conventional endoscopic endonasal aproach was used in all surgeries. Tumor consistency was classified in hard tumors when they were difficult to remove with ring curettes and required sharp dissection, bipolar cautery and/or surgical aspirator and the rest were classified as soft tumors [22].

Surgically removed specimens were immediately fixed in 10% buffered formalin and subsequently embedded in paraffin. Standard H & E–stained sections were used for diagnosis. Immunohistochemical complementary techniques were performed in addition to morphological evaluation to classify specimens based on the 2017 WHO Classification. The following antibodies were used: GH (clone A0570, Dako), cytokeratin (clone CAM5.2, Roche) and Ki67 (clone MIB-1, Dako).

Statistical analysis

The statistical analysis was performed with STATA.15. In the descriptive analysis, categorical variables were expressed as absolute and relative (%) frequencies; quantitative variables were expressed as mean ± standard deviation or median and range if normal assumption was not fulfilled. The normality assumption was studied with Shapiro-Wilk test and the variance homogeneity assumption with the Levene test. For the comparison of differences in continuous parameters, Student's T tests and lineal regression analysis were performed, and for the comparison of categorical variables between independent samples, the chi-squared-test and the logistic regression analysis were performed. Nonparametric ROC curve analysis was used to determine which doses of SSA was the most effective for surgical remission. In all cases, a two-tailed P value < 0.05 was considered as statistically significant.

Figure 1. Flowchart of the study design.



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A total of 48 acromegalic patients were included in the study, 20 in the pre-treated group and 28 in the untreated group.

3. Results

Baseline characteristics

Baseline characteristics are reported in Table 1. Twenty patients were treated with SSA in the preoperative stage (Octreotide LAR intramuscular, 6 cases; Lanreotide Autogel subcutaneous, 14 cases) for at least 3 months preoperatively (median, 6.5 months; range, 3-84 months). Seventy percent (n=32) were treated with ≥ 90 or ≥30 mg/month of lanreotide or octreotide, respectively. Median doses were of 97.5 mg/month (range 60-120) with lanreotide and 20 mg/month (range 20-30) for octreotide. No differences were found in baseline characteristics between patients pre-treated with SSAs and untreated, but at diagnosis, headache and visual involvement were more common in untreated than in pre-treated patients ***(Table 1).***

Table 1. Baseline characteristics of patients pre-treated with somatostatin analogues and untreated.

Variable	Global (n=48)	Untreated (n=28)	Pretreated (n=20)	P value*
Age (years)	50.6±13.22	49.6±2.3	52.2±3.2	0.511
Female sex	66.7% (n=32)	64.3 % (n=18)	70 % (n=14)	0.679
Diabetes	18.8% (n=9)	10.7% (n=3)	30.0% (n=6)	0.091
Hypertension	39.6% (n=19)	35.7% (n=10)	45.0% (n=9)	0.517
Heart disease	8.3% (n=4)	10.7% (n=3)	5.0% (n=1)	0.480
Obesity	12.5% (n=6)	14.3% (n=4)	10.0% (n=2)	0.658
Sleep apnoea syndrome	22.9% (n=11)	21.4% (n=6)	25.0% (n=5)	0.772
Pituitary apoplexy	2.1% (n=1)	3.6% (n=1)	0.0% (n=0)	0.333
Visual involvement	10.4% (n=5)	17.9% (n=5)	0.0% (n=0)	**0.046**
Headache	20.8% (n=10)	32.1% (n=9)	5.0% (n=1)	**0.022**
Hypopituitarism	18.8% (n=9)	21.4% (n=6)	15.0% (n=3)	0.574
Presurgical GH (ng/mL)	11.5±13.50	12.3±3.1	10.5±1.9	0.664
Presurgical IGF1 (ng/mL)	667.1±303.57	653.2±58.0	686.5±67.7	0.711
Macroadenoma	83.3% (n=40)	82.1% (n=23)	85.0% (n=17)	0.793
Tumor size (mm)	15.3±8.39	16.1±1.7	14.3±1.7	0.451
Knosp grade 3-4	31.3% (n=15)	39.3% (n=11)	20.0% (n=4)	0.098

Presurgical GH and IGF1 levels refers to their values before somatostatin analogues treatment initiation.

*P Value refers to the differences between pre-treated and untreated patients

Surgical remission (2010 criteria)

Surgical cure was achieved in 54.2% (n=26) of patients, 87.5% (n=7) in microadenomas, 47.5% (n=19) in macroadenomas and 13.3% (n=2) in PA grade Knosp 3-4. We found that surgical remission was more than four times higher in patients treated with high SSAs doses (≥90 mg/month of lanreotide or ≥30 mg/month of octreotide) compared with those treated with lower doses or untreated (Table 2). Based on the ROC, the dose of 26.3 mg/months of octreotide (AUC=1.00,

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sensitivity and specificity of 100%) and of 90 mg/month of lanreotide (AUC=0.66, sensitivity 75.0% and specificity of 60.0%) were the most effective to achieve surgical remission ***(Table 2).***

Table 2. Surgical remission in patients with acromegaly pre-treated with somatostatin analogues and untreated.

Patients	2010 criteria			
	Pre-treated	Untreated	P	Odds ratio, 95%CI
All patients (n=48)	60.0% (n=12)	50.0% (n=14)	0.493	OR=1.50 [0.47-4.79]
Microadenomas (n=8)	100% (n=3)	80% (n=4)	0.408	NC
Macroadenomas (n=40)	52.9% (n=9)	43.5% (n=10)	0.554	OR=1.46 [0.41-5.15]
Knosp 2-3 pituitary adenomas (n=16)	0.0% (n=0)	18.2% (n=2)	0.360	NC
All patients (High SSAs doses) (n=48)	**78.6% (n=11)**	**44.1% (n=15)**	**0.029**	**OR=4.64 [1.09-19.7]**
Macroadenomas (High SSAs doses) (n=40)	**72.7% (n=8)**	**37.9% (n=11)**	**0.049**	OR=4.39 [0.95-20.03]
All patients (≥ 6 months SSA) (n=48)	63.6% (n=7)	51.4% (n=19)	0.473	OR=1.66 [0.41-6.64]
Macroadenomas (≥ 6 months SSA) (n=40)	55.6% (n=5)	45.2% (n=14)	0.583	OR=1.52 [0.34-6.76]
All patients (lanreotide) (n=48)	71.4% (n=10)	47.1% (n=16)	0.124	OR=0.38 [0.06-2.28]
Macroadenomas (lanreotide) (n=40)	63.6% (n=7)	41.4% (n=12)	0.208	OR=0.5 [0.08-3.10]
All patients (octreotide) (n=48)	33.3% (n=2)	57.1% (n=24)	0.274	OR=2.81 [0.74-10.75]
Macroadenomas (octreotide) (n=40)	33.3% (n=29	50.0% (n=17)	0.451	OR=2.48 [0.59-10.40]

SSAs= somatostatin analogues; Odds ratios make reference to pretreated versus untreated

Surgical and endocrine complications and tumor consistency.

No operative or perioperative deaths occurred. Surgical morbidity was recorded in 9 patients and was similar in pre-treated and untreated, independently of the doses or the duration of SSA pre-treatment. Neither differences in the risk of postoperative anterior pituitary dysfunction were observed between pre-treated and untreated patients (***Table 3).***

The proportion of patients with hard tumors between pre-treated and untreated patients was similar, even when long duration of treatment was considered. However, the proportion of hard tumors decreased in pre-treated patients when high doses were considered (Table 3). Tumors of soft consistency were significantly more common in Knosp 0-2 PAs (87.9% vs 53.3%, P=0.008) ***(Table 3 and Figure 2).***

Figure 2. Histological images of pituitary tumours with different tumors consistencies

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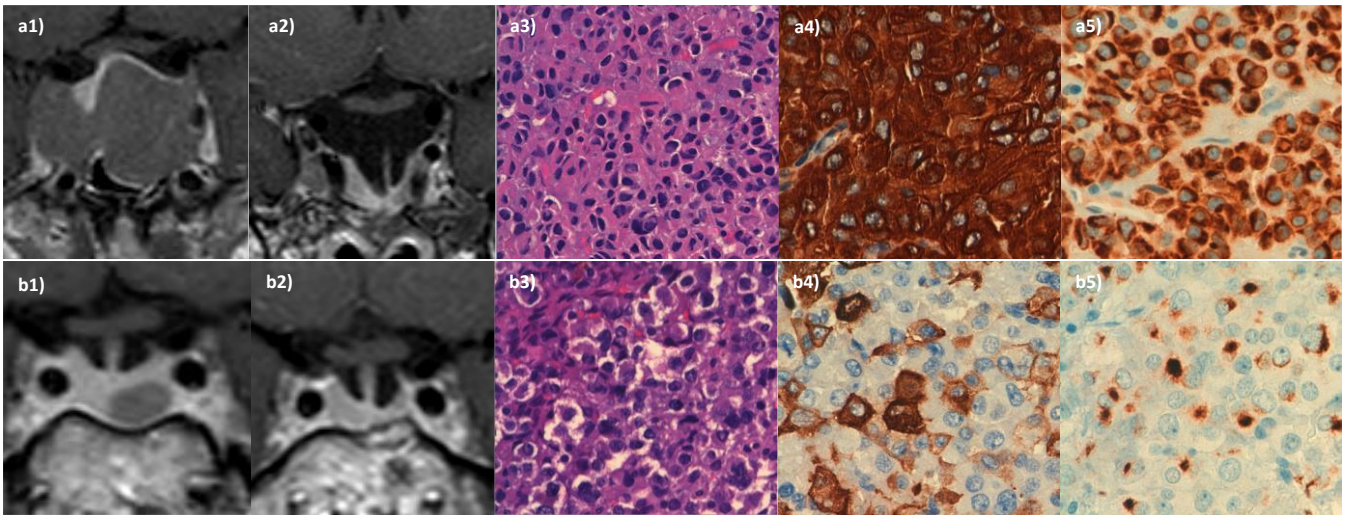

Case 1. Invasive pituitary adenomas (Knosp grade 4) of very hard consistency in the preoperative (a1) and (a2) small remnant in right cavernous sinus in the postoperative (coronal sections). The specimen was a densely granulated somatotroph tumor. Hematoxylin-eosin (a3) showed an acidophilic tumor, that stained strongly for GH (a4). Cytokeratin CAM5.2 (a5) staining was diffuse with a reinforce perinuclear pattern. Case 2. Knosp grade O pituitary adenomas of soft consistency in the preoperative (b1) and postoperative with complete tumoral resection (b2) (coronal sections). The lesion was a sparsely granulated somatotroph tumor. Hematoxylin-eosin (b3) revealed a chromophobic tumor with focal GH staining (b4). Cytokeratin CAM5.2 (b5) showed a dot-like perinuclear pattern corresponding to fibrous bodies.

Table 3. Surgical and endocrine morbidity in pre-treated with somatostatin analogues and untreated

Variable	Pretreated (n=20)	Untreated (n=28)	P value	OR and 95% CI
Surgical complications	15.0% (n=3)	21.4% (n=6)	0.574	OR=0.65 [0.14-2.96]
New APD	38.9% (n=7)	42.9% (n=9)	0.802	OR=0.85 [0.24-3.06]
Diabetes insipidus*	15.0% (n=3)	21.4% (n=6)	0.574	OR=0.65 [0.14-2.97]
Hospitalization length stay	6.7±2.0	6.9±1.4	0.937	NC
Hard tumors	15.0% (n=3)	28.6% (n=8)	0.270	OR=0.44 [0.10-1.93]
Variable	**Pre-treated with high doses (n=**	**Untreated or low doses (n=**	**P value**	**OR and 95% CI**
Surgical complications	14.3% (n=2)	20.6% (n=7)	0.611	OR=0.64 [0.11-3.56]
New APD	25.0% (n=3)	48.2% (n=13)	0.175	OR=0.36 [0.08-1.62]
Diabetes insipidus	21.4% (n=3)	17.7% (n=6)	0.760	OR=1.27 [0.27-6.00]
Hospitalization length stay	7.46±10.6	6.5±6.20	0.711	NC
Hard tumors	7.1% (n=1)	29.4% (n=10)	0.095	**OR=0.18 [0.02-0.87]**
Variable	**Pre-treated > 6 months**	**Untreated or pre-treated <6 m**	**P value**	**OR and 95% CI**
Surgical complications	18.2% (n=2)	18.9% (n=7)	0.956	OR=0.95 [0.17-5.42]
New APD	33.3% (n=3)	43.3% (n=13)	0.593	OR=0.65 [0.14-3.12]
Diabetes insipidus	18.2% (n=2)	18.9% (n=7)	0.956	OR=0.95 [0.17-5.42]
Hospitalization length stay	7.0±10.99	6.72±6.38	0.918	NC
Hard tumors	18.2% (n=2)	24.3% (n=9)	0.670	OR=0.69 [0.13-3.81]

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APD= anterior pituitary deficit; NC= not calculable; OR=odds ratio. *Diabetes insipidus refers to transient diabetes insipidus (no cases of permanent diabetes insipidus were reported).

4. Discussion

In this study, we found that preoperative long-acting SSA treatment with monthly doses equal or higher than 90 mg of lanreotide or 30 mg of octreotide for at least 3 months was associated with a global higher surgical remission rate according to the 2010 criteria. However, we did not observe any benefits of presurgical SSAs treatment in terms of surgical and endocrine complications.

In our study, no differences in surgical remission according 2010 were found between pre-treated and untreated patients when all doses of SSAs were considered. Based on the 2000 criteria, similar results were reported in several previous studies [18][23]. However, to the best of our knowledge, no previous studies have observed similar result as ours based on the 2010 criteria. On the other hand, an improvement in surgical outcomes with presurgical SSAs therapy has been described in a previous study based on this criteria [24]. Differences in these studies could be justified by different study populations as not in all studies important variables such as age, baseline GH and Knosp grade are comparable between pre-treated and untreated group, or even patients operated by different neurosurgeons were included in the analysis [17]. Different surgical remission definitions and variables formulations and doses of SSAs have been used in each study.

When the different tumor volumen were compared, we could not demonstrate a significant difference between pre-treated and untreated cases for microadenomas, macroadenomas, and invasive adenomas in terms of surgical cure when conventional doses were used. This is in line with the reported by other authors [18][23]. Nevertheless, a recent meta-analysis [25] found that patients with macroadenomas in the SSAs pre-treatment groups have had a more significantly cure rate than those untreated (RR=2.27, 95% CI= 1.34-3.84), although no differences were found in long-term surgical remission (RR=1.03, 95% CI=0.86-1.24). This observation was also reported in other previous individuals studies [13], and even in two randomised clinical trials [26][13]. So, in general, most studies, and different meta-analysis [27][16][28], supported that patients with macroadenomas are more likely to benefit in terms of improved surgical remission.

No differences were found between both formulations of long acting SSA in terms of surgical outcomes in our study. Similar results were reported by several previous studies [16][29], including one randomized clinical trial [30] . On the other hand, in a recent meta-analysis [6], the efficacy of octreotide LAR was greater than lanreotide. On the other hand, Zhang et al [29] in their meta-analysis proving benefits from lanreotide (RR 2.27, 95% CI= 1.34-3.84), but not from octreotide (RR 1.51, 95% CI= 0.82-2.75) in short term postoperative biochemical remission.

We observed a clear benefit of high doses of SSA based on the 2010 criteria, as pre-treated patients with high doses achieved surgical remission near to five-times more commonly than untreated or treated with lower doses. This finding is supported by the PRIMARYS study [7], which showed that primary treatment with lanreotide Autogel at maximal doses provides clinically significant reductions (>20%) in tumor volume in 62.9% of patients at 1 year; and by the Caron clinical trial [31], which found that GH hypersecretion was reduced to ≤ 2.5 μg/l in 68% of patients with titrated dose lanreotide Autogel compared with 56% with fixed-dose (P <0.005). This results are in accordance with those described by previous studies that have shown that the serum concentrations of SSAs correlate with their long-term efficacy against GH hypersecretion [32]. Higher SSA doses may be associated with tumor shrinkage and softening of their consistency, facilitating surgical removal. Moreover, presurgical GH levels and tumor size are well-known predictive factors of surgical remission [3].

We also did not detect any difference in the occurrence or severity of perioperative complications, in the hospitalization time, or in the risk of pituitary insufficiency. This in accordance with the reported by several previous studies where no differences were found, either. However, Colao et al. [33] reported a significantly shorter period of postoperative hospitalization in patients with acromegaly who underwent treatment with octreotide before surgery (5.6±0.5 days) compared with those who did not (8.6±0.7 days), suggesting that it could be related to a lower frequency of cardiac arrhythmia, respiratory impairment, and respiratory infections in the treated group.

The study has some limitations. First, the study is retrospectively designed from 2008 to 2012, and the number of patients was relatively small, so the possibility of a type 2 error should be considered. Nevertheless, all patients with missing data in the main variables were excluded of the study, and most patients (n=34) were prospectively included in the study. It is a two-center study performed mostly in a Pituitary Center of Excellence (Ramón y Cajal Hospital)[5], so surgical outcomes cannot be extrapolated to other centers with a low-pituitary tumour surgery volume and operated by other neurosurgeons with less experience. Moreover, we had not analyzed other aspects that can be improved with presurgical SSA such as hemodynamic parameters and quality of life, and only patients with first long-acting SSA were included in the study, so it could be expected that, in patients not adequately controlled on first generation-SSA pasireotide would be more adequate [34] and a benefit of presurgical treatment would be achieved.

5. Conclusions

The dose of SSAs is a key factor during pre-surgical treatment since the beneficial effects in surgical remission were observed with doses equal or higher than 90 mg/month of lanreotide and 30 mg/month of octreotide, but not with lower doses.

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Institutional Review Board Statement: All procedures performed in the participants of the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study has been approved by the Ethical Committee of the Ramón y Cajal University Hospital and Hospital HM Madrid

Informed Consent Statement: Due to the retrospective nature of the study, the Ethical Committee has approved the need of informed consent only in those patients who continued in follow-up in our center.
Conflicts of Interest: The authors declare no conflict of interest

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