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Pretreatment with somatostatin analogs does not affect the anesthesiologic management of patients with acromegaly

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Abstract

Purpose Acromegaly may be associated with an increased risk of complex intraoperative management and anesthetic complications. No study addressed whether pretreatment with somatostatin receptor ligands (SRLs) affects anesthesiologic management.

Methods We studied 211 consecutive acromegalic patients who had a recorded intraoperative computerized anesthetic record (ICAR) available for analysis. Ninety-six (45.5%) patients were SRL-pretreated while 115 patients were treatment naïve.

Results Treatment with SRLs reduced mean basal growth hormone level from 23.8 ± 4.2 to 5.9 ± 1.3 µg/L. Normalization of insulin-like growth factor-1 was achieved in 26 patients (27.1%). The frequency of comorbidities at surgery was similar in the two groups. Five patients with difficult intubation were naïve (4.3%) as compared with 5 SRL-pretreated patients (5.2%; $P = 1.0$). ICAR registration did not show any significant change of intraoperative vital parameters in the two groups of patients as well as in the intraoperative utilization of drugs. Total duration of anesthesia and surgery were similar in the two groups. Four patients with an intraoperative adverse event were naïve (3.5%) as compared with 4 SRL-pretreated patients (4.2%; $P = 1.00$). Remission of disease occurred in 83 of 114 naïve patients (72.8%) and in 57 of 93 SRL-pretreated patients (61.3%; $P = 0.11$).

Conclusions SRL-pretreatment of patients with acromegaly had no significant impact on intraoperative anesthesiologic management. Despite a better Cormack–Lehane score in SRL-pretreated than in naïve patients, the rate of difficult intubation was similar in both groups. SRL-pretreatment did not affect the rate of surgical remission or complications as well.

Keywords Acromegaly · Pituitary surgery · Pituitary neoplasm · Anesthesia · Somatostatin analogs

Introduction

Acromegaly is a rare, chronic, and debilitating disease that is caused in almost all cases by a growth hormone (GH)-secreting pituitary adenoma. Treatment options in patients with acromegaly include transsphenoidal surgery (TSS), radiation therapy, and drugs. TSS is usually considered the first therapeutic option with the goal of attempting complete tumor removal, when feasible, and reversal of GH hypersecretion [1]. There is wide agreement that surgery should be performed by a pituitary-dedicated neurosurgeon [2–4]. Indeed, surgical expertise in pituitary tumors is one of the most important determinants of surgical outcome in patients with acromegaly and rates of surgical remission approach 85–90% for microadenomas and 40–60% for macroadenomas in large series from single institutions [5–8]. Recently, the concept of a pituitary center of excellence has been widened to include a multidisciplinary team to improve the integrated management of patients with pituitary diseases [9].

The availability of effective drugs, namely, dopamine agonists, somatostatin receptor ligands (SRLs), and GH receptor antagonists, has further improved the clinical outcome of patients with acromegaly who have not been cured by TSS. In particular, the effectiveness of SRLs in reducing not only GH secretion but also tumor size in naïve patients is well recognized [10–12]. The latter effect, in particular, arose the hope that presurgical treatment with SRL might improve surgical outcome [13]. However, very conflicting

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results have been reported on this issue [14–19] and, at present, there are still different points of view on presurgical treatment with SRL [20]. The Endocrine Society Guidelines for acromegaly suggest against the routine use of presurgical SRLs to improve surgical remission rates [1]. A possible role of SRLs pretreatment in patients with severe pharyngeal thickness, sleep apnea, or severe cardiopathy to reduce surgical risk is not excluded, even though the evidence for such an effect is rated as very low quality [1]. Indeed, it is well accepted that acromegaly may increase the risk of anesthetic complications, especially of difficult intubation, because of laryngeal and pharyngeal soft tissue swelling and vocal cord swelling [21–25]. However, no study addressed this particular topic so far, probably because of the difficulty to implement a trial of large sample size and to define an objective endpoint.

Recently, we reported the usefulness of an intraoperative computerized anesthetic record (ICAR) to objectively monitor clinical and management characteristics of patients undergoing TSS for Cushing's disease [26]. Taking advantage of the data prospectively recorded in ICAR, we studied a large cohort of patients with acromegaly to investigate whether pretreatment with a first generation SRL altered intraoperative variables and affected anesthesiologic management. Moreover, we conducted a secondary analysis reporting surgical results and complications in this group of patients.

Materials and methods

Patient population

We retrospectively reviewed 307 patients with acromegaly who had TSS at our center between September 2007 and December 2016. We included into the present study all consecutive patients who had a recorded ICAR available for analysis. All surgical procedures were performed by a single pituitary-dedicated neurosurgeon (PM) using a standard microsurgical technique that has been described in detail elsewhere [27]. Eighty-six patients (28.0%) were excluded from the study because ICAR was not available. In the remaining 221 patients, 10 cases (4.5%) were excluded, in accordance with the criteria already defined in a previous paper [16], because long-acting SRL treatment had been stopped for whatsoever reason more than 3 months before surgery (9 cases) or because duration of SRL treatment before surgery was less than 3 months (1 case).

Age at surgery, sex, body mass index (BMI), body surface area (BSA), patients' comorbidities, hormonal characteristics, and history of previous treatments for acromegaly were prospectively recorded. Moreover, preoperative anesthesiologic evaluation of physical status was classified according to the American Society of Anesthesiology (ASA) score and upper airway morphology (macroglossia, prognathism, and Mallampati score) were also prospectively recorded soon before surgery.

Diagnosis of active acromegaly was confirmed by typical clinical features, GH hypersecretion, elevated serum levels of insulin growth factor-1 (IGF-1) adjusted for age and sex, and magnetic resonance imaging (MRI) visualization of a pituitary adenoma. Postsurgical remission of disease was defined as the presence of a GH level below 1 ng/mL at baseline or during an oral glucose tolerance test and age- and sex-adjusted normal IGF-1 level [1]. Moreover, to avoid misclassification of the surgical outcome because of a carry-over effect of previous SRL therapy, pretreated patients were classified on the basis of hormonal evaluation performed at least 6 months after surgery.

Diseases or injuries following TSS that were potentially fatal, resulted in a permanent defect, or required reoperation or readmission to the hospital were considered as major complications, whereas less serious side-effects were considered as minor complications. Water and electrolyte disturbances after TSS were classified as described previously [26].

Standard informed consent was obtained from all individual patient included in the study.

Intraoperative vital parameters monitoring and drugs administration

All patients undergoing TSS received a standardized intra- and peri-operative anesthetic protocol, described previously [26]. Briefly, intraoperative monitoring included V2 electrocardiogram, heart rate, non-invasive automated arterial blood pressure, and peripheral oxygen saturation (SpO_2). Throughout anesthesia, end-tidal CO_2 ($EtCO_2$) was monitored. End-tidal concentrations of nitrous oxide (N_2O) and sevoflurane were also continuously monitored with an infrared analyzer when these agents were used.

After induction of anesthesia (propofol 2 mg/Kg) and myorelaxation (rocuronium bromide 0.5 mg/Kg), orotracheal intubation was performed through standard direct laryngoscopy. Flexible fiberoptic laryngoscopy was considered for orotracheal intubation in anticipated difficult cases. The Cormack–Lehane score, which describes what is seen through direct laryngoscopy during the intubation process itself, was prospectively recorded. Intubation was defined as difficult (or impossible) if—albeit correct head positioning, external laryngeal manipulation, and use of a tube stylet—one of the following was reported by the attending anesthesiologist: (a) difficult laryngoscopy; (b) necessity of three or more attempts for intubation; (c) need for laryngeal mask or fiberoptic laryngoscopy; (d) withdrawal and procedure re-planning because of impossible airway management [28].

Mechanical ventilation was set to maintain $EtCO_2$ values in the range of 30 to 35 mm Hg. Anesthesia was maintained by continuous iv infusion of either propofol or inhaled sevoflurane together with continuous iv remifentanil infusion. Throughout the surgical procedure, patients received 40–50% O_2. No further muscle relaxants were administered. To limit intraoperative bleeding that could impair the surgical maneuver, we aimed at maintaining systolic arterial blood pressure between 80 and 120 mmHg. The first tier intraoperative therapy for episodes of relative hypotension (systolic blood pressure < 80 mmHg for more than 3 min) or relative hypertension (systolic blood pressure > 120 mmHg for more than 3 min) was an adjustment of the anesthetic regimen. The second tier intervention included administration of crystalloids for hypotension and administration of iv labetalol for hypertension. No prophylactic antibiotic therapy was routinely administered, except when clinically indicated. At the end of the surgical procedure, patients were awaked and extubated in the operating room. Thereafter, patients were kept for about an hour in a recovery room nearby the operating room and then they were transported to the neurosurgical ward.

Intraoperative monitoring data were automatically stored in the ICAR, a computerized dedicated system described in detail in a previous publication [26].

Endpoints

The primary endpoint of the study was to compare patients naïve to medical treatment with patients who had received SRL treatment before surgery with respect to difficult intubation, intraoperative blood pressure and heart rhythm control, duration of the surgical procedure, and any complications of the anesthesiological management.

A secondary analysis was also performed to verify the effect of SRL pretreatment on the rate of surgical remission and postoperative complication rates.

Statistical analysis

Continuous variables' normality was assessed by the Kolmogorov–Smirnov test. Continuous variables with a normal distribution are reported as mean (± SE) and compared with the unpaired Student t-test, while variables not normally distributed are presented as median and interquartile ranges (IQR) and compared with the Wilcoxon rank sum test. Categorical variables are reported as number (percentage) and compared with the Pearson's χ^2 test with Yates' correction or Fisher's exact test, as appropriate. Multiple logistic regression analysis was used to determine which variables independently predicted remission of disease after surgery. A probability value less than 0.05 was considered to be statistically significant and all reported analyses are two-tailed. All calculations were performed using IBM SPSS Statistics, version 23.0 (IBM corp., Armonk, New York, USA).

Results

Patients' characteristics

The main clinical characteristics of the study population at diagnosis are summarized in Table 1. Despite the lack of randomization, these characteristics were well balanced

Table 1 Clinical characteristics at diagnosis of 211 patients with acromegaly who received transsphenoidal surgery

Variables	All patients (n = 211)	Naïve (n = 115)	SRL-pretreated (n = 96)	*P* value
Age at presentation—year	47.9 ± 0.9	46.4 ± 1.2	49.0 ± 1.2	0.13
Male sex—no. (%)	96 (45.5%)	52 (45.2%)	44 (45.8%)	1.00
Basal GH level—μg/L	23.9 ± 3.0	24.0 ± 4.1	23.8 ± 4.2	0.97
Previous surgery—no. (%)	9 (4.3%)	3 (2.6%)	6 (6.2%)	0.34
Microadenoma—no. (%)	42 (19.9%)	25 (21.7%)	17 (17.7%)	0.58
Maximum tumor diameter—mm	16.2 ± 0.5	16.2 ± 0.8	16.3 ± 0.7	0.97
Cavernous sinus invasion—no. (%)	42 (19.9%)	20 (17.4%)	22 (22.9%)	0.41
Sphenoid sinus invasion—no. (%)	9 (4.3%)	4 (3.5%)	5 (5.2%)	0.78
Hypothyroidism—no. (%)[a]	8 (4.1%)	6 (5.5%)	2 (2.4%)	0.47
Hypogonadism—no. (%)[b]	89 (43.4%)	53 (46.9%)	36 (39.1%)	0.33
Hypoadrenalism—no. (%)	5 (2.4%)	2 (1.7%)	3 (3.1%)	0.84

Plus-minus values are means ± standard error of the means

GH growth hormone, *SRL* somatostatin receptor ligand

[a]Thyroid function was not applicable in 18 patients (6 naïve and 12 SRL-pretreated)

[b]Gonadal function was not applicable in 6 patients (2 naïve and 4 SRL-pretreated)

between the two groups. In particular, tumor size and extension, as well as basal GH levels, were similar in the two groups.

Among patients pretreated with SRL, 68 patients (70.8%) received octreotide LAR, whereas the remaining 28 patients (29.2%) received Lanreotide. The median duration of SRL treatment before surgery was 12 months (IQR 6–24 months, range 3 to 156 months) and was similar in patients who received octreotide LAR compared with those who received lanreotide, respectively ($P=0.90$). The estimated median total dose of SRL received by the patients before surgery was 360 mg (IQR 150–720 mg, range 60 to 4680 mg) for octreotide LAR and 1440 mg (IQR 615–2520 mg, range 180 to 5760 mg) for lanreotide. The median interval between the last administration of SRL and surgery was 20 days (IQR 13–28 days, range 3 to 90 days) and was not different in patients who had received octreotide LAR or lanreotide ($P=0.57$).

Treatment with SRLs reduced mean basal GH level from 23.8 ± 4.2 to 5.9 ± 1.3 µg/L. Normalization of IGF-1 levels during medical treatment was achieved in 26 patients (27.1%). Probability to achieve remission of disease during SRL treatment was similar for octreotide LAR and lanreotide (27.9% and 25.1%, respectively; $P=0.97$). Paired baseline and MRI examinations during treatment with SRL were available for review in 55 patients. A reduction of tumor diameter greater than 2 mm occurred in 34 of the 55 patients (61.8%) and was similar in patients treated with octreotide LAR or lanreotide (63.2%, 58.8%, respectively; $P=0.97$).

Presurgical evaluation

The principal characteristics of the study population at surgery are summarized in Table 2. Patients pretreated with SRL were slightly older than naïve patients (50.8 ± 1.3 years vs. 46.4 ± 1.2 years; $P=0.011$), which is accounted for by the period of SRL treatment before surgery. According to BMI, 32.2% of the patients had a normal weight, 45.5% were overweight, 18.0% were obese, and 4.3% were severely obese. No patient had a BMI lower than 18. Both BMI and BSA were distributed similarly in the two groups of patients.

Clinical examination showed the expected spectrum of comorbidities in this group of patients with acromegaly. More than 40% of patients had hypertension, which was under pharmacotherapy in 90% of the patients, 15.2% had diabetes mellitus, which was under pharmacotherapy in 78%

Table 2 Clinical characteristics and comorbidities of the patients at the time of the surgical procedure

Variables	All patients (n = 211)	Naïve (n = 115)	SRL-pretreated (n = 96)	*P* value
Age at surgery—year	48.4 ± 0.9	46.4 ± 1.2	50.8 ± 1.3	0.011
Weight—Kg	78.4 ± 1.1	77.8 ± 1.5	79.2 ± 1.5	0.53
BMI—Kg/heigth^2	27.2 ± 0.3	26.9 ± 0.4	27.7 ± 0.4	0.16
BSA—m^2	1.89 ± 0.01	1.88 ± 0.02	1.90 ± 0.02	0.68
Hypertension—no. (%)	92 (43.6%)	45 (39.1%)	47 (49.0%)	0.15
Diabetes mellitus—no. (%)	32 (15.2%)	15 (13.0%)	17 (17.7%)	0.35
Cardiopathy—no. (%)	11 (5.2%)	5 (4.3%)	6 (6.2%)	0.55
Lung pathology—no. (%)	37 (17.6%)	16 (13.9%)	21 (21.9%)	0.15
Current smoker—no. (%)	54 (25.6%)	33 (28.7%)	21 (21.9%)	0.26
Macroglossia—no. (%)	104 (49.3%)	54 (46.9%)	50 (52.1%)	0.33
Mallampati score—no. (%)[a]				
1	65 (32.0%)	36 (31.9%)	29 (32.2%)	0.98
2	119 (58.6%)	66 (58.4%)	53 (58.9%)	
3	19 (9.4%)	11 (9.7%)	8 (8.9%)	
ASA score—no. (%)				
1–2	187 (88.6%)	104 (90.4%)	83 (86.5%)	0.36
3–4	24 (11.4%)	11 (9.6%)	13 (13.5%)	
Cormack–Lehane score—no. (%)[b]				
1–2	50 (23.9%)	19 (16.5%)	31 (33.0%)	0.009
3–5	159 (76.1%)	96 (83.5%)	63 (67.0%)	

Plus-minus values are means ± standard error of the means

SRLs somatostatin receptor ligands, *BMI* body mass index, *BSA* body surface area, *ASA* American Society of Anesthesiology

[a]Eight patients (2 naïve and 6 SRLs-pretreated) had missing information

[b]Two SRLs-pretreated patients had missing information

of the patients. Clinically relevant cardiac disease, consisting mostly of ischemic heart disease, atrial fibrillation, or severe valvular disease, was recorded in 4.7% of the patients, whereas severe lung disease, mostly obstructive sleep apnea and bronchial chronic obstructive disease, was present in 17.6% of the patients. Pretreatment with SRL did not significantly affect the frequency of these comorbidities compared with naïve patients (Table 2). However, although there was no difference in the Mallampati score between the two groups, the Cormack–Lehane score was significantly better in SRL-pretreated patients than in naïve patients (Table 2).

Intraoperative vital parameters monitoring and anesthesiologic complications

There was no perioperative mortality.

Endotracheal intubation was completed successfully in all patients and none had to postpone surgery because of failed intubation. Intubation was deemed difficult in 10 patients (4.7%): three of them required fiberoptic intubation, and seven could be intubated with the standard technique after 3 attempts. Among the 10 patients with difficult intubation, 5 patients were naïve (4.3%) and the remaining 5 cases (5.2%) were SRL-pretreated ($P = 1.0$). In the latter group, no patient had normalization of IGF-I levels during SRL treatment but two of them had a decline of GH levels greater than 50%. All patients with difficult intubation had a Cormack–Lehane score of 3 or higher. As expected, difficult intubation was more frequent in patients with a Mallampati score of 3 (21.1%) than in patients with a Mallampati score of 1 or 2 (3.1% and 3.4%, respectively; $P = 0.003$).

Total anesthesia time was 89.0 ± 1.4 min (range, 46 to 165 min) and did not significantly differ between naïve and SRL-pretreated patients (90.6 ± 1.8 vs. 87.0 ± 2.1 min, respectively; $P = 0.76$). Similarly, the total duration of the surgical procedure was 37.6 ± 0.8 min (range 20 to 104 min) and was not different in naïve (37.3 ± 1.1 min) and SRL-pretreated patients (38.0 ± 1.1 min; $P = 0.81$).

Intraoperative vital parameters (systolic arterial pressure, heart rate, peripheral oxygen saturation pressure, and end-tidal CO_2), as registered in ICAR, were not significantly different in naïve as compared with SRL-pretreated patients (Table 3). The frequency of administration of inhalatory drugs, nitrous oxide, atropine, antibiotics, and hypotensive agents during anesthesia was also not significantly different between the two groups (Table 3). Eight patients (3.8%) suffered an intraoperative adverse event recorded in ICAR. Two patients had arterial hypertension. Three patients exhibited $SpO_2 < 90\%$ at the end of surgery and required careful aspiration of prominent bronchial secretions. One patient had bradycardia (HR 35/min) and recovered promptly after iv atropine administration. One patient presented transitory ST-segment elevation on electrocardiogram monitoring without subsequent elevation of cardiac enzymes. The remaining patient had a skin rash upon general anesthesia induction. The skin reaction was self-limited. Among the 8 patients with an intraoperative adverse event, 4 patients were naïve (3.5%) and the remaining 4 cases (4.2%) were SRL-pretreated ($P = 1.00$). No clinical or anesthesiologic characteristics were predictive of the occurrence of an intraoperative adverse event.

Table 3 Intraoperative vital variables and drugs administration in 211 patients with acromegaly

Variables	Naïve (n = 115)	SRL-pretreated (n = 96)	*P* value
Systolic arterial pressure			
Mean	106.0 ± 2.0	101.4 ± 2.5	0.15
Maximal	141.3 ± 2.9	136.8 ± 3.2	0.30
Minimal	80.1 ± 1.9	76.2 ± 2.4	0.19
Heart rate (bpm)			
Mean	70.9 ± 1.0	71.2 ± 1.2	0.86
Maximal	89.3 ± 1.6	88.9 ± 1.6	0.88
Mean peripheral oxygen saturation pressure (%)	99.3 ± 0.8	99.4 ± 1.0	0.67
Mean end tidal CO_2 (mmHg)	27.0 ± 0.3	26.9 ± 0.3	0.90
Inhalatory drugs (%)	42 (36.5%)	37 (38.5%)	0.87
Nitrous oxide (%)	35 (30.4%)	22 (22.9%)	0.28
Hypotensive drugs (%)	28 (24.3%)	17 (17.7%)	0.32
Atropine (%)	12 (10.4%)	16 (16.7%)	0.26
Antibiotic therapy (%)	7 (6.1%)	11 (11.5%)	0.25

Plus-minus values are means ± standard error of the means

SRLs somatostatin receptor ligands

Early surgical results and postoperative complications

Surgical remission of acromegaly occurred in 140 of the 208 patients (67.3%) for whom the hormonal evaluation at 6 months after surgery was known. Remission of disease occurred in 82 of 114 naive patients (71.9%) and in 58 of 94 SRL-pretreated patients (61.7%; $P = 0.16$). To control for the possible imbalance between the two groups, we next performed a multivariate logistic regression analysis. The final model, that included 202 patients with all dataset available, showed that early surgical failure was very strongly associated with cavernous sinus invasion on MRI at diagnosis (OR 36.1; 95% CI 10.8–120.3; $P < 0.001$), while younger age at surgery, high basal GH levels, and invasion of the sphenoid sinus retained a weak association with surgical failure ($0.01 < P < 0.05$). On the contrary, sex, previous pituitary surgery, tumor size (categorized as macroadenoma vs.

microadenoma) and SRL-pretreatment were not significantly associated with surgical outcome.

The overall rate of postoperative complications was 3.3% (7 out of 211 patients) and was equally distributed between naïve (4 cases, 3.5%) and SRL-pretreated patients (3 cases, 3.1%; $P = 1.00$). Major complications occurred in four patients (1.9%): major epistaxis requiring rehospitalization and nasal packing 14 days after surgery (1 SRL-pretreated patient), rhinoliquorrhea occurring 8 days after surgery requiring rehospitalization and surgical repair (1 naïve patient), and severe hyponatremia after discharge that required rehospitalization for management (2 patients, 1 naïve and 1 SRL-pretreated patient). Minor complications were reported in three patients (1.4%) and included a hypothensive crisis on the day of discharge (1 naïve patient), a urinary tract infection successfully treated with antibiotics (1 SRL-pretreated patient), and an episode of epistaxis that resolved spontaneously (1 naïve patient).

Water and electrolyte disturbances were reported after surgery in 11 patients (5.2%), including the two patients with severe hyponatremia already counted as major complications (see above). Diabetes insipidus of at least 2 months of duration occurred in 4 patients (1.9%) and was equally distributed among naïve patients (3 cases, 2.6%) and SRL-pretreated patients (1 case, 1.0%; $P = 0.63$). Hyponatremia was detected in 7 patients (3.3%) of whom three were naïve (2.6%) and four SRL-pretreated (4.2%; $P = 0.70$).

Discussion

The main goal of our study was to verify the impact of SRL-pretreatment on anesthesiologic management in a large cohort of unselected patients with acromegaly undergoing TSS removal of the GH-secreting pituitary adenoma. While the surgical technique to remove the pituitary adenoma is not affected by the specific tumor type but only by tumor size, invasiveness, and consistency, the anesthesiologic management of patients with acromegaly undergoing TSS has been considered much more demanding than in other types of pituitary tumors [22–24]. Considering that most of the anesthesiologic risk is secondary to the characteristic morphological changes of acromegaly, such as macroglossia, prognathism, and soft tissue swelling, it has been proposed that a multidisciplinary team including neurosurgeons, experienced anesthetists, respiratory physicians, and radiologists should perform a comprehensive evaluation of the patient with acromegaly before surgery to predict those patients with a high risk of difficult intubation [25]. While the proposal of implementing an ad hoc multidisciplinary team to plan the anesthesiologic management in acromegaly seems very complicated to realize for logistic constraints and the rarity of the disease, the idea to reduce macroglossia, soft tissue swelling, and other comorbidities in preparation of surgery seems more attractive and feasible. Since the improvement of symptoms in patients with acromegaly is associated with the decline of GH and IGF-1 levels independently of the treatment modality, medical therapy prior to surgery might translate into easier anesthesiologic management. Again, the type of drug used to reduce GH hypersecretion should be irrelevant to this aim. The debate on this issue is, nevertheless, centered exclusively on the use of SRLs but, despite several years of clinical use of these drugs, clinical data that specifically report the effect of presurgical treatment on anesthesiologic management are lacking.

Our study included 96 patients that had received SRLs before referral for TSS to our department. The decision to initiate SRL or not was exclusively taken by the referring endocrinologist, as we have no preference pro or against presurgical treatment. Despite the lack of randomization, the main clinical, hormonal, and radiological characteristics at presentation between naïve and SRL-pretreated patients were well balanced, which reasonably excludes a significant selection bias. Even the hormonal and radiological responses to SRLs are those expected in a series of unselected patients with acromegaly. Indeed, normalization of IGF-1 levels during SRL therapy occurred in 27.1% of our patients, which is similar to that reported previously in a different group of 143 patients that received SRLs, including older formulations, before surgery [16]. Moreover, a prospective, randomized trial comparing Pasireotide with Octreotide LAR reported that the latter normalized IGF-1 levels in 21.2% of 182 unselected acromegalic patients [29].

Clinical variables that may affect the anesthesiologic risk in patients with acromegaly did not significantly differ between naïve and SRL-pretreated patients, apart from age (Table 2). The age difference is explained by the interval between begin of medical therapy and the decision to perform surgery, as the two study groups were of comparable age at presentation. The similar frequency of important comorbidities, like hypertension, diabetes mellitus, severe cardiomyopathy, or respiratory disorders, in the two groups of patients, seems, at first sight, surprising. Indeed, SRL-induced decrease in GH levels would be expected to lead to a general improvement of health conditions. This expectation has not been completely confirmed. Annamalai and coworker [30] prospectively treated 30 naïve patients with Lanreotide for 6 months before surgery and found that, despite a marked reduction of GH and IGF-1 concentrations, several metabolic, vascular, cardiac, and respiratory sequelae did not ameliorate uniformly. Moreover, improvement of acromegalic complications in response to therapy varied considerably between individuals, without a clear association with biochemical control [30]. Our data support the possibility that SRL treatment in the presurgical setting might not end in a clinically relevant improvement of many comorbidities.

However, we had no paired evaluation of the patients before and during SRL treatment and we cannot completely exclude that SRL-pretreated patients had a significantly greater burden of comorbidities at baseline than naïve patients.

It is well known that patients with acromegaly may present a very important challenge for anesthetists because of difficult intubation [21–25]. Two scores largely used to predict difficult intubation in surgical patients, namely the Mallampati score and the Cormack–Lehane score, had divergent results in our population. In the general population, the Mallampati score is usually predictive of the Cormack–Lehane score. On the contrary, in acromegalic patients, SRL-pretreatment did not improve the Mallampati score, while the Cormack–Lehane score was better in the group of SRL-pretreated patients (Table 2). This might be explained by a more pronounced effect of medical therapy on the reduction of soft tissue imbibition at the level of the glottal plane rather than of tongue and soft palate. With relevance to this issue, our data suggest that the Mallampati score could be inadequate in predicting difficult intubation in acromegalic patients. Nevertheless, caution is needed in drawing this conclusion, mainly because it is impossible for us to ascertain whether the better Cormack–Lehane score in SRL-pretreated patients is the result of medical treatment or not because no similar assessment has been done before starting SRL treatment. We are not aware of data on this topic in the literature. It should be noted that difficult intubation did not produce clinically prominent problems in our series. Indeed, a complicated laryngoscopy represents only one aspect required to define difficult intubation [28]. Undoubtedly, the expertise of anesthetists in the management of acromegalic patients helps reduce the number of attempts at intubation and the need of non-standard devices and/or procedures regardless of medical presurgical therapy, which may explain our findings. Comparison with data in the literature is complicated because the definition of difficult intubation is highly variable. Failure of first intubation was recently reported in 2 of 16 (12.5%) patients in one study [25] and in 4 of 32 (12.5%) acromegalic patients in another study [24].

The data on intraoperative variables, the first reported in such a systematic way thanks to the ICAR system, showed no significant difference in the two groups of patients. This means that SRL-pretreatment does not seem to contribute to a meaningful improvement of intraoperative management in patients with acromegaly. The same reasoning applies to anesthesiologic complications, which were similar in both groups.

The secondary endpoints of our study confirmed that presurgical SRL treatment did not improve surgical outcome and the risk of complications. The rate of surgical remission in naïve patients (72.8%) was slightly but not significantly higher than in SRL-pretreated patients (60.7%) and this result was also confirmed by multivariate analysis. Different opinions exist in the literature [14–20]. Nevertheless, based on our extensive experience on this topic, which combines two different and not overlapping datasets of patients with acromegaly (16 and the present study), we can conclude that SRL-pretreatment does not affect either the probability of disease remission or the risk of complications when surgery is performed by an experienced pituitary neurosurgeon.

In conclusion, SRL-pretreatment of patients with acromegaly had no significant impact on intraoperative anesthesiologic management as compared with naïve patients. Despite a better Cormack–Lehane score in SRL-pretreated than in naïve patients, the rate of difficult intubation was similarly low in both groups of patients. SRL-pretreatment did not affect the rate of surgical remission or complications as well.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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