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Comparison between somatostatin analog injections

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SUMMARY

OBJECTIVE: Long-acting depot formulations of somatostatin analogs, i.e., octreotide and lanreotide, are the first-line medical therapies for patients with acromegaly to whom surgery/radiotherapy cannot be performed or who have inadequate response. In this study, we aimed to evaluate the short-term local and systemic adverse reactions developed after the somatostatin analogs injections in the patients with acromegaly, in order to compare the side effects of somatostatin analogs injections.

METHODS: Patients diagnosed with acromegaly who were referred to our endocrinology clinic for monthly somatostatin analogs injections were questionnaired. Wong-Baker Faces Pain Rating Scale was used to evaluate the injection-site pain at the time of injection. The existence of leg pain, nausea, diarrhea, and abdominal pain following the previous injection was also investigated during the next injection.

RESULTS: A total of 49 patients were included in the study. The statistical difference could not be shown between the injection-site pain, anorexia, and leg pain frequencies of the groups, while the frequency of gastrointestinal disturbances, i.e., diarrhea and abdominal pain, was significantly lower in the octreotide group ($p<0.001$ and $p=0.015$, respectively).

CONCLUSIONS: This is the first prospective study that compared the severity of the injection-site pain by using a scoring scale, following the long-acting somatostatin analogs injections. We have shown that there was no significant association of the injection-site pain severity with the somatostatin analogs regimen nor the dose differences within each somatostatin analogs treatment.

KEYWORDS: Octreotide. Lanreotide. Injection site reaction. Drug-related side effects and adverse reactions.

INTRODUCTION

Long-acting depot formulations of somatostatin analogs (SSA), i.e., octreotide (OCT) and lanreotide (LAN), are the first-line medical therapies for patients with acromegaly to whom surgery/radiotherapy cannot be performed or who have inadequate response to surgery/radiotherapy[1,2]. The comparison between both short- and long-acting formulations of SSA has been evaluated in various studies, which generally have focused on the efficacy of therapies[3-8]. To date, only one head-to-head clinical trial, of which the primary aim was to evaluate the patient-reported outcomes of the SSA injections, including the injection-site pain duration, has been reported[9].

The most commonly reported local and systemic adverse reactions of SSA injections include erythema, injection-site and leg pain, impaired glucose metabolism, biliary gallstones, diarrhea, nausea, vomiting, and abdominal pain[10]. We designed a prospective study evaluating the short-term local and systemic adverse reactions developed after SSA injections in the patients with acromegaly who have been followed up by our clinic, in order to compare the side effects of SSA injections, particularly the pain severity at the injection site.

METHODS

Patients diagnosed with acromegaly who were referred to our endocrinology clinic for monthly SSA injections between April 2021 and August 2021 were questionnaired. The outcomes of the three consecutive monthly injections that had been performed by the same nurse were evaluated. The injections had been performed at a different site (left/right), considering the previous injection site. Wong-Baker Faces Pain Rating Scale was used to evaluate the injection-site pain at the time of injection, and the patients were asked to choose the exact pain score on the scale (Figure 1)[11]. This pain scale displays a series of faces, ranging from a happy face (0) to a crying face (10). The patients were expected to choose a face that best described their level of pain. The existence of leg pain, nausea, diarrhea, and abdominal pain within 3

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consecutive days following the previous injection was investigated during the next injection.

In addition to local and systemic side effects, name and dose of SSA, the duration of the treatment, and the site location of the current injection were noted. Since patient-reported pain is a subjective entity that could be affected by the psychological status, demographic features of the patients such as, age, sex, marital, and educational status were also noted. The average of local pain scores of three injections was calculated. The occurrence of side effects was evaluated according to the reports from the patients. The presence of an adverse effect during or after any injection(s) was recorded as positive in terms of that side effect. The patients who were above 18 years old and with acromegaly were eligible for inclusion in the study if they were admitted to our clinic for at least four times consecutively for injection and able to respond to the questions by which our nurse had asked during their injections. Patients with any neuromuscular disease that could cause a sensory impairment on the lower extremities (n=1) and patients who were under the current dose of SSA for less than 3 months (n=4) and whose injections were more than a month apart, such as 45 days (n=3), were excluded.

All statistical analyses were performed using the IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean ± standard deviation or (in case of no normal distribution) median (25th–75th percentile). Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were carried out using the independent samples t-test, the Mann-Whitney U test and the Kruskal-Wallis test, whichever was appropriate. Association between two categorical variables was examined by the chi-square test. All statistical analyses were carried out with 5% significance, and a two-sided $p<0.05$ was considered statistically significant. Ethics approval was obtained from the ethics committee of the National Ministry of Health (date: March 19, 2021, no: E-66175679-514.05.01-375015).

RESULTS

After the exclusion of 8 patients, a total of 49 patients were included in the study, consisting of 27 (55.1%) men and 22 (44.9%) women, with a mean±SD age of 51.1±11.3 years. Thirty-four (69.4%) patients were on OCT, while 15 (30.6%) were on LAN. General demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients (n=49).

	Mean±SD
Age (years)	51.1±11.3
Height (cm)	172.8±11.3
Weight (kg)	87.5±17.7
Body mass index (kg/m^2)	29.26±5.05
Waist circumference (cm)	106.2±11.9
Hip circumference (cm)	105.2±16.9
Duration of treatment (month)	73.4±55.4
	n (%)
Sex	
Male	27 (55.1)
Female	22 (44.9)
Marital Status	
Married	42 (85.7)
Single	7 (14.3)
Education	
Nonliterate	4 (8.2)
Primary school	24 (49.0)
High school	15 (30.6)
College	6 (12.2)

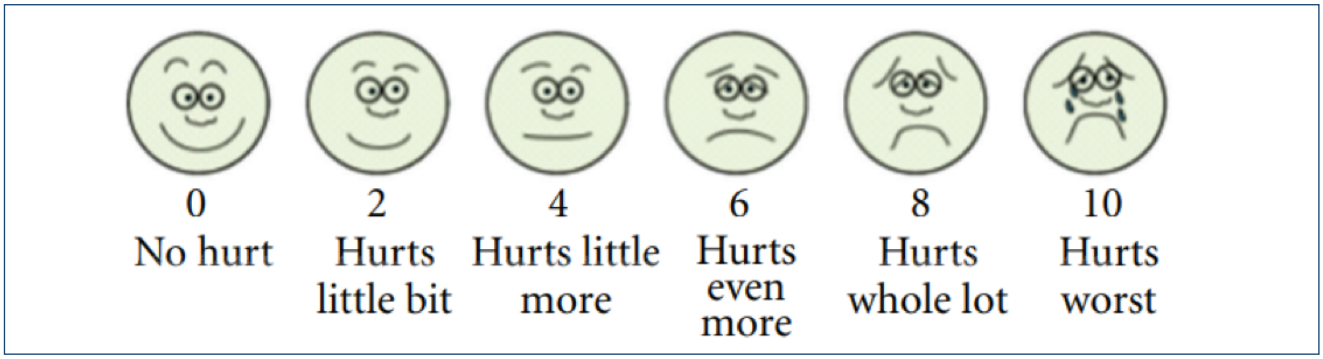

Figure 1. Wong-Baker faces pain rating scale.

As described in Table 2, there was no statistical difference between age, sex, marital, and educational status distribution of the two groups. The waist circumference medians of the groups were similar (p=0.527). The statistical difference could not be shown between the injection-site pain, anorexia, and leg pain frequencies of the groups, while the frequency of gastrointestinal (GI) disturbances, i.e., diarrhea and abdominal pain, was significantly lower in the OCT group (p<0.001 and p=0.015, respectively) (Table 2). Statistical analysis could not be performed for the comparison of the nausea frequencies,

Table 2. Comparison of demographic characteristics' distribution and the side effects of somatostatin analogs.

	Somatostatin analogs		p
	Octreotide (n=34)	Lanreotide (n=15)	
Age (years) mean±SD	50.3±10.5	52.7±12.8	0.503*
Sex, n (%)			
Male	19 (59.4)	8 (47.1)	0.601**
Female	13 (40.6)	9 (52.9)	
Marital status, n (%)			
Married	27 (84.4)	15 (88.2)	1.000**
Single	5 (15.6)	2 (11.8)	
Education, n (%)			
Nonliterate	1 (3.1)	3 (17.6)	0.212**
Primary school	18 (56.3)	6 (35.3)	
High school	10 (31.3)	5 (29.4)	
College	3 (9.4)	3 (17.6)	
Side effects, n (%)			
Diarrhea$^{\beta}$			
Yes	2 (6.3)	10 (58.8)	**<0.001****
No	30 (93.8)	7 (41.2)	
Nausea$^{\beta}$			
Yes	0 (0.0)	2 (11.8)	Not Available
No	32 (100.0)	15 (88.2)	
Leg pain$^{\beta}$			
Yes	3 (9.4)	3 (17.6)	0.405**
No	29 (90.6)	14 (82.4)	
Abdominal pain$^{\beta}$			
Yes	2 (6.3)	6 (35.3)	**0.015****
No	30 (93.8)	11 (64.7)	
Anorexia$^{\beta}$			
Yes	3 (9.4)	3 (17.6)	0.405**
No	29 (90.6)	14 (82.4)	
	Median (25th–75th)	Median (25th–75th)	
Pain at the injection siteα	1.00 (0.00–2.00)	1.00 (0.00–1.67)	0.766***
Hip circumference (cm)	102.0 (100.0–110.0)	102.0 (96.5–108.0)	0.527***
Duration of treatment	66.0 (36.0–120.0)	48.0 (21.0–84.0)	0.084***

*Evaluated by independent samples t-test. **Evaluated by chi-square test. ***Evaluated by Mann-Whitney U test. αMedian of mean injection-site pain score of three injections. $^{\beta}$Total of responses regarding 3 injection days.
Bold values indicate statistically significance.

due to insufficient number of patients who experienced nausea in the OCT group (n=0).

In the OCT group, there was no significant association between the maximum treatment doses (10 [n=6], 20 [n=9], 30 [n=17] mg) and the injection-site pain (p=0.682). Similarly, the treatment doses of LAN (60 [n=7] and 120 [n=8] mg) had no statistically significant effect on the injection-site pain (p=0.336) (Table 3). Due to insufficient number of patients, LAN 90 mg group (n=2) could not be included in the analysis.

DISCUSSION

Our prospective study has demonstrated that there was no difference in the local adverse effects such as the severity of injection-site pain and leg pain, which developed following SSA injections between OCT and LAN groups, while bowel problems, i.e., diarrhea and abdominal pain, were significantly lower in the OCT group. These results are in agreement with the only head-to-head comparative study investigating the outcomes of SSA therapies in 195 acromegalic patients published in the literature[9]. Strasburger et al. have reported that the incidence of bowel problems was significantly higher in patients on LAN (p=0.0076). The study has also evaluated the duration of pain following the injections, instead of the severity of pain, and the authors have stated that the duration of injection-site pain following OCT injection was longer than that in the LAN group (p=0.0007). In another study published in 2012, 68 patients with acromegaly have been evaluated in terms of efficacy and side effects of SSA[5]. In the LAN group, the number of patients experiencing diarrhea was higher than that in the OCT group (5/32 to 1/36). In contrast to the difference between GI side effects of SSA therapies in our study, two other studies that examined 25 and 54 patients with acromegaly have reported similar GI adverse reactions between the two treatments[4,8]. Similarly, in other two studies evaluating the efficacy and side effects of the short-acting SSA, which were designed as switching between SSA drugs, the occurrence of the side effects, including the intensity of diarrhea, was similar in both therapies[6,7].

Table 3. Association of injection-site pain with the doses of somatostatin analogs.

	Doses	Injection-site pain*	p
Octreotide	10	1.00 (0.00–2.42)	0.682¥
	20	1.00 (0.00–1.67)	
	30	1.00 (0.67–2.33)	
Lanreotide	60	1.67 (1.00–2.00)	0.336Ω
	120	0.67 (0.08–2.83)	

*Data are expressed as median of mean injection-site pain score of three injections (25th–75th). ¥Evaluated by Kruskal-Wallis test. ΩEvaluated by Mann-Whitney U test.

The most frequent side effect of LAN treatment was diarrhea (58.8%) in our study, which was similar to that reported by Chanson et al.[12]. In various studies investigating the outcomes of LAN therapy, GI disturbances, most prominently diarrhea, have been reported as the most common adverse reaction of the treatment, of which the incidence rate varied between 19% and 76%[12-16]. In a comprehensive review on the adverse events associated with SSA in acromegaly by Grasso et al.[10], it has been stated that the treatment discontinuations due to the side effects were generally related to GI problems. The possible mechanism responsible for that side effect of SSA has been attributed to the drug-induced impairment of gastroenteropancreatic hormones that causes exocrine pancreatic insufficiency[10,17].

In multiple studies, local pain at the injection site has been reported as the most frequent side effect of OCT treatment[18-20]. In our study, we have evaluated the severity of pain using a scoring scale, instead of the frequency of pain, and found that the median of the average injection-site pain score of the three consecutive monthly injections was 1.00 (0.00–2.00) out of 10, with no significant difference from LAN injection (p=0.766). Vance et al. have evaluated the outcomes of short-acting OCT treatment in 189 patients with acromegaly and found local pain at the injection site as one of the common side effects[20]. In contrast, a meta-analysis assessing the efficacy and tolerability of the long-acting OCT has demonstrated that diarrhea, gallstone formation, headache, and abdominal discomfort were the general side effects of the therapy, and the local pain has not been emphasized[17]. Combining that analysis with the low injection-site pain scores reported in our study, it can be stated that the local side effects may be trivial during the long-acting SSA injections. Additionally, we have also found that the doses of SSA treatments were not significantly related to the local site pain, which may be considered another negligible factor during the management of patients with acromegaly.

The strength of our prospective study was that all 147 injections were performed by the same specialist nurse and all questionnaire forms were completed by the patients under the supervision of our nurse. The low sample size, which was 49 patients, has been the main limitation of our study. The association of the SSA doses with the side effects was one of our end points; however, the statistical analysis could not be performed for the majority of side effects other than the injection-site pain, due to the lack of enough patients experiencing each side effect.

CONCLUSIONS

To the best of our knowledge, this is the first prospective study that compared the severity of the injection-site pain by using a scoring scale, following the long-acting SSA injections. We have shown that there was no significant association of the injection-site pain severity with the SSA regimen nor the dose differences within each SSA treatment. Additionally, the frequency of GI disturbances, i.e., diarrhea and abdominal pain, was significantly lower in the OCT group. During the management plan of patients with acromegaly, it may be beneficial to consider the GI disturbances as a possible adverse event following SSA treatments, particularly after LAN injections.

AUTHORS' CONTRIBUTIONS

EG: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. **YD:** Investigation, Methodology, Visualization, Writing – review & editing. **AS:** Data curation, Investigation, Supervision, Visualization, Writing – review & editing. **ZC:** Data curation, Formal Analysis, Supervision, Visualization, Writing – review & editing. **BÇ:** Data curation, Formal Analysis, Software, Supervision, Writing – original draft. **MS:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **DK:** Methodology, Investigation, Visualization, Writing – original draft. **APK:** Formal Analysis, Methodology, Visualization, Writing – original draft.

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