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Abstract: Epistaxis, particularly in Hereditary Hemorrhagic Telangiectasia (HHT) patients, is a common otolaryngological emergency, often requiring complex management. A hierarchy of increasingly invasive interventions, from external compression of the nasal pyramid to nostril closure, is typically proposed and applied. We conducted a retrospective study on HHT patients to assess the effectiveness and longevity of invasive procedures postoperatively. Data were collected using the Epistaxis Severity Score (ESS) questionnaire. The primary focus was on changes in the frequency and intensity of epistaxis, while the secondary focus was on the overall quality of life. The study found that invasive procedures initially improved the frequency and intensity of epistaxis in HHT patients. However, within one to 9 months postoperatively, these benefits often diminished, with hemorrhagic symptoms recurring at similar or worsened levels. Facial trauma further negated the advantages of these procedures. The findings suggest a need for a gradual and increasingly invasive approach to managing epistaxis in HHT patients. Highly invasive procedures should be reserved for cases where less invasive methods fail, due to their limited temporal effectiveness and the risk of causing anatomical-functional changes in the rhino-sinus area, complicating future management of severe epistaxis.

Keywords: hereditary hemorrhagic telangiectasia; rhinology; epistaxis

1. Introduction

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant disorder characterized by abnormal vascular development and multiple arteriovenous malformations (AVMs) [1,2]. These AVMs can be small, like cutaneous or mucosal telangiectasias, or larger visceral malformations. . The underlying pathology is a defect in the vascular wall [3]. The disorder is commonly manifested by spontaneous and recurrent nosebleeds (epistaxis), gastrointestinal bleeding, and pulmonary and cerebral arteriovenous malformations [4]. Approximately 1 in 5,000 to 8,000 individuals are affected by HHT, making it the second most common inherited bleeding disorder [5,6]. With a similar incidence HHT belongs to the so called orphan diseases being mainly treated in specialized centers [7,8]. The genetic underpinnings involve mutations in genes that modulate the transforming growth factor (TGF)-β superfamily signaling in vascular endothelial cells, with mutations related to endoglin (HHT type 1) and activin receptor-like kinase (ALK1) (HHT type 2) identified through genetic testing.

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Management of epistaxis in HHT includes a range of medical and surgical interventions, based on the severity of epistaxis [9]. Surgical options like endoscopic surgery using argon plasma coagulation, lasers, and quantum molecular resonance technology, as well as intranasal dermoplasty and estrogen therapy, have been employed to control epistaxis [10,11]. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor, has also been explored for its potential in treating epistaxis, though further study is required to establish its efficacy [12]. Pazopanib is another VEGF inhibitor that targets the enzyme tyrosine kinase [13]. However, despite these treatment options, a definitive "gold standard" for epistaxis management in HHT is yet to be established.

Topical therapies, including tranexamic acid, selective estrogen modulators (SERMs), propranolol, rose geranium oil, and N-acetylcysteine, have demonstrated promise in small trials [14–17]. However, their long-term effectiveness and impact on the Epistaxis Severity Score (ESS) remain unclear.

The ESS is a gold-standard, patient-reported outcome measure specifically designed to evaluate nosebleed severity in patients with Hereditary Hemorrhagic Telangiectasia (HHT) [18]. It was proposed by Hoag et al. for the International HHT Foundation in 2010 and has been used in various studies to assess the severity and impact of epistaxis in HHT patients [19]. This score is typically documented in patient charts and is confirmed based on documented patient histories [20]. Patients are assigned a score from 1 to 10 based on their answers to six questions; mild (0-4), moderate (4-7), or severe epistaxis [21–23], with patients having higher ESS scores often requiring more invasive tratments. Furthermore, the ESS has been shown to have a negative correlation with the physical component score (PCS), indicating that a higher severity of nosebleeds can significantly impact the patients' physical health and quality of life. As a matter of fact, a study from 2015 [24] highlighted the minimal important difference of the ESS in HHT patients, and this threshold, known as the *minimal important difference* (MID), was established at 0.71.

Our study aims to critically reassess the widely held belief that surgical interventions are the optimal approach for treating epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT). We propose the hypothesis that surgeries and certain interventional procedures, particularly when performed without precise criteria and specific indications, may not only be suboptimal but could also worsen the condition. In our findings there is a potential risk that these interventions could lead to an increased frequency and severity of nosebleeds over the long term. Through a comparative analysis of long-term outcomes between patients who underwent surgical treatments and those who received targeted topical therapies, our research intends to highlight the possible adverse effects of indiscriminate surgical interventions. This study advocates for a more cautious and conservative approach in managing HHT-related epistaxis, emphasizing the need for careful evaluation and selection of treatment strategies [25].

2. Materials and Methods

Our study on Hereditary Hemorrhagic Telangiectasia (HHT) included 56 adult patients (aged 18 and above) with a confirmed diagnosis of HHT. The diagnosis is definite if 3 to 4 of the criteria match with a positive predictive value of 100% [26]. The patients were divided into Surgical Group (16 females, 14 males; mean age 45.83 ± 16.63), who were part of a follow-up program post-surgical interventions and demonstrated compliance with telemedicine for ongoing evaluation, and a Control Group (13 females, 13 males; mean age 43 ± 16.37), with patients who had never undergone surgery and who were assigned with a topical therapy (nasal washes, nasal sprays and ointments). Informed consent was a prerequisite for all participants, ensuring their awareness and agreement to the study's procedures and objectives.

At the Complex Operational Unit of Ear, Nose and Throat Science of Policlinico Universitario A. Gemelli in Rome, within the framework dedicated to Hereditary Hemorrhagic Telangiectasia, from November 2021 to October 2023, we systematically collected clinical data from 130 patients using the validated Epistaxis Severity Score (ESS) questionnaire. Out of these, 44 patients had undergone interventional procedures in their medical history. Only 30 of these patients met the following inclusion and exclusion criteria; additionally, a control group of 26 subjects with a confirmed

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diagnosis of HHT was selected, essentially homogeneous in age and sex to those belonging to the Surgical Group, for whom the ESS was collected at similar times

Patients undergoing therapy with biological drugs were excluded. This decision was made to eliminate potential variables that could arise from the effects of these medications. Secondly, patients who had undergone procedures but lacked accessible documentation were also excluded. The availability of comprehensive medical records was crucial for accurate assessment and follow-up in the study.

In our study, we utilized changes in the ESS over time to evaluate the long-term efficacy of surgical interventions and topical therapies in managing epistaxis in HHT patients. Specifically, the observation times for the ESS included T0, which for surgical patients represented the pre-surgical moment, T1 at *1 month post-surgery*, and finally T2 at *nine months post-surgery*. The same ESS collection timelines were maintained for the control group, with T0 set as the time before starting the topical therapy.

The patients were stratified into two groups: Group A (invasive interventional procedures) and Group B (minimally invasive interventional procedures) [16]. The demographics of our population are described in Table 1. By invasive surgical procedures, we refer to coagulation techniques (diode laser, argon plasma), embolization, and we have included sclerotherapy in this group as well. Minimally invasive procedures encompassed cauterizations with Silver Nitrate (AgNO3) and with mono/bipolar tool.

Table 1. demographic for the selected groups.

Sex Distribution			
	Control Group	**Surgery Group A**	**Surgery Group B**
Total Females	13	9	7
Total Males	13	8	6
Age Distribution			
	Control Group	**Surgery Group A**	**Surgery Group B**
Total Patients	25	17	13
Mean Age	43	50.94	39.15
Age Std Dev	16.37	15.86	15.74

3. Results

In our analysis, we aimed to assess the differences in the change of Epistaxis Severity Scores (ESS) between a surgical group and a control group at two distinct time intervals: from baseline (T0) to one month (T1), and from baseline to nine months (T2). The surgical group comprised patients undergoing invasive or minimally invasive treatments, while the control group received no surgical intervention, while being assigned with a topical therapy instead. Our objective was to evaluate the effectiveness of surgical interventions in reducing the severity of epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT). We conducted statistical analyses to determine whether there were significant differences in age and sex distributions between the surgical group (which includes both minimally invasive and invasive surgeries) and the control group. The purpose was to ascertain the comparability of these groups in terms of basic demographic characteristics. *Sex Distribution Analysis:* We employed the Chi-Square test to assess the differences in sex distribution between the groups. The test yielded a p-value of 1.0, indicating no statistically significant difference in sex distribution between the surgical and control groups. This result suggests that both groups were well-matched in terms of gender representation. *Age Distribution Analysis:* Prior to comparing the age distributions, we verified the normality of age data in each group. Both groups demonstrated normally distributed age data, allowing us to use the Student's t-test for independent samples. The t-test resulted in a p-value of 0.5246. This lack of statistical significance indicates that there were no substantial differences in age distribution between the surgical and control groups.

Prior to statistical comparison, we examined the normality of the distributions of the changes in ESS scores (Δ T1-T0 and Δ T2-T0) for both groups. The Shapiro-Wilk test revealed that the Δ T1-T0

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scores for both groups and the Δ T2-T0 scores for the surgical group did not follow a normal distribution, while the Δ T2-T0 scores for the control group were normally distributed. Given these findings, we elected to use the Mann-Whitney U test, a non-parametric test, for all comparisons to ensure consistency and reliability in the presence of non-normally distributed data.

To ensure an accurate analysis, we aimed to determine whether there were statistically significant differences in the ESS at baseline (T0) across three distinct groups (Group A, Group B and Control Group). To achieve this, we first ensured that the data met the necessary assumptions for ANOVA. The homogeneity of variances was verified using Levene's test, which resulted in a p-value of 0.222, suggesting that the variance across the groups was homogenous. Subsequently, a one-way ANOVA was conducted to compare the mean ESS scores at T0 among the three groups. The results of the ANOVA indicated no significant differences in the ESS scores at T0 across the groups ($F = 1.387$, $p = 0.259$). Therefore, based on our analysis, we conclude that there are no statistically significant differences in the ESS scores at T0 among the three groups studied.

The results of the Mann-Whitney U test indicated no statistically significant difference between the groups in the short-term change in ESS scores (Δ T1-T0) with a p-value of 0.1243. This suggests that both groups experienced similar changes in the severity of epistaxis in the initial three weeks. However, in the long-term comparison (Δ T2-T0), a statistically significant difference was observed ($p = 0.00016$), indicating a disparity in the impact of surgical intervention over a nine-month period. Specifically, the control group exhibited a more substantial reduction in ESS scores compared to the surgical group (Table 2).

These findings highlight that, while the surgical interventions had an immediate effect on reducing the severity of epistaxis, this effect was not sustained over a longer period. In contrast, the control group, which did not undergo surgical treatment, showed a greater improvement in ESS scores over nine months. This outcome raises important considerations about the long-term management of epistaxis in HHT patients and suggests that surgical interventions, while beneficial in the short term, may not provide sustained improvement in comparison to non-surgical management strategies.

Furthermore, the Mann-Whitney U test was employed to compare the efficacy of two treatment groups, categorized as minimally invasive (Group B) and invasive (Group A), in terms of changes in ESS scores. The ESS delta values, calculated as the differences between ESS scores at different time points (T1-T0 and T2-T0), were used as the primary metric for assessing clinical improvement, with lower or more negative deltas indicating greater improvement.

The results of the Mann-Whitney U test for the ESS T1-T0 delta yielded a U statistic of 117.0 and a p-value of 0.802, while the test for the ESS T2-T0 delta produced a U statistic of 102.5 with a p-value of 0.750. These p-values indicate no statistically significant difference in the clinical improvement between the two treatment groups. Consequently, the data suggest that neither treatment method demonstrated a superior outcome in terms of ESS score changes over the observed time periods (Table 3).

Table 2. Mann-Whitney Test for differences between Surgical Group and Control Group in terms of ESS at different times (ESS T1-T0 and ESS T2-T0). Dif T1-T0 indicates the difference between the mean ESS at T1 and T0; Dif T2-T0 indicates the mean difference between ESS at T2 and T0;.

Group	*ESS (mean ± SD)*		*p value (Mann- Whitney U test)*
Surgical Group	T0	*5.21 ± 2.59*	
	T1	*3.39 ± 2.09*	
	T2	*5.14 ± 2.42*	
Control Group	T0	*4.67 ± 1.79*	
	T1	*3.50 ± 0.98*	
	T2	*2.78 ± 1.05*	
Surgical Group	Dif. T1 - T0	*-1.17 ± 1.37*	*0.1243*
Control Group	Dif T1 - T0	*-1.83 ± 3.36*	
Surgical Group	Dif T2 - T0	*-0.08 ± 3.08*	*0.00016*

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Control Group	Dif T2 - T0	*-1.89± 1.51*

Table 3. Mann-Whitney Test for differences between Group A and B, showing no statistical difference between the two treatments (mini-invasive and invasive surgery).

Comparison	Mann-Whitney U Statistic	p-value
Δ ESS T1-T0	117	0.8015
Δ ESS T2-T0	102.5	0.7502

4. Discussion

In this study, our primary objective was to evaluate the long-term efficacy of the therapeutic approaches for managing epistaxis in patients with Hereditary Hemorrhagic Telangiectasia (HHT). We focused on comparing the outcomes between a surgical group and a control group over two specific timeframes: one month (T1) and nine months (T2) post-initiation of therapy. The analysis of changes in Epistaxis Severity Scores (ESS) from baseline (T0) to these time points provided insights into the short-term and long-term effectiveness of the treatments.

For the control group, the treatment regimen consisted of conservative management strategies frequently utilized at our center. These included nasal washes with saline solutions, the application of nasal sprays, mainly administered as drops, (composed of hyaluronic acid), and the use of nasal ointments following episodes of epistaxis.

Our statistical analysis revealed no significant differences between the surgical and control groups in the short-term (T1) change in ESS (Δ T1-T0), as indicated by a Mann-Whitney U test p-value of 0.1243. However, a significant difference emerged in the long-term (T2) analysis (Δ T2-T0) with a p-value of 0.00016, suggesting a disparity in the impact of the surgical intervention over a nine-month period. Interestingly, while the surgical group exhibited immediate benefits, indicated by the changes in ESS at T1, these benefits were not sustained at T2. In fact, the control group, which adhered to conservative management, showed greater improvement in ESS scores at the nine-month mark. This observation underscores that, although surgical interventions provide immediate relief from epistaxis, their benefits might diminish over time, potentially resulting in conditions worse than the baseline.

We also evaluated the differences in terms of ESS over time for the different assessments (T1, one month, and T2, nine months) between the two surgery groups, Group A (invasive treatments) and Group B (minimally invasive treatments), with the absence of statistically significant differences between the two groups.

These findings hold significant implications for the long-term management of epistaxis in HHT patients. They suggest that conservative treatment strategies, though less aggressive than surgery, may offer more sustainable benefits over time. This represents a further step towards confirming that surgical therapy should be considered a rescue tool in conditions that are substantially irrecoverable with medical therapy.

5. Conclusions

Although the sample size in this study is not extensive in numerical terms, it's important to consider the strict inclusion criteria implemented to mitigate potential selection bias, especially given that Rendu-Osler-Weber syndrome (HHT) is a rare disease with limited case numbers compared to other otolaryngological conditions. The study indicates that surgical treatments initially provide short-term benefits (one month post-treatment); however, these advantages appear to diminish over time (nine months post-treatment). On the other hand, conservative treatments like nasal washes, sprays, and ointments show consistent improvement in managing epistaxis over this period, suggesting they may offer more enduring benefits than surgery.

The findings suggest that surgical intervention in HHT patients should generally be considered as a last resort, especially when conservative medical treatments are ineffective. Our data advocates for a more conservative initial approach to epistaxis management, focusing on preservation and

minimal intervention. In situations where surgery is necessary, it should be specifically targeted at treating particular conditions, such as larger or more actively bleeding telangiectasias, and conducted with extreme caution to minimize damage to the nasal mucosa.

This research contributes to the increasing evidence favoring conservative management in HHT-related epistaxis and highlights the need for long-term outcome evaluations to judge treatment efficacy. Future studies with larger, more diverse samples are essential to strengthen these findings and help establish comprehensive treatment protocols for HHT. Notably, current interventional procedures in both groups do not seem to provide lasting benefits; in fact, they may worsen epistaxis over time. Therefore, expanded studies and the creation of an international, or at least European, registry for this rare disease would be desirable. Such a registry would allow for the evaluation of a larger caseload and the development of updated, effective international guidelines for treating epistaxis in HHT, which, unfortunately, is still too often based on personal experience.

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Data Availability Statement: The datasets presented in this article are not readily available because the data are part of an ongoing study. Requests to access the datasets should be directed to giuliocesare.passali@unicatt.it

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