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Somatostatin analogs in the treatment of gastrointestinal angiodysplasia bleeding: a systematic review

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ABSTRACT

Aim: We aimed to perform a systematic review to gather evidence on the efficacy of somatostatin analogs (SA) in managing bleeding gastrointestinal angiodysplasias (GIADs).

Background: Some usual treatment modalities for bleeding caused by GIADs include endoscopic or surgical management. However, considering their availability and side effects, they may not be feasible for every patient. On that account, pharmacological management may become a safe and effective option.

Methods: In January 2024, a systematic review of the literature was conducted using the PubMed/Medline, Cochrane Library, and Scopus databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework was followed. Inclusion in this review was restricted to randomized clinical trials (RCTs) or observational studies comparing the use of SA as the main or complementary therapy in patients with GIADs. The outcomes of interest were hemoglobin levels, transfusion requirements, bleeding, and safety/adverse effects.

Results: Seven studies were included in the systematic review, two RCTs and five observational studies. There were 682 patients, of which 166 (24.3%) received any form of treatment involving SA. The studies varied greatly regarding follow-up, SA of choice, and other treatments associated with SA or as a control. Lanreotide appears to be able to significantly improve hemoglobin levels when associated with various treatments, whereas octreotide does not. One RCT found a significant reduction in blood or iron transfusion units when comparing SA to a standard of care, but other studies had mixed results. Lanreotide may be useful in reducing bleeding episodes in patients treated with argon plasma coagulation with double-balloon enteroscopy. Gastrointestinal adverse events such as diarrhea, vomiting, and abdominal pain were commonly reported across studies.

Conclusion: The majority but not all included studies suggest that SA may improve hemoglobin levels and reduce bleeding in patients with GIAD. However, the studies included small sample sizes and were not of strong statistical power. Further RCTs with larger populations are necessary to validate the effectiveness of SA in managing patients with GIAD.

Keywords: Somatostatin analogs, Angiodysplasia, Bleeding, Hemoglobin.

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Introduction

Gastrointestinal angiodysplasias (GIADs) are arterial or venous vascular malformations composed of dilated and tortuous vessels located in the mucosal and submucosal layers of the gastrointestinal tract (1). This condition is associated with various clinical scenarios and is especially frequent among adults over 60 years (2). They are reportedly the most common cause of

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small bowel hemorrhage (3, 4), being responsible for about 10% of all gastrointestinal bleeding (GIB) cases (1). The resulting iron deficiency anemia is usually managed with iron supplementation and, in some cases, blood transfusions (5), which may impair the quality of life of those affected and increase healthcare costs (6).

Some of the usual treatment modalities of GIB caused by GIADs are argon plasma coagulation (APC), mechanical clip placement, multipolar electrocoagulation (MPEC), laser photoablation, angiography with embolization, and surgical resection. However, considering most patients are elderly, such endoscopic or surgical management may not be the best option (7, 8). In addition, a meta-analysis evaluating endoscopic therapy for GIADs showed a pooled recurrence rate of 34% within 2 years (9). Therefore, pharmacological management may become a safe and effective option.

Somatostatin analogs (SA) emerge as a possible alternative therapy for bleeding due to GIADs. They have been shown to have anti-angiogenic effects, reduce splanchnic blood flow, and improve platelet aggregation (1, 10-12). Despite promising results regarding decreased recurrence rates and the need for red blood cell (RBC) transfusion, studies showing the benefits of these analogs still may present a high risk of bias, considering their retrospective approach, small samples, and lack of control groups (8-10). Therefore, we aimed to perform a systematic review to gather evidence on the efficacy of SA in managing bleeding GIADs.

Methods

Search strategy and selection of articles

In January 2024, a comprehensive systematic review of the literature was conducted using the PubMed/Medline, Cochrane Library, and Embase databases with the terms: ‘angiodysplasia’, ‘gastrointestinal bleeding’, and ‘somatostatin analogs’ with synonyms for each term. The search was based on the Medical Subject Headings (MeSH) the National Library of Medicine provided.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework was followed (13). Inclusion in this review was restricted to studies that met all the following eligibility criteria: (1) randomized trials or nonrandomized cohorts; (2) enrolling patients with confirmed angiodysplasia; (3) comparing the use of SA as the main or complementary therapy; and (4) reporting at least one of the clinical outcomes of interest.

Two authors (V.A.L.J. and M.F.V.) conducted individual reviews of the title and abstract of each study, adhering to the predetermined inclusion criteria. Subsequently, full texts were examined for those abstracts that either met the criteria or lacked sufficient information. Discrepant cases were resolved through consensus or analyzed by a third evaluator (T.C.). Additionally, the included articles' references were reviewed to identify studies that may not have been identified through the initial process. The language was not limited to English, and there were no publication date restrictions. This study is registered at the International Database of Prospectively Registered Systematic Reviews (PROSPERO) under CRD 42024505301.

Data Extraction and Assessment of Study Quality

Data extraction and risk of bias were executed independently by two reviewers (V.A.L.J. and M.F.V.) using a specially developed structured form. Divergences were solved by consensus or discussed with a third author (T.C.).

The data extraction form contained the following data regarding study-level characteristics: author's last name, study year, country, study design, number of cases and controls, ascertainment of exposure, and follow-up time. The following patient-level characteristics were also extracted: mean age, sex, total number and percentage in each treatment group, SA type and dosage, and mean baseline hemoglobin. The outcomes of interest were hemoglobin levels, transfusion requirements, bleeding, and safety/adverse effects.

The Cochrane Collaboration's tool for evaluating the risk of bias in randomized trials (RoB 2) was utilized for the quality evaluation of RCTs (14). We evaluated five domains for each selected study: (1) bias in the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing data; (4) bias in outcome measurement; and (5) bias in the selection of the reported results. The risk of bias assessment for each trial outcome was based on individual domain judgments. The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used for evaluating the risk of bias in non-randomized studies (15).

Results

As detailed in Figure 1, the initial search yielded 2,018 results. After removing duplicate records and ineligible studies, 50 remained and were fully reviewed based on inclusion criteria. Of these, a total of 7 studies were included, comprising 114 patients from 2 randomized controlled trials (RCTs) (16, 17) and 568 from 5 non-randomized cohorts (18-22). A total of 166 patients received treatments involving SA (62 SA alone (17-20), 27 SA plus ablation (18), 25 SA plus iron (18), 23 SA plus transfusions of iron and red blood cells (16), 29 SA plus argon plasma coagulation and double balloon enteroscopy (21, 22), 594 patients received treatments without SA (63 ablation (18), 147 iron (18, 22), 324 red blood cells and iron transfusion (16, 22), 60 argon plasma coagulation (APC) and double-balloon enteroscopy (DBE) (21, 22) and 99 patients received placebo or no treatment (17, 19, 20). The studies had great variations in follow-up time and SA of choice: three used lanreotide (18, 21, 22), two used octreotide (19, 20); sandostatin and pasireotide-LAR were used in one study each (16, 17). More information on study characteristics can be found in Table 1.

Hemoglobin levels

Five included studies reported hemoglobin levels as an outcome (16, 18, 19, 21, 22). One observational study found a significant improvement from baseline hemoglobin levels for the combination of iron supplementation and lanreotide at 12 months and for the combination of ablation and lanreotide at 6 months ($p<0.05$), but not at 12 months ($p = 0.6$) (18). Zammit et al. compared APC plus DBE and lanreotide with APC plus DBE without it and found statistically significant improvement of hemoglobin levels in the first group ($p=0.043$) (21); Tai et al. also found a significant hemoglobin increase from baseline with this intervention (22).

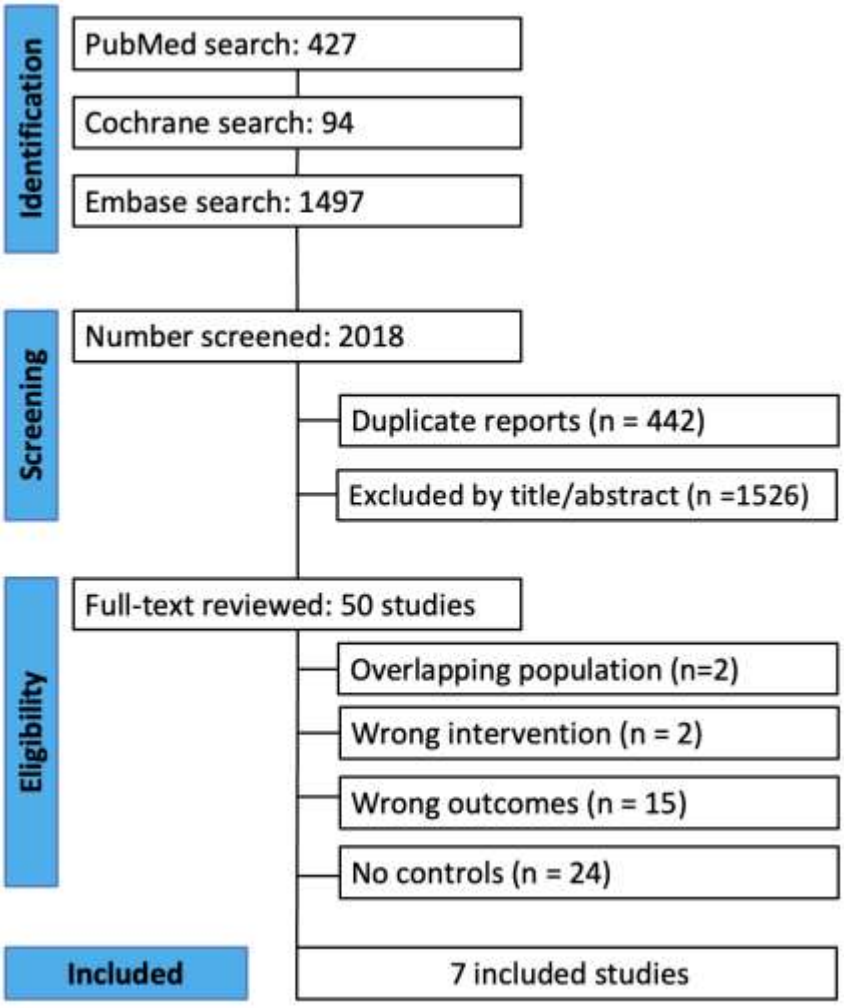

Figure 1. PRISMA flow diagram of study screening and selection

Table 1. Design and characteristics of the studies included in the systematic review.

First author, year	Country	Study design	Groups	Number of patients	Age, years*	Male, %	SA Administration	Follow-up	Hemoglobin, g/dL*
Gutierrez, 2023	USA	Observational	Ablation Ablation + SA Iron Iron + SA SA	312	69 69.7 68.9 64.96 63.7	-	Lanreotide 90-120 mg every month for 12 months	24 months	11.01 9.13 10.59 10.03 11.91
Goltstein, 2023	Netherlands	RCT	SA + Transfusion + Iron Transfusion + Iron	62	72.5 71.8	48 55	Sandostatin LAR 40 mg IM every 28 days for 52 weeks	60 weeks	10.15 10.15
Del Cueto-Aguilera, 2022	Mexico	Observational	SA No treatment	52	73.5 66.1	50 44.4	Octreotide SC 100 mcg/24 h for 10.5 months*	12.9 months	6.9 6.72
Benamouzig, 2018	France	RCT	SA Placebo	22	70.4 72	70 75	Pasireotide-LAR IM 60 mg every 28 days for 6 months	12 months	9.6 9.2
Chetcuti Zammit, 2017	UK	Observational	DBE + APC SA + DBE + APC	49	68.7 74	51.4 33.3	Lanreotide 60-120 mg SC every 4 weeks or 6 weeks for 19 months*	32.7 months	10.33 86.8
Junquera, 2007	Spain	Observational	SA Placebo	70	71 71	71.8 52.6	Octreotide SC 50 mcg/12 h for 1-2 years	1 year	-
Tai, 2023	UK	Observational	SA + APC APC Iron + Transfusion Iron	85	76 70 76 75	56 50 36 58	30-120 mg SC every month for 8 months**	1 year	8.47 9.84 10.21 11.08

* Mean; ** Median. APC, argon plasma coagulation; DBE, double balloon enteroscopy; Hb, hemoglobin; IM, intramuscular; IQR, interquartile range; LAR, long-acting release; RCT, randomized controlled trial; SA, somatostatin analog; SC, standard of care; UK, United Kingdom; USA, United States of America.

One RCT compared standard care (iron supplementation and RBC transfusions) with standard care plus octreotide but did not find statistically significant differences between groups in hemoglobin levels (16), whereas an observational study reported a decreased hemoglobin reduction in treated patients (19). More details from the results above can be found in Table 2.

Transfusion requirements

Six studies evaluated RBC and/or iron transfusions as an outcome. One RCT with 60 weeks of follow-up showed a significant reduction in both types of transfusions when comparing octreotide to standard of

Table 2. Summary of results for each study regarding hemoglobin levels

Study	Design	Patients/Group	Main results
Gutierrez, 2023	Observational	72 Ablation + Lanreotide 25 Iron + Lanreotide 8 Lanreotide	Hb in g/dL* Ablation + SA: 9.13±0.40 to 10.84±0.49 at 6 months (p<0.05) and 10.85±0.50 at 12 months (p=0.06) Iron + SA: 10.03±0.61 to 12.40±0.42 at 12 months (p<0.05)
Goltstein, 2023	RCT	61 SC + Octreotide 31 SC	Hb in mmol/L There was a numerical difference between SC + SA [7.2 (95%CI 6.7 – 7.8)] and SC [6.6 (95%CI 6.1 – 7.1)], but this result was not statistically significant
Chetcuti Zammit, 2017	Observational	12 DBE + APC + Lanreotide 37 DBE + APC only	Hb in g/L The Hb improvement in the Lanreotide group was statistically significant (11g/L vs 3.2g/L, p=0.043)
Tai, 2023	Observational	17 DBE + APC + Lanreotide	Hb in g/L Mean Hb at one year after treatment (94, IQR 12) was greater than at baseline (85, IQR 14)
Del Cueto-Aguilera, 2022	Observational	16 Octreotide 36 Control	Treated patients had less Hb reduction (25% vs 58.3%, p=0.037)

* Mean ± SEM. APC, argon plasma coagulation; CI, confidence interval; DBE, double balloon enteroscopy; Hb, hemoglobin; IQR, interquartile range; RCT, randomized controlled trial; SA, somatostatin analog; SC, standard of care.

Table 3. Summary of results for each study regarding transfusion requirements

Study	Design	Patients/Group	Main results
Goltstein, 2023	RCT	61 SC + Octreotide 31 SC	Octreotide patients had 11.0 (95% CI, 5.5–16.5) transfusion units in the study year*, while SC patients had 21.2 (95% CI, 15.7–26.7)*, resulting in a mean reduction of 10.2 (95% CI, 2.4-18.1; p=0.01) Octreotide: 8.2 (95% CI, 3.2-13.2) RBC transfusions and 2.8 (95% CI, 1.3-4.3) iron infusions* SC: 16.8 (95% CI, 11.8–21.8) and 4.6 (95% CI, 3.1–6.0)*
Del Cueto-Aguilera, 2022	Observational	16 Octreotide 36 Control	Octreotide patients required less blood transfusions (6.3% vs 38.9%, p=0.021)
Benamouzig, 2018	RCT	10 Pasireotide-LAR 12 Placebo	83% (36–99%) in the SA group and 25% (3–65%) in the placebo group had at least a 30% reduction in RBC transfusion
Chetcuti Zammit, 2017	Observational	12 DBE + APC + Lanreotide 37 DBE + APC only	SA patients had lower blood transfusion requirements per month (0.8 vs 4.7 p=0.052)
Junquera 2007	Observational	32 Octreotide 36 External control	No difference was found in RBC transfusion requirements (1.1 ± 2.6 vs 0.7 ± 1.5 units) Iron requirements were lower in the SA group (22 ± 62 *versus* 166 ± 267 units, p<0.001)
Tai, 2023	Observational	17 DBE + APC + Lanreotide	No difference was found in blood transfusion episodes (p=0.07) or in the mean number of iron infusions (from 2 episodes, IQR 5 prior to treatment, to 3 episodes, IQR 9 after starting SA)

* Mean. APC, argon plasma coagulation; CI, confidence interval; DBE, double balloon enteroscopy; IQR, interquartile range; LAR, long-acting release; RBC, red blood cell; RCT, randomized controlled trial; SA, somatostatin analog; SC, standard of care; UK, United Kingdom; USA, United States of America.

care (oral, then parenteral iron supplementation, if not effective, RBC transfusion for anemia) (16). Another RCT evaluating Pasireotide-LAR had as its main outcome a 30% reduction in RBC transfusion, for which it did not find a significant result, but the sample size was very small (17). Two observational studies also reported RBC transfusion reduction in patients using SA (19, 21), while only one found a significant reduction in iron transfusion requirements (20), and the other did not find a difference in any transfusion (22) (Table 3).

Bleeding

Five included studies analyzed the risk of bleeding. The RCT that reported this outcome found a non-significant reduction in bleeding episodes in patients treated with octreotide compared to those not (16). Two observational studies found statistically significant reductions, Aguillera et al. for bleeding episodes in general ($p < 0.02$) (19) and Junquera et al. only for chronic bleeding ($p = 0.41$) (20). Two studies reported the risk of bleeding using lanreotide with DBE plus APC. Zammit et al. reported a significant reduction between the SA and the DBE plus APC alone groups ($p = 0.032$) (21), while Tai et al. did not directly compare the two groups but found a reduction in bleeding episodes in the SA group comparing to baseline ($p = 0.002$) (22). More information can be found in Table 4. There were great variations in what was considered a bleeding episode that could explain the different results between studies; for example, Goldstein et al. considered a bleeding episode as an episode of anemia that required a visit to the hospital (16), while Aguillera et al. defined bleeding as the presence of at least one of many parameters (decrease of hemoglobin > 2 g/dl, visible blood in stools; blood transfusion or iron parenteral requirement) (19).

Safety

Six studies included safety outcomes in their report. The most reported adverse events were gastrointestinal adverse events, such as diarrhea - in some cases requiring pancreatic enzyme replacement -, vomiting, and abdominal pain (16, 17, 19, 20, 22); some patients had to adjust their antidiabetics doses (16, 17); in an RCT, two patients had to discontinue octreotide due to serious adverse events: acute cholangitis and hypoglycemic episode with loss of consciousness (16). Other serious adverse events were intractable abdominal pain (1 patient, octreotide) (19), hypoglycemia associated with diarrhea (1 patient, pasireotide) (17), and stroke (1 patient, octreotide) (20). Two studies reported symptomatic gallstone disease as an adverse event of lanreotide (21, 22). Junquera et al. found a significant increase in patients presenting adverse events in the octreotide group ($p = 0.012$) (20). No treatment-related deaths were reported among the studies.

Quality assessment

Regarding the risk of bias in individual studies, one RCT was classified with some concerns (16) and the other as low risk (17). As for the observational studies,

Table 4. Summary of results for each study regarding bleeding events

Study	Design	Patients/Group	Main results
Goltstein, 2023	RCT	61 SC + Octreotide 31 SC	Although not significant, during the study year, patients on SA experienced fewer bleeding episodes than patients on SC - adjusted difference 3.2 (95% CI -0.2-6.6)
Del Cueto-Aguilera, 2022	Observational	16 Octreotide 36 Control	The rebleeding rate in SA patients (25%) was significantly lower than in the control group (72.2%) (p=0.002)
Junquera, 2007	Observational	32 Octreotide 36 External control	For all bleeding, there was no significant difference between the groups (SA 0.4 ± 0.7; placebo 0.9 ± 1.5. p=0.070). SA patients had fewer chronic bleeding than control (SA 0.03 ± 0.8; placebo 0.2 ± 0.5. p=0.041)
Chetcuti Zammit, 2017	Observational	12 DBE + APC + Lanreotide 37 DBE + APC only	SA patients had fewer bleeding episodes than DBE + APC only (1.08; 2.6. p=0.032, respectively)
Tai, 2023	Observational	17 DBE + APC + Lanreotide	The median number of bleeding episodes per year reduced from 3.5 (IQR 4) to 1.0 (IQR 2) comparing to baseline (p=0.002)

* Mean. APC, argon plasma coagulation; CI, confidence interval; DBE, double balloon enteroscopy; IQR, interquartile range; RCT, randomized controlled trial; SA, somatostatin analog; SC, standard of care.

two presented critical risks of bias (20, 21): Zammit et al. had a critical risk of bias regarding the selection of the participants, whereas Junquera et al. had a critical risk of bias in the classification of interventions. The remaining studies were classified as having moderate risk (18, 19, 22). The overall risk of bias evaluation for each domain can be found in the Supplementary Appendix - Tables S1 and S2.

Discussion

From the five studies assessing hemoglobin levels, three found statistically significant improvement in patients treated with SA, while one had no significant difference, and one found a reduction in Hb levels. While the studies are still non-conclusive, there is a tendency for more studies to show an improvement in Hb levels in patients treated with SA. Also, all five studies found fewer bleeding episodes in the SA group than their respective controls; however, this difference was significant in only three. Our results are by those from a previous review from 2010 on the effects of SA on gastrointestinal vascular malformations, which found it reasonable to administer octreotide, especially in patients with refractory bleeding, inaccessible lesions, and patients at high risk for other interventions. (8).

The possible mechanisms for this effect include the SA anti-angiogenic activity by inhibition of growth factors like vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and the growth hormone (GH)/insulin-like growth factor-I (IGF-I). (11). Additionally, octreotide has been shown to reduce the proliferation of human HUV-EC-C endothelial cells as well as the density of the vascular network in vitro and in vivo experiments (23). SA induces biological effects by interacting with specific G protein-coupled receptors, the Somatostatin Receptors (SSTR1–SSTR5) (24).

The adverse events related to SA included in the studies were gastrointestinal adverse events (diarrhea, abdominal pain, and vomiting), abnormal glucose metabolism, gallstone disease, cholangitis, and acute stroke. There is a special concern regarding the potential risk of thromboembolic events among elderly patients, particularly those who are typically prescribed anticoagulation or antiplatelet medications (25). By inhibiting gallbladder contractions, approximately 27% of patients treated with SA may develop gallstones. (26). Therefore, SA treatment can be associated with an increased discontinuation rate in patients taking the medicine (27).

Our study has limitations related to the heterogeneity of the studies included in the review. In addition, there were different definitions of the control groups and outcomes among the studies, which may have made the populations not very similar. The small sample size, the lack of randomization, and variations in the dose and form of the medications and control groups make it difficult to generalize the results.

Considering the lack of robust evidence on its superiority and the potential adverse effects of SA, particularly on the elderly, it seems prudent to evaluate the risks and benefits of SA and endoscopic therapies on an individual basis, taking into account the degree of bleeding, clinical status, and associated comorbidities of each patient.

Conclusion

The majority, but not all, included studies suggest that SA may improve hemoglobin levels and reduce bleeding in patients with GIAD, although it comes with potential risks and adverse effects. However, the studies included small sample sizes and were not of strong statistical power.

Further multicenter randomized controlled trials with larger populations are necessary to validate the effectiveness of SA in managing patients with GIAD. We suggest future studies standardizing the interventions and control groups to make it feasible to compare and generalize the results.

Conflict of interests

The authors declare no conflict of interest.

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