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Refractory Anaemia Secondary to Small Bowel Angioectasias - Comparison between Endotherapy Alone versus Combination with Somatostatin Analogues

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ABSTRACT

Background & Aims: Patients with small bowel angioectasias (SBAs) can be difficult to manage as they are generally elderly with multiple co-morbidities. Angioectasias are multiple and tend to recur. Argon plasma coagulation (APC), despite being a commonly used method to treat these patients has an associated persistent rate of re-bleeding necessitating additional treatment to manage these patients.

Methods: All patients with refractory iron deficiency anaemia secondary to SBAs were retrospectively subdivided into two groups. Patients in group 1 were managed with double balloon enteroscopy (DBE) and APC alone and those in group 2 received Lanreotide in addition to DBE and APC.

Results: A total of 49 patients were included in this study: group 1: 37 patients (75.5%), group 2: 12 patients (24.5%). All had significant comorbidities and the mean duration of anaemia was 114.3, SD 307.0 months. Significant improvements in haemoglobin (Hb) (11g/L vs 3.2g/L p=0.043), transfusion requirements per month (0.8 vs 4.7 p=0.052) and mean bleeding episodes (1.08 vs 2.6 p=0.032) were demonstrated in group 2 when compared to group 1. One patient developed symptomatic gallstone disease and one patient stopped Lanreotide due to a lack of response.

Conclusions: This is the first study comparing endotherapy to a combination of endotherapy and pharmacotherapy. It shows a significantly better outcome in patients receiving a combination of endotherapy and Lanreotide. Lanreotide can be a safe additional treatment in patients not responding to APC alone.

Key words: Argon plasma coagulation (APC) – double balloon enteroscopy (DBE) – Lanreotide – small bowel bleeding.

Abbreviations: APC: argon plasma coagulation; CE: capsule endoscopy; DBE double balloon enteroscopy; Hb: hemoglobin; OGIB: over gastrointestinal bleeding; SBAs: small bowel angioectasias.

INTRODUCTION

Small bowel (SB) bleeding accounts for up to 10% [1] of the patients who present with occult or overt gastrointestinal bleeding (OGIB) with a negative gastroscopy and colonoscopy. Small bowel angioectasias (SBAs) (50%) are the most common finding on capsule endoscopy (CE) in patients with OGIB [2]. Angioectasias are ectatic blood vessels with or without endothelial lining that have a tendency to bleed [3]. They are most commonly located in the proximal SB [4] and are often multiple [5].

Management of patients with SBAs can be challenging due to several reasons. Small bowell angioectasias commonly occur in elderly patients [6] with several underlying co-morbidities such as cardiovascular disease, chronic liver and kidney disease [7]. In addition, these patients are very often on anticoagulants or anti-platelets which increase the bleeding tendency of the vascular lesions [8]. Patients with aortic stenosis have a higher tendency to have SBAs [9]. In this phenomenon there is an increased consumption of high molecular weight multimers of von Willebrand Factor (vWF) due to high shear forces across the stenotic aortic valve thus predisposing patients to bleeding [10]. Von Willebrand Factor normally plays a role in homeostasis by stabilizing factor 8 and aiding binding of factor 8 to platelets [11].

Argon plasma coagulation (APC, non-contact thermal therapy) has been the traditional method of treating SBAs at double balloon enteroscopy (DBE) [12]. The diagnostic and therapeutic yield of device-assisted enteroscopy for OGIB was

reported to be 69% and 52% in a multi-centre retrospective study [13]. The presence of an overtube at DBE allows deeper examination of the small bowel. Mean depth of small bowel insertion of antegrade DBE varies between 200 cm and 360 cm and between 100 and 167 cm for the retrograde route [14-20]. Few studies report a relatively high complete enteroscopy rate of 57% and 66% [14, 21]. The complication rate of DBE is 0.9 to 1.2% [22, 23]. Argon plasma coagulation is a safe therapeutic procedure with very few side effects [24].

Studies on patients receiving APC to treat SBAs report a rise in haemoglobin (Hb) and a decrease in transfusion requirements [25, 26]. However, recent evidence suggests a persistently high rate of rebleeding despite endotherapy. Jackson et al. reported a rebleeding rate of 45% over a mean (±SD) of 22±13 months in patients with SBAs despite endotherapy [27]. In a systemic review of angioectasias in patients with OGIB, the pooled rebleeding rate from 24 studies (n=490) of patients who underwent endoscopic therapy was 42.7% over an average / median follow up of 0.25 to 4.6 years. This was not dissimilar to the rebleeding rate of 49.2% from 6 natural history studies over 1 to 3 years (n=130) [28]. In another study by Pinho et al., rebleeding occurred in 40% of patients during a median follow-up of 23 months. Rebleeding increased during the subsequent years of follow up: 32.7, 38.3, 46.0, 53.7, and 63.0% at 1, 2, 3, 4, and 5 years respectively [26]. Endoscopic therapy is discussed in the ACG review on the management of SBAs. Authors state that data on endoscopic therapy is limited due to lack of studies comparing it to sham therapy [1]. Some explanations for the persistent rebleeding rate include the fact that SBAs are not always accessible at DBE and that there might be incomplete examination of the small bowel at DBE. Therapeutic and prolonged endoscopic procedures such as DBE are frequently challenging in the elderly due to underlying comorbidities.

Somatostatin analogues such as Octreotide and Lanreotide have been used in the management of patients with SBAs as rescue therapy in addition to endotherapy [29, 30]. Whilst there is some evidence for endoscopic intervention versus somatostatin analogues, no direct comparisons have been made between the two modalities.

The aim of this study was to evaluate the efficacy of Lanreotide in the management of patients with SBAs in addition to DBE and APC in comparison to patients who underwent DBE and APC alone.

METHODS

All patients with refractory iron deficiency anaemia secondary to SBAs who were treated with DBE and APC ± Lanreotide between 2010 and 2016 at the Royal Hallamshire Hospital in Sheffield were included in this retrospective study. Patients were subdivided into group 1: patients who were managed with DBE and APC alone, and group 2: patients who received Lanreotide in addition to DBE and APC. Patients in group 2 were commenced on Lanreotide due to persistent refractory anaemia that had not improved following endoscopic ablation using DBE. Patients in both groups had underlying refractory anaemia despite iron therapy and required blood transfusions.

Lanreotide was administered by deep subcutaneous injection at the following doses: 120mg at 4 weekly intervals if there was no renal or liver impairment. The dose was adjusted to 90mg or 60mg and the frequency was decreased to 6 weeks depending on the severity of the previously mentioned disorders [31, 32].

Demographic data were recorded. The data for this study was part of the STH15364, DBE Diagnosis & Treatment Multicenter Outcomes Study in UK, which was approved by the Sheffield Ethics Committee. Efficacy was evaluated by comparing the following parameters in the 2 groups: mean Hb, transfusion requirements, bleeding episodes (defined as >2g/dl drop in Hb or overt bleeding both requiring blood transfusion).

Statistical analysis was carried out using SPSS version 24. Mean Hb level, mean transfusion requirements and bleeding episodes were compared using the Mann-Whitney U test. Mean Hb, transfusion requirements and bleeding episodes before and after treatment were compared using Wilcoxon Signed Ranks Test. Spearman's correlation analysis was used to assess any correlation between the time from APC to starting Lanreotide and other parameters such as Hb, blood transfusion requirements and bleeding episodes.

RESULTS

Demographic data

A total of 49 patients were included in this study: 37 patients (75.5%) were treated with DBE and APC and 12 patients (24.5%) were given Lanreotide in addition to DBE, APC. Fifty-three per cent (n=26) were females. Patients were followed up for a median duration of 32.7 (SD 23.6) months. The mean age of the cohort was 70.1 (SD 11.4) years. There was no statistical difference between the mean age at which the treatment was started in both groups: group 1: 68.7±9.65; group 2: 74.0±15.4 years, p=0.3). There was also no statistically significant difference in the gender of patients in both groups. The mean duration of anaemia was 114.3±307.0 months before treatment was started. Table I summarizes demographic differences between the two groups.

Table I. Characteristics of both treatment groups

	Group 1 (DBE & APC)	Group 2 (DBE, APC, Lanreotide)	p value
Number of patients	37	12	
Males, n (%)	19 (51.4)	4 (33.3)	0.3
Mean age (years)	68.7	74.0	0.3
Anaemia (months)	123.2	87.5	0.6

Table II shows the underlying co-morbidities of this group of patients.

The mean Hb level before treatment was started, was significantly lower in group 2 (86.8 g/L) than group 1 (103.3 g/L) (p=0.001). A greater number of patients in group 2 (n=11; 91.7%) had underlying cardiovascular co-morbidities compared to group 1 (n=23; 62.2%) (p=0.036). Other co-morbidities were similar in both groups. A larger number of patients in group 2 were on warfarin (n=6; 50.0%) compared

Table II. Co-morbidities in the group of patients with small bowel angioectasias

Co-morbidities	Group 1 Number of patients (%)	Group 2 Number of patients (%)	p value
Cardiovascular	23 (62.2)	11 91.7	0.036
Respiratory	15 (40.5)	758.3	0.282
Endocrine	11 (29.7)	7 58.3	0.078
Gastrointestinal	14 (37.8)	3 (25.0)	0.408
Renal	8 (21.6)	6 (50.0)	0.067
Haematological	6 (16.2)	4 (33.3)	0.219
Rheumatological	7 (18.9)	1 (8.3)	0.360
Neurological	3 (8.1)	3 (25.0)	0.146

to group 1 (n=4; 10.8%) (p=0.033). More patients in group 2 were on aspirin (n=4; 33.3%) than in group 1 (n=11; 29.7%) (p=0.0001) .

Six patients (12.2%) had upper gastrointestinal involvement and 4 patients (8.2%) had colonic involvement apart from SBAs.

Table III shows the number of patients who were on anti-coagulants, oral iron and tranexamic acid.

Group 1 patients underwent 60 DBEs in total. Patients in group 2 underwent 19 DBEs before and 11 DBEs after pharmacotherapy was started.

Table III. Co-existing medications in the cohort studied.

Medications	Group 1 - Number of patients (%)	Group 2 - Number of patients (%)	p value
Warfarin	4 (10.8)	6 (50.0)	0.033
Aspirin	11 (29.7)	4 (33.3)	0.0001
Clopidogrel	1 (2.70)	0 (0)	0.009
Low molecular weight heparin	0 (0)	1 (100)	
Oral iron	16 (43.2)	9 (75.0)	0.018
Tranexamic acid	0 (0)	4 (33.3)	

In our study, increasing age did not correlate with higher transfusion requirement (p=0.487) or more bleeding episodes (p=0.997).

Lanreotide administration

Lanreotide was administered for a mean of 45 months (±19.7), range 6 – 79 months. It was started at the following doses: 60mg in 41.7% of patients, 90mg in 33.3% of patients and 120mg in 25% of patients. Most patients (75.0%) received Lanreotide at a 4 weekly interval. Seventeen per cent of patients received the injection at 6 weekly intervals. One patient (8.3%) received only a single dose. Patients received a mean number of 16.6 doses (±13.3) and they were on Lanreotide for a mean duration of 19 months (±14.6).

Mean Hb, blood transfusion requirements and bleeding episodes in the two treatment groups

There was an improvement in mean Hb in group 1 post endotherapy at 1 month and 3 months but the improvement was not sustained at 6 months (p=0.011) (Table IV). There was no reduction in the mean number of blood transfusion units required (15.7 to 6.0) (p=0.602). There was also no significant reduction in the mean number of bleeding episodes (3.50 to 3.25) (p=0.564).

Table IV. Mean Hb in patients treated with APC;

Haemoglobin (g/L)	Pre-intervention	1 month	3 months	6 months
Mean	103.3	111.5	118.6	86.5

In group 2, the mean Hb before starting Lanreotide was 86.8 g/L. This improved to 98.1 g/L after Lanreotide was started (p= 0.012) (Fig.1). The patients received a mean 27.1 blood transfusion units before and 12.7 blood transfusion units after starting Lanreotide (p=0.006) (Fig. 2). Patients also had a reduction in the mean number of bleeding episodes from 4.2 to 1.1 (p=0.01). The patients had a total of 19 DBEs before and a significantly lower number of DBEs (11) whilst on Lanreotide (p=0.048).

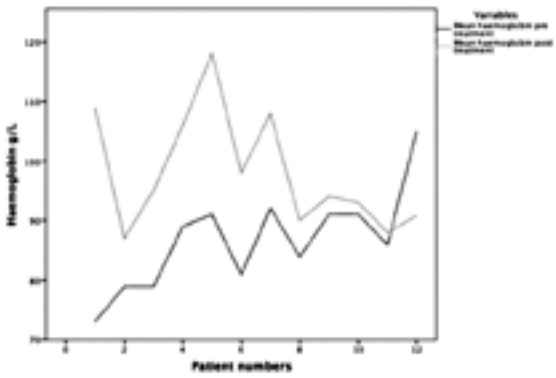

Fig. 1. Haemoglobin before and after treatment in group 2.

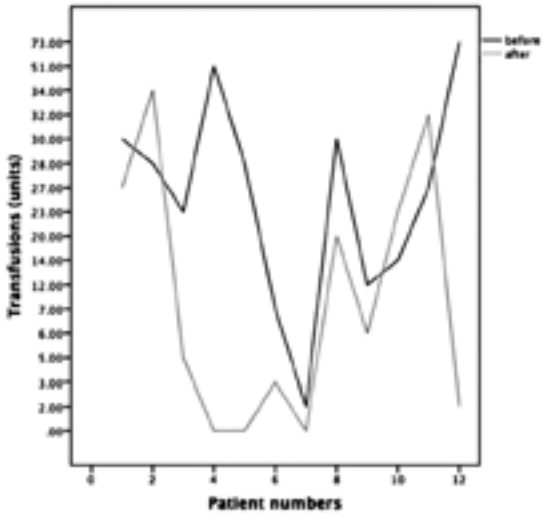

Fig. 2. Transfusion requirements before and after treatment in group 2.

The number of blood transfusions, number of DBEs, bleeding episodes and the mean Hb were not significantly related to the dose of Lanreotide given. There was also no

statistical correlation between the proximity of introduction of Lanreotide to DBE and APC and the mean Hb, bleeding episodes and transfusion requirements in group 2.

Comparison between the two groups

Hemoglobin level did not improve in 17 patients (45.9%) in group 1. Only 1 patient (8.33%) in group 2 had a lower Hb after treatment was started.

There was no statistical difference between the two groups in the length of the small bowel examined (median 165cm group 1 vs 175cm group 2; p=0.517) and the number of angioectasias treated (7 group 1 vs 5.25 group 2; p=0.740) at antegrade DBE. Data from small bowel capsule endoscopies was comparable to findings at DBE.

Improvements in Hb (11g/L vs 3.2g/L, p=0.043), transfusion requirements per month (0.8 vs 4.7 p=0.052) and bleeding episodes (1.08 vs 2.6, p=0.032) were significantly better in group 2 compared to group 1.

Only 1 patient developed symptomatic gallstone disease and had Lanreotide stopped. No other complications were recorded. One patient stopped Lanreotide due to a lack of response.

DISCUSSION

Double balloon enteroscopy with APC has been the traditional method of treatment of SBAs [33]. Argon plasma coagulation involves synchronised delivery of high frequency electrical current and ionized argon gas to the target angioectasia without direct contact.

This study has shown the lack of sustained significant improvement in Hb, blood transfusion requirements and bleeding episodes in patients treated with APC monotherapy at 6 months. There was no statistically significant difference in the length of small bowel examined between the two groups. Thus the length of the small bowel examined could not have been the reason for a different response to treatment in the two groups. One possible explanation is that some of the angioectasias might have been beyond the reach of DBE and therefore not eradicated at DBE. However, Table IV shows an initial improvement in Hb at 1 month and 3 months with a further drop in Hb at 6 months. Argon plasma coagulation can therefore result in an initial improvement in Hb but it does not contribute to a sustained maintenance of Hb. In addition, whilst many studies discuss rebleeding rate, detailed information on Hb measurements post endotherapy are not always provided [27, 34, 35].

A persistent high rate of rebleeding exists in the literature despite endotherapy [27, 28]. This can be explained by the multiplicity of SBAs in up to 60% of patients [5], the incomplete visualization of the small bowel at enteroscopy and the underlying co-morbidities [36] that persist and predispose patients to SBAs. All these factors would necessitate frequent repeat DBEs. Also, there is inadequate stratification of patients in most of the studies. There might be another possible diagnosis for iron deficiency anaemia outwith SBAs including angioectasias in the upper gastrointestinal tract and in the colon. Incomplete investigation, before small bowel investigation might be a significant contributing factor to persistent rebleeding following APC to SBAs. Only 22.1% of patients presenting with iron deficiency anaemia were investigated appropriately before being referred for small bowel studies [37].

The usefulness of Octreotide was first reported in 1993 when three patients with SBAs were treated successfully with Octreotide 0.1mg subcutaneously twice a day [38]. Holleran et al. demonstrated an improvement in Hb and transfusion requirements in a group of 24 patients with SBAs treated with long-acting Octreotide [30]. Bon et al. showed an improvement in Hb, bleeding episodes and transfusions in 15 patients treated with either 90mg of Lanreotide or 20mg of Octreotide [29].

The main mechanisms by which somatostatin analogues are thought to act in reducing bleeding include: platelet aggregation [39], decreased duodenal and splanchnic blood flow [40], increased vascular resistance [41], down-regulation of vascular endothelial growth factor (VEGF) expression [42] and inhibition of angiogenesis [42, 43]. Somatostatin analogues have a better side-effect profile than other drugs such as anti-angiogenic drug [44, 45] and hormonal treatment [46]. The main side effects include gastrointestinal disturbances, hypothyroidism, gallstone disease and pancreatic enzyme insufficiency [30, 47]. Lanreotide can be administered by deep subcutaneous injection unlike Octreotide. This avoids painful intramuscular administration and the risk of haematomas in patients with clotting abnormalities especially those with underlying cirrhosis or those on anticoagulants.

Therapeutic DBE with APC for the management of SBAs has not been compared to natural history cohorts directly except in a systematic review by Romagnuolo et al. where 24 studies (490 patients) receiving endoscopic therapy were compared to 6 natural history studies (9130 patients). There was a 42.7% rebleeding rate in the endoscopic therapy group and a 49.2% rebleeding rate in the natural history studies [19]. This is the first study comparing DBE and APC alone to DBE and APC in conjunction with somatostatin analogues in the management of SBAs. There is also a lack of studies comparing APC to other drugs such as anti-angiogenic therapy.

We have demonstrated the role of a somatostatin analogue as an adjunct therapy in selected patients with SBAs that had persistent refractory anaemia despite endoscopic ablation. Lanreotide led to an improvement in mean Hb, a reduction in the transfusion requirements, bleeding episodes and the number of DBEs when it was administered to patients in addition to APC. This study suggests that there is a useful role in combining endotherapy with pharmacotherapy in the management of patients with SBAs.

The mean Hb prior to treatment was lower in the Lanreotide group than in the APC group. This group also had a significantly higher rate of cardiovascular co-morbidities and more patients on warfarin and aspirin related to the underlying cardiovascular disease. This might have been indicative of a group of patients that were more challenging to treat and it explains why they needed additional treatment to endotherapy. Patients with SBAs and anaemia should be carefully considered for the dual therapy as evidenced by this study especially those with a significantly low Hb before therapy, those with cardiovascular comorbidities and those in whom anticoagulants cannot be stopped.

There are some limitations to this study including the fact that this is a retrospective study with a heterogeneous cohort. There was no specific time period to define the persistent rate of rebleeding following DBE and APC. Lanreotide commencement was based on a clinical decision supported by the severity of blood parameters on a case-to-case basis. However, this reflects current clinical practice in most institutions. A natural history cohort (no treatment) and a Lanreotide alone arm would have been useful to be included to strengthen the findings of this study.

The number of patients in the Lanreotide group is also visibly smaller than the endoscopic therapy alone group. This is because Lanreotide is still reserved for rescue therapy in a highly selective group of patients with minimal improvement with APC.

Group 2 included patients who had persistent anaemia requiring several blood transfusions despite APC treatment, necessitating additional treatment with lanreotide. They also had more underlying co-morbidities than group 1. Group 2 therefore was different from group 1, consisting of patients with more co-morbidities and more severe blood loss who failed monotherapy. This can also be considered a strength of the study as although group 2 presented a bigger challenge to manage, results obtained for group 2 with dual therapy were better than group 1.

CONCLUSIONS

Our study has demonstrated the persistent rebleeding rate in patients with SBAs despite endoscopic ablation, consistent with recent literature. This is the first study that shows the beneficial effects of Lanreotide in addition to APC in the management of SBAs. It is a good adjunct therapy with a safe adverse event profile that can be used in patients with multiple comorbidities who are often elderly. We have shown a reduction in the need for blood transfusions, bleeding episodes and an improvement in mean Hb. This will in turn translate into a better quality of life for the patients. Larger studies are required to define which group of patients would benefit the most from Lanreotide and the length and timing of the addition of pharmacotherapy in patients with SBAs.

Conflicts of interest: None.

Authors' contribution: S. Z.: data collection, analysis and interpretation of the data, statistical analysis and drafting of the manuscript. R .S. and D.S.: study concept and design, revision of the manuscript, and study supervision. All authors have approved the final submitted version of the manuscript.

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