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Gastrointestinal bleeding due to angiodysplasia in patients on hemodialysis. Treatment with conjugated estrogens

M. J. Manzanera, E. Gutiérrez, B. Domínguez-Gil, J. A. García, E. González and M. Praga
Nephrology Department. 12 de Octubre Hospital. Madrid.

SUMMARY

Gastrointestinal angiodysplasia is a very common cause of digestive hemorrhage among elderly patients with chronic renal insufficiency. Therapeutic possibilities are scarce, as well as information available. Here we present our experience with 8 cases of dialysis patients that were treated with conjugated estrogens because of digestive hemorrhage due to angiodysplasia. Dissapearance of bleeding was observed after the onset of estrogen therapy, with a significant decrease of blood transfusions. This type of non-invasive treatment can avoid aggressive therapeutic interventions in patients with a high prevalence of co-morbid conditions (old patients undergoing chronic dialysis).

Key words: ***Angiodysplasia. Estrogens. Chronic renal insufficiency. Hemodialysis. Digestive haemorrhage.***

HEMORRAGIA DIGESTIVA POR ANGIODISPLASIA EN PACIENTES EN HEMODIÁLISIS. TRATAMEINTO CON ESTRÓGENOS CONJUGADOS

RESUMEN

Las angiodisplasias son causa frecuente de sangrado digestivo en pacientes con insuficiencia renal crónica, sobre todo en ancianos. Existe escasa información a cerca de las posibilidades terapéuticas en estos enfermos. Presentamos nuestra experiencia con 8 pacientes con insuficiencia renal crónica que fueron tratados con estrógenos conjugados equinos por sangrado digestivo secundario a angiodisplasia demostrada mediante endoscopia. Se consiguió la remisión clínica reduciendo de forma significativa las necesidades transfusionales. El tratamiento hormonal evitaría procedimientos terapéuticos mucho más agresivos en pacientes que ya presentan alto riesgo de morbi-mortalidad (ancianos, insuficiencia renal crónica).

Palabras clave: ***Angiodisplasia. Estrógenos. Insuficiencia renal crónica. Hemodiálisis. Hemorragia digestiva.***

Correspondence: Manuel Praga
Servicio de Nefrología
Hospital 12 de Octubre
Avda. Andalucía, km. 5,400
28041 Madrid
E-mail: mpragat@senefro.org

INTRODUCTION

Angiodysplasia prevalence in the general population is not well known since there are many asymptomatic individuals that are not submitted to endoscopic procedures and thus are not diagnosed. This type of lesions may be multiple at a single region or coexist at different sites of the gastrointestinal tract.

There are particular clinical conditions with a higher angiodysplasia incidence. Therefore, this pathology represents the second most frequent cause of gastrointestinal bleeding in elderly patients with end-stage renal failure.[1] Half of recurrent bleedings in these patients are due to the existence of these lesions.[2]

There is scant information in the literature on long-term follow-up and therapeutic options of angiodysplasia in patients with chronic renal failure on replacement therapy (hemodialysis or peritoneal dialysis). Since 1984, some studies have shown a beneficial effect of estrogens in upper gastrointestinal bleeding (UGIB) in CRF patients, although the number of treated patients has been low.[3,4]

In this work, we present our experience with hormonal treatment in CRF patients on hemodialysis that present with UGIB secondary to angiodysplasia.

PATIENTS AND METHODS

Our aim was to retrospectively analyze the clinical course of patients with angiodysplasia submitted to hormonal treatment with conjugated estrogens.

We included in the study all patients on hemodialysis that were diagnosed with angiodysplasia by means of endoscopy at our department from 1992 to 2003 and that received conjugated equine estrogenic therapy (Equin®) at a 0.625 mg b.i.d dose during the first year. Thereafter, the dose was reduced to 0.625 mg q.d.

We excluded all patients that required surgical treatment, besides hormonal therapy. We do have considered all patients that have received some kind of endoscopic treatment.

These patients were followed-up for 12 months. In order to verify treatment effectiveness we observed two variables: number of GI hemorrhages pre- and post-treatment, considered as the occurrence of melena that prompted hospital admission, and the number of blood transfusions (packed red blood cells units) required before and after beginning of treatment. Results are expressed by the mean ± standard deviation.

RESULTS

There were 8 patients, 6 males (75%) and females (25%). Mean age was 69.12 _ 8.87 years (55-81). All suffered from end-stage renal failure and received renal replacement therapy with hemodialysis at the time of diagnosis. Renal failure etiology was classified into four categories: glomerulonephritis (mesangial IgA and membranoproliferative), diabetic nephropathy, nephroangiosclerosis, and unknown. Of them, nephroangiosclerosis was the most frequent.

Only one patient suffered from valvulopathy prior to angiodysplasia diagnosis. She was a patient with mitral and aortic regurgitation. Another aspect to be taken into account was the presence of any kind of treatment that would promote bleeding at the time of the study. This fact occurred in three patients (37.5%) that were on anti-aggregating agents for ischemic heart disease. Because of severity of this pathology, acetylsalicylic acid therapy was not interrupted in any of them.

All patients had the same clinical presentation: gastrointestinal bleeding as melena with severe anemia that, in all cases, had required repeated blood transfusions. The diagnosis of angiodysplastic lesions was obtained through endoscopy.

The most frequent site for the lesions was the stomach (50%) followed by the large bowel (37%). In one case, there were esophageal lesions. In half of the patients (4 patients) there were multiple lesions.

Patients were treated with equine conjugated estrogens at a 0.625 mg b.i.d. dose. Three patients additionally received direct treatment of the lesions with sclerotherapy. Average follow-up was 9.3 _ 3.7 months since 5 patients died (for other reasons than UGIB that had already stopped) without completing the one-year follow-up period: tow of them because of mesenteric ischemia and the remaining three for cardiologic cause.

Before starting hormonal therapy, the patients required 7 ± 3 units, on average, of packed red blood cells during hospital admissions for GI bleeding whereas, after treatment, none of them required transfusion, the decrease being statistically significant ($p = 0.01$).

All patients received post-hemodialysis intravenous erythropoietin at the beginning of the study. After the first follow-up month, the required dose could be reduced to keep hematocrit above 35%.

After the first year, estrogens dose was reduced to 0.625 mg q.d. in the three patients that remained followed-up. Only one of them (33%) had a new melena episode 16 months after reducing Equin® dose, not requiring hospital admission or blood transfusion.

In two patients adverse events related to estrogen therapy occurred. A lady started to have metrorrhagia, requiring gynecologic assessment and follow-up. One male patient developed gynecomastia. During the follow-up period, none of them withdrew from hormonal therapy for adverse events.

DISCUSSION

In our experience, hormonal therapy in CRF patients that present with GI bleeding due to angiodysplasia has been effective, significantly reducing the number of bleeding episodes as well as transfusion needs. In all treated cases, the improvement was strikingly rapid, with disappearance of UGIB and the need for transfusion in few days after estrogen therapy implementation.

The main advantage from this treatment versus sclerotherapy or surgery is that estrogens act, through a yet unknown mechanism, at multiple sites overcoming the difficulty of the multifocal distribution of these lesions, which limits other treatments efficacy.

During the follow-up period, our patients treated with conjugated estrogens, at a 0.625 mg b.i.d. dose, have not presented serious adverse events that would have led to early therapy interruption. The complications occurred might be related to the hormone dose used. It may be that with shorter treatment periods and/or a lower conjugated estrogens dose as good results as the ones presented with less related adverse events might be obtained.

The fact that it is a relatively safe therapy increases its benefit since, indirectly, mortality would decrease in this group of patients avoiding very aggressive treatments (endoscopy, colonoscopy, surgical excision) in high-risk patients (elderly, CRF, multiple morbidities).

The rationale of using hormone therapy to treat recurrent bleeding in patients with vascular malformations is based on Koch's observation in 1952.[5] He observed that a lady diagnosed with Osler-Rendu-Weber syndrome had recurrent epistaxis episodes with a different frequency depending on the time of the menstrual cycle she was. From then on, its role has been described in dialysis patients or with advanced renal failure.

In 1984, six CRF patients (4 on hemodialysis and 2 on peritoneal dialysis) with a history of GI bleeding were treated wit estrogens observing a significant reduction of hemorrhage time.[3] A not controlled study published in 1986 applies hormonal treatment to 7 CRF patients on hemodialysis and a history of melena. In four patients, the bleeding completely stopped within 3-5 days of treatment. In the other two patients, it the initial dose had to be increased. Two days after the dose increase there was no further evidence of GI bleeding.[4] In the same year, Livio M. *et al*. carried out a randomized, double blind, and prospective study in which hormone therapy was applied to 6 patients with CRF and GI bleeding. They conclude that conjugated estrogens at cumulative doses of 3 mg/kg significantly shorten hemorrhage time in these patients being more effective than placebo. Besides, this treatment was safer and provided several advantages over vasopressin or crioprecipates infusion, especially regarding the duration of the beneficial effects.[6]

Other studies tried to reproduce the therapeutic success obtained in patients with UGIB due to angiodysplasia but with normal renal function. The outcomes were mixed and the indication of its use in this type of patients remains controversial.[7,8,9,10]

This highly variable result in different groups of patients may relate with the theories that have been formulated about the pathogenesis of angiodysplastic lesions. It has been postulated that congenital malformations of the GI tract, vascular lesions in the elderly or in CRF patients would have a different morphology and, thus, would respond differently to the same treatment.[11,12]

The current reason because of angiodysplasia is more prevalent in CRF patients is unknown. A hypothesis suggests that the presence of angiodysplastic lesions in the GI tract may not be more frequent in CRF patients than in the elderly with normal renal function; however, the higher bleeding risk due to uremia-induced platelets dysfunction[11] might make evident these lesions, something that would not occur so frequently in the elderly with normal renal function. However, there are no objective data that allow corroborating the validity of this idea.

Another hypothesis to consider comes from recent studies on the pathogenesis of angiodysplasia-related UGIB in patients with cardiac valvular disease. In a recent publication it has been demonstrated the occurrence of and acquired von Willebrand syndrome type 2A in patients with Heyden's syndrome (aortic stenosis and intestinal angiodysplasia). Blood flow turbulence caused by the valvular pathology induced an increase in a specific von Willebrand protease expression, reducing von Willebrand multimers and predisposing the patients to bleeding through susceptible sites, such as angiodysplasia lesions. The degree of stenosis was directly related to the severity of the coagulopathy and with the frequency of intestinal bleeding; valve replacement was followed by an evident improvement.[13,14,15,16] It is possible that a similar pathogenic sequence may be present in patients on chronic dialysis in whom blood flow tur-

bulences are frequent (dialysis lines, vascular accesses with stenosis, endovenous catheters). However, there are no studies that have investigated this possibility. It is remarkable that estrogen therapy is effective in patients with von Willebrand's disease type 2B.[17,18,19]

CONCLUSION

Therapy with equine conjugated estrogens in hemodialysis patients with angiodysplasia-related gastrointestinal bleeding is effective, achieving clinical remission and canceling the need for blood transfusions. Although estrogens mechanism of action in this pathology is still unknown, our case series confirms that it is a safe treatment, with few adverse events and that may avoid the need for more aggressive therapies in patients usually old and with high co-morbidity.

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