Improvement of iron-deficiency anemia resulting from gastric antral vascular ectasia in patients with systemic sclerosis: cyclophosphamide versus argon plasma coagulation

Amr T. El-Hawary[a], Ehab F. Mostafa[a], Salem Y. Mohamed[a], Lobna I. Kotb[b]

[a]Internal Medicine Department, Hepatogastroenterology Division, [b]Rheumatology and Rehabilitation Department, Zagazig University, Zagazig, Egypt

Correspondence to Amr T. EL-Hawary, MD, Department of Internal Medicine, Zagazig University, Zagazig, 44519, Egypt. Tel: + +20 1003087983; fax: 0020552346461;. e-mail: dramrelhawary@yahoo.com

Received 17 February 2018
Accepted 29 March 2018

The Egyptian Journal of Internal Medicine 2018, 30:175–181

Background
Systemic sclerosis is an autoimmune disease characterized by multisystem affection that could involve the gastrointestinal tract in the form of gastric antral vascular ectasia (GAVE) that might cause iron-deficiency anemia.
Objective
Evaluation of the outcome and the experience of management of iron deficiency anemia resulting from GAVE in patients with scleroderma using cyclophosphamide therapy compared with argon plasma coagulation (APC).
Patients and methods
This study was conducted over a 2-year period from February 2015 to February 2017. Scleroderma patients with GAVE and iron deficiency anemia were treated with cyclophosphamide (group I) others with APC application to areas with mucosal vascular lesions (group II).
Results
In total, 14 scleroderma patients with iron deficiency anemia resulting from associated GAVE were enrolled into two groups: group I included seven patients who were treated with cyclophosphamide infusion and group II were exposed to APC in sessions. Patients were followed up at 3 and 6 months; the endpoint was a complete response with improved anemia [hemoglobin (HB) and blood indices], and it was achieved in both groups as we found in group I patients there was a highly significant improvement ($P<0.001$) in HB, 3 and 6 months after therapy and in group II patients there was a highly significant improvement ($P<0.001$) in iron level 3 and 6 months, HB 6 months after. On comparing both groups it was clear that there was a significant improvement in group I as regards HB and ferritin levels 3 and 6 months after treatment when compared with group II, and highly significant increase in serum iron level 6 months after treatment in group I when compared with group II.
Conclusion
We found that cyclophosphamide and APC are highly efficacious and safe in controlling anemia resulting from scleroderma-associated GAVE. Also, cyclophosphamide is more efficient than APC in improving in those patients.

Keywords:
argon plasma coagulation, cyclophosphamide, gastric antral vascular ectasia, systemic sclerosis

Egypt J Intern Med 30:175–181

1110-7782

Introduction

Scleroderma or systemic sclerosis (SSc) is collagen, autoimmune disease characterized by progressive skin thickening and tightness. Pulmonary interstitial fibrosis and kidney damage are the most critical indicators of mortality; however, the gastrointestinal (GI) tract is the most common damaged system. Virtually all parts of the GI tract can be involved, although the esophagus is the most frequently reported [1].

In the majority of patients with scleroderma GI manifestations are seen clinically, and gastric antral vascular ectasia (GAVE) is one of the recognized vascular changes seen in such patients. Although GAVE is a rare entity in the spectrum of manifestations of SSc, its real prevalence is probably higher as patients consult when they are symptomatic or when anemia of unknown origin is diagnosed [2].

Some SSc patients with gastric manifestations may experience frank hemorrhage or iron-deficiency anemia from GAVE.

GAVE is characterized by a unique endoscopic appearance of rough parallel folds and dilated blood vessels departing from the pylorus and converging in

the gastric antrum. This presentation is usually described as 'watermelon stomach'. GAVE has been associated with various medical conditions such as hepatic cirrhosis, chronic renal failure, hypertension, and chronic pulmonary disease. It has also been associated with autoimmune diseases, including Raynaud's phenomena, rheumatoid arthritis, polymyalgia rheumatica, primary biliary cirrhosis, and even SSc (diffuse and limited) [3].

Studies have suggested different medical risk factors for the development of GAVE, including hypergastrinemia, proliferation of neuroendocrine cells, and alterations in levels of prostaglandin E2 and vasoactive intestinal polypeptide, leading to local vasodilation and a tendency to bleed. Also antibodies such as anti-RNAP III are an essential risk factor in the progression of SSc and the apparition of GAVE [2].

In SSc patients with GAVE, therapeutic strategies have usually included blood transfusion, iron supplementation, and, occasionally, antrectomy. More recent reports have suggested that endoscopic laser ablation can be useful in as many as 75% of cases. The more straightforward and safer laser technique of argon plasma coagulation (APC) offers an additional option [4].

APC is an electrosurgical technique for the management of bleeding and the devitalization of tissue abnormalities. This is achieved by noncontact thermal coagulation in which a high-frequency current is applied to the target tissue through an argon plasma jet creating effective hemostasis and homogeneous surface coagulation with limited penetration depth. It was reported that the hemoglobin (HB) value improved, and transfusion requirements decreased in patients with PHG after therapy with APC [5].

This study aims to evaluate the efficacy of APC versus cyclophosphamide in making a significant improvement in GAVE and its resulting anemia occurring in scleroderma patients.

Patients and methods

Patient selection

This study was conducted at the Internal Medicine and Rheumatology and Rehabilitation Department, Zagazig University Hospital, Egypt, a tertiary referral center. Over a 2 years period from February 2015 to February 2017 all patients were reviewed and evaluated by full history taking, together with a general and local examination after written consent had been obtained from each patient. The study was performed on 14 patients fulfilling the criteria of SSc and having an iron deficiency that was proven to be caused by GAVE; they were selected from 27 patients admitted with SSc and iron-deficiency anemia in the predetermined period they were agreed to investigating the cause of iron deficiency anemia resistant to conventional therapy.

Patients were excluded from the study if they were noncooperative or refused the procedure or if they have any cause of anemia other than GAVE.

Thorough clinical examination

All patients were thoroughly examined for vital signs, signs of scleroderma including skin tightness, Raynaud's phenomenon, telangiectasia, and also for signs of renal, cardiac, or respiratory diseases.

Biochemical measurements

Complete blood count, iron, ferritin, occult blood in stool, Coomb's test, reticulocytes liver function, and kidney function prothrombin time and International normalized ratio.

Abdominal ultrasonography

All patients were examined using a real-time grayscale device with a transducer having a frequency of 3.5 MHz. The following were noted: splenic bipolar diameter liver and kidney states.

Upper gastrointestinal endoscopy

After an 8 h fast, all patients underwent gastroduodenoscopy using a video endoscopic system (Pentax EPM-3500, Japan) with sedation using intravenous midazolam in a titrated dose of up to 0.1 mg/kg (5–10 mg).

During endoscopy, the following were evaluated: degree and severity of GAVE, the presence of any other causes of blood loss such as esophageal or fundal varices, gastritis or duodenitis, erosions, and ulcerations.

Pulsed cyclophosphamide therapy

Group I patients received monthly infusions of 500–1000 mg cyclophosphamide over 6 months.

Argon plasma coagulation

Group II patients were treated with 4–5 sessions of APC over 6 months with 4–6 weeks interval. The APC equipment consisted of an APC probe (lumen 1.5 mm, outer diameter 2.0 mm) advanced since the end of the working, the therapeutic accessory channel of the

endoscope, a gas source, and a high-frequency generator. The argon gas flow was set at 2.5 l/min. The electrical power output was adjusted to 60–90 W, which was safe about the local risk of perforation.

APC was applied to all areas of visible mucosal vascular lesions for about 1–3 s, with ~5 mm distance between the APC probe and the gastric mucosal injury. The probe could be applied axially or laterally. The endpoint of successful endoscopic therapy was the production of a white coagulum which limits the depth of coagulation. The session duration was from 15 to 30 min. All patients received proton pump inhibitor therapy after the procedure to enhance mucosal healing.

Follow-up of patients

Patients were followed up 3 and 6 months after starting therapy by endoscopic surveillance, laboratory evaluation of HB level, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, iron, ferritin, and clinical assessment of improvement in the initial symptoms.

Definitive criteria for successful treatment were an improvement in HB and blood levels indices and the severity of GAVE from endoscopic evaluation, cessation of the patient's initial symptoms, and a decrease in blood transfusion requirements.

Statistical analysis

(1) The collected data were computerized and statistically analyzed using the statistical package for the social sciences program (SPSS) version 24 (SPSS Inc., Chicago, Illinois, USA).
(2) Data were tested for normal distribution using the Shapiro–Walk test.
(3) Qualitative data were represented as frequencies and relative percentages.
(4) χ^2-Test and Fisher's exact was used to calculate the difference between qualitative variables as indicated.
(5) Quantitative data were expressed as mean±SD.
(6) The independent *t*-test was used to calculate the difference between quantitative variables in the two groups.
(7) Paired sample *t*-test to compare the changes before and after the intervention method.

All statistical comparisons were two-tailed with a significance level of *P*-value up to 0.05 which indicates significant, *P* value of less than 0.001 indicates highly considerable difference while a *P* value of more than 0.05 indicates nonsignificant difference.

Results

A total of 14 scleroderma patients with iron deficiency anemia that was proved to be resulting from associated GAVE were enrolled in the study and were grouped into two groups.

Group I (*N*=7) (four women and three men) with age 49.4 ±13.5 years were treated with monthly cyclophosphamide infusion therapy and group II (*N*=7) (three women and four men) with age 45.9±12.9 years who were treated with multiple APC sessions.

Results showed that:

There was no significant statistical difference between both groups as regards age (*P*=0.33) and sex (*P*=0.53) (Table 1).

Baseline laboratory parameters showed that all patients in both groups had iron-deficiency anemia, with a mean HB value of 7.7±0.9 (Table 2).

For group I patients who were treated with monthly cyclophosphamide infusions and upon follow-up at 3 and 6 months durations, results show that there was a highly significant improvement ($P<0.001$) in HB, mean corpuscular hemoglobin concentration, transferrin saturation, and total iron binding capacity at 3 and 6 months and in mean corpuscular volume and iron levels at 6 months after therapy and also a significant improvement ($P<0.05$) in mean corpuscular volume and iron levels after 3 months and in mean corpuscular hemoglobin after 3 and 6 months of therapy (Table 3).

For group II patients in whom APC was used, results showed that there was a highly significant improvement ($P<0.001$) in iron level at 3 and 6

Table 1 Baseline clinicodemographic data of the studied population (*N*=14)

Parameters	Groups		Total (*N*=14)	*P*
	Group I (*N*=7)	Group II (*N*=7)		
Sex [*n* (%)]				
Female	4 (57.1)	3 (42.9)	7 (50.0)	0.539
Male	3 (42.9)	4 (57.1)	7 (50.0)	
Age (years)	49.4±13.5	42.4±12.3	45.9±12.9	0.330
Duration	7±2.2	6.3±2.9	6.6±2.5	0.613

All variables were compared using an independent *t*-test except (sex) the χ^2-test. There were no statistical differences between groups.

Table 2 Baseline laboratory parameters of the studied population

Parameters	Groups		Total (*N*=14)	*P*
	Group I (*N*=7)	Group II (*N*=7)		
Hemoglobin (g/dl)	7.8±0.9	7.6±0.9	7.7±0.9	0.690
MCV	64.5±8.1	60±6.9	62.3±7.6	0.275
MCH	22.9±4.2	23.4±1.6	23.2±3.1	0.795
MCHC	23.4±3.2	22.4±2.6	22.9±2.9	0.536
RDW	18.5±2.7	18.9±2.2	18.7±2.4	0.783
Iron (μg/dl)	45.7±6.5	42.1±5.2	43.9±5.9	0.277
Ferritin (ng/ml)	22.6±4.2	20.6±3.3	21.6±3.8	0.342
Transferrin saturation (%)	13±6.1	10.4±3	11.7±4.8	0.334
TIBC (μg/dl)	506.3±25.8	516±6.3	511.1±18.8	0.353

All data are reported as mean±SD and compared using an independent *t*-test.

Table 3 Iron profile and hematological parameters before, 3 and 6 months after intervention in group I (cyclophosphamide arm)

Parameters	Group I			P_1	P_2
	Before	After 3 months	After 6 months		
Hemoglobin	7.8±0.9	8.9±1.2	11.1±1.6	**<0.001**	**<0.001**
MCV	64.5±8.1	74.9±5.2	82.4±5.3	**0.001**	**<0.001**
MCH	22.9±4.2	25.9±2.3	28.3±1.7	**0.014**	**0.003**
MCHC	23.4±3.2	27.9±1.8	29.8±2.6	**<0.001**	**<0.001**
RDW	18.5±2.7	15±1.4	13.8±0.9	**<0.001**	**0.001**
Iron	45.7±6.5	70.1±13.6	95.7±21.1	**0.001**	**<0.001**
Ferritin	22.6±4.2	51.1±35.5	96.4±42.7	0.06	**0.002**
Transferrin saturation	13±6.1	21.4±4.4	26.9±2.5	**<0.001**	**<0.001**
TIBC	506.3±25.8	459.3±32.8	400.7±46.2	**<0.001**	**<0.001**

All data are reported as mean±SD and compared using paired *t*-test. P_1: *P*-value of before versus after 3 months. P_2: *P*-value of before versus after 6 months. *P*-value ≤0.05 indicates significant, $P<0.001$ indicates highly significant difference while, $P>0.05$ indicates Non-significant difference.

Table 4 Iron profile and hemoglobin parameters before, 3 and 6 months after intervention in group II (argon plasma coagulation arm)

Parameters	Group II			P_1	P_2
	Before	After 3 months	After 6 months		
Hemoglobin	7.6±0.9	8.2±0.8	9.4±0.8	**0.002**	**<0.001**
MCV	60±6.9	67±6.5	75.9±4.5	**0.001**	**<0.001**
MCH	23.4±1.6	25.1±1.6	27.2±1.3	**0.001**	**<0.001**
MCHC	22.4±2.6	24.6±2.2	27.3±1.8	**0.001**	**<0.001**
RDW	18.9±2.2	16.9±1.4	14.9±1.3	**0.001**	**<0.001**
Iron	42.1±5.2	49.4±5.4	61.3±9	**<0.001**	**<0.001**
Ferritin	20.6±3.3	24±1.9	42.8±15.3	**0.005**	**0.004**
Transferrin saturation	10.4±3	14.9±3.1	22.5±4.4	**0.001**	**<0.001**
TIBC	516±6.3	482.3±26.4	446.4±28.8	**0.005**	**<0.001**

All data are reported as mean±SD and compared using paired *t*-test. P_1: *P*-value of before versus after 3 months. P_2: *P*-value of before versus after 6 months. *P*-value ≤0.05 indicates significant, $P<0.001$ indicates highly significant difference while, $P>0.05$ indicates Non-significant difference.

months, HB, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, transferrin saturation, and total iron binding capacity at 6 months after APC application and also a significant improvement ($P<0.05$) after 3 months in HB, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and ferritin levels (Table 4).

On comparing both groups, it was clear that there was a significant improvement ($P<0.05$) after 3 months in MCHC, iron, transferrin saturation in group I as compared with group II (Table 5 and Fig. 2).

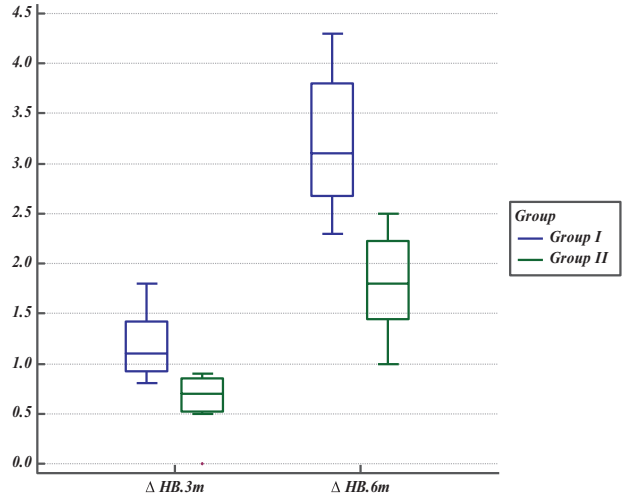
Results also showed significant improvement in group I as regards HB and ferritin levels 3 and 6 months after treatment when compared with group II, and highly significant improvement in serum iron level 6 months

Table 5 Comparison of the number of changes (Δ values) in iron profile and hematological parameters before, 3 and 6 months after intervention in group I (cyclophosphamide arm) and group II (argon plasma coagulation arm)

	Change from baselineand after 3 months		*P*	Change from baseline and after 6 months		*P*
	Group I	Group II		Group I	Group II	
ΔHemoglobin	1.2±0.4	0.6±0.3	0.007	3.3±0.7	1.8±0.5	0.001
ΔMCV	10.3±4.4	7±3	0.127	17.9±3.7	15.9±5.6	0.451
ΔMCH	2.9±2.2	1.7±0.8	0.202	5.4±2.9	3.8±1.1	0.208
ΔMCHC	4.5±1.7	2.2±1	0.008	6.4±1	4.9±1.7	0.075
ΔRDW	−3.6±1.4	−2±0.9	0.031	−4.7±2	−4±1.1	0.439
ΔIron	24.4±10	7.3±2.4	0.001	50±14.8	19.1±5.1	<0.001
ΔFerritin	28.6±32.6	3.4±2.1	0.001	73.9±38.8	22.3±13.1	0.006
ΔTransferrin saturation	8.4±2.5	4.5±1.8	0.005	13.9±4.1	12.1±3.7	0.407
ΔTIBC	−47±13.1	−33.7±20.6	0.175	−105.6±28	−69.6±24	0.024

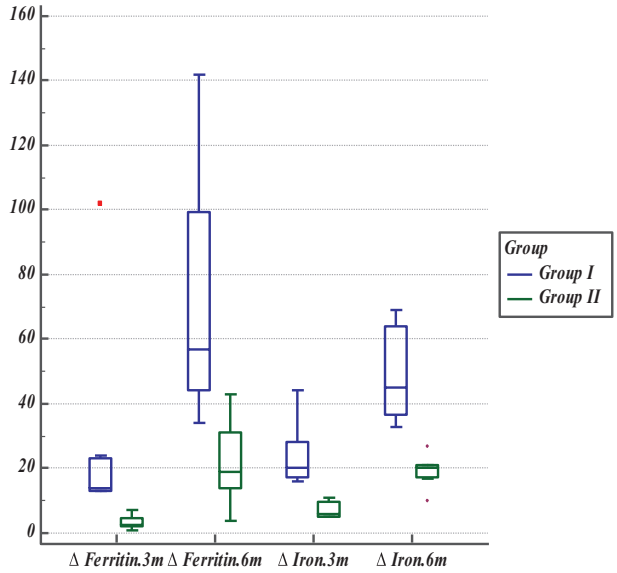
All data are reported as mean±SD and compared using independent *t*-test.

Figure 1



Box-plot diagram represents the range of Δhemoglobin (g/dl), 3 and 6 months after intervention in both groups; the upper and the lower line in each box represents the 75th and 25th percentile, respectively, while the path through each box indicates the median. Whiskers represent the range between the minimum and maximum values. The amounts of changes after treatment were higher for group I.

Figure 2



Box-plot diagram represents the range of Δferritin and iron, 3 and 6 months after intervention in both groups; the upper and the lower line in each box represent the 75th and 25th percentile, respectively, while the path through each box indicates the median. Whiskers represent the range between the minimum and maximum values excluding the outliers (rounded markers). The amount of changes after treatment was higher for group I.

after treatment in group I when compared with group II (Table 5 and Figs 1 and 2).

Discussion

Scleroderma is a chronic autoimmune disease with an unknown etiology. The most common clinical presentations include Raynaud's phenomenon, skin thickening, and tightness caused by widespread vasculopathy and excessive fibrosis. The GI tract is the most commonly involved internal organ in scleroderma. It is estimated that GI involvement occurs in ~70–90% of scleroderma patients [1].

GAVE, also known as 'watermelon stomach', has a unique endoscopic appearance that is characterized by multiple, parallel longitudinal columns of red vessels within the gastric antrum radiating to the pylorus, resembling the stripes on a watermelon [4].

Although GAVE is relatively rare, it causes up to 4% of nonvariceal upper GI bleeding, and is increasing in frequency among individuals with SSc and considered the principal cause of chronic, GI bleeding in SSc patients. Its clinical presentation ranges from asymptomatic anemia to severe bleeding and in some cases may be an early manifestation; its etiology remains unclear [6].

Management of GAVE differs from symptomatic therapy and noninvasive medical therapy to corrective

endoscopic procedures and surgical interventions. Symptomatic treatment includes iron-deficit correction, proton pump inhibitors, and blood transfusion if anemia is very characteristic and severe. Some patients might need multiple blood transfusions [2].

In the current study, we evaluated and compared the efficacy of using cyclophosphamide and APC in improving GAVE in patients with scleroderma.

In total, 14 patients fulfilling the criteria of SSc associated with iron-deficiency anemia that was proven to be caused by GAVE were enrolled and completed the study. They were divided into two groups:

Group I: patients who received cyclophosphamide therapy.
Group II: patients on whom APC was applied.

We found that using cyclophosphamide in monthly infusions had resulted in highly significant improvement in HB, MCHC, transferrin saturation, and TIBC at 3 and 6 months and MCV and iron on 6 months therapy.

This goes in agreement with Schulz *et al.* [7] who stated that in three cases of SSc-associated GAVE, two of these patients had been treated with cyclophosphamide for comorbid interstitial lung disease and the third for lymphoma. Improvement and stabilization of HB levels followed IV CYC and marked a reduction in blood transfusion requirements and the number and frequency of endoscopic laser treatments.

Papachristos *et al.* [8] also reported two cases of refractory GAVE in patients with diffuse scleroderma, which improved significantly after the administration of intravenous cyclophosphamide.

Applying APC in group II patients has shown to be effective in inducing a highly significant improvement in iron level at 3 and 6 months, HB, MCV, MCH, MCHC, transferrin saturation, and TIBC 6 months after initiation of sessions.

The same was observed by Bourke *et al.* [9] who reported APC treatment success in up to 77% in patients with GAVE.

This was also experienced by Kwan *et al.* [10] who found that APC has been equally useful in the treatment of GAVE and is superior in cost, convenience, and complication rates.

This also goes with Kar *et al.* [3] who reported employment of APC successfully in the treatment of GAVE in two patients, with different presentations, etiologies, and endoscopic appearances of GAVE.

Our study demonstrated that cyclophosphamide is more efficient than APC as there was a significant improvement after 3 months in MCHC, iron, transferrin saturation in group I as compared with group II.

And also there was a significant improvement in group I as regards HB and ferritin levels at 3 and 6 months after treatment when compared with group II.There was also a highly significant improvement in serum iron level at 6 months after treatment in group I when compared with group II.

Lorenzi *et al.* [11] also demonstrated this, he had reported a 72-year-old woman with severe transfusion-dependent GAVE that had undergone 19 sclerotherapeutic interventions in the 6 months and then received pulse methylprednisolone and cyclophosphamide given her lung and skin disease. The patients GAVE utterly resolved following immunosuppressive treatment subsequent to complete stabilization of HB and resolution of endoscopic abnormalities was unexpected. And although it is conceivable that this might have played a part in the resolution of her lesion, the temporal relationship between the administration of immunosuppressive treatment and the stabilization of her HB is impressive.

This goes in agreement with Shibukawa *et al.* [12] who reported a case of GAVE associated with SSc and interstitial pneumonitis and showed resistance to endoscopic treatment using APC. After initial recognition of GAVE as the origin of persistent anemia, three sessions of APC were performed, and dilated vessels on the antrum were eliminated entirely. Five months after primary treatment, follow-up endoscopy revealed deformity of the gastric antrum caused by ulcer scars induced by APC, with no vascular ectasia. Ten months later, the patient showed anemia and recurrence of GAVE on endoscopy. Ablation using APC was performed again, thereby eradicating recurrent GAVE. At a 2 months' follow-up, however, repeated GAVE was indicated. In spite of GAVE eradication by APC, the third recurrence of GAVE was observed after 32 months. During the follow-up period, SSc and interstitial pneumonitis were clinically controlled by the administration of immunosuppressives with no aggravation.

Conclusion

We have found that both IV cyclophosphamide and APC are highly efficacious in controlling anemia resulting from GAVE associated with scleroderma.

Also we concluded that cyclophosphamide therapy is superior to APC in making a significant improvement in HB, iron, ferritin, and other blood indices in those patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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