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Safety and Efficacy of Carbon Dioxide Angiography in the Endovascular Management of Critical Limb Ischemia Patients with Renal Insufficiency

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Abstract

Background: This study aims to achieve angioplasty in CLTI patients with renal impairment using CO2 angiography, to assess the clinical outcome with no risk of renal failure and to assess the procedure of CO2 angiography, whether it can be standalone procedure.

Methods: From October 2017 to May 2019, a prospective clinical trial enrolled 35 patients with CLTI associated with renal insufficiency. All were managed using automated CO2 angiography. The primary outcome was assessment of the safety and efficacy of CO2 angiography. The secondary outcome was freedom from renal events.

Results: No serious complications related to CO2 angiography occurred, while severe leg pain occurred in 9 cases (29.7%).Image quality using CO2 angiography was good in 36 lesions (65.5%), accepted in 10 (18%) and poor in 9 (16.5%). We used Iodinated contrast media (ICM) in 33 cases and did not use it in two case one of them due to allergy to iodine. CIN occurred in five patients out of 35 in our study; two out of five with CIN required dialysis while the others recovered to their baseline creatinine level preoperative. The two patients who required dialysis, one of them passed away 1month postoperative due to septic shock while the other required permanent dialysis and had below knee amputation. The only two factors that were statistically significant in predicting the incidence of CIN in our study preoperative creatinine level and amount of (ICM) (p value, 0.008 and 0.001 respectively). There were three cases of mortality in our study (8.5%).

Conclusions: CO2 angiography is safe in the endovascular management of CLTI patients. The diagnostic value of CO2 angiography is the most valuable in the femoropopliteal segment and the least in the infrapopliteal vessels especially in the more distal segments due to motion artefact caused by leg pain during injection. CO2 angiography is poor in showing dissections during endovascular interventions; however, it allows excellent visualization of stents and its struts. CO2 angiography may help to reduce the incidence of CIN by reducing total volume of iodinated contrast during endovascular intervention.

Keywords: Carbon dioxide, Angiography, Endovascular, Critical limb ischemia, renal impairment

Introduction

Revascularization constitutes the mainstay of therapy for chronic limb threatening ischemia CLTI patients, and the endovascular first approach is becoming the standard, including those with poor surgical risk or short life expectancy. **(Adam et al 2005)**

Angiography with iodinated contrast media (ICM) remains the most commonly used method for diagnostic and interventional vascular procedures. However, this approach is associated with an increased risk of contrast-induced nephropathy (CIN) among diabetic patients with renal insufficiency. **(Madhusudhan et al 2009)**

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CLTI Patients have associated cardiovascular and chronic kidney diseases, which places them at increased risk CIN after endovascular interventions using ICM. **(Fujihara et al 2015)**
To decrease procedure-related complications, such as CIN and allergic reactions, carbon dioxide (CO2) emerged as a contrast agent during endovascular interventions. **(Scalise et al 2015)**

The CO2 is widely available, nontoxic, of low cost and with much higher tissue solubility. Irvin F. Hawkins, widely acknowledged as a pioneer of modern CO2 angiography, described how an error led him to realize the potential of this technique when he inadvertently injected air into the celiac artery, luckily without ill consequences. **(Hawkins et al 2009)**

Materials and Method
From October 2017 to May 2019, a prospective clinical trial enrolled 35 CLTI patients with renal insufficiency (creatinine ≥ 1.4 mg/ dl) including different anatomical lesions (aorto-iliac, femoro-popliteal and infra popliteal diseases).

The aim of the study was toachieve angioplasty in CLTI patients with renal impairment using CO2 angiography, to assess the clinical outcome with no risk of renal failure and toassess the procedure of CO2 angioplasty, whether it can be standalone procedure or it is in need of supplementation by other modalities (that do not compromise the renal function).

Inclusion criteria:
All CLTI patients associated with renal insufficiency or at risk of angioplasty with iodinated contrast media (Cardiac and allergic patients)

Exclusion criteria:
Patients with end stage renal disease (ESRD) who are on regular dialysis and those with normal renal function tests who are not at risk of angioplasty with iodinated contrast media
We noted the demographic features in all patients, presentation by Rutherford stage, level of block and we measured renal function tests preoperative, 1-3 days, 1month and 3 months postoperatively.

We used automated CO2 angiography in the endovascular treatment of all patients in our study. We used (ICM) in variable amounts according to CO2 angiography image quality either to confirm the result of CO2 angiography or if the CO2 angiography appears bad in quality. When we used (ICM), we diluted it in ratio 2:1 with normal saline .

We explained the procedure of peripheral endovascular intervention using CO2 angiography, its benefits, possible risks, complications and other alternative interventions to all patients and they signed to an informed written consent.

We pretreated all patients with acetylsalicylic acid 75 mg twice daily, atorvastatin 20 mg once daily, clopidogerl 75 mg once daily as loading dose. Intravenous sodium bicarbonate 1ml/kg/hr started 1 hour before intervention and continued for 6 hours in 3ml/kg/hr after intervention to guard against CIN.

For CO2 angiography, we placed patients in a modified Trendelenburg position with the aid of a 30° transparent rubber wedge. We connected the automatic, digital Angiodroid injection system to the sidearm of the sheath. After obtaining an access to the CFA, we injected 10 mL

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of CO_2 to fill the tubing with gas and eliminate the air. The **injection pressure** would be set at 20 mm Hg over the patient's systolic blood pressure for each injection and the **injected CO_2 volumes** varied according to the arterial segment imaged.

The primary outcome is to assess the safety and efficacy of CO_2 angioplasty. Safety defined as freedom from serious CO_2 injection–related complications (Air contamination, aortic vapour lock, cardiac/pulmonary artery vapour lock, thrombotic atheroembolism, spinal cord ischemia and neurotoxicity). Efficacy defined as the procedure success (ability to cross and treat the lesion(s) with restoration of brisk ante grade flow through the treated artery, which is largely dependent on the quality of image taken by CO_2 angiography.

We defined the quality of image in our study subjectively according to the primary operator.

Accuracy of CO2Angiograms

We used Philips proprietary post processing software to obtain high-quality images after CO2angiography.Diagnostic accuracy was scored according to three predefined categories:

1. Good: All images were of high quality to establish the diagnosis and set up the revascularization without the need for further imaging.
2. Accepted: All images were adequate to establish the diagnosis and guide the treatment; however, complementary images with ICM were necessary prior to the intervention.
3. Bad: All images were insufficient or required the need to repeat the angiographic acquisition with ICM.

The secondary outcome was freedom from renal events (CIN, progressive renal insufficiency, and need for permanent renal-replacement therapy), so we measured creatinine level 1-3 days, 1 month and 3 month postoperative.

Statistical methods:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test (Chan, 2003a). P-values less than 0.05 were considered as statistically significant.

Results

1-Demographic data:-

Our study 35 included CLTI patients who use CO_2 angiography, 34 of them due to renal insufficiency and only one due to anaphylaxis from iodinated contrast media (ICM).There were 20 females (57%) and 16 males (43%).The mean age was 62.69 ± 10.19

As regards comorbidities, 97% had renal insufficiency, 85.7% were diabetic, 74.3% were hypertensive, 28.6% had cardiac comorbidities and 20% had cerebrovascular disease (Fig1).

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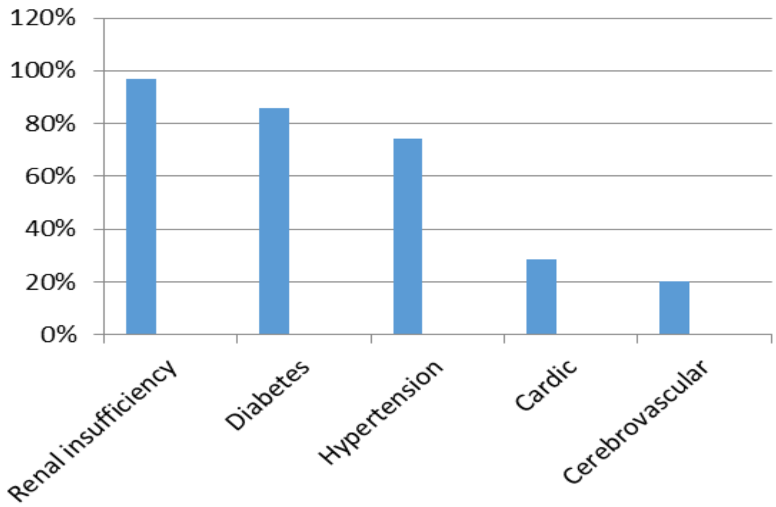

Figure1. Column chart showing the Percentage of comorbidities

2- Presentation:-

All patients had critical limb ischemia.22 presented with minor tissue loss (62.9%), 11 with major tissue loss (31.4%) and three with rest pain (5.7%) according to the Rutherford staging system (Fig2).

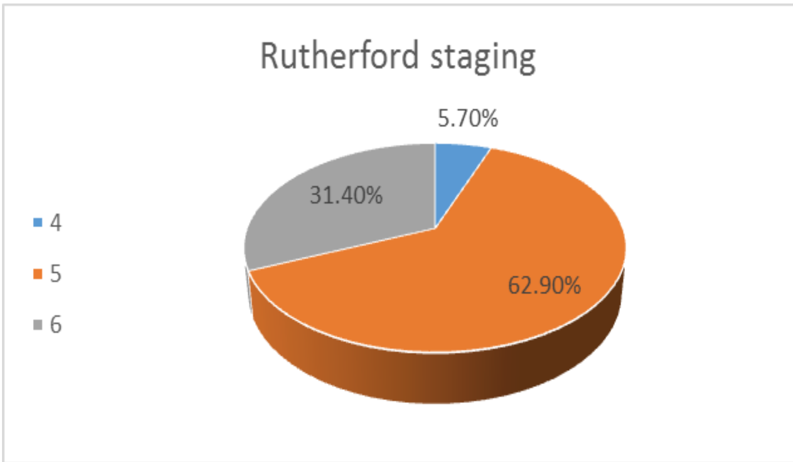

Figure 2.Pie chart showing patient presentations according to the Rutherford staging

3- Lesion distribution and endovascular procedures:-

There were 23 SFA lesions (42%), 13 popliteal lesions (23.5%), 15 infrapopliteal lesions (27.5%) and 4 iliac lesions (7%) (Total 55 lesions). We used diagnostic angiography only in one patient with infrapopliteal disease with no attempt of any endovascular intervention. We used percutaneous transluminal angioplasty (PTA) in all other lesions (54 lesions) with flow limiting dissections in six cases (5 SFA and 1 upper popliteal) in which we used self-expandable stents bare metal stents. CO_2 angiography was poor in showing these dissections (Fig 3). All iliac lesions required primary balloon mounted stents (Table1).

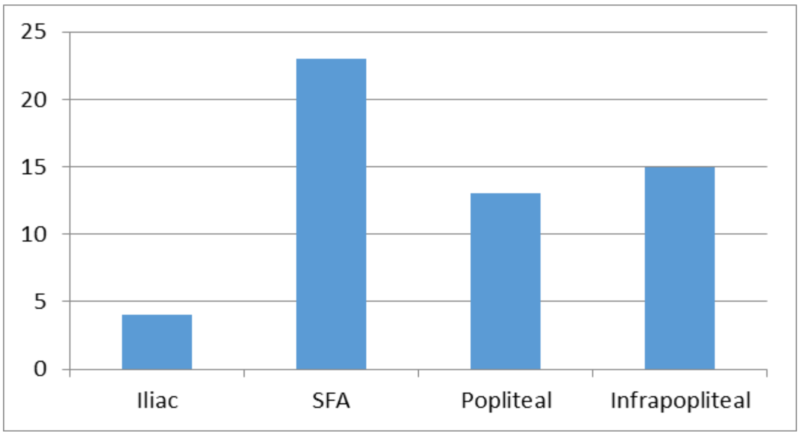

Figure3. Column chart showing lesion distribution

Table 1- Patient demographics, comorbidities, presentation, level of block, endovascular procedures, CO2 complications and quality of image by CO2 angiography

Cohort	Age	Weight	Presentation by Rutherford staging	Level of block	Comorbidities	ABI preoperative	Procedure	CO2 complications	Quality of image
1	75	80	5	SFA	DM, HTN, Renal	0.3	SFA,P1 angioplasty	No	Good
2	65	60	5	SFA	DM, HTN, Renal	0.3	SFA angioplasty	No	Good
3	31	120	6	SFA	DM, HTN, Renal and cardiac	0.6	SFA,P3 angioplasty	Leg pain	Poor
4	51	150	6	SFA	DM, HTN	0.3	SFA, ATA angioplasty	No	Accepted
5	55	60	5	SFA	DM, HTN and IHD	0.3	SFA,ATA angioplasty	No	Accepted
6	67	110	5	SFA	HTN and Renal	0.8	Infrapopliteal angioplasty	Leg pain	Poor
7	72	120	5	SFA	DM, HTN and renal impairment	0.3	SFA,PTA angioplasty	Leg pain	Poor
8	55	80	6	SFA	DM and renal	0.3	SFA angioplasty	No	Good
9	62	80	4	SFA	DM, HTN, Renal and Cardiac	0.3	SFA,P1 angioplasty	No	Good
10	72	70	5	Infrapopliteal	DM and HTN	0.3	P2,P3 angioplasty	No	Good
11	75	100	5	SFA	DM, HTN,Renal and Cerebrovascular	0.3	SFA,P1,P2 angioplasty	No	Accepted
12	70	80	5	Iliac	DM, HTN, renal and cerebrovascular	0.4	Iliac stenting,SFA,P3 angioplasty	Leg pain	Poor
13	70	80	5	SFA	DM, renal and previous SFA angioplasty	0.3	SFA stent in stent,P3 angioplasty	Leg pain	Poor
14	78	60	5	SFA	AF, renal and previous Popliteal angioplasty	0.3	Infrapopliteal angioplasty	No	Accepted
15	63	80	6	SFA	DM, HTN, renal and IHD	0.3	P3,TPT angioplasty	Leg pain	Poor
16	73	60	5	SFA	HTN, Renal	0.3	SFA,P1 angioplasty	No	Good
17	65	120	6	SFA	DM and Renal	0.4	SFA angioplasty	No	Good
18	74	120	5	SFA	DM, HTN and renal	0.4	SFA,PTA angioplasty	No	Good
19	60	80	6	SFA	HTN and Renal	0.3	SFA angioplasty and stenting	No	Accepted
20	61	60	5	Iliac	DM and Renal	0.3	Kissing iliac stenting	No	Accepted
21	60	60	6	SFA	DM, Renal, Cardiac and cerebrovascular	0.3	SFA angioplasty and stenting	No	Good
22	63	80	5	SFA	DM, HTN,IHD ,Cerebrovascular and Renal	0.3	SFA angioplasty and stenting	No	Accepted
23	70	80	5	SFA	DM,HTN,IHD,Cerebrovascular and Renal	0.4	SFA angioplasty and stenting and ATA angioplasty	No	Good
24	66	120	5	SFA	Allergy to Contrast	0.4	SFA angioplasty	No	Good
25	52	80	6	SFA	DM,HTN,IHD,cerebrovascular	0.4	SFA, Popliteal	No	Good

					and renal		and PTA angioplasty		
26	54	75	7	SFA	DM and Renal	0.5	SFA angioplasty	No	Good
27	54	120	6	Iliac	DM, Renal and HTN	0.35	Iliac stent and SFA angioplasty	No	Poor
28	72	80	5	Infrapopliteal	DM, Renal and HTN	0.7	ATA angioplasty	No	Accepted
29	48	80	6	Infrapopliteal	DM	0.3	ATA and peroneal angioplasty	No	Good
30	70	120	6	Infrapopliteal	DM, Renal, HTN and Cerebrovascular	0.3	Retrograde ATA and P1 angioplasty	Leg pain	Poor
31	71	60	5	SFA	DM, HTN and Renal	0.3	SFA and P1 angioplasty using DCB	No	Good
32	60	70	6	SFA	DM, HTN, IHD, cerebrovascular and Renal	0.3	SFA,P1,P2 and ATA angioplasty	Leg pain	Poor
33	61	100	5	Infrapopliteal	DM, HTN, Renal and IHD	0.3	Infrapopliteal diagnostic angiography	No	Accepted
34	55	60	5	Infrapopliteal	DM, HTN and Renal	0.3	ATA and PTA angioplasty	Leg pain	Poor
35	44	90	4	Iliac	HTN	0.3	Iliac stenting	No	Accepted

4- Contrast media:-

We used automated CO_2 angiography in all cases. The mean pressure for injection was 170 ± 18 mmHg and the mean total volume for each case was 220 ± 48 ml. No serious complications occurred from CO_2 injection, while severe leg pain during injection occurred in nine cases (29.7%).We identified the quality of image of CO_2 angiography subjectively according to the operator as good, accepted or poor. It was good in 36 lesions (65.5%), accepted in 10 (18%) and poor in 9 (16.5%) (Fig 3). The major disadvantage of CO_2 angiography as regard the quality of image is its susceptibility to motion artefact, this tends to be most problematic in the abdomen due to bowel peristalsis and infrapopliteal vessels due to leg motion, so control of respiration, patient motion, is therefore crucial (Fig 4,5,6 and 7).

(A) (B)

Figure 4.Diagnostic angiography of the lower popliteal artery and its trifurcation showing lower popliteal occlusion, ATA and PTA occlusion (A) CO_2 angiography (B) Iodinated contrast

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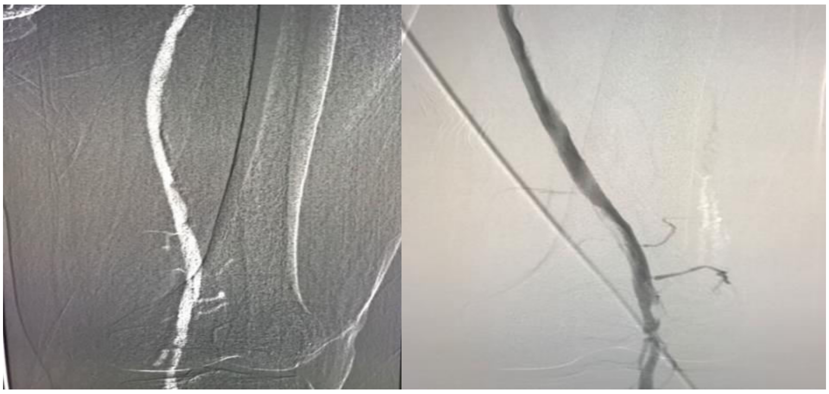

(A) (B)

Figure 5. Non flow limiting dissection after femoro-popliteal angioplasty couldn't be seen by CO2 angiography (A) and is visible by iodinated contrast angiography (B)

(A) (B)

Figure 6. Left CIA angioplasty and stenting (A) CO2 angiography (B) Iodinated contrast angiography

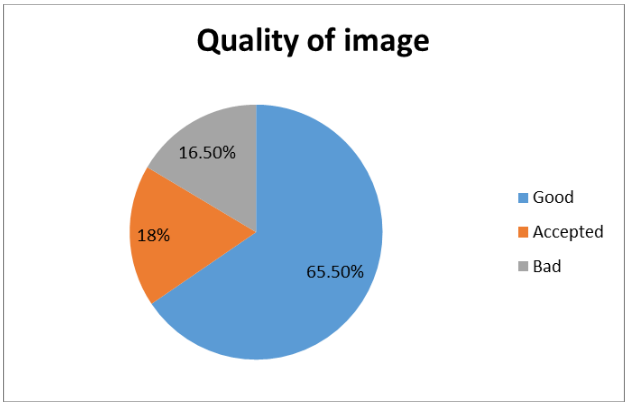

Figure 7.Pie chart showing the quality of image in all anatomical distributions using CO2 angiography.

Additional mask images, super selective CO2 injection, intravenous glucagon, patient cooperation, leg elevation, local vasodilators as well as sedation and analgesia may all be helpful. The negative effect of the CO2 angiography allows excellent visualization of the stent itself during angiography and may thus enable a better tool for angiographic assessment of stent integrity, patency, and in-stent restenosis **(Abdulghaffar et al 2012)**. Struts are easier

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to see, and therefore, abnormalities caused by poor expansion/ wall apposition, compression, distraction, and fractures are easier to see with CO_2 angiography (Fig 8). We used iodinated contrast media (ICM) in 9 cases due to ineffective CO_2 angiography image and in 24 cases as confirmatory to the CO_2 angiography image. The mean amount of (ICM) was 12.5 ml ± 10 ml (minimum 0 ml and maximum 35 ml).

5-Outcome measures:-

Safety and efficacy of CO2 angiography

The CO_2 angiography was safe in all cases 100% (no serious complications); while mild to moderate leg pain during injection occurred in 9 cases (95% CI, 13.6%-41.7%)

Renal function and CIN

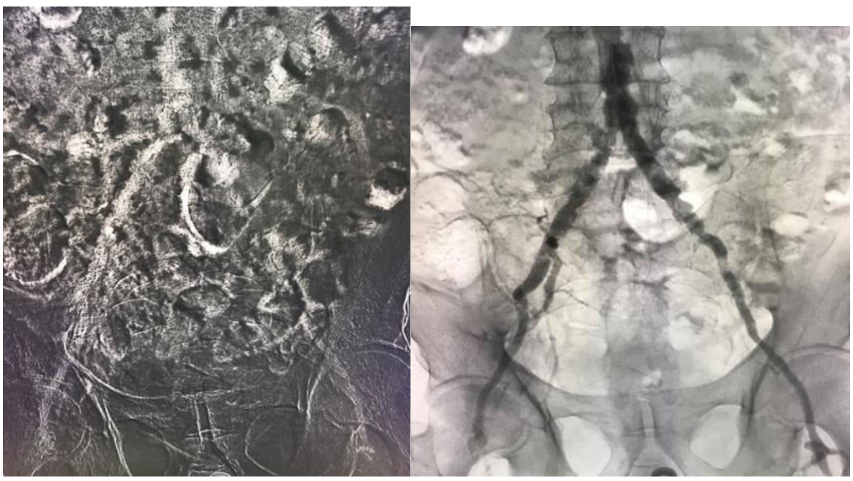
We measured Serum creatinine preoperatively, 1-3 days, 1month and 3-month post angiography. The mean serum creatinine (md /dl) was (2.27 ± 0.9), (2.36 ± 1.48), (2.19 ± 1.25) and (2.24 ± 1.18) respectively (Fig 8).

CIN occurred in five patients out of 35 in our study (14.5%) in which serum creatinine increased from (4.5 to 9), (3 to 3.7), (2.3 to 4.3), (3.2 to 4.75) and (2.7 to 3.5) respectively. The total amount of (ICM) was (30 ml, 25 ml, 25 ml, 30 ml and 35ml respectively.

Two patients out of five with CIN required dialysis while the others recovered to their baseline creatinine level preoperative. The two patients who required dialysis, one of them passed away1month postoperative due to septic shock while the other required permanent dialysis and had below knee amputation (BKA).

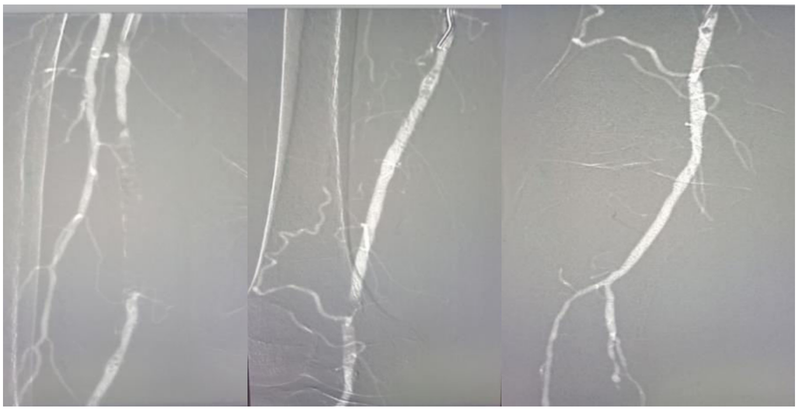
The only two factors that were statically significant in predicting the incidence of CIN in our study were creatinine level preoperative and amount of (ICM) (p value, 0.008 and 0.001 respectively).There were three cases of mortality in our study (8.5%).

Tables 2 and 3 summarizes the patient cohort and the outcome measures.



(A) **(B)**

Figure 8.Aorto-iliac visualization impaired by peristalsis artefacts using CO_2 angiography (A) in comparison to iodinated contrast angiography (B)

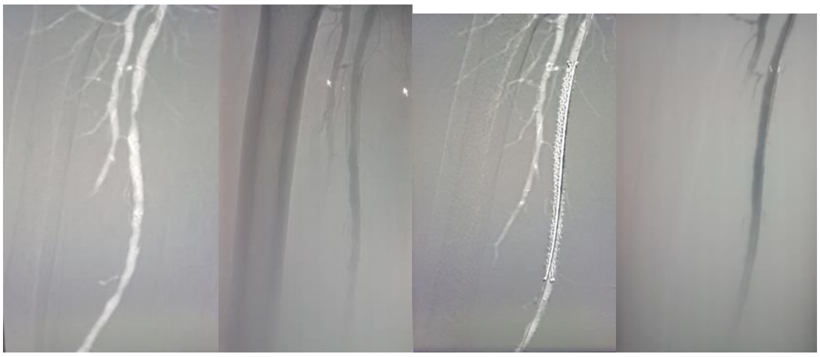


(A) (B) (C)

Figure 9. Bolus fragmentations by CO2 (A) SFA total occlusion (B) Bolus fragmentation “pseudo stenosis”. (C) Confirmation using additional runs with CO2, or use of DSA with stacking is mandatory to produce high diagnostic quality angiograms

(A) **(B)** **(C)** **(D)**

Figure10. CO2 angiography in the infrapopliteal disease (A) Total occlusion of TPT (B) Distal run off to the foot (C) confirmation using iodinated contrast angiography (D) Completion angiography



(A) **(B)** **(C)** **(D)**

Figure11. CO2 angiography in the femoropopliteal disease (A) Total SFA occlusion (B) SFA dissection by iodinated contrast (C) SFA stenting by CO2 angiography (D) Confirmation of the result by Iodinated contrast.

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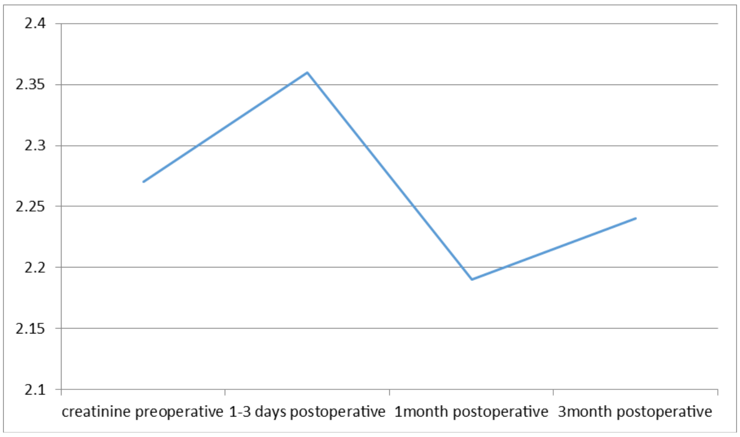

Figure 12. Line chart showing average serum creatinine measured preoperative, 1-3 days, 1m and 3m postoperative

Table 2Amount and purpose of ICM, renal outcomes and follow up

Cohort	Amount of contrast	Purpose of ICM	Creatinine Preoperative	Creatinine (1-3 days) post op.	Creatinine 1 month post op.	Creatinine 3 month post op.	CIN	Dialysis	Follow up
1	3 ml	Confirmatory	3.3	3	3.1	3.3	No	No	AKA
2	5 ml	Confirmatory	2.5	1.3	1.6	1.5	No	No	Intact pedal pulse
3	30 ml	In effective	4.5	9	-	-	yes	yes	mortality
4	10 ml	Confirmatory	1.56	1.3	1.4	1.6	No	No	mortality
5	10 ml	Confirmatory	1.2	1.3	1.13	1.33	No	No	AKA
6	25 ml	In effective	1.8	1.6	1.8	1.78	No	No	AKA
7	30 ml	In effective	2.6	2.04	2.2	2.45	No	No	Intact pedal pulse
8	10 ml	Confirmatory	1.8	1.49	1.74	1.79	No	No	Forefoot amputation
9	3 ml	Confirmatory	2.6	2.1	2.24	2.2	No	No	Intact DP pulse
10	5 ml	Confirmatory	1.8	1.9	1.78	1.8	No	No	Intact PTA pulse
11	10 ml	Confirmatory	2.39	1.6	1.5	1.3	No	No	Intact DP pulse
12	20 ml	In effective	1.9	2.2	1.7	1.76	No	No	Intact PTA pulse
13	25 ml	In effective	1.6	3.7	3	3.1	yes	No	Intact ATA pulse
14	10 ml	Confirmatory	1.6	1.4	1.6	1.5	No	No	Intact Popliteal pulse
15	25 ml	In effective	3	4.3	2.95	3.2	yes	No	Intact PTA pulse
16	10 ml	Confirmatory	1.7	2	2.2	2	No	No	Intact Popliteal pulse
17	10 ml	Confirmatory	2.3	2	1.8	1.6	No	No	Intact popliteal pulse
18	5 ml	Confirmatory	2	1.95	2.3	2	No	No	Intact PTA pulse
19	10 ml	Confirmatory	1.75	2	2.4	2.2	No	No	Intact PTA pulse
20	10 ml	Confirmatory	2	1.4	1.4	1.5	No	No	Intact

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									popliteal pulse
21	5 ml	Confirmatory	2.28	1.8	2	2	No	No	Intact DP pulse
22	10 ml	Confirmatory	1.58	2.3	3.5	3.78	No	No	Intact PTA pulse
23	3 ml	Confirmatory	1.99	2.1	1.8	2.2	No	No	Intact DP pulse
24	0 ml	Not used	3.92	0.5	0.7	0.6	No	No	BKA
25	8 ml	Confirmatory	2	1.8	1.55	1.9	No	No	Intact PTA pulse
26	15 ml	Confirmatory	1.8	1.89	1.15	1.9	No	No	Intact PTA pulse
27	20 ml	Confirmatory	1.9	2.3	1.8	2.2	No	No	Intact PTA pulse
28	10 ml	Confirmatory	4.6	4.5	4.7	4.65	No	No	Intact ATA pulse
29	0 ml	Not used	3.75	3.4	3.75	3.5	No	No	BKA
30	30 ml	In effective	1.7	1.8	1.8	1.8	No	No	BKA
31	3 ml	Confirmatory	1.6	1.14	1.4	1.5	No	No	Intact ATA and PTA pulses
32	30 ml	In effective	3.2	4	7	4.75	yes	yes	BKA
33	5 ml	Confirmatory	1.7	1.7	1.6	1.65	No	No	BKA
34	35 ml	In effective	2.7	3.5	4	6	yes	yes	mortality
35	10 ml	Confirmatory	2.5	2.2	2	1.9	No	No	Intact Pedal pulse

Table 3-Lesion distribution and endovascular procedure

Lesion	Quality of image	Dissections	Stents deployed	Complications related to CO2 injection
Iliac (n) 4	Good (0) 0%	NO	4	
	Accepted (3) 75%			
	Bad(1) 25%			
SFA (n) 23	Good (21) 91%	5	5	
	Accepted (2) 9%			
	Bad (0) 0%			
Popliteal (n) 13	Good (11) 85%	1	1	
	Accepted (2) 15%			
	Bad (0) 0%			
Infrapopliteal (n) 15	Good (4) 25%	No		(9) leg pain during injection

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Table 4- Risk factors relation with CIN

	CIN										
	Yes					No					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
age	55.80	14.89	60.00	31.00	70.00	63.83	9.04	65.00	44.00	78.00	0.237
weight	82.00	22.80	80.00	60.00	120.00	87.83	24.48	80.00	60.00	150.00	0.664
creat pre	3.14	0.83	3.00	2.30	4.50	2.12	0.83	1.90	0.60	4.60	0.008
Amount of ICM	29.00	4.18	30.00	25.00	35.00	9.90	7.79	10.00	0.00	30.00	< 0.001
C02 pressure	162.00	10.95	170.00	150.00	170.00	171.67	18.95	175.00	140.00	220.00	0.219
Total volume	208.00	57.62	240.00	120.00	260.00	223.67	46.94	240.00	120.00	280.00	0.536

Table 5- Risk factors relation with dialysis

	Dialysis										
	Yes					no					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
age	48.67	15.50	55.00	31.00	60.00	64.00	8.81	65.00	44.00	78.00	0.062
weight	83.33	32.15	70.00	60.00	120.00	87.34	23.76	80.00	60.00	150.00	0.635
creat pre	3.47	0.93	3.20	2.70	4.50	2.15	0.81	1.94	0.60	4.60	0.020
Amount of ICM	31.67	2.89	30.00	30.00	35.00	10.84	8.40	10.00	0.00	30.00	0.001
C02 pressure	163.33	11.55	170.00	150.00	170.00	170.94	18.73	170.00	140.00	220.00	0.446
Total volume	206.67	75.72	240.00	120.00	260.00	222.81	46.16	240.00	120.00	280.00	0.760

Discussion

As regards cohort demographics, our study included 35 CLTI patients who use CO2 angiography, 34 of them due to renal insufficiency and only one due to anaphylaxis from iodinated contrast media (ICM).The mean age of the patients in our study was 62.69 ± 10.19. 97% have renal insufficiency, 85.7% were diabetics, 74.3% were hypertensive, 28.6 % have cardiac comorbidities and 20% have cerebrovascular diseases. It was similar to **Palena et al** study**, which** included 36 diabetic patients with CKD.In their study, all have renal impairment (100%), all were diabetics (100%), 67% hypertensive, 53% have cardiac comorbidities and 17% were on regular dialysis. Diabetes is the most common risk factor associated with renal impairment in both studies. **(Palena et al 2016)**.

It was different to **Fujihara et al** study. The mean age of patients in their study was higher 75.66 ±7.88 (62.69 ± 10.19 in our study).All patients in their study have renal impairment with mean serum creatinine 1.68 ±0.92 (2.27 ± 0.9 in our study) and less diabetic patients 50% (85.7% in our study). **(Fujihara et al 2015)**

As regards patient presentations in our study, all were presenting by critical limb ischemia (CLI), 62.9% with minor tissue loss (Rutherford stage 5), 31.4% with major tissue loss

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(Rutherford stage 6) and 5.7% with rest pain (Rutherford stage 4). It was similar to **Palena et al study** where all patients were presenting by nonhealing pedal ulcers and/or gangrene (Rutherford stage 5/6**).**

It was different to **Dazio et al** study where 88% of patients were presenting with claudication, 7.5% with rest pain and 4.5% with tissue loss (no patients with claudication were included in our study which are known to have less morbidities than CLI patients). **(Dazio et al 2012)**

As regards lesion distribution in our study, there were 23 SFA lesions (42%), 13 popliteal lesions (23.5%), 15 infrapopliteal lesions (27.5%) and 4 iliac lesions (7%) (Total 55 lesions).In comparison to **Palena et al**, there were 14 patients in their study with superficial femoral artery (SFA) disease (22%), 17 patients with popliteal disease (26.5%), and 33 with below-the-knee disease (51.5%).

It was different to **(Dazio et al 2012)** study, where 62 lesions were in the iliac segment (42%) and 86 lesions were in the femoral segment (58%).Also, it was different to **De Almeidaet al study** that included 10 patients with TASC C and D femoropopliteal lesions. **(De Almeidaet al 2014**).

As regards accuracy of CO2 angiogram in all arterial segments in our study, it was good in 65% of lesions, accepted in 18% of lesions and bad in 16.5% of lesions.

It was better than **Dazio et al study** in the **femoral vessels** where the accuracy of CO2 angiogram was good in 63% (91% in our study), fair in 37% (9% in our study) and poor in 0% (0% in our study).

Moreover, it was inferior to **Dazio et al study** in the **iliac vessels** where the accuracy of CO2 angiogram was good in 17% (0% in our study); fair in 83% (75% in our study) and poor in 0% (25% in our study).They did not assess the accuracy of the CO2 angiogram in the infrapopliteal vessels.

It was better than **Palena et al** study where the accuracy of angiogram in their study was good in 39% of lesions (65% in our study), accepted in 44% of lesions (18% in our study) and poor in 17% of lesions (16.5% in our study).

In the accuracy assessment, the most common factor that interfered with the quality of CO2 angiogram in their study was motion artefact introduced by the involuntary movement of limbs and/or feet during injections, which in some cases resulted in the need for additional images. Eleven (30%) patients in their study treated with ACDA complained of pain during CO2injections (25% in our study), which resulted in motion artefacts. They concluded that low-quality arteriograms lead to repeated contrast injections and higher doses of radiation, thus increasing the risk of complications. **(Palena et al 2016).**

In addition, it was better than **De Almeidaet al study** in the femoropopliteal lesions where their accuracy of CO2 angiogram was good in 40% (91%in our study); fair in 50% (9% in our study) and poor in 10% (0%in our study).They didn't measure the accuracy of the CO2 angiogram in the infrapopliteal vessels. Their study results showed that the use of CO2 in TASC C and D lesions needed iodine complementation in most of the cases (nine out of ten), in contrast to our study where the accuracy of CO2 angiogram in the femoral vessels reaches

91% and rarely needed iodine complementation unless confirmatory. They explained that extension of the arterial lesions was the factor that most contributed to the need for iodine supplementation due to the difficulty to visualize the refill after a long arterial occlusion. **(De Almeidaet al 2014**).

As regards the safety of CO2 angiography procedure in our study, it was safe in all cases (no serious complications); mild to moderate leg pain during injection occurred in nine cases (95% CI, 13.6%-41.7%) that required additional iodinated contrast to confirm the results of angiogram. The mean pressure for injection was 170 ± 18 mmHg and the mean total volume was 220 ± 48 ml.Similar to our study, **Palena et al study** confirmed the safety of CO2 angiography with only two cases of leg pain during injection. They used CO2 angiography with average injection pressure 171.1±24.3 mm Hg and average total volume 395.3±114.6 mL. Based on their observations, they suggest that the systolic blood pressure should ideally be kept at or below 140 mm Hg (which would generate a CO2 injection pressure not higher than 160 mm Hg) in order to decrease the incidence of pain and therefore motion; however, this was not statistically proven. **(Palena et al 2016).**Similar to our study, **De Almeidaet al** confirmed the safety of the procedure; there were no CO2 related complications in their study. As regards renal outcomes after ICM injection in our study, we measured the serum creatinine preoperatively, 1-3 days, 1month and 3 month post angiography to predict CIN and 2nd renal events. The mean serum creatinine (md /dl) was (2.27 ± 0.9), (2.36 ± 1.48), (2.19 ± 1.25) and (2.24 ± 1.18) respectively. The average amount if ICM injection in our study was 20 ml. CIN occurred in 5 patients out of 35 in our study (14.5%) in which serum creatinine rises from (4.5 to 9), (3 to 3.7), (2.3 to 4.3), (3.2 to 4.75) and (2.7 to 3.5) respectively. The total amount of (ICM) injection in these cases was (30 ml, 25 ml, 25 ml, 30 ml and 35ml respectively. Two patients out of five with CIN required dialysis while the others recovered to their baseline creatinine level preoperative.

In contrast to our study, **Fujihara et al** measured the eGFR in their study at 1–3 days, 1 month, and 3 months after the procedure to predict CIN and secondry renal event and it was (35.2±13), (36.7±14), (37.1±14) and (36±14) respectively. The average preprocedure serum creatinine level in their study was 1.68±0.92 mg/dl (2.27 ± 0.9 in our study).It did not show any statistical difference in their study. The average volume of ICM in their study was 15.0 ± 18.1 ml. The incidence of CIN in their study was 5.1% (14.5% in our study), with no case of worsening renal insufficiency and none of the patients required permanent renal replacement therapy. They concluded that CO2 angiography-guided angioplasty was effective to prevent CIN , the most effective strategy to prevent CIN is to reduce the volume of iodinated contrast media and the risk of CIN was directly associated with increasing iodinated contrast volume adjusted for renal function. **(Fujihara et al 2015).**

The only two factors that were statistically significant in predicting the incidence of CIN in our study were creatinine level preoperative and amount of (ICM) (p value, 0.008 and 0.001 respectively**).**

Similar to our study**, Dazio et al** measured the serum creatinine to predict CIN and 2nd renal event, however they measured it only 2 days and one month after the procedure and did not different from that at preprocedure in both groups.

Group **1**(with CKD)**: 2.20±1.13**, **2.06±1.01** vs. **2.19±1.05** mg/dl, respectively).
Group **2**(without CKD): **0.82±0.19, 0.82±0.16** vs. **0.81±0.18** mg/dl, respectively).

It was different to our study in that none of the patients in their study had CIN or required haemodialysis after the procedure. The mean volume of injected ICM in their study was:
In the femoral vessels (1.5±6 ml in group 1and 49±15 ml in group 2)
In the iliac vessels (0 ml in group 1 and 53±24 ml in group 2)

Conclusions

It is safe to use CO2 angiography in the endovascular management of CLTI patients. The quality of CO2 angiography is the most valuable in the femoropopliteal segment. The diagnostic value of CO2 angiography in the infrapopliteal vessels is the least consistent especially in the more distal segments due to motion artefact caused by leg pain during injection and occasionally in the iliac diseases due to peristalsis artefacts.CO2 angiography is poor in showing dissections during endovascular interventions; however, it allows excellent visualization of stents and their struts. CO2 angiography may help to reduce the incidence of CIN by reducing total volume of iodinated contrast during endovascular intervention.CO2 angiography, as a standalone procedure needs further evaluation.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions.

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References

1. **Abdulghaffar W**, Elganayni F, Saleh HA, Abou-Issa AH, Abouelcibaa O. Role of carbon dioxide angiography in management of below knee arterial lesions. Egypt J RadiolNucl Med 2012;43:549-54
2. **Adam DJ**, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet. 2005;366:1925–1934.
3. **Chan YH**: Biostatistics102: Quantitative Data – Parametric & Non-parametric Tests. Singapore Med J 2003; 44(8): 391-396.
4. **Daizo K**, Kenichi F, Masashi F, Motomaru M, Aya N, Tohru M; Safety and Efficacy of Endovascular Therapy With a Simple Homemade Carbon Dioxide Delivery System in Patients With Ileofemoral Artery Diseases. Circ J 2012; 76: 1722 – 1728
5. **De Almeida Mendes** C, de Arruda Martins A, PassosTeivelis M, et al. Carbon dioxide is a cost-effective contrast medium to guide revascularization of TASC A and TASC B femoropopliteal occlusive disease. Ann Vasc Surg. 2014;28: 1473–1478.
6. **Fujihara M**, Kawasaki D, Shintani Y, et al. Endovascular therapy by CO 2 angiography to prevent contrast-induced nephropathy in patients with chronic kidney disease: a

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

prospective multicenter trial of CO 2 angiography registry. Catheter CardiovascInterv. 2015;85:870–877.

7. **Hawkins I**, Cho KJ, Caridi JG. Carbon dioxide in angiography to reduce the risk of contrast-induced nephropathy. Radiol Clin North Am 2009;47:813-25.
8. **Madhusudhan KS**, *Sharma S, Srivastava DN, et al. Comparison of intra-arterial digital subtraction angiography using carbon dioxide by 'home made' delivery system and conventional iodinated contrast media in the* evaluation *of peripheral arterial occlusive disease of the lower limbs. J Med Imaging RadiatOncol. 2009;53:40–49.*
9. **Palena LM**, Diaz-Sandoval LJ, Candeo A, et al. Automated carbon dioxide angiography for the evaluation and endovascular treatment of diabetic patients with critical limb ischemia. J EndovascTher 2016;23:4048.