Carbon dioxide versus iodine contrast medium for endovascular revascularization of aortoiliac occlusive disease: a two-center randomized controlled trial

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Objectives

The objective of this study was to compare the quality of radiographic imaging obtained intraoperatively using carbon dioxide (CO_2) as a contrast medium with iodinated contrast media in patients undergoing endovascular revascularization of aortoiliac occlusive disease Trans-Atlantic Inter-Society Consensus A, B, and C in patients without renal impairment.

Patients and methods

Recruitment started from July 2015 and ended July 2018. Patients with aortoiliac occlusive disease who were eligible for endovascular treatment and lacked contraindications to either iodine contrast or CO_2 were offered to participate. After informed consent, they were randomized into the CO_2 arm (32) patients or iodine contrast medium (ICM) arm (32) patients. They underwent aortoiliac angioplasty blinded to the type of contrast type used. The primary outcome was the quality of image using one type of contrast agent to perform the needed interventions. The secondary outcomes were technical success rate and the safety of procedure. Imaging from all cases were analyzed within 12 weeks of conclusion of the study by two independent observers blinded to treatment arm.

Results

CO_2 angiography images were classified as very good in 27.4% (25.8 and 29%), whereas 39% (40.6 and 37.5%) of iodine arteriograms were classified as very good by two observers, with no statistical significance (P=0.158 and 0.176). Interoperator agreement analysis showed substantial agreement (kappa=0.712). Technical success was 100%, with no procedure-related deaths. The treatment time was longer when CO_2 was used as contrast medium (87±22 min) versus using ICM (77 ±28 min). The use of ICM was required in three (9%) CO_2 patients to complete the procedure.

Conclusion

Using CO_2 as a contrast medium in aortoiliac arterial occlusive disease in normal kidney function patients produces good-quality images and is practical and safe. It is a comparable alternative to ICM with minimum risk of affecting kidney function and complications.

Keywords:
Aortoiliac occlusive disease, carbon dioxide angiography, endovascular revascularization, iodine contrast medium

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Introduction

In the current era of endovascular intervention with the increasing numbers of endovascular procedures involving iodine-based contrast; it is important to laminate patients in consistence with risk of developing contrast-induced nephropathy (CIN) [1]. Although the infrainguinal disease can be diagnosed and planned with the use of duplex ultrasound assessment [2], the aortoiliac disease will usually need computed tomography angiography [3], followed by intervention, which if done via an endovascular approach will mean patients will be exposed to iodine contrast medium (ICM) twice in a short period of time.

CO_2 as a contrast medium in vascular intervention has been used for a long time mainly for patients with established renal impairment or hypersensitivity [4]. A number of studies have explored CO_2 quality of imaging and the possible advantages and disadvantages of carbon dioxide (CO_2) as an alternative contrast for invasive or diagnostic interventions in the peripheral arterial disease [5–10]. This has been done in only a few randomized controlled trials (RCTs) [5,8,11].

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Objectives

The objective of this study was to compare the quality of radiographic imaging obtained intraoperatively with the use of CO_2 as a contrast medium with iodinated contrast media in patients undergoing endovascular revascularization of aortoiliac occlusive disease Trans-Atlantic Inter-Society Consensus (TASC) A, B, and C in patients without renal impairment.

Patients and methods

Trial design and setting

The two centers collaborating in this RCT are Vascular Surgery Department in Zagazig University Hospitals, Egypt and Intervention Radiology Department in Alnoor Specialist Hospital, Makkah, Saudi Arabia. The study protocol was approved by the local ethical committee in accordance with the declaration of Helsinki on medical research involving human patients. The trial was registered in the clinical trials database. Registration number is NCT04458714.

Participants and eligibility criteria

Inclusion criteria were patients with aortoiliac arteries atherosclerotic disease (with arterial atherosclerotic disease classified as TASC A, B, and C (classified by computed tomography angiography), with good distal runoff, and were suitable for either types of contrast ICM or CO_2 (no history of allergy to contrast and normal kidney functions), who underwent endovascular aortoiliac revascularization. Exclusion criteria from this RCT included patients with TASC D aortoiliac lesions, patients requiring femoral endarterectomy, significant multilevel distal disease, patients younger than 18 years old, patients with severe chronic obstructive lung disease, patients with chronic kidney failure, patients with heart failure, or pregnant patients.

Sampling

The sample size was calculated by the intuitional review board statistician using open epi software (Open Source Epidemiologic Statistics for Public Health) [12]. It was based on the RCT done by De Almeida Mendes *et al.* [5]. Power of study as set at 80% and confidence interval set at 95%. The sample size was calculated to be 64 cases, with 32 cases in each arm.

Patient recruitment started in July 2015 and ended July 2018. Patients with aortoiliac arteries occlusive disease with arterial atherosclerotic disease classified as TASC A, B, and C with good performed distal runoff were assessed for eligibility to participate in the trial.

Randomization

All patients who met the inclusion and exclusion criteria were offered to participate in the trial after detailed explanation of steps, benefits, and risks of both contrast medium. Patients who agreed were asked to sign an informed consent. Patient data were encrypted for patient confidentially. After patient data input was done, randomization was done using a computer-generated method. Computer-generated random numbers were created with the use of randomly permuted blocks with two block sizes, after which they were sealed in sequentially numbered envelopes, and group allocation was independent of time and person delivering the treatment. Single blinding was used to recruit the patients. The patients were randomized into the following two arms: a CO_2 arm (treatment arm) and an ICM arm (control arm), according to the contrast medium selected for the intervention. Arm I included 32 patients who were randomized for using CO_2 as the contrast medium. Arm II involved 32 patients who were randomized for using ICM.

Study interventions

All procedures were performed in an endovascular suite. Cases in both arms were done under local anesthetic with sedation, except nine (28.1%) cases in the CO_2 arm, which were done under general anesthetic (GA) either due to patient request or anticipation that patient will not be able to stay still owing to body habitus or low pain threshold. After an ultrasound-guided arterial puncture and the insertion of a 6-Fr sheath was done, intravenous heparinization of 5000 IU heparin was performed followed by initial angiography. In the CO_2 arm, 10 (31.2%) cases needed bilateral retrograde access for kissing iliac stents, 13 (40.6%) cases needed ipsilateral retrograde access, and nine (28.1%) cases needed contralateral and ipsilateral access to cross the lesion. However, in the ICM arm, 11 (34.3%) cases needed bilateral retrograde access for kissing iliac stents, 15 (46.8%) cases needed ipsilateral retrograde access, and six (18.7%) cases needed contralateral and ipsilateral access to cross the lesion. At this stage, the sheath may be up sized according to stent size requirement. The lesion was crossed using hydrophilic guide wire assisted with guiding catheter and then a stiff wire was exchanged to support balloon dilation and stent deployment. This was followed by predilation by a semicompliant balloon in some cases before deployment of a self-expanding stenting and postdilatation with an angioplasty balloon.

In the CO_2 arm, we used manual injection of CO_2 from a medicinal CO_2 cylinder connected to a particle

Table 1 Technical aspects

Characteristic	CO_2 arm	ICM arm
Anesthetics	9 (28.1%) cases GA 23 (71.9%) cases LA	32 (100%) cases LA with sedation
Access	10 (31.2%) bilateral retrograde access for kissing iliac stents 13 (40.6%) ipsilateral retrograde access 9 (28.1%) contralateral access + ipsilateral to cross the lesion	11 (34.3%) bilateral retrograde access for kissing iliac stents 15 (46.8%) ipsilateral retrograde access 6 (18.7%) contralateral access + ipsilateral to cross the lesion

CO_2, carbon dioxide; GA, general anesthesia; ICM, iodine contrast medium; LA, local anesthesia.

filter under water aspiration to prevent air contamination. The appropriate amount of CO_2 was aspirated by a three-way tap using a 20-ml syringe and was accompanied by aspirating 3 ml of saline to provide a fluid barrier. In the ICM arm, the injection of contrast was performed using 10-ml syringes with 5 ml of iodinated contrast media and 5 ml of saline solution per injection. The ICM used in all cases was Omnipaque 300 (Iohexol), a nonionic low osmolar contrast media commonly in use in both hospitals. The technical aspects of procedures are summarized in Table 1.

Primary and secondary outcomes

The primary outcome was the quality of image using one type of contrast agent to perform the needed interventions. The secondary outcomes were technical success rate and the safety of procedure, which was defined as the freedom from procedural complications (procedure-related complications were the incidence of cardiac death, myocardial infarction, stroke, major amputation, nonocclusive mesenteric ischemia, extended hospitalization (>24 h) as a consequence of CO_2-guided treatment, hematomas, pseudoaneurysms, perforations, CIN, target lesion revascularization, and postoperative death within 3 months of surgery).

Postoperative assessment and follow-up

The endovascular equipment used in each intervention and the volumes of contrast used were accurately documented for analysis. Immediately after the intervention, all patients in both arms received intravenous fluids following a local guideline for renal protection, regardless of the contrast medium used. The protocol for renal protection included intravenous fluids preprocedure with N-acetyl cysteine and intravenous fluid maintenance for 24 h. Patients were discharged the next day, and outpatient renal functions were repeated 3 days after procedure, as well as at 1 week and 1 month. We analyzed creatinine levels between the two arms during the preoperative and postoperative periods. Any increase of serum creatinine by more than 25% or more than or equal to 0.5 mg/dl is described as CIN. Patients have been followed up for 1 year. One patient from the CO_2 arm decided to withdraw from the trial during the follow-up period and was excluded from the follow-up analysis.

Table 2 Interpretation of Cohen's kappa value

Cohen's kappa value	Interpretation of Cohen's kappa value
≤0	No agreement
0.1–0.20	Slight agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Near perfect agreement
1	Perfect agreement

Imaging of all cases has been analyzed within 12 weeks of conclusion of the study. The images were reviewed by two independent observers (radiologists with >5 years of experience in performing endovascular procedures) blinded to treatment arm. Image quality was assessed using Likert rating scale ranging from 1 (very poor) to 5 (very good) for each image. A score of 1 was defined as poor quality with loss of delineation of the vessel, a score of 2 was considered below average with poor delineation of the vessel, a score of 3 is for average quality image and medium delineation of the vessel, a score of 4 was considered good quality with clear delineation of the vessel, and a score of 5 was considered very good quality with very clear delineation of the vessel.'

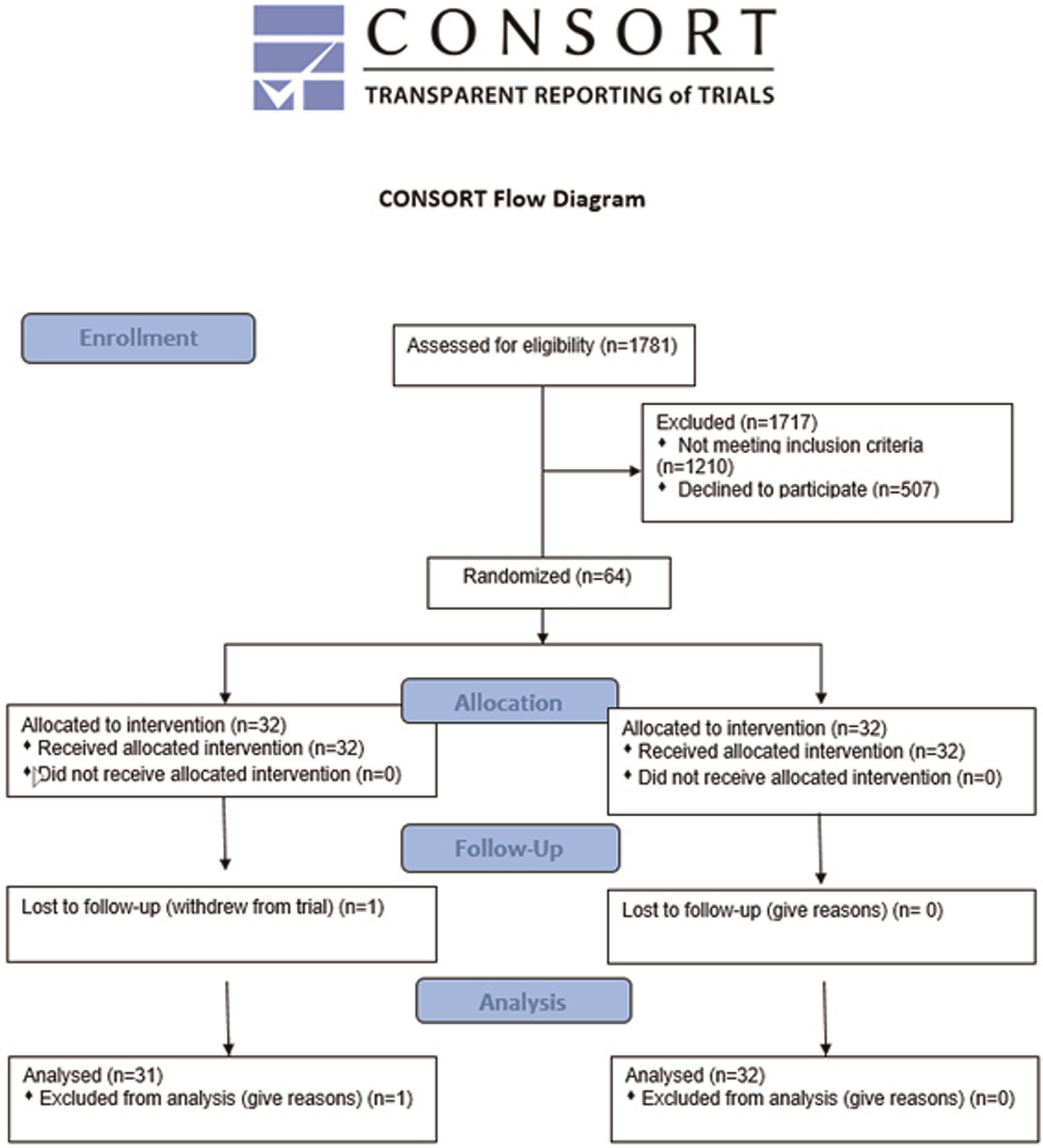
Statistical analysis

Statistical analysis was performed according to prespecified analysis plan using SPSS (SPSS for Windows, Version 23.0; SPSS Inc., Chicago, Illinois, USA). Continues variables were compared using Student's *t* test and Mann–Whitney *U* test as appropriate. Categorical variables were represented as frequencies and percentages. Categorical variables were compared between arms by Fisher's exact tests. The distribution of numerical variables was investigated by histograms and normality Shapiro–Wilk tests, analyzed separately in each arm. Numerical data were described by means and SDs or medians and interquartile as appropriate. The level of significance used was 5%. Interoperator agreement was assessed using Cohen's kappa (κ) statistics [13]. The interpretation of the strength of agreement is presented in Table 2.

Results

The trial flow diagram is demonstrated in Fig. 1.

Figure 1



Trial flow diagram.

Baseline data

Endovascular treatment was performed in 64 patients (32 patients in the CO_2 arm and 32 patients in the ICM arm) with aortoiliac occlusive disease. The demographic and preoperative data are demonstrated in Table 3.

Outcomes and estimation

The angiographic image quality is shown in details in Table 4. Overall, 25.8 and 29% (average of 27.4%) of the CO_2 angiography images were classified as very good by observer 1 and observer 2, respectively, whereas 40.6 and 37.5% (average of 39.05%) of iodine arteriograms were classified as very good by observer 1 and observer 2, respectively. There was no statistically significant difference in image quality (P=0.158 observer 1 and P value=0.176 observer 2). Of the 31 cases in the CO_2 arm, three (9%) cases needed supplementation with ICM to complete the procedure. The images with ICM in these three cases were removed from image quality analysis. Interoperator agreement was assessed using Cohen's kappa (κ) statistics. The interpretation of the strength of agreement is presented in Table 4. The interpretation of the strength of agreement was

Table 3 Demographic and preoperative data of both arm

Characteristic	CO_2 arm	ICM arm	*P* value
Average age, mean (SD)	54.3±9.8	56.3±9.7	0.43
Sex [*n* (%)]			
Male	22 (71)	15 (46.9)	0.07
Female	9 (29)	17 (53.1)	
BMI (kg/m^2)	30.1±5.8	29.2±5.5	0.52
Diabetes [*n* (%)]	17 (55)	12 (37.5)	0.2
Hypertension [*n* (%)]	21 (67.7)	19 (59.4)	0.6
IHD [*n* (%)]	19 (61.3)	17 (53.1)	0.51
Smoking [*n* (%)]	18 (58)	17 (53.1)	0.8
Dyslipidemia [*n* (%)]	15 (48.4)	17 (53.1)	0.8
TASC A [*n* (%)]	11 (35.5)	13 (40.6)	0.86
TASC B [*n* (%)]	11 (35.5)	9 (28.1)	
TASC C [*n* (%)]	9 (29)	10 (31.3)	
Preoperative ABI	0.48	0.43	0.334
Creatinine preoperative (mg/dl)	0.92±0.16	0.94±0.2	0.672

ABI, ankle-brachial index; CO_2, carbon dioxide; ICM, iodine contrast medium; IHD, ischemic heart disease; TASC, Trans-Atlantic Inter-Society Consensus.

0.712 in both arms of the study showing substantial agreement between the two observers.

The surgical results were satisfactory in both arms, with 100% overall technical success and no need to convert to open surgery. Clinical findings were satisfactory, with ischemia regression and an increase in ABI in both arms. The median ABI rates in the CO_2 arm increased from 0.48 to 0.96 and in the ICM arm from 0.43 to 0.98, without statistically significant differences between the arms. Intraoperative and postoperative data of both arms are demonstrated in Table 5.

No procedure-related deaths occurred. Two patients in the CO_2 arm and three patients in the ICM arm underwent major amputation during the follow-up period. None of the patients presented with any other major clinical or surgical complications, including cardiac death, myocardial infarction, stroke, and/or postoperative death within 3 months of surgery, except a single case of pseudoaneurysm in the CO_2 arm, which required surgical repair 1 week later.

There was a statistically significant difference between the two arms in the treatment time or length of the procedure (median period was 87±22 min for the CO_2 arm and 77±28 min for the ICM arm, P=0.04). This is owing to waiting up to 2–3 min between injections in CO_2 arm and the need for GA in some cases. The median volume of contrast in the CO_2 arm was 171 ml (range, 45–248 ml), and the median volume of ICM for the ICM arm was 78 ml (range, 29–121 ml). The use of ICM was required in three (9%) CO_2 patients to complete the procedure, and the median volume of ICM used was 10 ml (range, 7–12 ml).

Table 4 Qualitative image quality by two radiologists and interoperator agreement using Cohen's kappa (κ) statistics

Arm	Image quality 1 [*n* (%)]	Image quality 2 [*n* (%)]
Likert rating scale	Observer 1	Observer 2
CO_2 arm		
2 (below average)	2 (6.5)	2 (6.5)
3 (average)	7 (22.6)	8 (25.8)
4 (good)	14 (45.2)	12 (38.7)
5 (very good)	8 (25.8)	9 (29.0)
Total	31	31
ICM arm		
3 (average)	6 (18.8)	5 (15.6)
4 (good)	13 (40.6)	15 (46.8)
5 (very good)	13 (40.6)	12 (37.5)
Total	32	32
P value	0.158	0.176
Interoperator agreement for both arms		
Arm	Value	Approximate significance
Measure of agreement		
Kappa	0.712	0.000

CO2, carbon dioxide; ICM, iodine contrast medium.

Table 5 Intraoperative and postoperative data of both arms

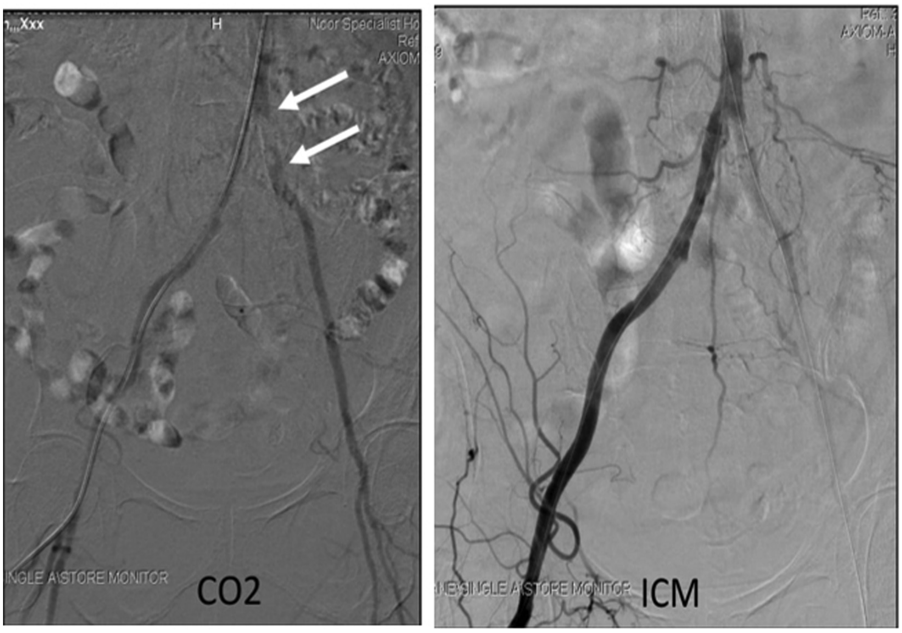
Characteristic	CO_2 arm	ICM arm	*P* value
Postoperative ABI median	0.96	0.98	0.710
Complications [*n* (%)]			
Groin hematoma	2 (6.5)	2(6.3)	0.752
Pseudoaneurysm	1(3.2)	0 (0)	
Major amputation	2(6.5)	3(9.3)	
Intervention time (min) (mean ±SD)	87±22	77±28	0.04
Creatinine day 3 (mg/dl)	0.93 ±0.17	0.98 ±0.24	0.410
Creatinine day 7 (mg/dl)	0.94 ±0.18	0.97 ±0.23	0.462
Creatinine 1-month (mg/dl)	0.90 ±0.15	0.97 ±0.21	0.144

ABI, ankle-brachial index; CO_2, carbon dioxide; ICM, iodine contrast medium.

There was no significant difference in preoperative creatinine level, 3 days, 7 days, and 1 month postoperatively in comparison between both arms. Two (6.25%) patients in the ICM arm showed elevation of serum creatinine of more than 25% in the third day creatinine level test but both recovered in the later tests, with no long-term affection of creatinine level.

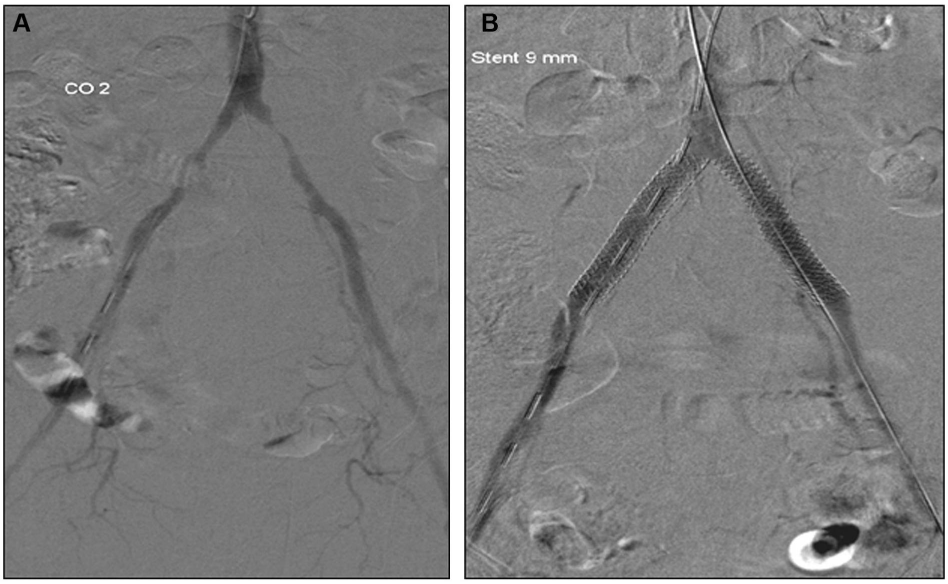
ICM has better image quality; however, the extent of obstructed segment is better appreciated on CO_2 image. This is because of low viscosity of CO_2 allowing better filling of collaterals and passing through very narrow channels, as seen in Figs 2 and 3.

Figure 2



CO_2 and ICM angiography for lower aorta and iliac arteries. ICM has better image quality; however, the extent of obstructed segment (white arrow) is better appreciated on CO_2 image. This is because of low viscosity of CO_2, allowing better filling of collaterals and passing through very narrow channel. Note simultaneous filling of common femoral arteries (CFA) in the CO_2 images and delayed filling of the left CFA with the ICM. CO_2, carbon dioxide; ICM, iodine contrast medium.

Figure 3



Bilateral common iliac stenosis. (a) Pre-intervention with CO_2 angiogram, and (b) postintervention with CO_2 angiogram. CO_2, carbon dioxide.

Discussion

CO_2 as a contrast medium in vascular intervention has been used for a long time, mainly for patients with established renal impairment or hypersensitivity. CO_2 was first described by Rosenstein in 1921. CO_2 was evaluated in patients, first via needle injection (Barrera, 1956) and then via catheter delivery [14]. Despite this fact, its use remained unpopular owing to unfamiliarity with its use and uncommon expertise.

Evaluation of image quality has been done in a few papers. One study concluded that CO_2 image quality is equal to ICM in iliac arteries, but quality gradually deteriorates in the distal arteries of the leg [15]. Another single-armed study with no comparator demonstrated good-quality images in 63% in SFA disease but only 22.6% in the aortoiliac disease [6]. The image quality was only graded by a simple 3 grade system. Another study involving 14 patients showed that CO_2 gives less quality images in comparison with ICM. CO_2 angiography image quality was better for the thigh segment in comparison with the distal runoff and pelvic regions [16].

Our study results showed CO_2 can be used with good visualization of the vessels in comparison with ICM, without compromising the quality or the outcome of the procedure. The rate of below average quality image was only 6.5% in our study. This can be explained by using of catheters to inject as close as possible to the lesions. Nine patients in CO_2 arm had GA either owing to patient request or anticipation that patient will not be able to stay still owing to body habitus or low pain threshold. GA was used in a number of studies [5,17]. Nitrous oxide must be avoided as an anesthetic agent in these cases [8]. We agree with Sharafuddin and Marjan [8] that motion artifact is the Achilles' heel of using CO_2. The patient has to be cooperative as well to cease respiratory movements while screening; using GA may improve the quality of images.

We used manual injection in the CO_2 arm, which was simple and safe to use as long as the steps are followed punctually, and the team was well trained. This has also be demonstrated in other studies with good results [5,10,18]. Some studies [9,19–21] showed the safety, efficacy, and better quality of images when using automatic injectors that automate volume, pressure of injection, and purity of CO_2 injection.

In ICM arm in our study, 6.25% of the patients had CIN, which is similar to other studies [6,7]. They recovered in the later tests, with no long-term affection of kidney function. A meta-analysis demonstrated no significant difference in acute kidney injury between CO_2 and ICM angiography in patients with baseline chronic kidney disease [22]. Although there is no clear explanation of the cause of this finding, we agree them that atheroembolization and vapor lock may potentially explain this finding. We always kept time between injections 2 min at least and used under water seal to decrease the risk of air contamination to avoid the vapor lock. All patients received intravenous fluids following a fixed protocol for renal protection, regardless of the contrast medium used.

A study published in 2020 involving 50 patients demonstrated that the incidence of CIN was halved, and renal function was largely maintained with the use of CO_2 compared with iodinated contrast medium [23]. Another study involving 128 patients showed 95% of patients did not have any deterioration of the renal parameters when using CO_2 compared with iodinated contrast [24]. The same authors published another study in 2019, which showed that in diabetic patients with peripheral arterial disease cohort, there was a high rate of undiagnosed chronic kidney disease, suggesting that CO_2 angiography should be used as a first choice [25].The merit of using CO_2 angiography in patients with normal kidney functions can be justified in relatively young patients with a background of hypertension and diabetes mellitus who are at risk of developing chronic kidney disease in the future.

The time of the procedure in CO_2 arm was longer in comparison with the ICM arm in our study. It is possible that the time was longer in the CO_2 arm owing to waiting up to 2–3 min between injections and the need for GA in some cases. Other studies did not show significant difference in the time of intervention [7,26].

Minor complications that could occur using CO_2 in peripheral interventions involve leg pain, abdominal pain, diarrhea, and even rare lethal complications, such as nonobstructive mesenteric ischemia [5–10,18,26]. We did not observe CO_2-related complications, although our study size is small, but this is consistent with other published studies [10,27]. Larger studies demonstrated complications related to CO_2 varying from rare up to 17% [6,22,28].

Study limitations

We found the concept of undergoing a trial is unfavorable among our local populations. Unavailability of automated CO_2 injector is another factor to consider, although we found manual injection to be simple and safe to use as long as the steps are followed punctually and the team is well trained. Using GA in some cases in the CO_2 arm may be considered as a confounder bias. We did explain to our patients in the recruitment phase that the discomfort/pain while using CO_2 is a known effect is some cases, hence GA was offered as an option before randomization.

Conclusion

The use of CO_2 as a contrast medium in aortoiliac arterial occlusive disease in normal kidney function patients produces good-quality images and is practical and safe. Moreover, the extent of obstructed segment is better appreciated on CO_2

image. This is because of low viscosity of CO_2, allowing better filling of collaterals and passing through very narrow channels. It is a comparable alternative to ICM with minimum risk of affecting kidney function and complications.

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Conflicts of interest

There are no conflicts of interest.

References

1 Hossain M, Costanzo E, Cosentino J, Patel C, Qaisar H, Singh V, *et al.* Contrast-induced nephropathy: pathophysiology, risk factors, and prevention. Saudi J Kidney Dis Transplant 2018; 29:1–9.

2 Artazcoz AV. Diagnosis of peripheral vascular disease: current perspectives. J Anesth Clin Res 2015; 06:2.

3 Ahmed S, Raman SP, Fishman EK. CT angiography and 3D imaging in aortoiliac occlusive disease: collateral pathways in Leriche syndrome. Abdom Radiol. 2017; 42:2346–2357.

4 Hawkins IFJ, Wilcox CS, Kerns SR, Sabatelli FW. CO2 digital angiography: a safer contrast agent for renal vascular imaging? Am J kidney Dis Off J Natl Kidney Found 1994; 24:685–694.

5 De Almeida Mendes C, De Arruda Martins A, Teivelis MP, Kuzniec S, Nishinari K, Krutman 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, Fukunaga M, Nakama T, Koshida R, *et al.* Endovascular therapy by CO2 angiography to prevent contrast-induced nephropathy in patients with chronic kidney disease: a prospective multicenter trial of CO2 angiography registry. Catheter Cardiovasc Interv 2015; 85:870–877.

7 Stegemann E, Tegtmeier C, Bimpong-Buta NY, Sansone R, Uhlenbruch M, Richter A, *et al.* Carbon dioxide-aided angiography decreases contrast volume and preserves kidney function in peripheral vascular interventions. Angiology. 2016; 67:875–881.

8 Sharafuddin MJ, Marjan AE. Current status of carbon dioxide angiography. J Vasc Surg 2017; 66:618–637.

9 Giordano A, Messina S, Polimeno M, Corcione N, Ferraro P, Biondi-Zoccai G, Giordano G. Peripheral diagnostic and interventional procedures using an automated injection system for carbon dioxide (CO2): case series and learning curve. Hear lung Vessel. 2015; 7:18–26.

10 Kawasaki D, Fujii K, Fukunaga M, Masutani M, Nakata A, Masuyama T. 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.

11 Bettmann MA, D?agostino R, Juravsky LI, Jeffery RF, Tottle A, Goudey CP. Carbon dioxide as an angiographic contrast agent: a prospective randomized trial. Invest Radiol 1994; 29(Supplement 2):S45–S46.

12 Dean AG, Sullivan KM, Soe MM. OpenEpi: open source epidemiologic statistics for public health. Available at: https://www.openepi.com/Menu/OE_Menu.htm. [Accessed August 2, 2018].

13 Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas 1960; 20:37–46.

14 Hawkins IF. Carbon dioxide digital subtraction arteriography. Am J Roentgenol 1982; 139:19–24.

15 Rolland Y, Duvauferrier R, Lucas A, Gourlay C, Morcet N, Rambeau M, Chaperon J. Lower limb angiography: a prospective study comparing carbon dioxide with iodinated contrast material in 30 patients. Am J Roentgenol 1998; 171:333–337.

16 Ho CF, Chern MS, Wu MH, Wu HM, Lin WC, Chang CY, *et al.* Carbon dioxide angiography in lower limbs: a prospective comparative study with selective iodinated contrast angiography. Kaohsiung J Med Sci 2003; 19:599–606.

17 Gallitto E, Faggioli G, Vacirca A, Pini R, Mascoli C, Fenelli C, *et al.* The benefit of combined CO2 automated angiography and fusion imaging in preserving perioperative renal function in fenestrated endografting. J Vasc Surg 2020; 72:1906–1916.

18 Madhusudhan KS, Sharma S, Srivastava DN, Thulkar S, Mehta SN, Prasad G, *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 Radiat Oncol 2009; 53:40–49.

19 Palena LM, Diaz-Sandoval LJ, Candeo A, Brigato C, Sultato E, Manzi M. Automated carbon dioxide angiography for the evaluation and endovascular treatment of diabetic patients with critical limb ischemia. J Endovasc Ther 2016; 23:40–48.

20 Scalise F, Novelli E, Auguadro C, Casali V, Manfredi M, Zannoli R. Automated carbon dioxide digital angiography for lower-limb arterial disease evaluation: safety assessment and comparison with standard iodinated contrast media angiography. J Invasive Cardiol 2015; 27:20–26.

21 Bisdas T, Koutsias S. Carbon dioxide as a standard of care for zero contrast interventions: when, why and how? Curr Pharm Des 2019; 25:4662–4666.

22 Ghumman SS, Weinerman J, Khan A, Cheema MS, Garcia M, Levin D, *et al.* Contrast induced-acute kidney injury following peripheral angiography with carbon dioxide versus iodinated contrast media: a meta-analysis and systematic review of current literature. Catheter Cardiovasc Interv 2017; 90:437–448.

23 Diamantopoulos A, Patrone L, Santonocito S, Theodoulou I, Ilyas S, Dourado R, *et al.* Carbon dioxide angiography during peripheral angioplasty procedures significantly reduces the risk of contrast-induced nephropathy in patients with chronic kidney disease. CVIR Endovasc. 2020; 3:9.

24 Alexandru T, Fraunhofer S. Carbon dioxide (Co2) angiography in diabetic patients with peripheral arterial disease and chronic renal insufficiency as a standard procedure. Eur J Vasc Endovasc Surg 2019; 58:400.

25 Alexandru T, Fraunhofer S. Infrapopliteal carbon dioxide (CO2) angiography in diabetic patients with critical limb ischemia. Limb rescue and prevent kidney failure. Eur J Vasc Endovasc Surg 2019; 58:769.

26 Hawkins IF, Cho KJ, Caridi JG. Carbon dioxide in angiography to reduce the risk of contrast-induced nephropathy. Radiol Clin North Am 2009; 47:813–825.

27 Moos JM, Ham SW, Han SM, Lew WK, Hua HT, Hood DB, *et al.* Safety of carbon dioxide digital subtraction angiography. Arch Surg 2011; 146:1428–1432.

28 Prasad A. CO2 angiography for peripheral arterial imaging: the good, bad, and ugly. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv 2015; 85:878–879.