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Original Studies

Contrast Induced-Acute Kidney Injury following Peripheral Angiography with Carbon Dioxide versus Iodinated Contrast Media: A Meta-Analysis and Systematic Review of Current Literature

Saad S. Ghumman,1 MD, Jonathan Weinerman,1 BS, Aazib Khan,1 MD, Mubeen S. Cheema,1 MD, Marlene Garcia,1 MD, Daniel Levin,1 MD, Rajeev Suri,2 MD, and Anand Prasad,1*, MD, FACC, FSCAI, RPVI

Objective: We conducted a meta-analysis to compare the incidence of acute kidney injury (AKI) with carbon dioxide (CO2) versus iodinated contrast media (ICM). Background: Contrast induced-acute kidney injury (CI-AKI) is a known complication following endovascular procedures with ICM. CO2 has been employed as an alternative imaging medium as it is nontoxic to the kidneys. Methods: Search of indexed databases was performed and 1,732 references were retrieved. Eight studies (7 observational, 1 Randomized Controlled Trial) formed the meta-analysis. Primary outcome was AKI. Fixed effect model was used when possible in addition to analysis of publication bias. Results: In this meta-analysis, 677 patients underwent 754 peripheral angiographic procedures. Compared with ICM, CO2 was associated with a decreased incidence of AKI (4.3% vs. 11.1%; OR 0.465, 95% CI: 0.218-0.992; P = 0.048). Subgroup analysis of four studies that included granular data for patients with chronic kidney disease (CKD) did not demonstrate a decreased incidence of AKI with CO2 (4.1% vs. 10.0%; OR 0.449, 95% CI: 0.165–1.221, P = 0.117). Patients undergoing CO2 angiography experienced a higher number of nonrenal events including limb/abdominal pain (11 vs. 0; P = 0.001) and nausea/vomiting (9 vs. 1; P = 0.006). Conclusions: In comparison to ICM, CO2 use is associated with a modestly reduced rate of AKI with more frequent adverse nonrenal events. In studies that use CO2 as the primary imaging agent, the average incidence of AKI remained high at 6.2%—supporting the concept that factors other than renal toxicity from ICM may contribute to renal impairment following peripheral angiography.

Key words: contrast agents; angiography; peripheral/renal; acute kidney injury

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Acute kidney injury (AKI) and more specifically, iodinated contrast induced-acute kidney injury (CI-AKI), remains a concern in patients undergoing invasive endovascular procedures. Most recent studies have suggested an incidence of AKI in the context of endovascular procedures to be at least 10% [1,2]. Given the well-established nephrotoxic effect of iodinated contrast media (ICM), the use of carbon dioxide (CO2) imaging has emerged as an alternative method of peripheral vascular angiography [3]. The attractive qualities of CO2 angiography include no potential for allergic reactions and no direct renal toxicity. However, concerns about air contamination, variable image quality, and induction of ischemic symptoms have all limited ubiquitous use of this modality. In general, there exists a paucity of randomized data reporting AKI outcomes with CO2 as compared to ICM-based angiography. The purpose of this systematic review and meta-analysis was to collect and evaluate the published data regarding the comparative impact of each imaging medium on renal function and adverse reactions in patients undergoing abdominal and lower extremity endovascular procedures.

METHODS

Cohorts and Outcomes

The investigators developed a data extraction protocol that detailed the specific objectives, study selection criteria, clinical outcomes and statistical methods. This protocol was centered on three prospectively defined cohorts. The first cohort (cohort A) included randomized and nonrandomized double arm studies that compared outcomes with CO2 versus ICM angiography, cohort B included single arm studies reporting outcomes with CO2 as the primary imaging agent and cohort C included studies reporting outcomes with ICM as primary agent. The primary outcome studied was AKI as defined by the secondary to trapped bolus of gas in a blood vessel), nausea/vomiting, cholesterol emboli, and need for dialysis were also extracted where available. The following protocol was applied to all three cohorts.

Data Sources and Searches

We identified all published studies that reported outcomes for patients undergoing angiography with CO2 and ICM using MEDLINE (1984 to week 2 of February 2016) and EMBASE (1985 to week 2 of February 2016) electronic databases. Search Terms included “AKI,” “CO2,” “ICM,” “CI-AKI,” and “angiography.” We supplemented our search strategy by manually reviewing all references in the retrieved articles.

Study Selection

Two reviewers (S.S.G and J.W) performed study selection. Studies were considered for an initial review if they met any of the following selection criteria: all randomized controlled trials (RCT) comparing primary outcomes with CO2 in one arm and ICM in the other arm, all double arm prospective and retrospective observational studies comparing CO2 and ICM, all single arm observational studies reporting incidence outcomes with CO2 and all observational and randomized studies reporting incidence outcomes with ICM.

Data Extraction

Data extraction was carried out per the PRISMA (Providing Innovative Service Models and Assessment) criteria [4]. The reviewers independently extracted data on study (year of publication, PubMed ID, design, population demographics, comorbidities (smoking, coronary artery disease, diabetes mellitus, hypertension, chronic kidney disease [CKD]), type and details of procedure (diagnostic, therapeutic, anatomical site involved), type of contrast used (CO2, ICM), amount of contrast used (ml), injection technique, and the definition of AKI used. If outcomes or relevant data were missing in the publication the reviewers contacted the primary authors for source data.

Statistical Analysis

Statistical analysis was carried out using Comprehensive Meta-Analysis software (Biostat; Englewood, NJ) version 3.3.070. We determined pooled Odds Ratio (OR) and corresponding 95% Confidence Intervals (CI) for the development of CI-AKI for cohort A. To calculate incidence data for cohorts B and C an aggregate effect size weighted by sample size was computed to provide overall effect size across studies. The adequacy of pooling data across studies was assessed using the Cochran Q and the Higgins and Thompson I^2 test for heterogeneity where a significant Q statistic suggests that the distribution of effect size around the mean is greater than would be predicted from sampling error alone, whereas I^2 provides an estimate of the proportion of the variance in the aggregate effect size that is attributable to between-studies heterogeneity [5]. We preferred to employ fixed effect model based on the Mantel–Haenszel method. Results from our analysis were compared to the random effects model (DerSimonian and Laird) [6].
employed where interstudy heterogeneity was a concern. A probability value of $<0.05$ was considered statistically significant. Publication bias was addressed using funnel plots of effect size versus standard error and Eggers regression intercept where a $P$ value of $<0.20$ was considered statistically significant for publication bias [7]. Subgroup analysis was performed for studies reporting data specific to patients with baseline CKD as defined in each study.

RESULTS

Study Identification and Selection

This meta-analysis included three different sets of studies identified as separate cohorts as described above. Figure 1 represents an illustration of the search strategy.

Analysis

Cohort A (comparative studies of ICM vs. CO$_2$).
The characteristics of eight studies are shown in Table I and Table S1 (Supporting Information), respectively. Overall, we identified seven nonrandomized comparative studies and 1 RCT. These eight studies contained a total of 677 patients who underwent 754 procedures, year of publication ranged from 1995 to 2015. Of the 677 patients, the number of individuals in the CO$_2$ and ICM groups was 185 and 492, respectively. The mean age for the CO$_2$ group was 69 ($\pm 6.1$) years while that for ICM group was 69.5 ($\pm 4.8$) years. As shown in Table I, the definition of CI-AKI varied across studies with the majority ($n = 4, 50\%$) of them using more than 25% rise in serum creatinine from baseline as a parameter and 48 hr as the cutoff for measuring post procedure creatinine. As shown in Table S1 Supporting Information, all studies employed use of preprocedure hydration, however, volume and technique was variable and often not precisely reported. Gross incidence of AKI for CO$_2$ was 4.3% while that for ICM was 11.1%. Pooled odds ratio favored CO$_2$ over ICM (OR 0.465; CI 0.218–0.992; $P = 0.048$) as shown in Fig. 2. Test for heterogeneity showed a $Q$ value of 6.998, $P = 0.429$ and $I^2 < 0.001$ and since there was no evidence of heterogeneity we used the fixed model analysis for this cohort. Overall, six studies reported a decreased incidence of AKI in the CO$_2$ group when compared to the ICM group. A subgroup analysis (Fig. 3) of four studies that included patients with baseline CKD (defined as serum creatinine $>1.5$ mg/dl in two studies, $>1.8$ mg/dl in one study, and not defined in one study) did not show a statistically significant difference between the two contrast media (4.1% vs. 10.0%; OR 0.449; CI 0.165–0.1221; $P = 0.117$).

Patients undergoing CO$_2$ angiography experienced a higher number of nonrenal adverse events versus ICM, such as limb/abdominal pain (11 vs. 0, OR 77.185; CI 4.049–182.969).
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Group</th>
<th>n</th>
<th>Anatomy</th>
<th>Procedure</th>
<th>CI-AKI definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stegemann et al., 2015 [8]</td>
<td>R</td>
<td>CO2</td>
<td>37</td>
<td>IF=21, Pop=6, BTK=10</td>
<td>PTA=53</td>
<td>rise in serum creatinine of &gt;25% or &gt;0.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IF=126, Pop=7, BTK=21</td>
<td>PTA=203</td>
<td>rise in serum creatinine of &gt;25% or &gt;0.5 mg/dL</td>
</tr>
<tr>
<td>Knipp et al., 2010 [9]</td>
<td>R</td>
<td>CO2</td>
<td>4</td>
<td>Abd=4</td>
<td>Evar=4</td>
<td>Not Defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abd=7</td>
<td>EVAR=7</td>
<td>Not Defined</td>
</tr>
<tr>
<td>Chao et al., 2007 [10]</td>
<td>R</td>
<td>CO2</td>
<td>16</td>
<td>Abd=16</td>
<td>EVAR=16</td>
<td>&gt;20% rise in serum creatinine at 24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abd=84</td>
<td>EVAR=84</td>
<td>&gt;20% rise in serum creatinine at 24 hours</td>
</tr>
<tr>
<td>Liss et al., 2005 [11]</td>
<td>RCT</td>
<td>CO2</td>
<td>37</td>
<td>Renal=37</td>
<td>Diagnostic=10, PTA=27</td>
<td>increase in serum creatinine of more than 25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal=45</td>
<td>Diagnostic=13, PTA=32</td>
<td>increase in serum creatinine of more than 25%</td>
</tr>
<tr>
<td>Dowling et al., 2003 [12]</td>
<td>R</td>
<td>CO2</td>
<td>51</td>
<td>Abd=7, Renal=2, IF=36, Pop=1, BTK=0</td>
<td>Diagnostic=51</td>
<td>rise in creatinine of 1.0 mg/dL over baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abd=22, Renal=3, IF=37</td>
<td>Diagnostic=49, PTA=10</td>
<td>rise in creatinine of 1.0 mg/dL over baseline</td>
</tr>
<tr>
<td>Sterner et al., 2001 [13]</td>
<td>R</td>
<td>CO2</td>
<td>8</td>
<td>Abd=4, Renal=4</td>
<td>Diagnostic=4, PTA=8</td>
<td>rise in serum creatinine of &gt;25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abd=21, Renal=24, IF=29, Other=35</td>
<td>Diagnostic=48, EVAR=37, PTA=73</td>
<td>rise in serum creatinine of &gt;25%</td>
</tr>
<tr>
<td>Spinosa et al., 1999 [14]</td>
<td>P</td>
<td>CO2</td>
<td>24</td>
<td>Renal=24</td>
<td>Diagnostic=15, PTA=10</td>
<td>Increases in serum creatinine of more than 0.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal=25</td>
<td>Diagnostic=12, PTA=13</td>
<td>Increases in serum creatinine of more than 0.5 mg/dL</td>
</tr>
<tr>
<td>Frankhouse et al., 1995 [15]</td>
<td>R</td>
<td>CO2</td>
<td>8</td>
<td>IF=8</td>
<td>Diagnostic=8</td>
<td>rise in serum creatinine of &gt;25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal=2, IF=15, BTK=2</td>
<td>PTA=19</td>
<td>rise in serum creatinine of &gt;25%</td>
</tr>
</tbody>
</table>

**Note:** ICM = Iodinated Contrast Media; PTA = Percutaneous Transluminal Angioplasty; CI-AKI = Contrast-Induced Acute Kidney Injury; F/u = Follow-up; Pop = Population; BTK = Brachiofemoral Technique; ICM type and volume (ml) are listed for each study.
8.905–668.981, \( P = 0.001 \)) was nausea/vomiting (9 vs. 1, OR 12.306; CI 2.081–72.773, \( P = 0.001 \)), with no differences in death (2 vs. 2, OR 3.271; CI 0.495–21.633, \( P = 0.219 \)). No statistical differences were noted between CO2 and ICM regarding the need for renal replacement therapy (0 vs. 2, OR 0.384; CI 0.037–4.009, \( P = 0.424 \)). Meta-regression analysis between incidence of AKI and multiple covariates including year of publication (\( P = 0.758 \)), supplemental ICM dose (\( P = 0.991 \)) and definition of CI-AKI used (\( P = 0.258 \)) did not show any significant associations. Egger’s regression analysis for cohort A revealed a \( P \) value of 0.248. Hence there was no evidence of publication bias. Figure S1 Supporting Information shows the corresponding funnel plot. Given the possibility that AKI pathophysiology has changed overtime, an addition analysis was conducted with studies published after the year 2000, no significant changes were found in the results, data is not reported.

**Cohort B (CO2 only outcomes).** Thirteen studies identified a total of 1,414 patients who underwent 2,006 procedures using CO2 as the primary imaging agent. The characteristics of the studies are shown in Table II and CI-AKI in patients undergoing angiography with CO2 vs ICM.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Anatomy</th>
<th>Procedure</th>
<th>CI-AKI Definition</th>
<th>f/u renal function (hours)</th>
<th>Mean Volume of CO₂ (ml)</th>
<th>ICM used</th>
<th>Mean ICM volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawasaki et al., 2015 [16]</td>
<td>R</td>
<td>18</td>
<td>Renal=18</td>
<td>PTA=18</td>
<td>increase of 20% in the serum creatinine</td>
<td>48</td>
<td>244</td>
<td>none</td>
<td>*</td>
</tr>
<tr>
<td>Fujihara et al., 2015 [17]</td>
<td>P</td>
<td>98</td>
<td>Renal=16, IF=93</td>
<td>PTA=109</td>
<td>increase in creatinine level 0.5 mg/dL or greater than 25%.</td>
<td>72</td>
<td>281.4</td>
<td>yes</td>
<td>15</td>
</tr>
<tr>
<td>Palena et al., 2015 [18]</td>
<td>P</td>
<td>36</td>
<td>IF=14, Pop=33, BTK=17</td>
<td>Diagnostic=72, PTA=72</td>
<td>rise in serum creatinine of &gt;0.5 mg/dL.</td>
<td>24</td>
<td>395</td>
<td>yes</td>
<td>54</td>
</tr>
<tr>
<td>Sueyoshi et al., 2015 [19]</td>
<td>P</td>
<td>40</td>
<td>Abd=40,</td>
<td>Diagnostic=40</td>
<td>Not defined</td>
<td>24</td>
<td>*</td>
<td>yes</td>
<td>128</td>
</tr>
<tr>
<td>Scalise et al., 2015 [20]</td>
<td>P</td>
<td>40</td>
<td>IF=25, BTK=15</td>
<td>Diagnostic=5</td>
<td>Not defined</td>
<td>48</td>
<td>240</td>
<td>yes</td>
<td>150</td>
</tr>
<tr>
<td>Penzafer et al., 2014 [21]</td>
<td>P</td>
<td>5</td>
<td>Renal=5</td>
<td>Diagnostic=1, 007, EVAR=62, EVAR=18, Other=296, PTA=94, Other=343</td>
<td>rise in serum creatinine of &gt;0.5 mg/dL.</td>
<td>48</td>
<td>186</td>
<td>yes</td>
<td>8.5</td>
</tr>
<tr>
<td>Moos et al., 2011 [22]</td>
<td>R</td>
<td>991</td>
<td>Abd=527, Renal=164, IF=347, Venous=375, Other=296, PTA=94, Other=343</td>
<td>Not defined</td>
<td>24</td>
<td>*</td>
<td>yes</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2010 [23]</td>
<td>P</td>
<td>17</td>
<td>Renal=17</td>
<td>EVAR=18, Other=5</td>
<td>increase in creatinine level 0.5 mg/dL or greater than 25%.</td>
<td>24</td>
<td>363</td>
<td>yes</td>
<td>44</td>
</tr>
<tr>
<td>Criado et al., 2008 [24]</td>
<td>R</td>
<td>18</td>
<td>Renal=23</td>
<td>EVAR=18, Other=5</td>
<td>Not defined</td>
<td>24</td>
<td>363</td>
<td>yes</td>
<td>44</td>
</tr>
<tr>
<td>Spinosa et al., 2001 [25]</td>
<td>P</td>
<td>95</td>
<td>Renal=95</td>
<td>Diagnostic=26, PTA=69</td>
<td>increase in creatinine level 0.5 mg/dL or greater than 25%.</td>
<td>48</td>
<td>250</td>
<td>none</td>
<td>*</td>
</tr>
<tr>
<td>Fitridge et al., 1999 [26]</td>
<td>P</td>
<td>28</td>
<td>Renal=7, IF=21</td>
<td>Diagnostic=28, PTA=8</td>
<td>rise in serum creatinine of &gt;0.5 mg/dL.</td>
<td>72</td>
<td>23</td>
<td>yes</td>
<td>23</td>
</tr>
<tr>
<td>Caridi et al., 1999 [27]</td>
<td>P</td>
<td>15</td>
<td>Renal=23</td>
<td>PTA=23</td>
<td>rise in serum creatinine by 0.044 mmol/litre or an overall increase of 20%</td>
<td>48</td>
<td>129</td>
<td>yes</td>
<td>15</td>
</tr>
<tr>
<td>Spinosa et al., 1998 [28]</td>
<td>P</td>
<td>13</td>
<td>Abd=11, IF=2</td>
<td>Diagnostic=9, PTA=4</td>
<td>rise in serum creatinine of &gt;0.5 mg/dL.</td>
<td>24</td>
<td>40</td>
<td>none</td>
<td>*</td>
</tr>
</tbody>
</table>
Supporting Information Table S2, respectively. Studies were published from the year 1998 to 2015. The meta-analysis found an overall event rate of AKI in patients undergoing angiography with CO₂ of 6.2% (95% CI 0.050–0.076; \( P < 0.001 \)) as shown in Fig. 4. Heterogeneity was low (\( Q \) value = 9.070, \( I^2 < 0.001 \)) hence we used the fixed effect analysis for this cohort. Egger’s regression analysis for cohort B demonstrated a \( P \) value of 0.05 which suggested publication bias. Figure S2 Supporting Information shows the corresponding funnel plot.

**Cohort C (ICM only outcomes).** The 15 studies identified a total of 11,354 patients who underwent 11,525 procedures with the use of ICM as the contrast agent. The characteristics of the studies are shown in Table III and Supporting Information Table S3, respectively. Studies were published between 2003 and 2016. The meta-analysis found an overall event rate for AKI of 9.4% (95% CI 0.068–0.127) in patients undergoing angiography with ICM as shown in Fig. 5. This indicated an incidence of 9.4 for every 100 (or 9.4%) patients undergoing angiography with ICM. Heterogeneity was high in this cohort (\( Q \) value = 177.364, \( I^2 = 92.10 \)) hence the random effect analysis was used. Egger’s regression analysis for cohort C demonstrated a \( P \) value of 0.002, suggesting publication bias. Figure S3 Supporting Information shows the corresponding funnel plot.

**DISCUSSION**

This is the first meta-analysis to describe the renal and safety outcomes of ICM and CO₂ and their clinical application as contrast agents for peripheral angiography. Cohort A, our primary cohort, suggests a modest decrease in the incidence of AKI with CO₂ as compared to ICM (OR 0.465, \( P = 0.048 \)). The overall incidence of AKI as reported separately (cohorts B, C) following CO₂ and ICM angiography was 6.2% and 9.4%, respectively. There was no significant difference in AKI between CO₂ and ICM angiography in patients with baseline CKD. The analysis also demonstrated a higher incidence of nonrenal events including limb and abdominal pain, nausea and vomiting with CO₂ as compared to ICM. There was no difference in mortality between the two modalities.

**CO₂ as an Imaging Agent**

As the prevalence of diabetes, CKD, and peripheral arterial disease (PAD) continues to rise, an increasing number of patients will present for endovascular therapy and be exposed to the risk of CI-AKI [44]. The use of digital subtraction imaging with ICM remains the most common angiographic approach in patients with symptomatic PAD [45]. Pharmacologic measures to reduce the incidence of CI-AKI have been largely ineffective—with volume expansion and minimization of ICM as the most adopted techniques to prevent this complication.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Procedure type</th>
<th>Procedure type</th>
<th>CI-AKI definition</th>
<th>F/u renal function (hours)</th>
<th>ICM type</th>
<th>Mean ICM volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peng et al., 2016</td>
<td>P</td>
<td>204</td>
<td>Peri=204</td>
<td>Procedure</td>
<td>Increase in serum creatinine level ≥ 25% or ≥ 0.5 mg/dL at 72 hours post procedure</td>
<td>72</td>
<td>Iodixanol</td>
<td>138.7</td>
</tr>
<tr>
<td>Kim et al., 2015</td>
<td>R</td>
<td>240</td>
<td>Peri=240</td>
<td>Procedure</td>
<td>Increase in serum creatinine level ≥ 25% or ≥ 0.5 mg/dL</td>
<td>48</td>
<td>Iodixanol</td>
<td>158.4</td>
</tr>
<tr>
<td>Yang et al., 2014</td>
<td>P</td>
<td>305</td>
<td>Peri=305</td>
<td>Procedure</td>
<td>Increase in serum creatinine level ≥ 25% or ≥ 0.5 mg/dL</td>
<td>48</td>
<td>Iohexol Iodixanol</td>
<td>97.7</td>
</tr>
<tr>
<td>Arora et al., 2013</td>
<td>R</td>
<td>684</td>
<td>Peri=744</td>
<td>Procedure</td>
<td>Acute Kidney Injury Network (AKIN) criteria</td>
<td>192</td>
<td>Iodixanol</td>
<td>*</td>
</tr>
<tr>
<td>Hafiz et al., 2012</td>
<td>RCT</td>
<td>320</td>
<td>Coro=195, Peri=105, Other=20</td>
<td>Procedure</td>
<td>Increase in serum creatinine level ≥ 25% or ≥ 0.5 mg/dL</td>
<td>48</td>
<td>Iodixanol Iopamidol Ioversol</td>
<td>110</td>
</tr>
<tr>
<td>Karlsberg et al., 2011</td>
<td>P</td>
<td>253</td>
<td>Peri=253</td>
<td>Procedure</td>
<td>Increase in serum creatinine level ≥ 25%</td>
<td>24</td>
<td>Iodixanol Low osmolar contrast</td>
<td>235</td>
</tr>
<tr>
<td>Plaisance et al., 2011</td>
<td>R</td>
<td>7, 769</td>
<td>Peri=7, 769</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 0.5 mg/dL</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Sadat et al., 2011</td>
<td>RCT</td>
<td>40</td>
<td>Peri=40</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 25%</td>
<td>72</td>
<td>Iopamidol</td>
<td>73</td>
</tr>
<tr>
<td>Karlsberg et al., 2010</td>
<td>P</td>
<td>250</td>
<td>Peri=250</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 25%</td>
<td>24</td>
<td>Iodixanol Iopamidol Ioversol</td>
<td>235</td>
</tr>
<tr>
<td>Lawlor et al., 2007</td>
<td>RCT</td>
<td>78</td>
<td>Peri=78</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 25%</td>
<td>48</td>
<td>*</td>
<td>162</td>
</tr>
<tr>
<td>Sandhu et al., 2006</td>
<td>RCT</td>
<td>106</td>
<td>Visc=32, Peri=74</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 25%</td>
<td>48</td>
<td>Iodixanol Iopamidol</td>
<td>137</td>
</tr>
<tr>
<td>Erley et al., 2004</td>
<td>RCT</td>
<td>11</td>
<td>Peri=11</td>
<td>Procedure</td>
<td>Decrease in estimated glomerular filtration rate of &gt; 50%</td>
<td>48</td>
<td>Iohexol</td>
<td>49</td>
</tr>
<tr>
<td>Rashid et al., 2004</td>
<td>RCT</td>
<td>94</td>
<td>Peri=94</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 20%</td>
<td>48</td>
<td>Iohexol</td>
<td>143</td>
</tr>
<tr>
<td>Srodon et al., 2003</td>
<td>P</td>
<td>191</td>
<td>Peri=302</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 25%</td>
<td>72</td>
<td>Iohexol Iodixanol</td>
<td>*</td>
</tr>
<tr>
<td>Alamartine et al., 2003</td>
<td>P</td>
<td>809</td>
<td>Coro=404, Peri=138, Other=266</td>
<td>Procedure</td>
<td>Increase in serum creatinine level &gt; 25%</td>
<td>*</td>
<td>Iomeprol Oxaglic acid Iodixanol Oxitalamic acid</td>
<td>80gm</td>
</tr>
</tbody>
</table>
The renal toxicity of ICM has been well described and for these reasons CO\textsubscript{2} represents an attractive alternative contrast medium. The ability of CO\textsubscript{2} to provide vascular imaging is related to its chemical properties, which permits it to rapidly dissolve into the target vessel lumen where it displaces the blood pool, allowing for a negative X-ray image to be produced [17]. Due to potential neurotoxicity and risk of cardiac arrhythmias, it is avoided in the thoracic aorta, coronary arteries and cerebral circulation.

Initially employed in radiologic procedures to outline retroperitoneal structures, CO\textsubscript{2} gained use in the 1970s to support imaging during infra-diaphragmatic procedures of the lower extremity, abdominal, renal and hepatic vasculature [3,46]. More recently it has been explored as an alternate contrast medium of choice for peripheral angiographic procedures in patients who are high risk for CI-AKI [3].

**Review of Literature: Incidence of CI-AKI across Multiple Levels of Evidence**

While the aforementioned theoretical advantages of CO\textsubscript{2} are clear, implementation of this imaging modality into clinical practice has been limited. Few well-constructed studies are available to guide the utility of CO\textsubscript{2} angiography with the aims of AKI prevention and to rigorously yet safety and image quality. In the literature review, we found three RCTs that compared renal outcomes between CO\textsubscript{2} and ICM. Despite variable definitions for AKI, these studies appeared to favor the use of CO\textsubscript{2} with regards to renal injury [11,47,48]. A small number of nonrandomized prospective and retrospective studies have also compared the two contrast agents. In 2015, Stegemann et al. studied the safety and efficacy of CO\textsubscript{2} and found that the supplemental use of CO\textsubscript{2} decreased the total volume of ICM used for each procedure [8].

Single arm retrospective or prospective studies make up the larger body of reported literature with respect to CO\textsubscript{2}. While four contemporary studies have reported 0\% incidence of AKI in their subjects, Fujihara et al. recently reported the results of a multicenter prospective registry of patients undergoing peripheral angiography with CO\textsubscript{2} as the primary contrast agent. This study noted the incidence of AKI with CO\textsubscript{2} to be 5.1\% [17]. These findings are comparable to data from Moos et al. who reported outcomes in 991 patients undergoing various vascular procedures with CO\textsubscript{2} as the only contrast or used in supplement with ICM. These authors found an overall 6.6\% incidence of CI-AKI [22]. The etiology of AKI in patients receiving CO\textsubscript{2} as the primary imaging medium is not clear. CO\textsubscript{2} does not have direct renal toxicity and as a physiologic corollary supporting this statement, Palm et al. studied medullary blood flow in the rat kidney after injection of CO\textsubscript{2} or ICM (ioxaglate), and noted a pronounced decrease in medullary blood flow and renal O\textsubscript{2} concentration after injection of ICM while this effect was not seen with CO\textsubscript{2} [49]. There are, however, numerous practical considerations which may...
explain AKI development following the use of CO₂ in patients. The vapor lock phenomena, which occurs when rapid or excessive administration of gas leads to air trapping within the vascular column subsequently causing obstruction of blood flow, could lead to organ ischemia and air trapping involving the renal arteries. Nearly ubiquitous and poorly characterized is the phenomenon of atheroembolization, which occurs as a result of catheter and equipment manipulation in the peripheral circulation. Showering of debris into the systemic circulation and into the renal vascular bed may be an important mechanism of AKI—indeed, in patients with CKD undergoing invasive angiography, is reported to be as high as 40–50% [52]. In the present meta-analysis, we did not find any statistical difference in the incidence of AKI between CO₂ and ICM in patients with baseline CKD. This finding should be taken in light of some limitations. The cumulative sample size for the studies with specific data on subgroup of patients with CKD was relatively small (n = 349). Granular details on overall AKI risk for the subjects, specifics on periprocedural hydration and medication management were not provided in these studies.

CO₂ Use in Patients with CKD

Patients with CKD are vulnerable to CI-AKI and the use of preventive measures and/or alternative contrast has been extensively studied for these individuals [51]. Depending on risk factors and definition, the incidence of CI-AKI in patients with CKD undergoing invasive angiography is reported to be as high as 40–50% [52]. In the present meta-analysis, we did not find any statistical difference in the incidence of AKI between CO₂ and ICM in patients with baseline CKD. This finding should be taken in light of some limitations. The cumulative sample size for the studies with specific data on subgroup of patients with CKD was relatively small (n = 349). Granular details on overall AKI risk for the subjects, specifics on periprocedural hydration and medication management were not provided in these studies.

Nonrenal Adverse Events with CO₂

Our analysis of the literature noted a higher incidence of limb and abdominal pain as well as nausea and vomiting in patients receiving CO₂ versus ICM. Fujihara et al. reported an overall 17.3% rate (17 events out of 98 cases) of nonrenal events (limb pain/abdominal pain)—including two deaths attributable to CO₂ use [17]. Kawasaki et al. reported that 14.6% of patients undergoing CO₂ angiography complained of transient lower extremity pain, while Madhusudan reported this incidence to be 4.8% employing the use of a customized delivery system for intra-arterial injections [53,54]. The mechanisms underlying these effects in individual studies were not elucidated but likely involved either the vapor lock phenomenon or transient symptoms from blood displacement. It should be noted that potential air contamination of gas has also remained a concern with CO₂ injection and can contribute to the development of more severe ischemic effects.

Imaging Quality with CO₂

A challenge with CO₂ has been inferior imaging quality when compared to ICM-based angiography. The use of quantitative contrast opacification analysis or blinded qualitative review of CO₂-based images has not been performed in the majority of studies [2]. Fujihara et al. attempted semiquantitative analysis of angiographic sequences using two independent observers and graded the images from Types 1–3 (Type 1: the vessel and stenosis are completely visualized, Type 2: the vessel can be evaluated but the degree of stenosis cannot be measured, Type 3: no evaluation can be made). The authors reported that clinically acceptable evaluation of the vessel lumen and stenosis (Type 1 angiograms) by CO₂ alone in the majority (63%) of the superficial femoral artery cases [17]. However, only 22.6% of aortoiliac and 31.2% of renal artery stenosis angiograms had Type 1 angiograms—with an overall Type 3 (uninterpretable) rate of 12%. The need for adjuvant contrast administration and augmentation of lesion interrogation by intravascular ultrasound and pressure wires was required in several cases. The authors also noted that the limitations in the abdominal imaging (aortoiliac and renal beds) were often due to the presence of bowel loops and gas. It has been observed that in many studies, above the knee CO₂ imaging results are superior to infra-popliteal imaging—with diagnostic accuracy reported as low as 50% in this latter anatomical region [21,23]. However, Palena et al. reported 89.8% accuracy in patients with severe infra-popliteal arterial disease (vs. 94.4% for supra-popliteal lesions)—attributing this higher accuracy to the use of an automated CO₂ injection system as opposed to a conventional hand injection system [18]. Despite the lack of rigorous image analysis in the literature, the sum of the data would suggest that CO₂ angiography has significant challenges with respect to consistent high quality vessel imaging.

Study Limitations

The present meta-analysis has a number of limitations—including a lack of available data from RCTs with respect to outcomes with CO₂. Given the paucity of data, we had to pool the outcomes from all available observational and randomized trials that were available in published literature. Second, we also found that some authors chose not to report incidences of nonrenal events including limb ischemia/pain, nausea, vomiting, allergic reactions and mortality rate. Many studies also lacked data on subject baseline characteristics, periprocedural

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studies that use CO2 as the primary imaging agent, the reduced occurrence of AKI in patients with CKD. In patient level data and relied on published data only. pret comparative data. Last, we were unable to obtain the reported outcomes and can make it difficult to interpret comparative data. In the previously reported literature, the definition of AKI can significantly impact baseline as the definition. In the present meta-analysis that CO2 imaging may also contribute to renal impairment following peripheral angiography.

REFERENCES


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