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Review

A meta-analysis of the risk of total cardiovascular events of isosmolar iodixanol compared with low-osmolar contrast media

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ABSTRACT

Background: The iso-osmolar contrast agent iodixanol may be associated with a lower incidence of cardiac events than low-osmolar contrast media (LOCM), but previous trials have yielded mixed results.
Objective: To compare the risk of total cardiovascular events of the iso-osmolar contrast medium, iodixanol, to LOCM.
Methods: Medical literature databases were searched to identify comparisons between iodixanol and LOCM with cardiovascular events as a primary endpoint. A random-effects model was used to obtain pooled odds ratio (OR) for within-hospital and 30-day events.
Results: A total of 2 prospective cross-sectional studies and 11 randomized controlled trials (RCTs) (covering 6859 subjects) met our criteria. There was no significant difference in the incidence of within-hospital and 30-day cardiovascular events when iodixanol was compared with LOCM, with pooled OR of 0.72 (95%CI 0.49–1.06, $p = 0.09$) and 1.19 (95%CI 0.70–2.02, $p = 0.53$), respectively. Subgroup analysis showed no relative difference when iodixanol was compared with ioxaglate (OR = 0.92, 95%CI 0.50–1.70, $p = 0.80$) and iohexol (OR = 0.75, 95%CI 0.48–1.17, $p = 0.21$). However, a reduction in the within-hospital cardiovascular events was observed when iodixanol was compared with LOCM in the RCT subgroup (OR = 0.65, 95%CI 0.44–0.96, $p = 0.03$). Sensitivity analyses revealed that three studies had a strong impact on the association of within-hospital cardiovascular events between iodixanol and LOCM. Meta-regression analysis failed to account for heterogeneity. No publication bias was detected.
Conclusions: This meta-analysis demonstrates that there is no conclusive evidence that iodixanol is superior to LOCM overall with regard to fewer cardiovascular events.

Contents

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Introduction

The contribution of contrast media to major complications during coronary angiography or coronary angioplasty has been debated [1–3]. Compared with high osmolar contrast media (HOCM), nonionic low osmolar contrast media (LOCM) have been shown to decrease the incidence of major complications associated with diagnostic cardiac catheterization [4].

Today we have a third category of contrast media, the nonionic dimers, iodixanol with an osmolarity close to that of plasma. In experimental studies, iodixanol induced only minor changes in cardiac function [5]. In the first comparative clinical studies with iodixanol, it was shown that iodixanol had generally no electrophysiological or hemodynamic effects, or these effects were less pronounced when compared with the other contrast media [6]. Subsequent trials also demonstrated that iodixanol significantly decreased the incidence of cardiac events in patients undergoing coronary angiography when compared with different types of LOCM [7,8]. However, other investigations have given conflicting results and raised doubts about the usefulness of iodixanol [3,9]. In view of these differences, the objective of this meta-analysis was to provide a comprehensive comparison of the risk of cardiovascular events of the iso-osmolar agent iodixanol and the currently available LOCM.

Methods

Searches

MEDLINE, Embase, ISI Web of Knowledge, Google Scholar, clinical trials.gov, and international conference abstracts (from 1980 until April 30, 2013) were searched using the medical subject headings (MeSH) "iso-osmolar," "iodixanol," "low-osmolar," "iohexol," "iopamidol," "iopromide," "iomeprol," and "cardiovascular disease." The reference lists of pertinent articles were also reviewed.

Selection

We performed initial screening of study titles or abstracts, while the second screening was based on full-text review. A study was included if it randomized patients undergoing contrast media application to either LOCM or iodixanol, and if data on cardiac events were routinely ascertained in all patients. The search was performed without any language restrictions but was limited to human subjects. When an abstract from a meeting and a full report referred to the same study, only the full report was included in the analysis. When multiple reports were available from the same study, we used the most complete and/or recently reported data.

Definition of cardiovascular disease events

Cardiovascular disease events were defined as a composite of death, stroke, myocardial infarction (MI), angina pectoris, new arrhythmias, congestive heart failure, and emergent need for revascularization.

Data extraction

Two independent investigators (Zhang and Wu) reviewed each report to determine its eligibility and then extracted and tabulated all of the relevant data. Disagreement was resolved by consensus between the two authors. The following information was obtained from each article: first author, year of publication, total number of patients, mean age, average contrast volume, information about sex, diabetes, and type of LOCM used.

Statistical analysis

The primary end point was the incidence of total cardiac events as defined by each individual study protocol. Data from all the selected studies were combined to estimate the pooled odds ratio (OR) for iodixanol versus LOCM using a random-effects model. Significant between-study heterogeneity was expected regarding study populations and because different LOCM were used as comparators; therefore, a random-effects model was used to produce across-study summary OR with 95% confidence intervals (CI). The Cochrane x^2 test and the I^2 test were used to evaluate heterogeneity among studies, with a threshold value of $p = 0.10$ being considered significant [10]. To investigate the dynamic trend of the association, cumulative meta-analysis was performed by assortment of publication times [11]. Publication bias was evaluated by creating a funnel plot of each study's effect size versus the SE. Funnel plot asymmetry was assessed by Begg's test and Egger's test.

Meta-regression analyses were performed to explore sources of heterogeneity. Variables such as total number of patients, mean age, and average contrast volume were examined to detect any significant influence on the risk of total cardiovascular disease events. To assess the effect of individual studies on the summary estimate of effect, we performed an influence analysis, in which the pooled estimates were recalculated by omitting 1 study at a time. All statistical tests were performed with the STATA software, version 11.0 (Stata Corporation, College Station, TX, USA) and Review Manager 5.0.4 software (available from The Cochrane Collaboration at http://www.cochrane.org). A value of $p < 0.05$ was considered statistically significant.

Results

Search results

Fig. 1 shows a flow diagram of study selection. We identified a total of 213 citations. Of these citations, 166 were excluded by reviewing the title and abstract, leaving 47 studies for further evaluation. After full-text evaluation, 34 of these 47 studies were excluded. Most of the excluded studies did not contain pertinent data. A total of 13 studies [1–3,7–9,12–18] that covered 6859