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Pharmacologic and non-pharmacologic interventions to prevent hypersensitivity reactions of non-ionic iodinated contrast media: a systematic review protocol

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ABSTRACT

Introduction Iodinated contrast media are commonly used in medical imaging and can cause hypersensitivity reactions, including rare but severe life-threatening reactions. Although several prophylactic approaches have been proposed for severe reactions, their effects remain unclear. Therefore, we aim to review systematically the preventive effects of pharmacologic and non-pharmacologic interventions and predictors of acute, hypersensitivity reactions.

Methods and analysis We will search the PubMed, EMBASE and Cochrane Central Register of Controlled Trials databases from 1 January 1990 through 31 December 2019 and will examine the bibliographies of eligible studies, pertinent review articles and clinical practice guidelines. We will include prospective and retrospective studies of any design that evaluated the effects of pharmacological and non-pharmacological preventive interventions for adverse reactions of non-ionic iodinated contrast media. Two assessors will independently extract the characteristics of the study and intervention and the quantitative results. Two independent reviewers will assess the risk of bias using standard design-specific validity assessment tools. The primary outcome will be reduction in acute contrast media-induced hypersensitivity reactions. The secondary outcomes will include characteristics associated with the development of contrast media-induced acute hypersensitivity reactions, and adverse events associated with specific preventive interventions. Unique premedication regimens (eg, dose, drug and duration) and non-pharmacological strategies will be analysed separately. Average-risk and high-risk patients will be considered separately. A meta-analysis will be performed if appropriate.

Ethics and dissemination Ethics approval is not applicable, as this will be a secondary analysis of publicly available data. The results of the analysis will be submitted for publication in a peer reviewed journal.

PROSPERO registration number CRD42019134003

Strengths and limitations of this study

- ► This will be the first systematic review and meta-analysis to assess and compare the preventive effectiveness of pharmacologic and non-pharmacologic interventions for preventing acute hypersensitivity reactions caused by non-ionic iodinated contrast media.
- ► Comprehensive literature searches and up-to-date systematic review methodologies will be used to identify actionable evidence.
- ► If the number of studies is too small, or clinical or statistical across-study heterogeneity is deemed too great, a quantitative synthesis may not be feasible.

INTRODUCTION

Iodinated contrast media are commonly used to enhance CT examinations for diagnosis and treatment monitoring. However, non-ionic iodinated contrast media cause adverse reactions ranging from mild nausea or pruritus to haemodynamic shock and cardiopulmonary arrest in approximately 3% of patients.[1 2] Life-threatening reactions occur in approximately 4 in 10 000 cases.[1] As millions of doses of iodinated contrast media are administered annually, severe reactions are expected to occur commonly within a population.[3]

The mechanism underlying adverse reactions induced by contrast media is not fully understood and is likely multifactorial.[2] However, based on a general framework for the classification of adverse drug reactions, the reactions induced by contrast media can be divided into two types—commonly referred to as type A and type B reactions.[4 5] Type A reactions are physiologic and often dose-dependent reactions that are expected

from the pharmacologic properties of the administered contrast media. Type B reactions are hypersensitivity reactions that are neither physiologic nor dose-dependent, and are usually unpredictable. Distinction between type A and type B reactions can facilitate designing prophylactic strategies for preventing contrast media-induced adverse reactions; nevertheless, the distinction is not straightforward, and some professional societies have discordant classification systems.[4]

No perfect strategy has been established to mitigate the risk of acute severe contrast media-induced hypersensitivity reactions. Only weak evidence supports pharmacological interventions including corticosteroids and/or antihistamines.[2] For example, premedication often fails[6] and can induce adverse effects such as corticosteroid-induced hyperglycaemia and indirectly contributed to prolonged hospitalisation.[7 8] Purported risk factors for contrast media-induced reactions predict reactions of any severity; they do not specifically predict acute life-threatening reactions.[2 9] Further, the comparative effectiveness of alternative preventive strategies involving pharmacological and non-pharmacological interventions has not been systematically evaluated.[6–8 10–12] Although professional societies including the American College of Radiology (ACR) propose several premedication regimens,[2] only one has been tested in a randomised design, and that study had methodological challenges.[13] Premedication practice varies,[14 15] which precludes a standardised comparative assessment among alternative pharmacological and non-pharmacological interventions. Given this uncertainty, the 2019 European Society of Urogenital Radiology (ESUR) Guideline on Contrast Agents indicates that 'premedication is not recommended because there is not good evidence of its effectiveness (page 7, A1.1).'[9]

Since the publication of two systematic reviews in 2006 that evaluated the effectiveness of premedication regimens,[16 17] several relevant studies of pharmacological and alternative, non-pharmacological strategies (eg, exchanging one contrast medium for an alternative) have been published and have influenced the ACR and ESUR guidelines.[18 19] In addition, the two prior systematic reviews on this topic included pharmacological prophylaxis only in the context of now-outdated high-osmolality iodinated contrast media that are no longer used in clinical practice. Therefore, we planned a comprehensive quantitative synthesis of clinical data on the effects of pharmacological and non-pharmacological prophylactic strategies for the prevention of acute adverse reactions to non-ionic iodinated contrast media.

METHODS AND ANALYSIS

This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.[20] Based on the analytic framework shown in figure 1, we have formulated the following three key research questions and related subquestions:

Key question 1

What is the effect of interventions to reduce acute (<1 hour) hypersensitivity (type B) reactions in patients receiving contrast media?

Key question 1a: What is the preventive effect of guideline-recommended oral (12 or 13 hours), guideline-recommended accelerated intravenous

Key Question 1. What is the effect of interventions to reduce acute (<1 hour) hypersensitivity (Type B) reactions in patients receiving CM?
Key Question 2. What are the patient-level and intervention-level characteristics (i.e., predictors) associated with CM-induced acute hypersensitivity (Type B) reactions?
Key Question 3. What are the complications and adverse events associated with specific interventions to reduce CM-induced adverse reactions?

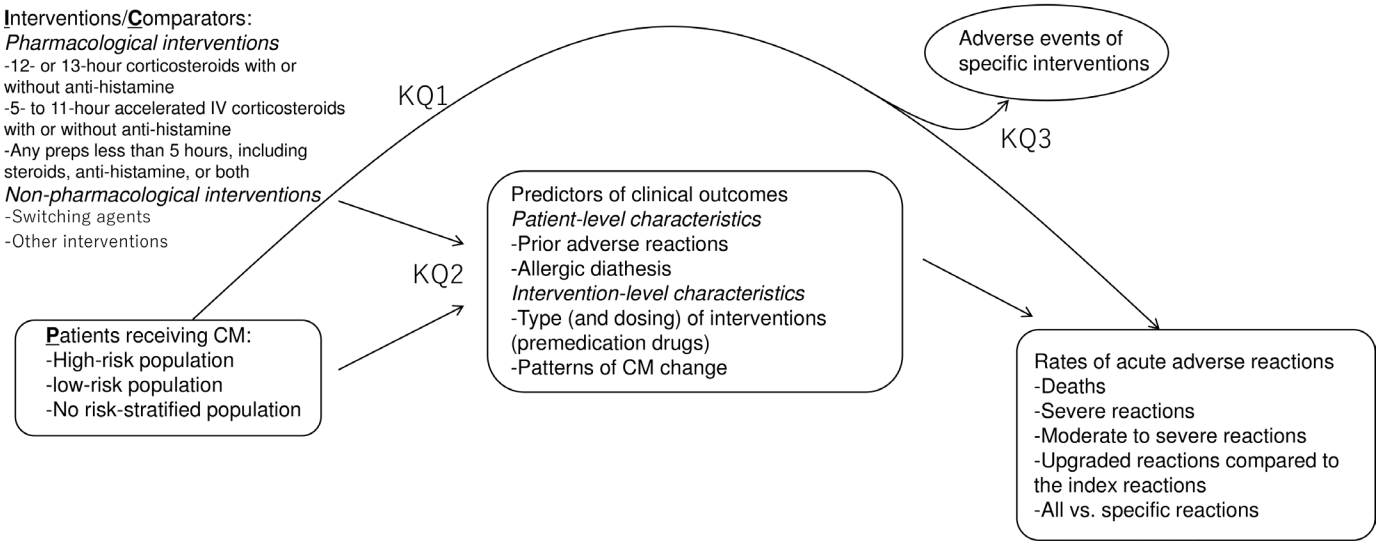

Figure 1 Analytic framework. CM, contrast media; KQ, key question.

(5–11 hours) or non-guideline emergent intravenous (<5 hours) premedication on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key question 1b: What is the preventive effect of a change of contrast media alone on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key question 1 c: What is the preventive effect of combining standard oral (12 or 13 hours) premedication and a change of contrast media on acute (<1 hour) hypersensitivity reactions in patients receiving contrast media?

Key question 1d: What is the preventive effect of other interventions (other than the above listed) on acute (<1 hour) hypersensitivity reactions?

Key question 1e: What is the preventive effect of any interventions for acute (<1 hour) adverse reactions of any type (ie, both type A and B reactions)?

Key question 2

What are the patient-level and intervention-level characteristics (ie, predictors) associated with contrast media-induced acute hypersensitivity (type B) reactions?

Key question 3

What are the complications and adverse events associated with specific interventions to reduce contrast media-induced adverse reactions?

Literature search

We will search the PubMed, EMBASE and Cochrane Central Register of Controlled Trials databases from 1 January 1990 through 31 December 2019 for both English-language and non-English-language publications, using search terms such as 'iodinated contrast media', 'premedication', 'adverse reaction', 'breakthrough reactions' and their synonyms. The complete search strategy and full list of databases are available in online supplementary file. We will include studies published after 1990, when non-ionic contrast media were developed and disseminated widely. We also will examine the references of eligible studies, relevant review articles and existing clinical practice guidelines developed by professional societies such as the ACR and ESUR.[2 9] All potentially eligible non-English publications will be translated into English before full-text assessment.

Inclusion and exclusion criteria

We will include studies that assessed patients who received intravenous or intra-arterial non-ionic iodinated contrast media and any interventions to reduce contrast media-induced adverse reactions. Table 1 presents our detailed inclusion criteria, which follow a generally accepted framework to formulate a systematic review question comprising five key components: populations, interventions, comparator interventions, outcomes and study designs.[21] Regarding pharmacological prophylactic interventions, we will focus on premedication based on corticosteroids, antihistamines, or both, and exclude studies that tested other medications (eg, ephedrine, diazepam, atropine) because these are not relevant to current clinical practice. We also will exclude studies that assessed patients who received high-osmolality contrast media because they are no longer used in clinical practice. Both prospective and retrospective studies of any design that evaluated at least 10 patients will be included.

Several frameworks for categorising clinical symptoms and severity induced by pharmacological agents including contrast media exist. We will employ an accepted general two-group framework (type A and type B) to classify acute contrast media-induced adverse reactions reported in primary studies in the main analysis.[5] We then will reclassify the reported acute adverse reactions using the current ACR categorisation system[2] in a sensitivity analysis to assess the applicability and difference between the two frameworks. Delayed reactions occurring more than 1 hour after contrast media administration will not be assessed. A breakthrough reaction will be defined as an acute type B reaction of any severity that occurs despite premedication. We will operationally classify any randomised controlled trials (RCTs) and any studies with a non-randomised design that compared two or more intervention groups (ie, so-called non-randomised studies of intervention (eg, quasi-RCTs, cohort studies, case–control studies)) as 'comparative studies.' 'Non-comparative studies' will include single-group studies and case series.

We will exclude editorials, comments, letters to the editor and review articles. Multiple publications with potentially overlapping patient populations can overestimate the volume of evidence. Therefore, for overlapping study populations, we will only include the publication with the largest sample size. We will contact the study authors by email if the publications do not report adequate information about the patient characteristics and reaction classifications. We will consider our request to be rejected if two email request reminders sent separately 14 days after the initial contact attempt are not returned.

The results of our electronic searches will be imported into reference management software and duplicate results will be removed. Multiple paired investigators will independently double-screen non-overlapping sets of abstracts (eg, the first half of the abstracts will be assigned to team A (two investigators) and the second half of the abstracts will be assigned to team B (two investigators) in the case of two paired teams) and examine full-text articles for potentially eligible citations. We will use Abstrackr (Center for Evidence Synthesis in Health, Brown University, available at abstrackr.cebm.brown.edu), a free, open-source, citation screening programme for abstract screening. A third investigator will adjudicate any discrepant results if consensus cannot be reached between the two reviewers.

Table 1 Inclusion criteria based on the PICOD framework

PICOD	Specific details
Population	Patients who received intravenous or intra-arterial non-ionic iodinated CM* ► High-risk population ► Low-risk population ► No risk-stratified population
Interventions /Comparators and co-interventions	Pharmacological interventions† ► 12 or 13 hours oral corticosteroids with or without antihistamine ► 5–11 hours IV corticosteroids with or without antihistamine ► Any premedication less than 5 hours using corticosteroids, antihistamine or both Non-pharmacological interventions ► Change of CM that caused prior type B hypersensitivity reaction
Outcomes	Rates of acute (<1 hour) type B hypersensitivity reactions‡ ► Acute reaction-related deaths within 30 days ► Severe reactions only ► Moderate and severe reactions only ► Upgraded reactions compared with the index reactions ► All hypersensitivity reactions Rates of adverse events induced by preventive interventions
Predictors of acute adverse reactions	Patient-level characteristics ► Prior type B hypersensitivity reactions ► Prior type A physiologic reactions§ ► Allergic diathesis (eg, asthma, food or drug allergy, etc) Intervention-level characteristics ► Types and regimens of interventions ► Dosing of specific premedication drugs ► Change of CM (specific class/product and/or dosing)
Designs	Any study designs including at least 10 patients ► Randomised controlled trials ► Non-randomised trials ► Prospective and retrospective cohorts – Comparative (two or more-group) design – Single-group design

*Per-study defined risk criteria are allowed.
†Both guideline-recommended and ad-hoc regimens are allowed, but will be analysed separately. Guideline-recommended oral regimens are defined as follows[2]: 13 hours regimen: prednisone 50 mg PO at 13, 7 and 1 hours before CM injection+/−optional diphenhydramine 50 mg IV, IM or PO at 1 hour before CM injection; 12 hours regimen: methylpredonisolone 32 mg PO at 12 and 2 hours before CM injection+/−optional antihistamine. Guideline-recommended urgent regimens are: methylprednisolone 40 mg or hydrocortisone 200 mg IV every 4 hours until CM injection (minimum cumulative duration 5 hours)+/−diphenhydramine 50 mg IV at 1 hour before CM injection. Any premedication that does not include corticosteroids or that is less than 5 hours in duration is non-standard.
‡Grades of type B hypersensitivity reactions are defined as follows[2]: mild reactions include limited urticaria/pruritus, cutaneous oedema, limited 'itchy'/'scratchy' throat, nasal congestion, sneezing, conjunctivitis and rhinorrhea; moderate reactions include diffuse urticaria/pruritus, diffuse erythema with stable vital signs, facial oedema without dyspnoea, throat tightness or hoarseness without dyspnoea, and wheezing/bronchospasm with mild or no hypoxia; and severe reactions include diffuse oedema, facial oedema with dyspnoea, diffuse erythema with hypotension, laryngeal oedema with stridor and/or hypoxia, wheezing/bronchospasm with significant hypoxia and anaphylactic shock (hypotension+tachycardia).
§Grades of type A physiologic reactions are defined as follows[2]: mild reactions include limited nausea/vomiting, transient flushing, warmth, chills, headache, dizziness, anxiety, altered taste, mild hypertension and vasovagal reaction that resolves spontaneously; moderate reactions include protracted nausea/vomiting, hypertensive urgency, isolated chest pain and vasovagal reaction that requires and is responsive to treatment; and severe reactions include vasovagal reaction resistant to treatment, arrhythmia, convulsions, seizures and hypertensive emergency.
CM, contrast medium; IM, intramuscularly; IV, intravenously; PICOD, populations, interventions, comparator interventions, outcomes and study designs; PO, orally.

Data extraction

We will extract the following descriptive data from eligible studies. Study characteristics will include first author, year of publication, journal and study design (prospective vs retrospective, comparative study vs non-comparative study). Participant characteristics will include age, sex, history and severity and type of any prior acute adverse reaction to iodinated contrast media, allergic diathesis including severe allergy(-ies) to other substances and asthma,[2] and other known risk factors for adverse reactions. Contrast media characteristics will include brand and generic names and doses of contrast

media administered. Intervention characteristics will include premedication strategies including drugs, doses, duration and change in contrast media. Outcome characteristics will include details of and change in adverse reactions (kinds and severity), assessors of adverse reactions (number and experience), and categorisation system to classify and grade acute adverse events. We will operationally define guideline-recommended regimens as the 12–13 hours oral administration of corticosteroids with or without use of an antihistamine, and standard accelerated regimen as a 5–11 hours intravenous administration of corticosteroids with or without the use of an antihistamine.[2] If a study adopted ad-hoc definitions or categorisation systems other than the two-group classification framework or those proposed by the ACR, we will specify these differences in sufficient detail. One primary investigator will extract the descriptive data, which will be verified by a second investigator.

Two reviewers will independently double-extract quantitative data from each publication. We will determine the relative risk of a hypersensitivity reaction between two (or more) groups in comparative studies. We will extract the number of patients in each group, as well as the number of patients who developed a hypersensitivity reaction. If relevant count data cannot be determined from the publication, we will instead extract the reported point estimates and their confidence intervals.

We will extract quantitative measures (eg, risk ratios, ORs) of the association of the presence or absence of a predictor with the development of a breakthrough reaction. We will prefer adjusted values over unadjusted values if both are reported. A priori candidate predictors selected for extraction include specific index type B reactions and their grades, and any allergic diathesis and its severity.

Assessment of risk of bias

For RCTs, we will use the revised tool to assess risk of bias in randomised trials (RoB 2 tool).[22] We will assess five domains of RCT study validity (ie, randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes, selective reporting) and then assign an overall risk of bias for each trial.

For non-randomised intervention studies, we will use the Risk Of Bias In Non-randomised Studies of Interventions tool for cohort studies,[23] and the Cochrane Risk Of Bias Assessment Tool for Non-Randomised Studies of Interventions for case–control studies.[24] We will assess seven domains of study validity (ie, confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selective reporting) and then assign an overall risk of bias for each study.

For single-group observational studies that assessed a predictor in a specific clinical context (eg, development of a breakthrough reaction under a premedication regimen), we will use a revised version of the Quality in Prognosis Studies tool (the QUIPS-2).[25] We will assess six domains of study validity (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis and reporting) and then assign an overall risk of bias for each study.

Two reviewers will independently assess each item and rate the domain-specific and overall risks of bias. Discrepant ratings will be resolved by consensus. A third independent investigator will adjudicate any unresolved discrepancies. The complete list of modified operational definitions used to rate each item will be available from the authors on request.

Data synthesis

The primary outcome of interest will be the relative risk of an acute type B (hypersensitivity) reaction between specific prevention strategies. Secondary outcomes will include the breakthrough reaction rate of each specific strategy and the predictive performances of covariates for overall and severe breakthrough reactions. For all outcome measures, we will first construct an evidence map by performing qualitative syntheses based on graphs and tables to examine the diversity and volume of available evidence on this topic.[26 27] If feasible, we will then perform a quantitative synthesis.

For summary relative measures (eg, relative risk of an acute type B reaction) based on count data, we will perform a random-effects meta-analysis using the binomial likelihood with logit link in a generalised linear modelling framework (ie, random-effects logistic regression).[28] If already-estimated relative measures are the only extractable formats, we will utilise the log-transformed estimates and their variances as 'plug-in' estimates. If appropriate, the meta-analytical model for a specific pairwise comparison will be extended to a network meta-analysis to synthesise data from both direct and indirect comparisons of all available studies in a single analysis.[28]

For summary estimates of the proportion measures in non-comparative studies, we will perform a random-effects meta-analysis of proportions using the binomial likelihood and logit link (ie, so-called the binomial-normal model).[29]

Additional analyses

We will estimate the between-study SD parameter, tau, and I^2 statistic and corresponding 95% credible intervals as measures of statistical heterogeneity. An I^2>50% will indicate intermediate heterogeneity, while an I^2>70% will indicate high heterogeneity.[30]

To explore statistical heterogeneity, we will perform subgroup analyses and, if feasible, a univariable random-effects meta-regression.[28] Preplanned candidate factors will include the use of guideline-recommended premedication regimens (vs non-guideline-recommended or ad-hoc regimens), alterations of the culprit contrast media (vs not), use of the general two-group classification framework versus the ACR categorisation systems for the classification and grading of reactions (vs others), and

severity and type of prior reactions to iodinated contrast media. We will consider conducting sensitivity analyses by reclassifying and/or re-grading the reported reactions based on the two-group classification system and the ACR classification system for studies not using these classification frameworks, if pertinent individual-level data are presented.

We will assess funnel-plot asymmetry if at least 10 studies are included.[31] To address potential biases derived from missing outcome data, we will apply the approach proposed by Turner *et al*.[32] We will assess the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach.[33]

Statistical software

We will conduct all analyses using Stata V.14/SE (Stata Corp.) and OpenBUGS V.3.2.3 (members of OpenBUGS Project Management Group; see www.openbugs.net). All tests will be two-sided, and statistical significance will be defined as a p value <0.05.

Patient and public involvement

We did not involve patients or the public in the preparation of this systematic review protocol.

DISCUSSION

The revised 2019 ESUR guidelines on contrast agents retracted recommendations for the premedication of patients at an increased risk of contrast reaction due to a lack of scientific evidence of efficacy.[9] This position is inconsistent with the latest guidelines of other professional societies, including the ACR (ACR Manual on Contrast Media V.10.3),[2] the Canadian Association of Radiologists[34] and the Japan Radiological Society.[35] Also, concerns have been raised on the relevance and impact of the classification systems and nomenclature of contrast media-induced adverse reactions, and their recommended management proposed in guidelines.[4] Given the wide application of iodinated contrast media in medical imaging and interventional procedures, the uncertainty surrounding the optimisation of prevention strategies based on the proposed framework, and the absence of recently published evidence reviews, we believe that it will be worthwhile to conduct a new systematic review that critically examines the existing evidence on interventions to reduce acute contrast media-induced adverse reactions. Using a comprehensive evidence map of the published literature on the effects of pharmacologic and non-pharmacologic interventions and, if feasible, new meta-analytic results, we hope to clarify the actionable evidence regarding the use of preventive interventions.

ETHICS AND DISSEMINATION

The findings from the review will be disseminated through publications in peer-reviewed journals, and presentations at conferences.

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Contributors HU and TN originated the idea; HU, TN and TT drafted the initial version of the protocol; HU, TN and TT developed the search strategy; HS, TY, HI, AT, NH, SI, YT, SN and MD reviewed the protocol and suggested amendments. All authors read and approved the final version of the protocol. HU, TN and TT are guarantors of the review.

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Patient consent for publication Not required.

Ethics approval As this is a systematic review, we are not planning to obtain a formal ethical approval.

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