Continuing versus Withholding renin angiotensin aldosterone system antagonists before non-cardiac surgery: A protocol of a systematic review and meta-analysis

Poursuite versus arrêt des antagonistes du système rénine-angiotensine-aldostérone en préopératoire de chirurgie non cardiaque: Protocole d'une revue systématique et d'une méta-analyse

Mohamed Ali Chaouch[1], Faten Haddad[2], Emna Kammoun[2], Henri Clautiaux[3], Mohamed Aziz Daghmouri[3]

1. Department of Visceral and Digestive Surgery, Monastir University Hospital, Monastir, Tunisia
2. University Tunis El Manar, Faculty of medicine of Tunis, Mongi Slim Hospital, Department of anesthesia and intensive care, Tunis, Tunisia.
3. Department of Anesthesiology, Montreuil Intercommunal Hospital Center, France

Abstract

Introduction: Perioperative use of ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) has been linked to early postinduction hypotension requiring vasopressor use under general anesthesia, potentially leading to complications like acute renal injury, myocardial injury, or stroke. However, the relationship between perioperative ACEI/ARB use and major morbidity remains uncertain.
Aim: This meta-analysis assessed the differences between the continuation or discontinuation of ACE inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) therapy during the perioperative period and hemodynamical instability, mortality, and major morbidity outcomes.
Methods: The protocol was registered in the PROSPERO database (ID: CRD42024519162). Literature searches of electronic databases and manual searches on the Medline, Embase, Scopus, and Web of Science databases up to August 30, 2024, will be performed. Case-control studies, cohort studies, non-randomized controlled trials, and randomized controlled trials (RCTs) involving adult patients aged over 18 years, who were chronically using ACEIs or ARBs due to chronic hypertension, undergoing non-cardiac surgery, where ACEIs or ARB therapy was either withheld or continued less than 10 hours before surgery will be included.
The primary outcome will be the incidence of intraoperative hypotension. Secondary outcomes will be the intraoperative use of vasoactive agent (incidence, dose of ephedrine (mg) and dose of phenylephrine (ng)), the incidence of severe hypotension, hospital length of stay, intraoperative and postoperative hypertension, the incidence of acute kidney injury, 30-day postoperative all-cause mortality and incidence of major cardio-cerebral events.
Conclusion: The results of this systematic review and meta-analysis should provide evidence for withholding or continuing perioperative ACE-I or ARB in noncardiac surgery.

Key words: Angiotensin-converting enzyme inhibitors, renin-angiotensin system inhibitor, continuing, with holding, pre-operative, non-cardiac surgery, meta-analysis, systematic review

Résumé

Introduction: L'utilisation périopératoire d'inhibiteurs de l'enzyme de conversion (IEC) ou d'inhibiteurs des récepteurs de l'angiotensine II (ARA II) a été associée à une hypotension peropératoire, pouvant entraîner des complications telles que rénales, myocardiques ou céracrales. Cependant, la relation entre l'utilisation périopératoire d'IEC/ARA II et les morbidités reste incertaine. L'objectif était d'évaluer les effets de la poursuite ou l'arrêt de l'IEC ou ARA II en préopératoire et l'instabilité hémodynamique, la mortalité et les morbidités postopératoires.
Méthodes: Le protocole a été enregistré dans PROSPERO (ID : CRD42024519162). Des recherches documentaires dans les bases de données électroniques et des recherches manuelles dans Medline, Embase, Scopus et Web of Science seront effectuées jusqu'au 30 août 2024. Seront inclus les études cas-témoins, les études de cohorte, les essais contrôlés non randomisés et les essais contrôlés randomisés impliquant des patients adultes âgés de plus de 18 ans, recevant un traitement chronique type IEC ou ARA II pour hypertension artérielle, subissant une chirurgie non cardiaque, où les IEC ou les ARA II étaient soit interrompu, soit poursuivi moins de 10 heures avant la chirurgie.
Le critère de jugement principal sera l'incidence de l'hypotension peropératoire. Les critères de jugement secondaires seront le recours à un agent vasoactif, l'hypotension sévère, la durée du séjour à l'hôpital, l'hypertension peropératoire et postopératoire, l'insuffisance rénale aigue, la mortalité à 30 jours postopératoires et les événements cardio-cérébraux majeurs.
Conclusion: Les résultats devraient fournir des preuves concernant l'arrêt ou de la poursuite de l'IEC ou de l'ARA II en préopératoire de chirurgie non-cardiaque.

Mots clés: Angiotensin-converting enzyme 2, inhibiteur système rénine angiotensine, Période préopératoire, chirurgie non cardiaque, méta-analyse, revue systématique, continuation, arrêt.

Correspondance

Faten Haddad

University Tunis El Manar, Faculty of medicine of Tunis, Mongi Slim Hospital, Department of anesthesia and intensive care, Tunis, Tunisia.
Email: Faten.haddad@fmt.utm.tn

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Introduction

Renin-angiotensin-aldosterone system (RAAS) inhibitor is a widely used treatment. Roughly one-third of surgical patients are on antihypertensive drugs annually, particularly RAAS inhibitors(1,2). However, evidence supporting the use or discontinuation of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEI) on the day of surgery is still lacking. Perioperative use of ACEIs and ARBs has been associated with early postinduction hypotension requiring the use of vasopressors under general anesthesia (3,4). This can result in acute renal injury, myocardial injury, or stroke as postoperative complications. Nonetheless, the potential association between perioperative ACEI/ARBs and major morbidity has not been eluded (5–8). Moreover, continuation of ACE-Is/ARBs in the perioperative period may also be associated with improved outcomes in vascular surgical patients who have sustained a perioperative myocardial infarction (9).

Accordingly, we aim to assess in this meta-analysis the differences between the continuation or discontinuation of ACE inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) therapy during the perioperative period and hemodynamical instability, mortality, and major morbidity outcomes.

Methods

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) Guidelines 2020 (10) and checked according to the AMSTAR 2 (Assessing the methodological quality of systematic reviews) guidelines (11). The protocol is registered in the PROSPERO database (ID: CRD42024519162).

Search strategy

Bibliographic sources

We will perform an electronic search of the relevant literature and will limit our search to data published until August 30, 2024. We will not use language restrictions. We will seek trials in the United States National Library of Medicine, Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, National Institutes of Health PubMed/MEDLINE, Web of Science, and Google Scholar databases. The MEDLINE and Embase strategies will be run simultaneously as a multi-file search in Ovid, and the results will be de-duplicated using the Ovid duplication tool. We will use the following keywords: “angiotensin-converting enzyme inhibitors ACEIs”, “angiotensin-converting enzyme inhibitors ACEI, “renin-angiotensin system inhibitor”, “renin-angiotensin-aldosterone system inhibitor”, “continuing”, “withholding”, “pre-operative” and “non-cardiac surgery”. We will check the reference list of included trials manually to identify additional studies. Additionally, we will search several clinical trial registries (ClinicalTrial.gov, Current Controlled Trials, Australian New Zealand Clinical Trials Registry (www.actr.org.au), Prospero registration and University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr) to identify ongoing trials. The different research strategies will be as follows:

1. **PubMed/MEDLINE**: ("Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR ACEIs OR ACEI) AND ("Renin-Angiotensin System Inhibitors" OR "Renin-Angiotensin-Aldosterone System Inhibitor") AND (Continuing OR Withholding) AND ("Preoperative Care"[Mesh] OR pre-operative) AND ("Noncardiac Surgery" OR "Non-cardiac surgery")
2. **Cochrane Library**: (Angiotensin-Converting Enzyme Inhibitors OR ACEIs OR ACEI) AND (Renin-Angiotensin System Inhibitors OR Renin-Angiotensin-Aldosterone System Inhibitor) AND (Continuing OR Withholding) AND (Preoperative OR Pre-operative) AND (Noncardiac Surgery)
3. **Embase**: ('angiotensin-converting enzyme inhibitor'/exp OR ACEIs OR ACEI) AND ('renin-angiotensin system inhibitor'/exp OR 'renin angiotensin aldosterone system inhibitor') AND (continuing OR withholding) AND ('preoperative care'/exp OR pre-operative) AND ('non-cardiac surgery')
4. **Web of Science**: TS=("Angiotensin-Converting Enzyme Inhibitors" OR ACEIs OR ACEI) AND TS=("Renin-Angiotensin System Inhibitors" OR "Renin-Angiotensin-Aldosterone System Inhibitor") AND TS=(Continuing OR Withholding) AND TS=(Preoperative OR Pre-operative) AND TS=("Noncardiac Surgery" OR "Non-cardiac Surgery")
5. **Google Scholar:** Search Strategy: "Angiotensin-Converting Enzyme Inhibitors" "ACEIs" "ACEI" "Renin-Angiotensin System Inhibitors" "Renin-Angiotensin-Aldosterone System Inhibitor" "Preoperative" "Non-cardiac Surgery" "Continuing" "Withholding".
6. **Clinical Trial Registries**
   - ClinicalTrials.gov:
     - Keywords: "Angiotensin-Converting Enzyme Inhibitors", "Preoperative", "Non-cardiac Surgery"
   - Australian New Zealand Clinical Trials Registry:
     - Search terms: "Angiotensin-Converting Enzyme Inhibitors", "Surgery"
   - University Hospital Medical Information Network Clinical Trials Registry (UMIN):
     - Search terms: "Renin-Angiotensin System Inhibitors", "Preoperative"

Study selection

Two authors will perform independent and blinded record screening. Disagreements will be resolved by discussion after consulting a third review team member. Then the full texts of all selected studies will be screened according to predefined inclusion and exclusion criteria. Included studies will be case-control studies, cohort studies, non-randomized controlled trials and randomized controlled trials (RCTs). Only articles published in peer-reviewed journals will be considered. Data from non-comparative studies, review articles, editorial letters, abstracts only, comments, and case series (fewer than ten cases) will be excluded.

Data extraction and outcomes

Data, including the first author's name, year of publication, country, type of study, age, gender (female/male), population, sample size (continuing group versus withholding group), angiotensin system inhibitors, outcomes, and follow-up duration. We will conduct our search based on the

Population, Intervention, Comparator, and Outcome (PICO) approach. In case of unclear bias domains or missing primary outcomes information, authors will be contacted by e-mail.
Population: adult patients (aged ≥ 18 years), who were chronically using ACEIs or ARBs due to chronic hypertension, undergoing scheduled or emergency non-cardiac surgery.
Intervention: Continuing to receive ACEIs or ARBs to the day of surgery (< 10 hours preoperatively)
Control group: Patients who did not receive these treatments on the day of surgery (> 10 hours preoperatively)
Outcomes: The primary outcome will be the incidence of intraoperative hypotension. Secondary outcomes will be the intraoperative use of vasoactive agent (incidence, dose of ephedrine (mg) and dose of phenylephrine (ng)), the incidence of severe hypotension, hospital length of stay (LOS), intraoperative and postoperative hypertension, the incidence of acute kidney injury (AKI), 30-day postoperative all-cause mortality and incidence of major cardio-cerebral events (MACCE).

Statistical analysis

We will use the RevMan 5.4 statistical package from the Cochrane Collaboration for meta-analysis (13). We will select the mean difference (MD) as an effective measure for continuous data. Odds ratios (OR) with 95% confidence intervals (95% CI) will be calculated for dichotomous variables. The random-effects model will be used, and the significance threshold will be fixed at 0.05. When mean and standard deviation (SD) won't be reported, they will be estimated from the provided range (R) and median based on the formula described by Hozo et al. (14).

Assessment of heterogeneity

To assess heterogeneity, three strategies will be used:

1. The Cochrane Chi² test (Q-test), the Tau² which is the variance of true effects, and 95% predictive interval (index of dispersion) to estimate the degree of heterogeneity (15). We will calculate the predictive interval using a Comprehensive Meta-analysis prediction interval. The values less than 25% indicate no heterogeneity, between 25% and 50% indicate moderate heterogeneity and more than 50% indicated substantial heterogeneity.
2. Graphical exploration with funnel plots (16).
3. Sensitivity analysis with a subgroup analysis when applicable (17). If feasible, subgroup analyses will be carried out to assess potential sources of heterogeneity.

Assessment of risk of bias

The Cochrane tool for bias assessment will be used to assess the risk of bias in RCTs (RoB2) (12). We will evaluate the bias in five distinct domains (A. randomization process, B. deviations from intended interventions, C. the bias in the measurement of outcome, D. bias to missing outcome data, and E. bias in selecting the reported results). Within each domain, one or more signaling questions will lead to judgments of "low risk of bias," "some concerns," or "high risk of bias". Regarding controlled clinical trials, the Newcastle-Ottawa Scale (NOS) will be used.

Summary of findings

Two authors independently will assess the evidence of the primary outcomes using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (18). We will consider the study limitations regarding the constancy of effect, imprecision, indirectness, and publication bias. We will assess the certainty of the evidence as high, moderate, low, or very low. If appropriate, we will consider the following criteria for upgrading the evidence: large effect, dose-response gradient, and plausible confounding effect. We will use the methods and recommendations described in sections 8.5 and 8.7 and chapters 11 and 12 of the Cochrane Handbook for Systematic Reviews of Interventions. We will use GRADEpro GDT software to summarize the findings tables. We will explain the reasons for downgrading or upgrading the included studies using footnotes and comments.

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