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Is perioperative beta-blockade effective and safe in patients undergoing noncardiac surgery?

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Abstract

Beta-blockade in patients undergoing noncardiac surgery has been widely recommended as a way to reduce cardiovascular adverse events during the perioperative period. However, studies have shown contradictory results. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified 22 systematic reviews comprising 131 studies addressing the question of this article, including 112 randomized trials. We extracted data, combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded perioperative use of beta-blockers in patients undergoing noncardiac surgery, although probably decreases the risk of myocardial infarction, increases the risk of stroke and total mortality.

Problem

The increase of catecholamines that occurs during noncardiac surgery [1] causes an elevation of blood pressure and heart rate [2],[3],[4], which contributes to the occurrence of cardiovascular adverse events. Beta-blockers suppress the effect of the rise of catecholamines, thus it is thought its administration during perioperative period could prevent these events. Initial studies showed very promising results, which led this intervention to be widely recommended for a wide range of patients undergoing noncardiac surgery. However, further trials not only cast doubts about the benefits of administering beta-blockers during the perioperative period, but also warned of possible adverse effects such as stroke, hypotension and bradycardia, among others. Furthermore, some trials on which previous recommendations were based, have been questioned due to scientific misconduct of their authors. For all these reasons, the decision whether or not to use this intervention is debated up to this day.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Perioperative use of beta-blockers in patients undergoing noncardiac surgery, although probably decreases the risk of myocardial infarction, increases the risk of stroke and total mortality.
- The existence of trials whose data are potentially fraudulent would be the main explanation for the conflicting results between earlier and subsequent trials.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 22 systematic reviews [5],[6],[7],[8],[9],[10],[11],[12],[13], [14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24], [25],[26], including 131 primary studies, of which 112 correspond to randomized controlled trials. Fifty-five randomized trials [27],[28],[29],[30],[31], [32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45], [46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59], [60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73], [74],[75],[76],[77],[78],[79],[80],[81] reported some of the outcomes of interest. This table and the overall summary are based on the latter.
What types of patients were included	The 55 trials included adult patients undergoing any type of noncardiac surgery: gastrointestinal (22%), vascular (22%), gynecological (14.6%), chest (12.2%), trauma (7.3 %), neurological (7.3%), ENT (4.9%), maxillofacial (4.9%), oral (2.4%) and emergency surgery (2.4%). All of the trials included both patients with and without previous use of beta-blockers.
What types of interventions were included	The type of beta-blocker most commonly used was metoprolol (35.1%), then esmolol (24.1%), atenolol (16.9%), labetalol (7.4%), bisoprolol (7.4%), propranolol (3.7%) and others (landiolol, nadolol and timolol, 5.4%). In all of the trials, the route of administration was preoperative oral beta-blockers, intraoperative intravenous and oral postoperative. All of the trials compared the intervention against placebo plus standard therapy.
What types of outcomes were measured	The systematic reviews identified grouped outcomes as follows: • All-cause mortality • Cardiac-cause mortality • Perioperative myocardial infarction • Myocardial ischemia • Stroke • Arrhythmias • Heart failure • Heart attack • Hospital stay • Hypotension • Bradycardia • Bronchospasm • Atrioventricular block • Acute pulmonary edema • Postoperative follow-up of patients in different trials varied from the day of hospital discharge until 30 days after surgery.

Summary of findings

The information on the effect of beta-blockers is based on the 29 randomized trials involving 12,644 patients, whose data could be included in a meta-analysis. All of the trials reported mortality [27],[28],[29],[31],[32],[33],[34],[36],[37],[38],[39],[40],[41],[42],[45],[46],[47],[52],[54],[56],[58],[59],[60],[62],[72],[74],[75],[77],[78], 26 trials reported perioperative myocardial infarction [27],[28],[29],[31],[33],[34],[39],[40],[41],[42],[45],[46],[47],[52],[54],[56],[58],[59],[60],[62],[63],[72],[74],[75],[77],[78] and 16 perioperative stroke [27],[28],[29],[40],[41],[42],[47],[56],[58],[59],[62],[72],[74],[75],[77],[78].

The summary of findings is the following:

- Perioperative use of beta-blockers in patients undergoing noncardiac surgery increases mortality. The certainty of the evidence is high.
- Perioperative use of beta-blockers in patients undergoing noncardiac surgery probably decreases the risk of myocardial infarction. The certainty of the evidence is moderate.
- Perioperative use of beta-blockers in patients undergoing noncardiac surgery increases the risk of stroke. The certainty of the evidence is high.

Beta-blockers for adults undergoing noncardiac surgery				
Patients	Adults undergoing noncardiac surgery			
Intervention	Perioperative beta-blockade			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT beta-blockade	**WITH beta-blockade**		
	Difference: patients per 1000			
Mortality	22 per 1000	28 per 1000	RR 1.25 (1.00 to 1.55)	⨁⨁⨁⨁[1] High
	Difference: 6 patients more per 1000 (Margin of error: from 0 to 12 more)			
Acute myocardial infarction	46 per 1000	32 per 1000	RR 0.71 (0.60 to 0.85)	⨁⨁⨁◯[1] Moderate
	Difference: 14 patients less per 1000 (Margin of error: 7 to 18 less)			
Stroke	4 per 1000	8 per 1000	RR 1.75 (1.10 a 2.79)	⨁⨁⨁⨁[1] High
	Difference: 4 patients more per 1000 (Margin of error: from 1 to 8 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT beta-blockers** is based on the risk in the control group of the trials. The risk **WITH beta-blockers** (and its margin of error) is calculated from the relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded because of suspected publication bias. In the case of mortality and stroke outcomes unpublished trials would probably favor the conclusion, therefore the certainty was not decreased.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to adult patients undergoing any type of noncardiac surgery, especially those with cardiovascular risk factors (such as diabetes, hypertension, peripheral arterial disease, among others) and with known coronary artery disease.
- This evidence applies to patients with or without previous use of beta-blockers.

About the outcomes included in this summary

- The outcomes selected for the summary of findings table correspond to those critical for decision-making according to the opinion of the authors of this summary. This is generally in line with the outcomes used by the identified reviews and main clinical guidelines.
- Other outcomes mentioned in the trials include adverse effects such as myocardial ischemia, bradyarrhythmia, hypotension, bronchospasm, pulmonary edema, among others. These probably are part of the pathophysiological mechanism by which the critical outcomes mentioned in this summary originate.

Balance between benefits and risks, and certainty of the evidence

- While there is a likely benefit on acute myocardial infarction in the perioperative period, this is offset by an increase in mortality and the risk of stroke.
- The balance between benefits and risk is unfavorable to the intervention.

What would patients and their doctors think about this intervention

- All patients and clinicians should lean against the use of this intervention based on the existing evidence.

Resource considerations

- Although beta-blockers are inexpensive and are widely available, they carry more risks than benefits, so a benefit/risk balance is not appropriate.

Differences between this summary and other sources

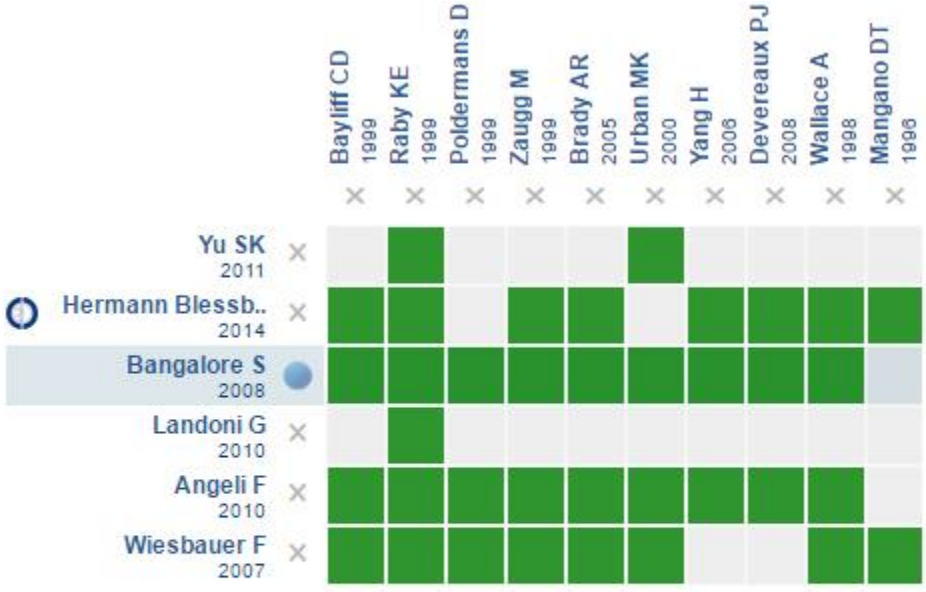
- The above findings differ with some systematic reviews included in this summary. The main explanation why some reviews concluded beta-blockade reduces the incidence of perioperative mortality and myocardial infarction is because they considered trials [44],[53] whose reliability has been questioned, based on accusations of data manipulation and omissions in reported results [82],[83]. In addition, the results were not reproduced by subsequent trials.
- Systematic reviews that take into account this fact did not include the previously mentioned trials. Their conclusions are consistent with this summary.

Could this evidence change in the future?

- The probability that the conclusions of this summary change with future information is very low, because of the certainty of existing evidence.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Perioperative beta-blockers for noncardiac surgery

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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