



Efficacy of prophylactic doses of intravenous nitroglycerin in preventing myocardial ischemia under general anesthesia: A systematic review and meta-analysis with trial sequential analysis[☆]



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ABSTRACT

Study Objective: To evaluate the efficacy of intravenous nitroglycerin (TNG) in preventing intraoperative myocardial ischemia (MI) under general anesthesia. Moreover, we analyzed the hemodynamic changes in heart rate (HR), mean blood pressure (MBP), and pulmonary capillary wedge pressure (PCWP) associated with TNG administration both before and after the induction of anesthesia.

Design: Meta-analysis.

Setting: Operating room, cardiac surgery or non-cardiac surgery, all surgeries were elective measurements.

We performed a computerized search of articles on PubMed, Scopus, and the Cochrane Central Register of Controlled Trials. Meta-analysis was performed using Review Manager. The data from the individual trials were combined using a random-effects model to calculate either the pooled relative risk (RR) or the weighted mean difference (WMD) with 95% confidence interval (CI). We conducted trial sequential analysis (TSA). The primary outcome was the incidence of MI and the secondary outcomes were hemodynamic changes (HR, MBP, and PCWP).

Main Results: Using electronic databases, we selected 10 trials with a total of 353 patients for our review. Prophylactic intravenous TNG did not significantly decrease the incidence of MI (RR = 0.61; CI, 0.33 to 1.13; P = 0.12; I² = 55). TSA corrected the CI to 0.05 to 7.39 and showed that 9.5% of the required information size was achieved. In terms of hemodynamic changes, intravenous TNG significantly reduced MBP in comparison with the placebo (MBP pre-induction: WMD = -7.27; 95% CI -14.2 to -0.33; P = 0.04; I² = 97%; MBP post-induction: WMD = -5.13; 95% CI -9.17 to -1.09; P = 0.01; I² = 73%).

Conclusions: Our analyses showed that prophylactic intravenous TNG does not reduce the incidence of intraoperative MI. Moreover, TSA suggests that further studies are necessary to confirm the results (GRADE: very low). Prophylactic doses of intravenous TNG significantly reduced the MBP both pre and post anesthesia induction (GRADE: very low).

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[☆] We have no conflicts of interest.

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Contents

1.	Introduction	17
2.	Materials and methods	17
2.1.	Inclusion and exclusion criteria	17
2.1.1.	Search strategy	17
2.2.	Selection of included studies	18
2.2.1.	Data extraction	18
2.3.	Critical appraisal of study quality	18
2.3.1.	Risk of bias assessment	18
2.3.2.	Quality of evidence assessment	18
2.4.	Data synthesis and analysis	18
3.	Results	18
3.1.	Characteristics of studies included in the meta-analysis	18
3.2.	Result of the meta-analysis	18
4.	Discussion	20
4.1.	Explanation of results	20
4.2.	Limitations of the meta-analysis	21
4.3.	Conclusions	21
	References	21

1. Introduction

Myocardial ischemia (MI) is one of the most frequent causes of morbidity and mortality in the perioperative setting. Perioperative cardiac complications are a concern for the 230 million patients worldwide who undergo surgery each year [1]. Postoperatively, 2% of these patients experience major cardiac complications [2] and 8% develop signs of substantial myocardial injury [3]. Preventing perioperative MI is therefore critically important.

Nitroglycerin (TNG) reverses MI intraoperatively by improving coronary arterial blood flow [4]. However, intraoperative prophylactic use of TNG in high-risk patients may have negligible benefits or may even be harmful, leading to cardiovascular decompensation through decreased preload [5]. Previous observational studies have suggested that prophylactic intravenous TNG is effective for reducing the incidence of intraoperative MI [6,7], but the evidence from randomized controlled trials (RCTs) is less convincing [8–11]. In a meta-analysis by Divatia et al. [12], prophylactic intravenous TNG did not reduce the incidence of intraoperative MI. However, three subsequently published RCTs gave conflicting results [7,11,13]. A recent meta-analysis of nitrates for prevention of cardiac morbidity in patients undergoing non-cardiac surgery was published in 2016 [14]. The analysis showed that administration of TNG did not reduce the incidence of MI. However, there were only four studies in this meta-analysis, which included surgery under epidural anesthesia. Thus, the preventive effect of TNG for MI was unclear. For these reasons, the efficacy of prophylactic TNG for the prevention of intraoperative MI remains controversial.

Several studies suggest that TNG administered as a prophylactic against MI caused hemodynamic changes (hypotension, bradycardia, and decreased pulmonary capillary wedge pressure [PCWP]) that may have led to an increased incidence of intraoperative MI. Prophylactic intravenous TNG was suggested to alter hemodynamic responses intraoperatively [15,16], although the results of the previously mentioned RCTs were not as convincing [6,10].

Against this background, we conducted a systematic review and meta-analysis of RCTs to evaluate the efficacy of intravenous TNG in preventing intraoperative MI under general anesthesia. Moreover, we analyzed the hemodynamic changes in heart rate (HR), mean blood pressure (MBP), and PCWP associated with TNG administration both before and after the induction of anesthesia.

2. Materials and methods

This quantitative systematic review was performed according to the criteria of the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) statement [17]. We specified and documented the analysis methods and inclusion criteria used in this meta-analysis and registered the study protocol in the UMIN Clinical Trials Registry (registration number: UMIN 000021467; principal investigator: H. Hoshijima; date of registration: 14 March 2016).

2.1. Inclusion and exclusion criteria

Inclusion and exclusion criteria were established a priori. This review included all RCTs investigating the incidence of MI associated with TNG compared with placebo in elective cardiac or non-cardiac surgical patients under general anesthesia. We excluded pediatric patients, observational studies, reviews, case reports, animal studies, and studies published as an abstract and did not restrict the articles due to language or publication type.

The primary outcome of this meta-analysis was the effect of TNG administration compared with control to prevent MI under general anesthesia. The secondary outcomes were HR, MBP, and PCWP as indicators of whether the administration of TNG reduced preload.

2.1.1. Search strategy

We performed a comprehensive literature search with the aid of PubMed, Scopus, and the Cochrane Central Register of Controlled Trials. The following strategy, which combined free text and Medical Subject Headings (MeSH) terms, was devised for the PubMed search: (((("nitroglycerin"[MeSH Terms] OR "nitroglycerin"[All Fields]) AND ("myocardial ischaemia"[All Fields] OR "myocardial ischemia"[MeSH Terms] OR "myocardial"[All Fields] AND "ischemia"[All Fields]) OR "myocardial ischemia"[All Fields] OR "coronary artery disease"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields] OR ("myocardial"[All Fields] AND "ischemia"[All Fields]))) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields])) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields])). We started the literature search on March 15, 2016. The references of the reviews and reports found were also searched manually with the most recent search being performed in April 2016.

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