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The Cardiac Protective Effects of Calcium Channel Blockers and Nitroglycerin in Cardiac Surgery: A Meta-analysis of Random Controlled Trials

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Abstract: Background: Myocardial ischemia is one of the most common postoperative complications in Cardiac surgery. Calcium channel blockers and nitroglycerin have some degree of protection against myocardial ischemia and are widely used in cardiac surgery. To compare the effects of calcium channel blockers and nitroglycerin on blood pressure, heart rate, and myocardial protection, a meta-analysis was conducted. Methods: The PubMed (Medline), Embase, and Cochrane Library databases were systematically searched, with the search period from database creation to April 2024. The study type was randomized controlled trial (RCT), and the comparisons were made between calcium channel blockers and nitroglycerin for myocardial protection during the perioperative period of cardiac surgery. Continuous variables were evaluated using the combined weighted mean difference (WMD) and 95% confidence interval (CI) or the risk ratio (RR) and 95% confidence interval. Results: A total of six randomized controlled trials (RCTs) were included, with a total of 608 patients. There was no statistically significant difference in postoperative systolic blood pressure between the two groups (WMD = 2.66, 95% CI: - 1.70 - 7.02, P = 0.23; heterogeneity test: P = 0.002, I^2 = 70%). There was a statistically significant difference in postoperative heart rate (WMD = -2.53, 95% CI: -4.71 - -0.36, P = 0.02; heterogeneity test: P = 0.05, I^2 = 52%). There was no statistically significant difference in the incidence of myocardial ischemia between the two groups (RR = 1.13, 95% CI: 0.88 - 1.45, P = 0.33; heterogeneity test: P = 0.96, I^2 = 0%). Conclusion: The meta-analysis suggests that calcium channel blockers and nitroglycerin do not have a significant difference in their effects on myocardial protection, but the nitroglycerin group has a higher heart rate.

Keywords: Calcium Channel Blockers; Nitroglycerin; Cardiac Surgery; Cardiac Protective Effects.

1. Introduction

Myocardial ischemia is one of the most prevalent complications during the perioperative period and represents a significant cause of mortality among surgical patients [1]. Among approximately 230 million surgical patients, 8% experience complications related to cardiac injury[2; 3]. Patients undergoing cardiac surgery are particularly vulnerable to myocardial ischemia due to compromised cardiac function and underlying cardiovascular conditions, which exacerbate hemodynamic fluctuations during procedures. To mitigate the risk of myocardial ischemia, anesthesiologists primarily employ strategies such as maintaining hemodynamic stability, minimizing the use of coronary vasoconstrictors, ensuring adequate oxygen supply, preventing tachycardia, and administering vasodilators that target coronary arteries.

Notably, nitroglycerin and calcium channel blockers (CCBs) are prominent agents in inducing coronary artery vasodilation. Nitroglycerin not only dilates the venous system to reduce preload but also expands coronary arteries—an effect beneficial for preventing myocardial ischemia[4]. CCBs inhibit extracellular calcium influx through voltage-gated L-type calcium channels; this blockade prevents calcium entry into vascular smooth muscle cells leading to relaxation and subsequent vascular dilation along with blood pressure reduction. Additionally, CCBs diminish myocardial contractility while reducing sinus tachycardia rates and atrioventricular conduction velocity thereby slowing heart rate[5]. Based on their distinct binding sites on L-type calcium channels, CCBs can be categorized into dihydropyridines (e.g., nifedipine and amlodipine) and non-dihydropyridines (e.g., diltiazem and verapamil)[6]. Given their ability to lower heart rate while promoting coronary artery dilation, CCBs confer protective effects on cardiac function.

Hiroshi et al. 's meta-analysis suggested that prophylactic use of nitroglycerin in patients undergoing noncardiac surgery did not reduce the incidence of intraoperative myocardial infarction[1]. In patients undergoing cardiac surgery, the question of whether intraoperative nitroglycerin or calcium-channel blockers have myocardial protection and whether there is a difference between the two agents remains unanswered. In the perioperative management of cardiac surgery, it is possible to use calcium channel blockers and nitroglycerin to control acute hypertension or myocardial protection. Both drugs are widely used in clinical practice, which drug is more obvious myocardial protection and hemodynamic stability is a question that needs to be determined by research. The results of clinical studies are different, so it is necessary to conduct a meta-analysis to integrate relevant studies. We compared changes in blood pressure and heart rate after cardiac surgery, the incidence of myocardial ischemia, and the total ST-segment change during the perioperative period to compare myocardial protection between the two groups.

2. Materials and Methods

2.1. Inclusion Criteria

2.1.1. Type of Research

Published or ongoing randomized controlled trials (RCTs) with complete data.

2.1.2. The Objectives of Studies

Cardiac surgery; Use of calcium channel blockers (no limited type) and nitroglycerin; Adults: >18 years old and not limited to gender; Use of both types of drugs before, during, or after surgery.

2.1.3. Types of Interventions

Calcium channel blockers (clovedipine, diltiazem, verapamil, nicardipine, etc.); nitroglycerin.

2.1.4. Outcome Indicators

Postoperative systolic blood pressure, postoperative heart rate, ST-segment elevation, and incidence of myocardial ischemia.

2.2. Exclusion Criteria

(1) non-RCTs; (2) non-cardiac surgery; (3) not in Chinese or English; (4) The full text was not available; (4) case-control and cohort studies; (5) case reports; (6) non-myocardial protection; (7) non-adult surgery; (8) excluding calcium channel blockers and nitroglycerin; (9) systematic reviews.

2.3. Search Strategy

2.3.1. Computer Search

Medline (Pubmed), Cochrane Library, and Embase were mainly searched. The search strategy mainly adopts the method of subject terms plus free words. The search time is up to April 2024, and regular searches were conducted to check for updates on relevant studies weekly. The search strategy for Pubmed was presented in Box 1. Similar search strategies were formulated for the other two databases based on this.

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#1 ((((((((((Cardiac Surgical Procedures[MeSH Terms]) OR (Procedure, Cardiac Surgical)) OR (Procedures, Cardiac Surgical)) OR (Surgical Procedure, Cardiac)) OR (Surgical Procedures, Cardiac)) OR (   Surgical Procedures, Heart)) OR (Cardiac Surgical Procedure)) OR (Heart Surgical Procedures)) OR (Procedure, Heart Surgical)) OR (Procedures, Heart Surgical)) OR (Surgical Procedure, Heart)) OR (Heart Surgical Procedure)
#2 (((((((((((Blockers, Calcium Channel Channel Blockers, Calcium Calcium Channel Blocking Drugs Calcium Channel Antagonists Antagonists, Calcium Channel Calcium Antagonists, Exogenous Antagonists, Exogenous Calcium Exogenous Calcium Inhibitors Exogenous Calcium Antagonists Exogenous Calcium Blockaders Calcium Blockaders, Exogenous Calcium Inhibitors, Exogenous[MeSH Terms]) OR (Blockers, Calcium Channel)) OR (Channel Blockers, Calcium)) OR (Calcium Channel Blocking Drugs)) OR (Calcium Channel Antagonists)) OR (Antagonists, Calcium Channel)) OR (Calcium Antagonists, Exogenous)) OR (Antagonists, Exogenous Calcium)) OR (Antagonists, Exogenous Calcium)) OR (Exogenous Calcium Antagonists)) OR (Exogenous Calcium Blockaders)) OR (Calcium Blockaders, Exogenous)) OR (Calcium Inhibitors, Exogenous)
#3 (((((((((((((((((((((((((((((Nitroglycerin[MeSH Terms]) OR (Glyceryl Trinitrate)) OR (Trinitrate, Glyceryl)) OR (Nitrolan)) OR (Nitrospan)) OR (Nitrostat)) OR (Perlinganit)) OR (Nitrong)) OR (Susadrin)) OR (Sustac)) OR (Sustak)) OR (Sustonit)) OR (Transderm Nitro)) OR (Nitroglyn)) OR (Trinitrin)) OR (Trinitrolong)) OR (Anginine)) OR (Dynamite)) OR (Gilustenon)) OR (Nitrangin)) OR (Nitro-Bid)) OR (Nitro Bid)) OR (NitroBid)) OR (Nitro-Dur)) OR (Nitro Dur)) OR (NitroDur)) OR (Nitrocard)) OR (Nitroderm)) OR (Nitroderm TTS)) OR (Nitrol)) OR (Tridil)
#4((((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])
#5 (animals[MeSH Terms]) NOT (humans[MeSH Terms])
#6 #4 AND #5
#7 #1 AND #2 AND #3 AND #6
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Box 1. Search strategy for Pubmed.

2.3.2. Manual Search

References of relevant systematic reviews, included studies, and case reports were searched on the Web of Science or Pubmed.

2.4. Literature Screening and Data Extraction

2.4.1. Literature Screening

All the literature obtained through database and manual retrieval were initially screened by two authors of the systematic review by reading the titles and abstracts. The screening processes of the two authors were independent of each other. When there was a discrepancy in the exclusion or inclusion of the literature between the two authors, they would have a joint discussion to reach a decision. When the discussion failed to resolve the disagreement, the final decision would be made by the third author. After the initial screening, further screening was conducted by reading the full text. Literature for which the full text could not be obtained and remained unavailable despite efforts such as contacting the authors would be excluded.

2.4.2. Data Extraction

Data extraction was performed independently by two authors of the systematic review. The following informations were extracted: (1) Basic information: the first author's name; year of publication; number of patients; age; study region; and design of the included trials. (2) Information related to quality assessment: random sequence generation, concealment of allocation, blinding of participants and researchers, blinded measurement of outcomes, incomplete data on outcomes, selective reporting, and other biases. (3) Data related to the outcome indicators: hemodynamic parameters (blood pressure, heart rate, central venous pressure, pulse oxygen saturation); electrocardiographic changes (ST-segment elevation value, duration of elevation, specific details of arrhythmia, other electrocardiographic changes related to myocardial ischemia).

2.5. Risk of Bias Assessment of Included Studies

According to the Cochrane Handbook of Systematic Review of Interventions, the risk of bias was evaluated from seven perspectives: random sequence generation, concealment of allocation, blinding of participants and researchers, blinded measurement of outcomes, incomplete data on outcomes, selective reporting, and other biases. The quality bias risk of included studies was evaluated using Review Manager 5.3.

2.6. Statistical Analysis

A systematic review was conducted using Review Manager 5.3. Mean difference (MD) and 95% confidence interval (CI) were used for continuous variables. Risk ratio (RR) and 95% CI were used for dichotomous variables. Heterogeneity was evaluated using the P value and I^2 value of the chi-square test (considered to be significant heterogeneity: $P < 0.05$ or $I^2 > 50\%$). The significance level for meta-analysis was α=0.05. When $P>=0.05$, it was considered that there was no statistically significant difference, and when $P<0.05$, it was considered that there was a statistically significant difference.

3. Results

3.1. Literature Screening Process and Results

A total of 510 articles were retrieved from Pubmed (Medline), 610 articles from Embase, 248 articles from the Cochrane Library, and 15 articles were retrieved manually. After independent screening by two systematic review authors, 7 RCTS were finally included[7; 8; 9; 10; 11; 12; 13].

A total of 608 subjects were included. The specific screening process and results were shown in Fig. 1.

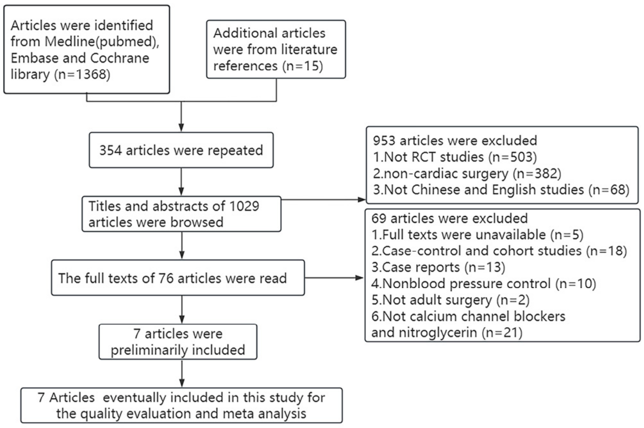

Figure 1. Flow chart of the literature selection process and results.

3.2. Basic Characteristics of Included Studies and Quality Bias Risk Assessment Results

Seven included studies were published between 1997 and 2017, with a total number of 608 patients. The patients in 2 of the studies were from the United States, 1 study from China, 1 study from Japan, 1 study from Austria, 1 study from India, and 1 study from Germany. All the seven included studies were RCTs, and the age of patients was mainly distributed between 52 and 64 years old. Calcium channel blockers included nicorandil, diltiazem, and nicardipine. Detailed information on basic characteristics was provided in Table 1. The quality risk assessment was shown in Fig. 2 and Fig. 3.

Table 1. Basic characteristics of the included studies. NIC: Nicorandil; NTG: Nitroglycerin; DLZ: Diltiazem; PPCI: Primary percutaneous coronary intervention; PTCA: Percutaneous Transluminal Coronary Angioplasty; CABG: Coronary Artery Bypass Grafting

Authors, years	intervention	type of Patients	Number	Country	Design	Age
Wang 2017	NIC/NTG	PPCI	105	China	RCT	NIC 63.0 NTG 61.6
Naoki 2002	NIC/NTG	PTCA	22	Japan	RCT	NIC 62.0 SNP 64.0
Lassnigg 2008	DLZ/NTG	CABG	40	Austria	RCT	DLZ 63.0 NTG 63.0
Hirnle 2000	DLZ/NTG	CABG	49	USA	RCT	DLZ 57.1 NTG 56.5
Apostolidou 1999	NIC/NTG	CABG	60	USA	RCT	NIC 59.0 NTG 64.0
Malhotra 1997	DLZ/NTG	CABG	71	India	RCT	DLZ 52.0 NTG 54.0
Keilich 1997	DLZ/NTG	CABG	211	Germany	RCT	DLZ 62.0 NIC 62.0

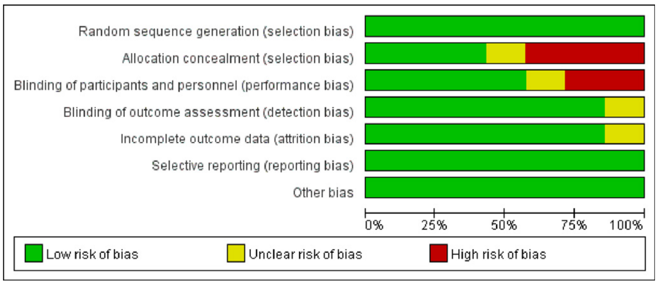

Figure 2. Risk of bias plot.

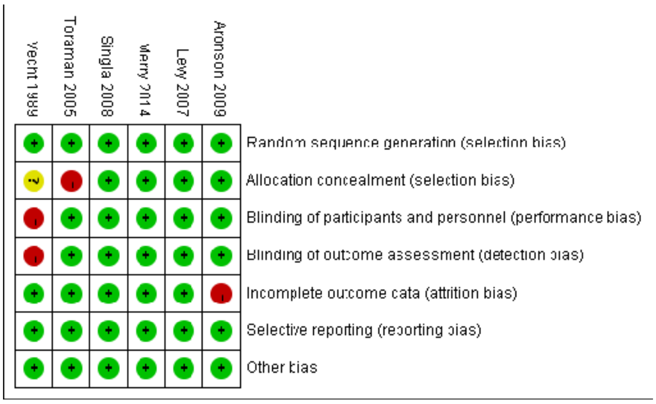

Figure 3. Summary of the risk of bias.

3.3. Results of Meta-analysis

3.3.1. Postoperative Systolic Blood Pressure

Seven studies were included in the analysis[7; 8; 9; 10; 11; 12; 13], with a total of 608 patients. The heterogeneity test showed P = 0.002, I^2 = 70% (Fig. 4), indicating significant heterogeneity, so a random effects model was used. The meta-analysis based on the random effects model showed that calcium channel blockers had slightly higher postoperative blood pressure than nitroglycerin, but the difference was not statistically significant: MD = 2.66, 95% CI (-1.70-7.02), P = 0.23 (Fig. 4). Despite the significant heterogeneity, the sensitivity analysis by excluding studies one by one showed no significant change in heterogeneity. Subgroup analysis by publication year (before 2000 and after 2000) showed that the heterogeneity was reduced in studies published between 2000 and 2017: I^2 = 34%, P = 0.21. This suggests that the source of heterogeneity may be the publication year. The subgroup analysis results are shown in Fig. 5.

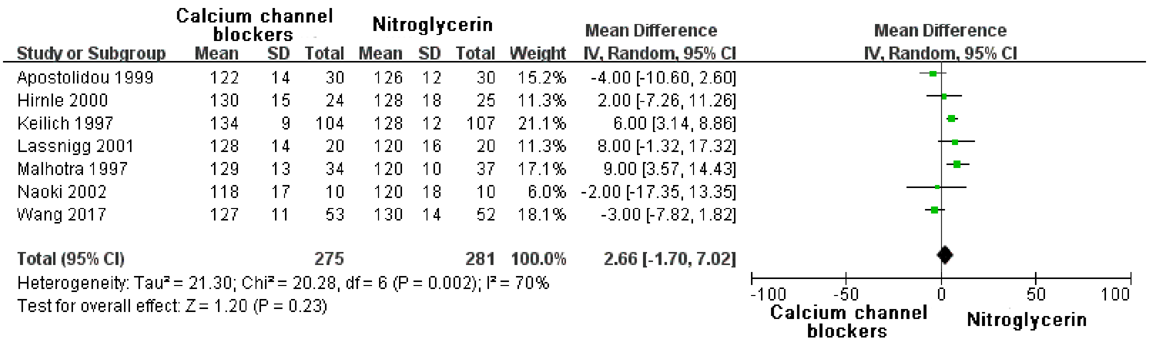

Figure 4. Meta-analysis of postoperative systolic blood pressure in cardiac protective effects with calcium channel blockers versus nitroglycerin.

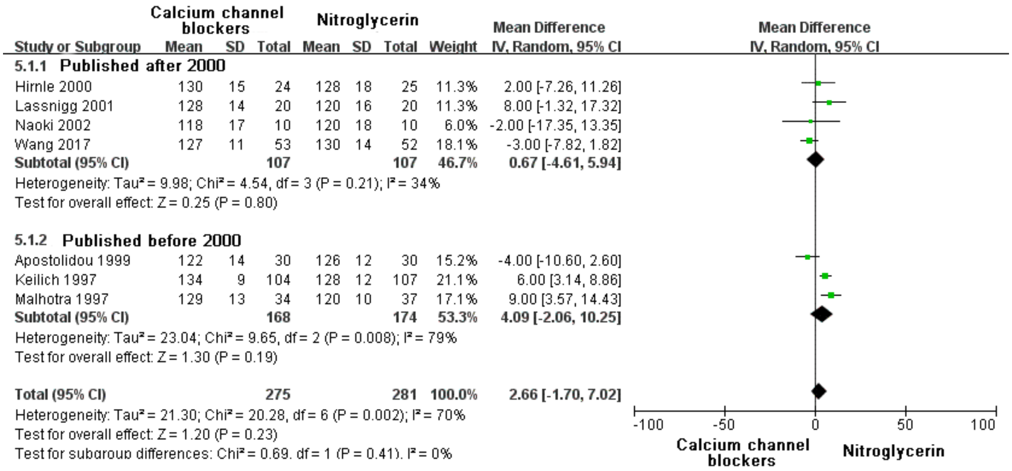

Figure 5. Results of subgroup analyses according to year of publication

3.3.2. Postoperative Heart Rate

Seven studies were included in the analysis[7; 8; 9; 10; 11; 12; 13], with a total of 608 patients. The heterogeneity test showed P = 0.05, I^2 = 52%, indicating significant heterogeneity, so a random effects model was used. The meta-analysis based on the random effects model showed that the postoperative heart rate was higher in the nitroglycerin group than in the calcium channel blocker group, and the difference was statistically significant: MD = -2.53, 95% CI (-4.71, -0.36), P = 0.02. Despite the significant heterogeneity, the sensitivity analysis by excluding studies one by one showed no significant change in heterogeneity.

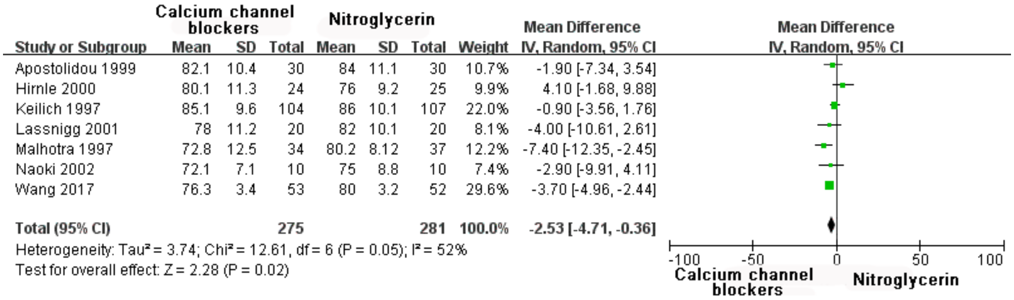

Figure 6. Meta-analysis of postoperative heart rate in cardiac protective effects with calcium channel blockers versus nitroglycerin.

3.3.3. ST-segment Elevation Value

Seven studies were included [7-13], involving a total of 608 patients. The heterogeneity test: P = 0.03, I^2 = 58%, with significant heterogeneity, thus a random effects model was adopted. The meta-analysis based on the random effects model indicated that there was no statistically significant difference in the ST segment elevation value between the two groups: MD = -0.01, 95% CI (-0.03, 0.02), P = 0.61 (Fig. 7). Due to the obvious heterogeneity, a sensitivity analysis was conducted by eliminating studies one by one, and no significant change in heterogeneity was found.

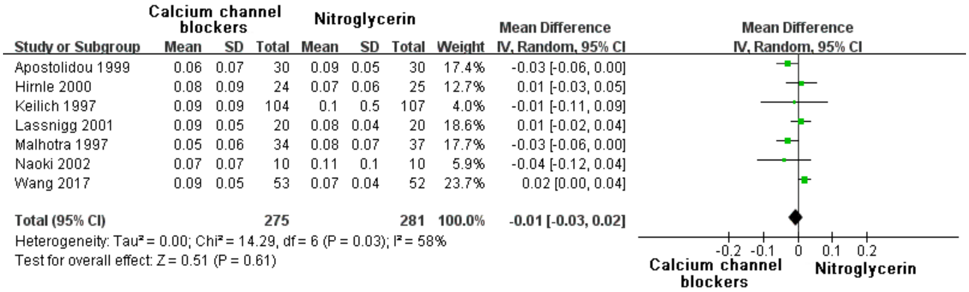

Figure 7. Meta-analysis of ST-segment elevation value in cardiac protective effects with calcium channel blockers versus nitroglycerin

3.3.4. Incidence of Myocardial Ischemia.

Seven studies were included [7-13], involving a total of 608 patients. The heterogeneity test: P = 0.96, I^2 = 0%, with no significant heterogeneity (Fig. 8), thus a fixed effect model was employed. The meta-analysis based on the fixed effects model demonstrated that there was no statistically significant difference in the incidence of myocardial ischemia between the two groups: RR = 1.13, 95% CI (0.88, 1.45), P = 0.33 (Fig. 8).

4. Discussion

The findings of the meta-analysis indicated no statistically significant difference in the effects of calcium channel blockers and nitroglycerin on postoperative systolic blood pressure during cardiac surgery. This suggests that both interventions exert similar influences on blood pressure, with each capable of achieving a degree of reduction. Furthermore, the meta-analysis concerning postoperative heart rate revealed that patients in the nitroglycerin group exhibited a higher heart rate, with this difference reaching statistical significance.

Study or Subgroup	Calcium channel blockers Events	Calcium channel blockers Total	Nitroglycerin Events	Nitroglycerin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Apostolidou 1999	12	30	9	30	11.2%	1.33 [0.66, 2.69]
Hirnle 2000	9	24	8	25	9.8%	1.17 [0.54, 2.53]
Keilich 1997	32	104	28	107	34.4%	1.18 [0.77, 1.81]
Lassnigg 2001	8	20	6	20	7.5%	1.33 [0.57, 3.14]
Malhotra 1997	8	34	7	37	8.3%	1.24 [0.51, 3.06]
Naoki 2002	2	10	3	10	3.7%	0.67 [0.14, 3.17]
Wang 2017	19	53	20	52	25.1%	0.93 [0.57, 1.53]
Total (95% CI)		**275**		**281**	**100.0%**	**1.13 [0.88, 1.45]**
Total events	90		81			

Heterogeneity: Chi² = 1.46, df = 6 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

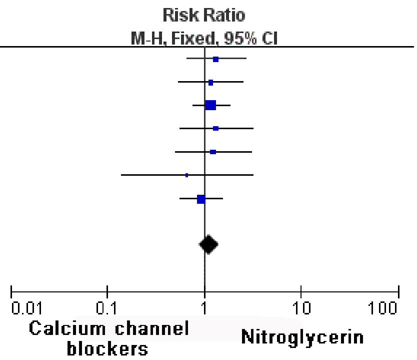

Figure 8. Meta-analysis of incidence of myocardial ischemia in cardiac protective effects with calcium channel blockers versus nitroglycerin

Nitroglycerin primarily induces venous dilation and lowers blood pressure by decreasing preload, which consequently leads to a reflexive increase in heart rate[14]. However, this elevation in heart rate shortens diastolic duration, potentially compromising myocardial perfusion since coronary artery opening predominantly occurs during diastole. Two principal theories have been proposed regarding the myocardial protective effect of nitroglycerin[15]. The first posits that nitrates positively influence myocardial oxygen balance through their impact on systemic hemodynamics—specifically via reduced venous return, diminished left ventricular wall tension, and slight afterload reduction—thereby lowering myocardial oxygen consumption[16] [16]. The second theory asserts that the essence of the nitroglycerin effect lies in its direct dilation of coronary arteries and subsequent redistribution of blood flow to the myocardium at risk due to coronary artery stenosis[17]. Calcium channel blockers target L-type calcium channels to decrease sinus pacing rates and atrioventricular conduction velocity, thereby reducing heart rate.

Indicators such as ST-segment elevation or high-pointed T waves observed on electrocardiograms are effective markers for suggesting myocardial ischemia; among these indicators, ST-segment elevation is most prevalent. All studies included in our research assessed total ST-segment elevation values during perioperative periods without revealing any statistically significant differences between groups; thus indicating minimal disparity between their effects on myocardial protection against ischemia.

Among seven studies analyzed for incidence rates of myocardial ischemia—determined through measurements of cardiac enzymes (CK-MB, troponin I, troponin T) alongside recorded instances indicative of ST-segment elevation—we found no statistically significant differences between groups according to meta-analytic results. Through our analysis encompassing both incidence rates and ST-segment elevations, we infer negligible differences exist regarding myocardial protective efficacy between calcium channel blockers and nitroglycerin. Nonetheless, existing literature indicates that nitroglycerin may induce reflex tachycardia postoperatively—a factor potentially detrimental to adequate myocardial perfusion during cardiac surgeries.

The meta-analysis of postoperative systolic blood pressure demonstrated considerable heterogeneity (P = 0.002; I^2 = 70%). A sensitivity analysis was performed by sequentially excluding individual studies; however, heterogeneity remained largely unchanged signifying individual study contributions were not responsible for variability observed within data sets. Heterogeneity assessments across different publication years revealed notable reductions: specifically those published from 2000-2017 showed decreased heterogeneity (I^2 = 34%; P = 0.21), implying temporal variations might contribute significantly towards overall heterogeneity attributed within analyses conducted herein.

The number of relevant literature included in this study is limited, and there are fewer relevant studies in the past five years. The total number of patients included is also relatively insufficient, which may lead to suboptimal test performance. Due to language limitations, this study only includes Chinese and English literature, which may result in language and regional bias. In addition, the types of cardiac surgery included coronary artery interventional surgery, which may have significant differences with open-chest surgery. Due to the limited number of included studies, this study was unable to conduct subgroup analysis by different calcium channel blockers.

5. Conclusion

Overall, the meta-analysis suggests that there is no obvious difference in the myocardial protective effect between calcium channel blockers and nitroglycerin, but the heart rate in the nitroglycerin group is higher.

Acknowledgments

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