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Efficacy of Clonidine for Prevention of Perioperative Myocardial Ischemia

A Critical Appraisal and Meta-analysis of the Literature

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Background: **There is a belief that clonidine may be effective in reducing perioperative myocardial ischemic events, although the results of several trials are conflicting. The aim of the current study was to provide a systematic review of randomized controlled trials that tested the efficacy of clonidine in this regard.**

Methods: **Data was collected from a MEDLINE search of English-language studies published from 1980 to 1999 and a manual search of bibliographies from retrieved articles. A total of 28 studies were assessed. According to the selection criteria (study design, population, intervention, and outcome) and a quality scoring system, seven studies were finally included in the meta-analysis. After homogeneity was established by $\dot{Q}$ value, the data were then combined using the fixed-effects model. The pooled odds ratio was calculated. A subgroup analysis based on the types of surgery and administration route was also performed to qualify the results. The results were expressed as odds ratio and 95% confidence interval.**

Results: **Heterogeneity of outcome data was negative in the trials. The pooled odds ratio was 0.49 (95% confidence interval 0.34–0.71). In the subgroup analysis, clonidine reduced the incidence of myocardial ischemia in patients undergoing cardiac and noncardiac surgery. Rates of bradycardia were similar in clonidine and placebo groups.**

Conclusion: **The meta-analysis suggests that perioperative clonidine reduces cardiac ischemic episodes in patients with known, or at risk of, coronary arterial disease without increasing the incidence of bradycardia. Therefore, these findings strongly justify planning and execution of a definitive study seeking the benefits of clonidine.**

HYPERTENSION and tachycardia, accompanied by increased sympathetic nervous system activity, may lead to an imbalance between myocardial oxygen demand and supply. This may lead to myocardial ischemia in patients who have coronary artery disease or in those with risk of ischemic heart diseases.[1,2] Myocardial ischemia increases the risk of myocardial infarction, which is a serious perioperative complication with an associated mortality rate of 17–42%,[3] and may compromise patients' functional status.[1,4]

Clonidine, a central acting α_2-agonist, was first introduced into clinical practice as an antihypertensive medication.[4,5] The drug was recently used for anesthetic premedication, providing sedative, anxiolytic, and analgesic effects.[6–11] Because clonidine attenuates hypertension, tachycardia, and norepinephrine release in response to stress induced by anesthetic and surgical procedures,[6–10,12] clonidine premedication may prevent perioperative myocardial ischemia by improving myocardial oxygen balance. However, there is controversy in the literature regarding the prophylactic effect of clonidine premedication on myocardial ischemic episodes. Therefore, we conducted a systematic review to determine whether clonidine premedication can reduce the occurrence of perioperative myocardial ischemia, a surrogate marker for myocardial infarction and cardiac death.

Methods

Searching

This work was conducted according to Quality of Reporting of Meta-analyses (QUOROM) recommendations for improving quality of meta-analysis.[13] We searched MEDLINE (from 1980 to 1999) using the following medical subject heading terms as the key and text words: (1) clonidine; (2) myocardial ischemia, coronary disease, myocardial infarction, coronary arteriosclerosis, coronary thrombosis, or angina pectoris; and (3) prospective studies, clinical trials, randomized controlled trials, controlled clinical trials, or intervention studies. Only English-language articles were searched. Personal files and the reference lists of all studies and review articles primarily retrieved were evaluated to search for other relevant studies. No attempt was made to obtain results of unpublished studies. Finally, we sent a list of relevant articles to the first authors of each study included in this systematic review to ask whether they knew of any other relevant published studies in this field.

Selection and Validity Assessment

Two investigators independently reviewed the titles and abstracts of all relevant articles; all potentially relevant studies were retrieved. Inclusion criteria were applied to the full manuscripts by three of the authors

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independently, two of whom were blinded to the journal in which the paper was published, the authors, the institution, and the magnitude and direction of the results; relevant information throughout the manuscript of each study was whited out. When disagreement occurred, the reviewers discussed the discrepancy, and it was resolved by consensus. Selection criteria to identify studies included (1) study design (controlled clinical trial); (2) population (adult patients undergoing surgery during general anesthesia); (3) intervention (treatment with perioperative clonidine); and (4) outcome (mortality rate, myocardial ischemia, or myocardial infarction).

Assessment of Methodological Quality

We used the methodological quality scoring system established by Cronin *et al.*[14] to critically appraise each of the primary studies. Two of the authors applied these criteria independently. To avoid bias in assessments, one reviewer was blinded to the journal, authors, institution, and the magnitude and direction of the results. We measured agreement among reviewers using the κ statistic with quadratic weights. Disagreements among reviewers were resolved by discussion and consensus. Studies with low-quality scores (4 points or lower) were excluded from further analysis.

Data Abstraction

Two investigators extracted data. Their disagreements were resolved by consensus. One reviewer was blinded to the journal, authors, and institution. Information in the Methods and the Results sections was abstracted separately. We recorded data in terms of the number of patients rather than the number of events. Finally, we sent a letter of inquiry to the first author of each study included in this systematic review to obtain missing data.

Statistical Analysis

The data were then combined using the fixed-effects model. Homogeneity was assessed from the $\dot{Q}$ value. The $\dot{Q}$ value was calculated using the following formula:

$$\dot{Q} = \text{sum}[\text{weight}i \times (\ln\text{OR}s - \ln\text{OR}i)^2],$$

where OR*s* is the odds ratio of summary. We planned to identify the reason for the heterogeneity when we found significant heterogeneity among studies. *A priori*, we decided to separately analyze the data according to other medication that causes bradycardia (β-adrenoceptor antagonists or calcium channel blockers) and the type of the surgery (cardiac or noncardiac surgery). The results were expressed graphically as the odds ratio and 95% confidence interval.

Results

Trial Flow

Figure 1 provides a meta-analysis profile summarizing trial flow. Our search retrieved 28 relevant trials, of which eight met the inclusion criteria (Appendix). The correlation between observers for the methodological quality of the articles was high (κ = 0.73–1). One study was excluded because of a low-quality score (score = 4).[15]

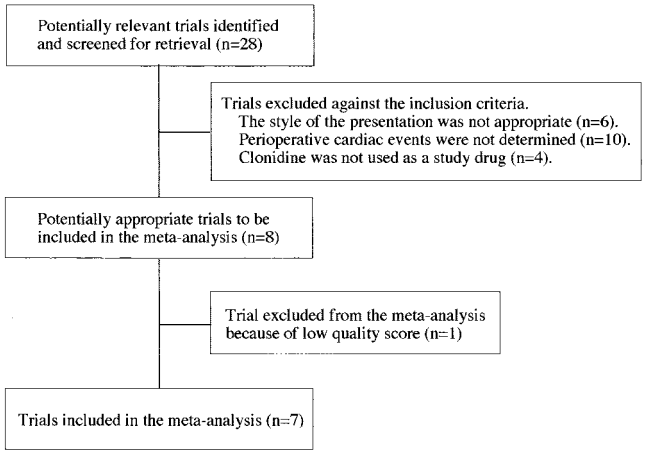

Fig. 1. Meta-analysis flow diagram.

Study Characteristics

Table 1 summarizes characteristics of seven studies included in our meta-analysis.[16–22] Mean age of each participant ranged between 59 and 70 yr. A total of 664 patients in seven studies was used. Five reports dealt with patients undergoing coronary artery bypass grafting (CABG), and patients in two reports underwent noncardiac surgery.

Quantitative Data Synthesis

Table 2 summarizes the outcome data. Heterogeneity of the data was negative ($\dot{Q}$ values: 6.45; $P \leq 0.05$). Figure 2 shows that the pooled odds of myocardial ischemia in patients receiving clonidine was lower than in those receiving placebo (odds ratio = 0.49, 95% confidence interval = 0.34–0.71). Heterogeneity of the data for subgroup analysis was negative ($\dot{Q}$ values: 5.20, 1.19, 4.29, and 2.03 for CABG, noncardiac, oral, and intravenous; $P \leq 0.05$). As shown in Figure 2, the pooled odds ratios were significant in the two subgroups of patients undergoing CABG (odds ratio = 0.52, 95% confidence interval = 0.29–0.93) or noncardiac surgery (odds ratio = 0.47, 95% confidence interval = 0.29–0.77). Figure 3 indicates that the incidence of myocardial ischemia was lower in patients who received clonidine orally (odds ratio = 0.48, 95% confidence interval = 0.32–0.71), not intravenously (odds ratio = 0.60, 95% confidence interval = 0.19–1.84). The adverse side effects were not reported in all of the studies. Bradycardia and hypotension were separately reported in five and three studies, respectively. Table 3 gives the odds ratios of the untoward reaction. There was no relation between development of bradycardia and the use of clonidine. Hypotension data could not be combined because of the heterogeneity ($\dot{Q}$ value = 6.57).

Table 1. Summary of Characteristics in Studies Included for the Meta-analysis

Author[Ref.]	No. of Patients	Observation Period (Until)	Clonidine Dose (Route)	Administration Timing
CABG				
Dorman[14]	43	2 hr after CPB	5 μg/kg, twice (oral)	−90 min and 10 min before CPB
Myles[15]	150	During operation	5 μg/kg, twice (oral)	−90 min and immediately before CPB
Abi-Jaoude[16]	24	Pre- and post-CPB	5 μg/kg (oral)	−120 min
Loick[17]	45	48 hr	4 μg/kg (IV) + 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (IV) + 0.2–0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (IV)	Preoperative/intraoperative/up to 48 hr
Boldt[18]	44	POD 3	3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (IV)	Induction of anesthesia ~ beginning CPB
Noncardiac surgery				
Ellis[19]	61	48 hr or until discharge	0.2 mg/d (TD) + 0.3 mg (oral)	Night before operation (TD) and −90 to −60 min (oral)
Stühmeier[20]	297	24 hr	2 μg/kg (oral)	−90 min

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; IV = intravenous; TD = transdermal; POD = postoperative day.

Discussion

This systematic review of randomized controlled trials has found that clonidine reduced the incidence of perioperative myocardial ischemia. This was evident in both CABG and noncardiac surgery. The main purpose of the current review was to assess the effect of clonidine on the incidence of perioperative ischemic episodes in patients at risk for myocardial infarction. Therefore, we conducted an overall analysis for a combination of cardiac and noncardiac cases. Overall analysis has the distinct advantage of a wide database. Many specific factors associated with CABG are largely responsible for perioperative myocardial ischemic events. Principal contributors include prolongation of cardiopulmonary bypass (CPB), aortic cross-clamp, poor myocardial protection, coronary air embolism, and thrombosis, vein graft failure, artery graft spasm, and inappropriate use of inotropic agents.[23] In patients with a history of myocardial ischemia, noncardiac surgery may provide a higher incidence of postoperative myocardial infarction than CABG, which improves postoperative coronary blood flow.[24] Because there is probably a difference in the influence on myocardial oxygen balance between CABG and noncardiac surgery, we conducted the subgroup analysis of the two populations. Furthermore, it is difficult to identify myocardial ischemia using electrocardiography in patients undergoing CABG. Several types of arrhythmia (*e.g.*, intraventricular conduction delay, bundle-branch block, ventricular escaped rhythm), electrolyte disturbances, and hypothermia, which are often observed in CABG, possibly lead to misjudgement of ST changes.[23] The potential difference in specificity for detection of ischemic changes may also justify our subgroup analysis. However, we do not believe that this analysis negates the significance of the overall analysis.

The reduction of myocardial ischemia in response to the administration of clonidine was found in the oral administration group, but not in the intravenous treatment groups. Although the reason for failure of intravenous clonidine is unclear, we will attempt to provide possible explanations for this result. One plausible interpretation is based on the low statistical power of the population that was provided intravenous clondine, in which 36 patients in total were enrolled. Power analysis indicates that more than 300 patients are needed to elucidate the efficacy of intravenous clonidine in decreasing the incidence of perioperative myocardial ischemia.[25] It would therefore be premature to conclude

Table 2. Summary of Characteristics in Studies Included for the Meta-analysis

Author[Ref.]	Quality Score[12]	Outcome Definitions ([1] ischemia, [2] infarction)
CABG		
Dorman[14]	9.25	[1] ST (II, V_5): >0.8 mm ↓ ↑ (20 sec)
Myles[15]	9.5	[1] ST (II, aVL, V_5): >1 mm ↓ or >2 mm ↑ (≥2 min) [2] new Q wave (II, aVL, V_5), CK-MB: >5% ↑
Abi-Jaoude[16]	7.5	[1] ST (aVF, V3R, V_5): >1 mm ↓ (≥3 min)
Loick[17]	6	[1] ST (II, V_5): ≥0.1 mV ↓ or ≥0.2 mV ↑
Boldt[18]	7	[1] ST (II, V_5): >0.1 mV ↓ or >0.2 mV ↑ (≥1 min) [2] new/deepened Q wave (II, V_5), CK-MB: >12 U/L ↑
Noncardiac surgery		
Ellis[19]	10.5	[1] ST (12-leads): >1 mm ↓ or >2 mm ↑; CK-MB: ≤40 IU [2] new Q wave, loss of R wave, ST (12-leads): >1 mm ↓ or >2 mm ↑, CK-MB: >40 IU
Stühmeier[20]	10.5	[1] ST (II, V_5): >0.1 mV ↓ or >0.2 mV ↑ (≥1 min) [2] CK-MB: >40 IU or >10% ↑

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; IV = intravenous; TD = transdermal; POD = postoperative day; −x min = clonidine administration × min before anesthesia (x = 60, 90, and 120); CK-MB = creatine kinase myocardial band.

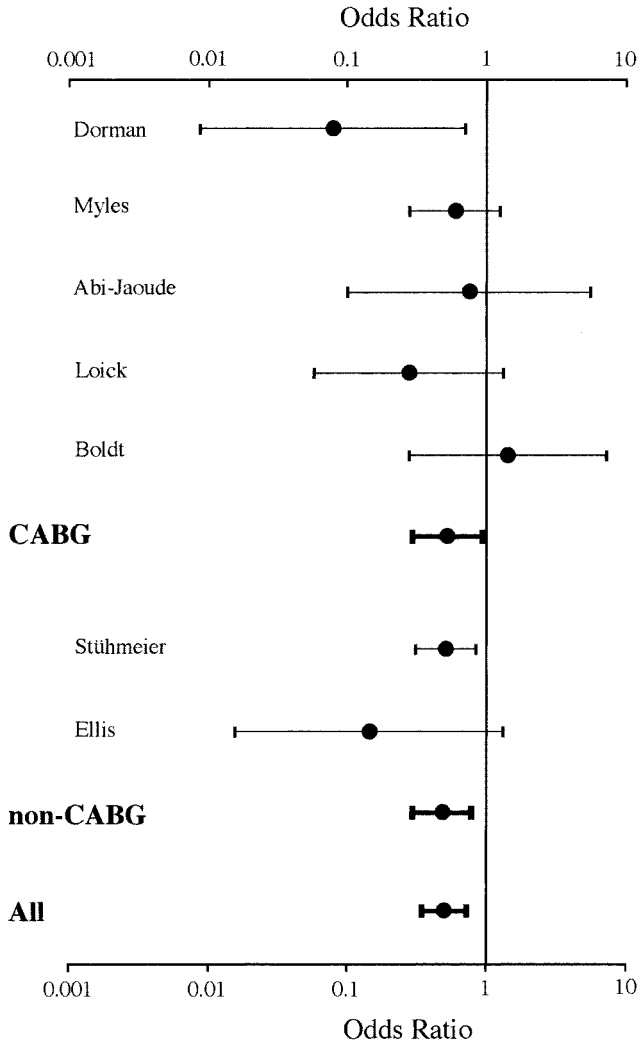

Fig. 2. The subgroup analysis based on surgery. The odds ratios are plotted on the *X*-axis on a logarithmic scale. Solid squares indicate odds ratio of each study and horizontal lines show 95% confidence interval of each study. CABG = coronary artery bypass grafting.

the inefficacy of intravenous clonidine. However, intravenous formula is not commercially available in many countries, including the United States. This may preclude clinical research seeking the beneficial effects of intravenous clonidine. Other explanations include the longer observation period. In a trial by Boldt *et al.*,[20] who monitored patients to detect ischemic episodes for 3 days after CABG, intravenous clonidine given intraoperatively failed to reduce events of myocardial ischemia. Because the pharmacologic effects of intraoperative clonidine disappear by postoperative day 3, such an observation period may finally have equalized the incidence in myocardial ischemic events between the clonidine and placebo groups.

None of the studies enrolled in our meta-analysis included patients undergoing prolonged clonidine treatment. Other medications administered long-term were not specified in detail in any study, although perioperative remedy using drugs other than clonidine was similar between the clonidine and the control groups. Therefore, we abandoned subgroup analysis based on preoperative medications other than clonidine.

Clonidine is most commonly distributed as a tablet. The bioavailability of clonidine 80% or more. In two studies,[16,17] this characteristic enabled anesthetists to give additional doses of clonidine through a gastric tube during general anesthesia. Clonidine has a long half-elimination time ($t_{1/2}$ = 12 ± 7 h).[26] A single dose before anesthesia is likely to maintain the effective concentrations over 24 h in some patient cohorts (*e.g.*, impaired liver metabolism). This is supported by evidence, which Myles *et al.* noted, that increased the requirement for temporary cardiac pacing for 24 h.[17] However, the protective effect from a single preoperative dose of

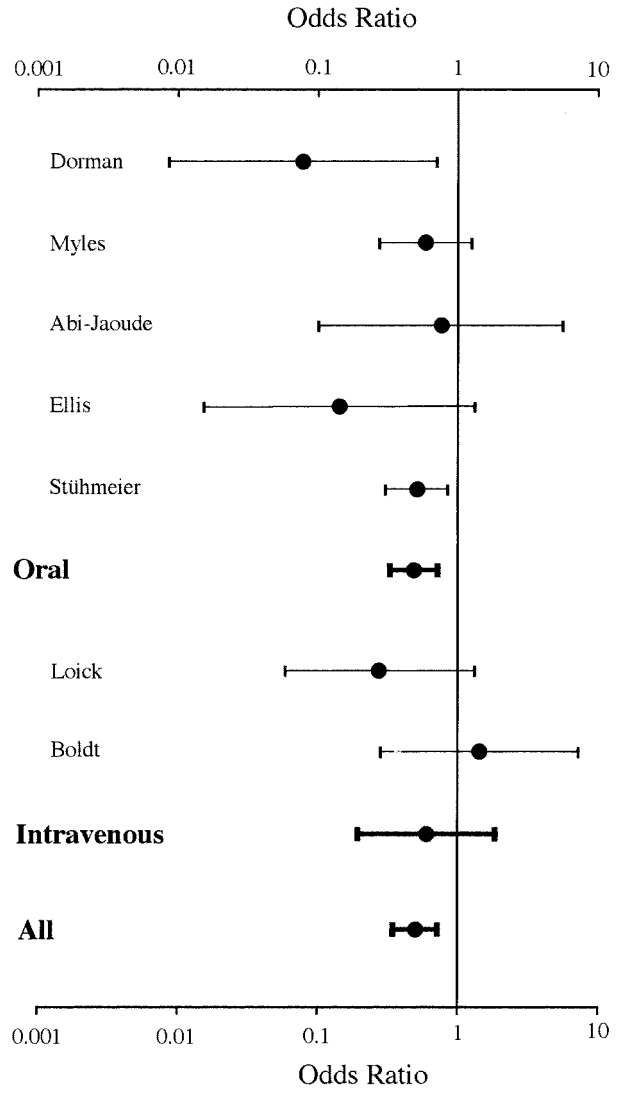

Fig. 3. The subgroup analysis based on the administration route of clonidine. The odds ratios are plotted on the *X*-axis on a logarithmic scale. Solid squares indicate odds ratio of each study and horizontal lines show the 95% confidence interval of each study.

Table 3. Summary of Outcome Data in Studies Included for the Meta-analysis

Author[Ref.]	Clonidine Group			Control Group		
	Ischemia	Infarction	Death	Ischemia	Infarction	Death
CABG						
Dorman[14]	4% of 22			38% of 21		
Myles[15]	15 of 76	8 of 76	0 of 76	22 of 74	11 of 74	2 of 74
Abi-Jaoude[16]	2 of 11	1 of 11	0 of 11	3 of 13	0 of 13	0 of 13
Loick[17]	40% of 14		1* of 24	>70% of 15		0 of 21
Boldt[18]		2 of 22	0 of 22		2 of 22	0 of 22
After CPB	6 of 22			5 of 22		
End of operation	3 of 22			5 of 22		
5 hr after CPB	4 of 22			3 of 22		
POD 1	3 of 22			1 of 22		
POD 3	2 of 22			1 of 22		
Total		2 of 22	0 of 22		2 of 22	0 of 22
Noncardiac surgery						
Ellis[19]						
Intraoperative	1 of 28			5 of 24		
Postoperative	6 of 28			5 of 26		
Perioperative	7 of 28	0 of 30	0 of 30	8 of 26	2 of 31	1† of 31
Stühmeier[20]	35 of 145	0 of 111	1 of 111	59 of 152	4 of 139	2 of 139

Percent values were counted as follows so as not to overestimate the efficacy of clonidine: 4% of 22 = 1/22; 38% of 21 = 8/21; 40% of 14 = 6/14; and >70% of 15 = 11.

* = died within 6 months after surgery; † = died after postoperative day 7.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; POD = postoperative day.

clonidine may not be expected to last sufficiently throughout the postoperative recovery period. Because dilution of blood associated with CPB further decreases blood clonidine concentrations, another dose of clonidine through a gastric tube may be necessary to reduce the incidence of ischemic change after CPB and during extended postoperative observation. Transdermal clonidine patches may be an alternative to this administration method.

Assessment of the timing of myocardial ischemia is also important. Boldt *et al.* reported the number of patients with ischemic episodes at 5 time points: immediately after CPB; at the end of the surgery; 5 h after CPB; 24 h postoperatively; and on postoperative day 3.[20] Ellis *et al*. reported the number of patients with ischemic episodes on three occasions: intraoperatively; postoperatively; and during the perioperative periods.[21] We have given the odds ratio using the data at 5 h post-CPB and the intraoperative data from reports by Boldt *et al*. and Ellis *et al.*, respectively. Smith *et al.* demonstrated that the highest rate of myocardial ischemia occurred most frequently on postoperative day 0.[27] We have also calculated the pooled odds ratio using the number of patients at other assessment points, except postoperative day 3, and have confirmed that our results did not change. Although myocardial ischemia was assessed by ST-segment changes in electrocardiography in all trials, differing definitions for the diagnosis of this complication were used; the types of electrocardiography lead, and the degree and duration of ST changes. Such a difference in the diagnostic definitions and sensitivity of the monitor may contribute to various incidences of perioperative myocardial ischemia (3.5–40%) in the trials of this review. Monitoring of ischemia using transesophageal echocardiography, which is more sensitive than electrocardiography, may have produced different results.

Table 4. Adverse Side Effects of Clonidine

Author[Ref.]	Clonidine	Control	Odds Ratio (95% Confidence Interval)
Bradycardia			
Dorman[14]	6/22	3/21	2.25 (0.48–10.5)
Myles[15]	9/76	2/74	4.84 (1.01–23.2)
Loick[17]	2/24	3/21	0.55 (0.08–3.63)
Boldt[18]	9/22	4/22	3.12 (0.79–12.4)
Stühmeier[20]	23/145	30/152	0.77 (0.42–1.40)
Pooled odds ratio			1.16 (0.72–1.87)
Hypotension			
Myles[15]	22/76	2/74	14.7 (3.31–65.1)
Abi-Jaoude[16]	2/11	1/13	2.67 (0.21–34.2)
Ellis[19]	2/30	3/31	0.67 (0.10–4.30)
Pooled odds ratio			Not applicable*

* heterogeneity (+).

Myocardial infarction or mortality associated with myocardial ischemia may have been the preferable end point in the current systematic review, although we used myocardial ischemia, which is a surrogate marker for the critical consequences. Because all of the studies reviewed in the current analysis used a small number of patients, the expected number of occurrences of myocardial infarction or death was not large enough to find a significant difference between the clonidine and the control groups. Thus, the low statistical power hindered us from using myocardial infarction or mortality as an end point of this systematic review. Power analysis reveals that a base of more than 5000 patients is required

to educe significant efficacy of clonidine in reducing these hard outcomes.[25]

Clonidine is well known to have side effects, including hypotension and bradycardia.[6–10,26] Our analysis revealed that clonidine had no effects on the incidence of bradycardia, although data of hypotension could not be combined because of heterogeneity. The adverse side effects of the drug were not fully documented in the studies reviewed in our meta-analysis, and the reported forms varied widely among the articles. Criteria for these side effects were arbitrarily determined. Five of seven articles indicated the incidence of hypotension, and only three article showed the occurrence of bradycardia.

Publication bias is an inevitable target of criticism concerning positive results in meta-analysis. In the current analysis, this publication bias is possible. To assess this problem, we calculated a fail-safe number (the number of unpublished studies with opposing conclusions needed to negate the reports in published literature) using the Orwin formula.[28] We found that, even though six studies averaging 91 subjects per study with an effect size of 0 for clonidine treatment were added to our meta-analysis, the studies could not nullify the positive result of clonidine. However, it is possible that a large, randomized, controlled trial with a substantial negative result could counteract the findings of this review.

In conclusion, our meta-analysis suggests that clonidine given pre- or intraoperatively reduces myocardial ischemic episodes in patients with coronary arterial disease and in those at risk for this disease and does not increase the incidence of bradycardia. Therefore, we should follow up this suggestion with firm recommendations for the design of a definitive prospective trial.

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Appendix

The appendix lists the 28 studies assessed and the specific reasons for their exclusion from the current meta-analysis.

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9. Helbo-Hansen S, *et al*: Acta Anaesthesiol Scand 1986; 30: 235–42. EX. (B)
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19. Aho M, *et al*: Anesth Analg 1992; 75:932–9. EX. (D)
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23. Kulka PJ, *et al*: Anesth Analg 1995; 80:263–8. EX. (B)
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25. Kulka PJ, *et al*: Crit Care Med 1996; 24:947–52. EX. (B)
26. Jalonen J, *et al*: ANESTHESIOLOGY 1997; 86:331–45. EX. (D)
27. McSPI-Europe research group. ANESTHESIOLOGY 1997; 86:346–63. EX. (D)
28. Dorman T, *et al*: Crit Care Med 1997; 25:1147–52. EX. (B)

IN. = included, EX. = excluded.

Reasons for exclusion: (A) = low-quality score (4 points), (B) = ischemic changes were not evaluated, (C) = abstract of a meeting, (D) = clonidine was not used, (E) = correspondence (letter), and (F) = editorial.