Randomized clinical trial

Randomized clinical trial of moxonidine in patients undergoing major vascular surgery

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Background: **Myocardial ischaemia is the leading cause of perioperative morbidity and mortality after surgery in patients with coronary artery disease. The aim of this study was to evaluate the effects of moxonidine, a centrally acting sympatholytic agent, on perioperative myocardial ischaemia and 1-year mortality in patients undergoing major vascular surgery.**

Methods: **In this double-blind, placebo-controlled two-centre trial, 141 patients were randomly assigned to receive moxonidine or placebo on the morning before surgery and on the following 4 days. Levels of cardiac troponin I (cTnI) were analysed before surgery and on days 1, 2, 3 and 7 thereafter. Holter electrocardiograms were recorded for 48 h starting before the administration of the study drug. Patients were followed daily during admission and by telephone interview 12 months after surgery.**

Results: **The incidence of raised perioperative cTnI levels or alteration in the ST segment in the Holter electrocardiogram or both was 40 per cent in the moxonidine group and 37 per cent in the placebo group ($P = 0{\cdot}694$). All-cause mortality rates within 12 months were 10 per cent in the moxonidine group and 11 per cent in the placebo group ($P = 0{\cdot}870$).**

Conclusion: **Small oral doses of moxonidine did not reduce the incidence of perioperative myocardial ischaemia and had no effect on mortality in patients undergoing vascular surgery. Registration number: NCT00244504 (http://www.clinicaltrials.gov).**

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Introduction

Cardiac ischaemic events are the leading cause of morbidity and mortality after non-cardiac surgery[1–3]. Patients with perioperative myocardial ischaemia are at especially high risk, because this is closely associated with adverse short- and long-term outcomes[4,5]. In patients undergoing major vascular surgery, the prevalence of coronary artery disease (CAD) is reported to be up to 50 per cent[6]. Therefore, these patients are at a particularly high risk of perioperative myocardial ischaemia[5,7,8].

Many studies have addressed the possible reduction of perioperative myocardial ischaemia by sympatholytic medication, and promising results have been reported from the use of β-receptor blockers[9,10]. However, recent trials[11,12] and two meta-analyses[13,14] have questioned the beneficial effect of these drugs. Other studies have investigated the effects of centrally acting α_2-receptor agonists. Wallace and colleagues[15] demonstrated a reduction in the incidence of myocardial ischaemia and a reduction in mortality from perioperative percutaneous administration of clonidine after a preoperative oral loading dose in patients having vascular surgery. Two meta-analyses that included approximately 2800 patients undergoing non-cardiac surgery showed similar effects from perioperative administration of α_2-receptor agonists[16,17]. However, two of the trials, including about 2200 patients, used mivazerol which is available only intravenously. The authors of the meta-analyses concluded that larger randomized studies

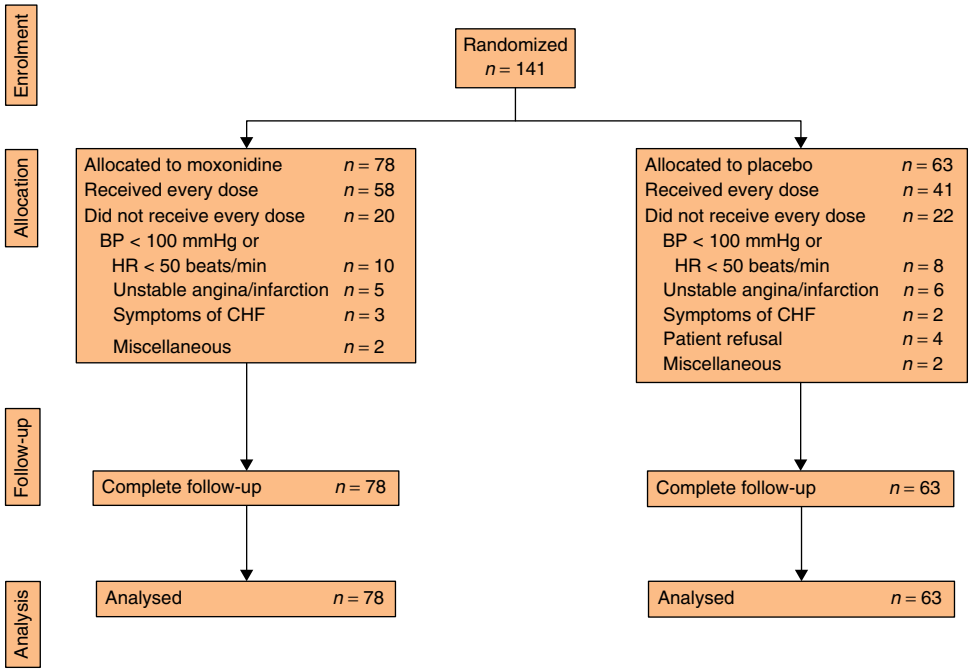

Fig. 1 CONSORT diagram for randomized clinical trial of moxonidine in major vascular surgery: randomization, allocation and follow-up for each group. BP, arterial blood pressure; HR, heart rate; CHF, congestive heart failure

were needed to evaluate the effects of perioperative centrally acting sympatholytic agents on cardiac morbidity and mortality in patients undergoing major surgery. In addition to the ambiguous evidence for perioperative β-receptor blockers and α_2-receptor agonists in patients at cardiac risk, these medications are not free from side-effects. Moxonidine (Physiotens®; Solvay Pharmaceuticals, Brussels, Belgium), an orally available drug, decreases sympathetic activity, reduces blood pressure and suppresses tachycardic episodes without affecting basal heart rate.

The hypothesis of the study was that, in patients undergoing major vascular surgery, oral moxonidine might reduce the risk of perioperative myocardial ischaemia, defined by increased levels of cardiac troponin I (cTnI) or alterations in Holter electrocardiography (ECG) ST segments, and therefore improve 1-year all-cause mortality.

Methods

The protocol of this randomized, double-blind, placebo-controlled, two-centre study was approved by the local ethics committees. Patients undergoing elective infrarenal abdominal aortic or major peripheral vascular surgery of the legs in a university and a tertiary care hospital were eligible (*Fig. 1*). Exclusion criteria were unstable angina, severe symptomatic heart failure (New York Heart Association class IV), systolic blood pressure at rest below 100 mmHg, heart rate below 50 beats/min, known sick sinus syndrome and secondary or tertiary atrioventricular block without cardiac pacemaker *in situ*, creatinine clearance below 30 ml/min, known allergy to moxonidine, pregnancy, urgent surgery and refusal or inability to give informed consent. The study included 141 patients, who each gave written informed consent.

Patients were stratified into those having aortic or peripheral vascular surgery, and into those with, and without, pre-existing β-blocker therapy. Using computer-generated lists, the patients were randomized to receive moxonidine (0·2 mg orally once a day) or placebo of identical shape and appearance the morning before surgery and on days 1 to 4 after surgery. Study medication was administered by a member of the team blinded to treatment allocation unless clinical examination revealed systolic blood pressure below 100 mmHg, heart rate below 50 beats/min, or symptoms and signs of angina pectoris or congestive left heart failure.

Levels of cTnI were measured the day before surgery, immediately after surgery and on days 1, 2, 3 and 7 after surgery, using an AxSYM® kit (Abbott Laboratories, Abbott Park, Illinois, USA). Based on the manufacturer's specifications and the authors' previous study[18], a cTnI

level higher than 2 μg/l was interpreted as evidence of myocardial cell necrosis secondary to cardiac ischaemia if there was no other obvious cause of myocardial injury[19].

Two-channel Holter ECG (MT-100/3; Schiller, Baar, Switzerland) was started before induction of anaesthesia and continued for 48 h after surgery. Two bipolar leads (V5, aVF) were recorded. Holter ECG data were analysed independently by two investigators blinded to treatment allocation and other study results. Holter ECG evidence of ischaemia was defined as a horizontal or down-sloping ST segment depression of at least 0·1 mV, or as a horizontal ST segment increase at 60 ms after the J point of at least 0·1 mV. If baseline ST segment alterations were present, an additional ST segment shift of at least 0·2 mV was required for diagnosis of ischaemia. If the amplitude of the QRS complex was less than 0·5 mV, the electrocardiogram was excluded from analysis[20]. Disagreement over ECG interpretation was resolved by a third reader. In addition, Holter ECG data were analysed for episodes of tachycardia (heart rate over 100 beats/min lasting for more than 20 min).

Anaesthetic care

With the exception of the study medication, the perioperative management of the patients, including preoperative evaluation, anaesthetic technique, postoperative pain management, and cardiac and antihypertensive medication, was guided by the physician in charge and not influenced by the study protocol. All patients were monitored with standard clinical monitors, and arterial and central venous lines were inserted as deemed appropriate by the physicians in charge of clinical care.

In-hospital patient review

A study team member blinded to treatment allocation examined all patients before surgery and daily for the first 7 days after surgery. Special attention was paid to symptoms of acute myocardial ischaemia and congestive heart failure. Patients were explicitly asked about potential adverse drug effects such as headache, nausea, vomiting, dizziness, dry mouth, fatigue or sleep disorders.

Follow-up interviews

Follow-up interviews were conducted by telephone after 30 days and again after 12 months by a member of the study group blinded to treatment allocation and all other data. Patients were asked about chest pain or shortness of breath, and about hospitalization of any cause. If patients were hospitalized, hospital charts were reviewed.

Study endpoints

The primary endpoint of this study was the perioperative occurrence of myocardial ischaemia, defined by alterations in Holter ECG ST segments or raised cTnI levels. The secondary endpoint was all-cause mortality within 30 days and 12 months after surgery.

In addition, the incidence of major adverse cardiac events was recorded, including any coronary intervention, acute coronary syndrome or congestive left heart failure requiring hospitalization within 30 days and 12 months after surgery.

Statistical analysis

Based on an incidence of myocardial ischaemia of 45 per cent found in a previous investigation at the Basel University Hospital[5] and an estimated effect size of 33 per cent (80 per cent power), the necessary sample size was calculated to be 180 patients per group. A blinded interim analysis was prospectively planned after one-third of the calculated study population had been enrolled.

Continuous variables were presented as mean(s.d.) or as median (range), and dichotomous variables were presented as numbers and percentages. $P < 0{\cdot}050$ was considered significant. Data were analysed using Student's t test (two-tailed) or ANOVA for repeated measures when normally distributed, or the Mann–Whitney U test (two-tailed) when not normally distributed. Dichotomous variables were analysed by the χ^2 test (two-tailed) or Fisher's exact test (two-tailed). Kaplan–Meier survival curves were compared using the log rank test. All analyses were performed using SPSS® 13·0 (SPSS; Chicago, Illinois, USA).

Results

This study recruited 141 patients between April 2002 and February 2005. Of these, 68 had abdominal aortic surgery (54 for aortic aneurysm and 14 for occlusive disease) and 73 had major peripheral vascular surgery of the legs. All analyses were performed on the basis of intention-to-treat. Patient characteristics appear in *Table 1* and surgery details in *Table 2*. General anaesthesia was used in 72 procedures (51·1 per cent), general anaesthesia combined with either epidural catheter placement or intrathecal opioid administration was used in 54 procedures (38·3 per cent) and regional anaesthesia was used in 15 procedures (10·6 per cent). Postoperative pain was managed with opioids and non-steroidal anti-inflammatory drugs in 131 patients (92·9 per cent) and epidural analgesia in ten (7·1 per cent). There were no intergroup

Table 1 Clinical characteristics

	Moxonidine ($n = 78$)	Placebo ($n = 63$)
Age (years)	67(10)	68(9)
Sex ratio (M : F)	68 : 10	52 : 11
BMI (kg/m^2)	26(4)	25(4)
Preoperative haemoglobin (g/l)	14·0(1·8)	13·8(2·1)
Preoperative haemodynamics		
Systolic BP (mmHg)	137(22)	134(16)
Diastolic BP (mmHg)	78(11)	75(11)
Heart rate (beats/min)	71(13)	71(13)
Risk stratification		
Lee index class III or IV*	29 (37)	31 (49)
ACC/AHA risk classification (intermediate or major risk)*	33 (42)	35 (56)
Diabetes mellitus, treated*	13 (17)	14 (22)
Smoker*	42 (54)	28 (44)
History of stroke or TIA*	8 (10)	10 (16)
Preoperative medication		
ß-receptor blockers*	40 (51)	32 (51)
Statins*	37 (47)	24 (38)

Values are mean(s.d.) or *number of patients (percentage). BMI, body mass index; BP, blood pressure; Lee index, Revised Cardiac Risk Index; ACC/AHA, American College of Cardiology/American Heart Association; TIA, transient ischaemic attack. There were no significant differences between the two groups.

differences in patient characteristics, anaesthetic care, surgery performed or postoperative pain management.

Perioperative ischaemia

The incidence of raised perioperative cTnI levels or ST segment alteration indicative of myocardial ischaemia in the Holter electrocardiogram was 40 per cent (31 of 78) in the moxonidine group and 37 per cent (23 of 63) in the placebo group ($P = 0·694$). The first occurrence of myocardial ischaemia was during surgery in nine patients taking moxonidine and four taking placebo, and within the first 12 h of surgery in nine and ten patients, between 12 and 36 h after surgery in nine and seven patients, and later than 36 h after surgery in four and two patients in the moxonidine and placebo groups respectively. Perioperative increase in cTnI was found in 14 per cent of patients in each group (11 of 78 *versus* nine of 63; $P = 0·975$). One patient in each group had raised cTnI levels before surgery; these were also raised after surgery. ST segments altered in 34 per cent (24 of 71) of the moxonidine group and in 30 per cent (18 of 61) of the placebo group ($P = 0·597$). ST segment analysis could not be performed in seven patients (9 per cent) in the moxonidine group and in two (3 per cent) in the placebo group ($P = 0·188$) because of left bundle branch block (in four patients), ventricular pacemaker rhythm (in two), or QRS complex less than 0·5 mV in both channels (in three).

Table 2 Surgical procedures

	Moxonidine ($n = 78$)	Placebo ($n = 63$)
Aortic surgery: occlusive disease		
Aortobifemoral graft	7 (9)	5 (8)
Aortic surgery: aneurysm		
Straight tube graft	13 (17)	6 (10)
Aortobi-iliac graft	17 (22)	11 (17)
Peripheral vascular surgery	37 (47)	36 (57)
Iliofemoral bypass	5 (6)	4 (6)
Femoropopliteal bypass	11 (14)	12 (19)
Femorocrural bypass	15 (19)	18 (29)
Miscellaneous*	6 (8)	2 (3)

Values are numbers of patients (percentage). *Miscellaneous peripheral vascular surgery included femorofemoral crossover bypasses, axillofemoral bypasses and vascular patch plastic surgery. There were no significant differences between the two groups.

The mean number of ST segment alterations during the 48 h of Holter ECG recording was 3 (range 1–16) in the moxonidine group and 3 (range 1–8) in the placebo group ($P = 0·433$). The mean duration of all ST segment alterations was 96 (range 5–619) min in the moxonidine group and 94 (range 5–851) min in the placebo group ($P = 0·279$).

Mortality after 30 days and 12 months

Follow-up was complete to February 2006: there were no differences in the all-cause mortality. Kaplan–Meier survival curves were similar for both groups ($P = 0·876$).

Mortality at 30 days was 4 per cent (three of 78) in the moxonidine group and 2 per cent (one of 63) in the placebo group ($P = 0{\cdot}628$). All-cause mortality at 1 year was 10 per cent (eight of 78) in the moxonidine group and 11 per cent (seven of 63) in the placebo group ($P = 0{\cdot}870$).

Cardiac events during follow-up

Six major adverse cardiac events were reported during follow-up: four myocardial infarctions and two episodes of congestive heart failure. One of these patients died later during follow-up. Of these six events, two occurred during hospitalization (within 3 days of surgery) and four occurred between 30 and 365 days after surgery. Five of the patients with a reported event had been taking moxonidine, and one had been taking placebo ($P = 0{\cdot}225$).

Perioperative haemodynamics

The incidence of intraoperative tachycardia was significantly lower in the moxonidine group (*Table 3*). Tachycardia (heart rate above 100 beats/min) was found in eight patients (10 per cent) in the moxonidine group compared with 15 (24 per cent) in the placebo group ($P = 0{\cdot}017$). This difference did not persist in the postoperative Holter ECG recordings that revealed tachycardia in 24 patients (31 per cent) in the moxonidine group and 24 (38 per cent) in the placebo group ($P = 0{\cdot}273$). During surgery, blood pressure and the incidence of bradycardia were similar between the two groups, as was the need for vasoactive medication. In the moxonidine group, 11 patients (14 per cent) needed continuous vasopressor support with norepinephrine or epinephrine compared with ten (16 per cent) in the placebo group ($P = 0{\cdot}769$). Small doses of ephedrine and phenylephrine were administered in 72 patients (92 per cent) from the moxonidine group and 56 (89 per cent) from the placebo group ($P = 0{\cdot}485$). Vasodilators (intravenous nitrates and urapidil) were administered in 28 patients (36 per cent) in the moxonidine group and 21 (33 per cent) in the placebo group ($P = 0{\cdot}751$). There were no other differences in haemodynamics during in-hospital follow-up.

Withholding study medication

Study medication was withheld at least once, according to the study protocol, in 21 patients (27 per cent) in the moxonidine group and 22 (35 per cent) in the placebo group ($P = 0{\cdot}305$). Withholding occurred on the morning before surgery in three patients (4 per cent) in the moxonidine group and two (3 per cent) in the placebo group, on the first postoperative morning in nine (12 per cent) and ten (16 per cent), on the second postoperative morning in eight (10 per cent) and six (10 per cent), on the third postoperative morning in ten (13 per cent) and ten (16 per cent), and on the fourth postoperative morning in eight (10 per cent) and ten (16 per cent) respectively. There were no differences in these values. Every patient received the study medication at least once before or within 48 h after surgery.

Table 3 Intraoperative haemodynamics

	Moxonidine ($n = 78$)	Placebo ($n = 63$)	P†
Heart rate			
Highest (beats/min)	82(14)	86(21)	0·302
Lowest (beats/min)	52(10)	53(11)	0·562
< 40 beats/min*	11 (14)	7 (11)	0·597‡
> 100 beats/min*	8 (10)	15 (24)	0·017‡
Blood pressure			
Highest systolic (mmHg)	157(21)	154(18)	0·512
Lowest systolic (mmHg)	89(13)	87(15)	0·611
< 80 mmHg*	7 (9)	9 (14)	0·323‡
≥ 180 mmHg*	13 (17)	11 (17)	0·901‡

Values are mean(s.d.) or *number of patients (percentage). †Comparisons by Student's *t*-test, except ‡χ^2 test.

Side-effects

There was no difference in any of the recorded potential side-effects between the moxonidine and the placebo procedures. The most frequent side-effects were dry mouth, reported in 66 (85 per cent) and 52 patients (83 per cent), sleep disorders in 62 (79 per cent) and 42 patients (67 per cent) and fatigue in 41 (53 per cent) and 30 patients (48 per cent) in the moxonidine and placebo groups respectively. Four patients from the moxonidine group were excluded from this analysis because they died within 3 days of surgery (two patients) or were transferred to another hospital on the third postoperative day.

Subgroup analyses

Because of early termination, predefined subgroup analyses were not fully reliable. However, in the 73 patients undergoing major peripheral vascular surgery, there was no difference in the rates of ischaemia between moxonidine and placebo groups. The only difference was a lower rate of tachycardia in the moxonidine subgroup during surgery (5 *versus* 28 per cent; $P = 0{\cdot}010$) and during the first 24 h in Holter ECG data (14 *versus* 33 per cent; $P = 0{\cdot}045$).

In the 68 patients undergoing abdominal aortic surgery, rates of perioperative ischaemia and perioperative haemodynamics were similar in the two groups.

In the 69 patients who were not taking β-blockers, preoperative patient characteristics and rates of ischaemia were similar in the two groups. The only difference was a lower rate of tachycardia in the moxonidine group during surgery (8 *versus* 42 per cent; $P = 0{\cdot}001$), but the rate was similar after surgery in the analysis of Holter ECG data during 48 h (39 *versus* 42 per cent; $P = 0{\cdot}821$).

In the 72 patients who were taking β-blockers, no differences were found in patient characteristics, rates of perioperative ischaemia or perioperative haemodynamics between the two groups.

Discussion

This randomized clinical trial found that small doses of oral moxonidine failed to change the rate of perioperative myocardial ischaemia in patients having major vascular surgery. Similarly, moxonidine did not alter long-term outcome. Because of the lack of effective evidence, the study was stopped after a predefined interim analysis.

The rates of perioperative ischaemia in the placebo and intervention groups corresponded to the sample size calculations and were comparable to previous studies, which found perioperative myocardial ischaemia, detected by Holter ECG in 31–46 per cent of high-risk patients undergoing major surgery[5,15,18]. Increase in cTnI, which is a stronger marker for myocardial necrosis including ischaemia, was evident in 14 per cent of the patients in each group. This rate of troponin increase was similar to studies by other authors, reporting raised troponin values in 14–19 per cent of cardiac-risk patients[18,21,22].

Evidently, the study drug had no effect on the rate of myocardial ischaemia. Potential reasons for the lack of clinical effect included a missing effect of moxonidine on perioperative ischaemia, too low a dosage, insufficient drug absorption and a lack of preoperative treatment. A daily oral dose of 0·2 mg moxonidine was chosen according to the manufacturer's recommendations that advise against increasing this within 3 weeks of starting treatment. In fact, a study that increased the moxonidine dosage in 1- to 2-week intervals was terminated prematurely because of excess mortality[23]. Therefore, starting moxonidine treatment just before surgery and using higher doses might have been unsafe. Nevertheless, the plasma levels of moxonidine in the study patients may have been inadequate. Contrary to this was the observation that intraoperative tachycardia was less frequent in the moxonidine group (*Table 3*), a difference that persisted at least 24 h after surgery in patients receiving moxonidine who had peripheral vascular surgery. Prevention of tachycardia with only minor effects on the resting heart rate is a typical effect of moxonidine. However, as the plasma levels of moxonidine were not measured, the question of whether moxonidine was sufficiently absorbed, particularly in patients undergoing abdominal surgery, remains unknown.

Although the incidence of cardiac ischaemia was similar to previous studies[5,15,18], the mortality in the present study was lower. All-cause mortality rates were 4 and 2 per cent after 30 days and 10 and 11 per cent after 12 months in the moxonidine and placebo groups respectively. In comparison, 30-day mortality in the placebo group of the clonidine trial by Wallace and colleagues[15] in a lower-risk patient population was 6·2 per cent, and in patients undergoing vascular surgery in a trial by Kim and colleagues[24] was 8 per cent. A previous study from the authors' group of similar patients showed a 1-year mortality of 16 per cent[18]. In elderly patients, one-third of whom had raised perioperative troponin T levels, Oscarsson and colleagues[25] found a 1-year mortality of 14 per cent.

One possible reason for the lower mortality rate in the present study could be the high proportion of patients taking β-blockers, statins and antiplatelet drugs; β-blockers in particular lower oxygen demand but, as with statins and antiplatelet agents, they have positive effects on coronary plaque stabilization. Therefore, they may reduce fatal myocardial infarction in the perioperative period and during follow-up. This might account for the lack of additional long-term effects of moxonidine. It might also call into question the value of troponin and ST segment alterations as surrogate markers for short- and long-term outcome.

The uneven number of patients in the two groups resulted from stopping the trial after the interim analysis, owing to a lack of statistical evidence for a difference in the main outcome variables. The resulting loss of statistical power does not diminish the validity of the main conclusion in this investigation. However, it rendered data insufficient for detailed subgroup analyses. Small doses of moxonidine started on the day of surgery and continued for 4 days after surgery affected the incidence of intraoperative tachycardia but did not reduce the incidence of perioperative myocardial ischaemia or survival in patients undergoing vascular surgery.

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The authors have no conflicts of interest to declare.

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