A randomized study to evaluate the effect of a perioperative infusion of dopexamine on colonic mucosal ischemia after aortic surgery

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Purpose: **Colonic ischemia after aortic surgery is associated with increased mortality and morbidity rates. This study was conducted as a single-center side arm to a multicenter, randomized, placebo-controlled study to evaluate the effect of dopexamine hydrochloride on its incidence.**

Methods: **Thirty patients, mean age 65.1 years (range, 46-84), undergoing elective infrarenal aortic surgery were entered. Preoperative hemodynamic and respiratory parameters were optimized. Patients were then randomly assigned to receive a perioperative infusion of dopexamine at 2 μg/kg per minute (n = 12) or 0.9% saline placebo (n = 18). All patients underwent colonoscopy and biopsy preoperatively and 1 week postoperatively. Specimens were assessed for evidence of mucosal ischemia, presence of mast cell tryptase, myeloperoxidase activity, and both the inducible and endothelial isoforms of nitric oxide synthase.**

Results: **There was no significant difference in perioperative fluid and blood requirements or hemodynamic and respiratory parameters between the two groups. However, there was significantly less evidence of mucosal ischemic changes in dopexamine-treated patients (n = 1) compared with placebo (n = 8) ($P = .049$). Furthermore, when preoperative biopsies were compared with those performed 1 week postoperatively, nine (50%) patients in the placebo group and two (16.7%) in the dopexamine group scored worse. Although there was no significant difference in inflammatory markers between the two groups, both mast cell tryptase and myeloperoxidase expression were increased in patients with histologic evidence of ischemia ($P < .05$). Furthermore, inducible nitric oxide synthase staining within the vascular ($P = .001$) and lamina propria ($P < .05$) components of the mucosa was also significantly greater.**

Conclusion: **A perioperative dopexamine infusion affords significant histologic protection to colonic mucosa after aortic surgery. (J Vasc Surg 2001;33:758-63.)**

Since the first report by Moore in 1954,[1] colonic ischemia, a well-recognized complication of abdominal aortic surgery, is associated with increased mortality and morbidity rates and has an incidence ranging from 2.8% to 60% depending on diagnostic criteria, case selection, and data collection.[2-6] In a recently reported prospective study, we found an incidence of 30% in a group of 56 patients undergoing elective infrarenal aortic surgery, when based on histologic findings.[7] As yet, the pathogenesis underlying this complication and its systemic consequences is not fully understood but is likely to be the result of an ischemia reperfusion (IR) injury. Although gut mucosa is exquisitely sensitive to a reduction in local tissue oxygen delivery, reperfusion of ischemic intestines will only compound any mucosal barrier dysfunction. Previous reports have implicated both mast cells and polymorphonuclear leukocytes in the pathogenesis of this type of IR injury. Furthermore, disturbances of the delicate intestinal microcirculation are known to be associated with the ultimate development of multiple organ dysfunction syndrome.[8]

Dopexamine hydrochloride, a synthetic catecholamine, has dopaminergic receptor agonist properties at both the dopamine 1 and 2 receptors combined with a potent β_2 receptor agonist activity. It has no α or direct β_1 effects but exhibits potent uptake-1 inhibition, thus potentiating neuronally released noradrenaline.[9-11] Its unique combination of pharmacologic properties translates into a clinical profile of afterload reduction, direct and indirect positive inotropism, and potentially both renal and splanchnic vascular bed dilatation. These beneficial effects have been applied to a variety of clinical settings in the past, including heart failure and low output states.[12-15] However, interest in dopexamine has grown, particularly following recent studies suggesting its anti-inflammatory role, both in humans and animals, in cases of sepsis and in critically ill surgical patients.[16-20] This role cannot be explained purely by its β_2 agonist properties.

The aim of our study, which was a single-center side arm of a multicenter, prospective, randomized, placebo-controlled study to examine the effect of dopexamine on renal function after elective aortic surgery, was designed to

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examine the effect of a perioperative infusion of dopexamine hydrochloride on colonic mucosa after infrarenal aortic cross-clamping.

METHODS

After ethical committee approval, written informed consent was obtained from all patients entered into the main study. Additional written consent was taken from patients for the side arm of the study. Of 36 patients included in the main study at this site, 30, with a mean age 65.1 years (range, 46-84) undergoing elective infrarenal aortic surgery, were entered to this side arm study. Exclusion criteria for the main study included a history of tachyarrhythmias or myocardial infarction within the previous 6 months, and those who had previous aortic surgery or a colonic pathologic condition were also excluded from entering the side arm study. Patients were randomly allocated by site, with the use of sealed envelopes, to receive an infusion of either dopexamine hydrochloride (Speywood Pharmaceuticals Ltd, Maidenhead, Berkshire, UK) at a rate of 2 μg/kg per minute (n = 12) or placebo (0.9% saline) at a similar rate (n = 18).

All patients were stabilized preoperatively with the aid of arterial and central venous catheters, blood assays, fluids, and supplementary oxygen to achieve predetermined goals: central venous pressure (CVP) of 8 to 10 cm H_2O, mean arterial blood pressure of 90 mm Hg, hemoglobin level of 10 g/dL, and oxygen saturation of 95%. An infusion of dopexamine or placebo was started at the induction of anesthesia and continued for 24 hours. A standard general anesthetic technique was used in all cases. The evening before surgery, patients were given a phosphate enema to evacuate the distal colon and rectum. After induction of anesthesia, patients were placed in the left lateral position, and a limited colonoscopy was performed with an Olympus CF-10L colonoscope (Olympus Optical, London, UK). Biopsies were then taken at 20, 30, and 40 cm from the anal verge and identified with different code numbers. A repeat biopsy was performed 1 week postoperatively in all patients to minimize discomfort. All operations were performed with a standard technique: aneurysms by inlay of a straight or bifurcated graft and occlusive disease by end-to-side proximal anastomosis. Operative details including cross-clamp time, patency or ligation of mesenteric and internal iliac vessels, and hemodynamic variables were recorded. All patients had preservation of at least one internal iliac artery. Routine postoperative management involved 24-hour observation and monitoring in the intensive care unit with intravenous morphine patient-controlled analgesia for pain control and fluids including blood products provided as necessary. Histopathologic specimens were fixed in 10% formalin and processed to paraffin wax. Three 5-μm sections were then cut and fixed on each slide. These were stained with hematoxylin and eosin and immunohistochemically with an indirect immunoperoxidase technique for expression of specific markers of inflammatory activation including: myeloperoxidase (DAKO Ltd, Cambridgeshire, UK); mast cell tryptase (MCT) (DAKO Ltd), which binds to secretory granules in degranulated mast cells; and isoforms of both the inducible nitric oxide synthase (iNOS) (Serotec, Oxford, UK) and endothelial nitric oxide synthase (eNOS) (Serotec). The primary antibody was omitted for negative controls. Positive controls included sections of inflammatory exudates for myeloperoxidase, normal tonsil and spleen for MCT, and scleroderma skin for both eNOS and iNOS. Clinical evaluation of specimens was performed independently by two histopathologists. A grade correlating the type and severity of ischemic changes was recorded (Table I). All immunohistochemical sections were assessed with a semiquantitative method and

Table I. Grading system applied to histopathologic appearance of colonic biopsies

Grading	*Histopathologic appearance*
1	Normal
2	Chronic inflammation
3	Active chronic inflammation
4	Acute inflammation
5	Ulceration
6	Perforation
7	Pus
8	Infarction

Table II. Patient demographic data (mean ± SD)

	Dopexamine group (n = 12)	*Placebo group (n = 18)*
Age (y)	67.7 ± 9.4	63.4 ± 8.1
Sex (male:female)	8:4	14:4
Mean weight (kg)	70.4 ± 6.9	69.8 ± 15.9
Aneurysmal disease	3	8
Occlusive disease	9	10

Table III. Evidence of mucosal ischemia as assessed with H+E and MPO: comparison between dopexamine-treated and placebo groups

	Dopexamine (n = 12)	*Placebo (n = 18)*
H+E		
Preoperative score (mean ± SD)	1.25 ± 0.45	1.11 ± 0.32
Postoperative score (mean ± SD)	1.25 ± 0.62	2.56 ± 2.01
Number better (%)	3 (25)	0 (0)
Number same (%)	7 (58.3)	9 (50)
Number worse (%)	2 (16.7)	9 (50)
MPO		
Preoperative score (mean ± SD)	0.17 ± 0.39	0.18 ± 0.39
Postoperative score (mean ± SD)	0.42 ± 0.67	0.76 ± 0.97
Number better (%)	1 (8.3)	1 (5.5)
Number same (%)	8 (66.7)	10 (55.6)
Number worse (%)	3 (25)	7 (38.9)

H+E, Hematoxylin and eosin; *MPO,* myeloperoxidase.

Table IV. Hemodynamic variables compared between dopexamine-treated and placebo groups (mean ± SD)

	Dopexamine group (n = 12)	*Placebo group (n = 18)*	P *value**
Preoperative baseline values			
CVP (cm H_20)	9.0 ± 1.2	8.7 ± 2.9	.7555
Mean blood pressure (mm Hg)	115.5 ± 13.5	116.4 ± 12.1	.8483
Mean oxygen saturation (%)	97.4 ± 1.1	96.7 ± 1.5	.1907
Mean hemoglobin (g/dL)	14.7 ± 1.1	14.3 ± 1.6	.4756
Perioperative values			
CVP (cm H_20)	6.6 ± 2.9	7.3 ± 3.5	.6577
Mean blood pressure (mm Hg)	101 ± 9.9	100 ± 13.1	.8305
Mean oxygen saturation (%)	97.9 ± 0.3	97.9 ± 1.2	.9487
Fluid input (mL)	2975.0 ± 720.1	3323.3 ± 1083.8	.3443
Blood given (mL)	225.0 ± 382.4	536.7 ± 430.3	.07
Postoperative values (24 h)			
CVP (cm H_20)	4.1 ± 4.1	6.6 ± 4.2	.156
Mean blood pressure (mm Hg)	109.6 ± 19.8	102.9 ± 13.6	.344
Mean oxygen saturation (%)	97 ± 2.1	96.9 ± 1.7	.904
Mean hemoglobin (g/dL)	10.9 ± 1.2	11.1 ± 1.8	.757
Fluid input (mL)	4256.0 ± 1905.2	4959.6 ± 2154.2	.39
Blood given (mL)	490.0 (840.8)	432.5 (463.8)	.837

*Student *t* test.

given a score according to the degree of the staining as absent (0), mild (1), moderate (2), and severe (3). In the case of both iNOS and eNOS, scores were assigned in a similar fashion to the degree of expression within the various elements of the mucosa (vascular endothelium—v, cytoplasm of epithelial cells—c, nucleus of epithelial cells—n, membrane of epithelial cells—m, lamina propria—l). In cases where scores given by both histopathologists did not concur, agreement was reached on reviewing and discussing the slide in question.

Summary data are expressed as mean ± SD. Differences in proportions were tested with the χ^2 or Fisher exact test as appropriate. The Student *t* test was used to compare quantitative data when the distribution was considered to be normal. The Mann-Whitney *U* test was used to compare the score representing the severity of mucosal ischemia, as determined histologically, and the degree of immunohistochemical staining, between treatment and placebo groups. Correlation between groups of ordinal data was assessed by calculating the Spearman rank correlation coefficient and its associated *P* value. The level for statistical significance was set at *P* less than .05.

RESULTS

The two groups were well matched in regard to age, sex, and weight (Table II). The dopexamine-treated group comprised nine patients with aortoiliac occlusive disease and three with abdominal aortic aneurysm (AAA); the placebo group included 10 patients with occlusive disease and eight with AAA. Although there was no significant difference between the two groups regarding preoperative patency of the inferior mesenteric artery, it was routinely ligated in 12 (100%) patients with aneurysmal disease and in six (32%) with occlusive disease. In all cases, at least one internal iliac artery remained patent, and no additional revascularization procedures were performed. All patients had preoperative biopsies with grades 1 or 2, but nine (30%) had histologic evidence suggestive of ischemia (grade ≥ 3) postoperatively of which only one was within the dopexamine-treated group ($P = .049$, Fisher exact test). Furthermore, the degree of mucosal ischemia was significantly greater in the placebo group than in those treated with dopexamine ($P = .025$, Mann-Whitney *U* test). When preoperative biopsies were compared with those performed 1 week postoperatively, nine (50%) patients in the placebo group and two (16.7%) in the dopexamine group scored worse (Table III). Although increased myeloperoxidase activity was seen in the placebo group 7 days postoperatively when compared with those receiving dopexamine, this was not statistically significant. There was one death in the placebo group from colonic infarction at 11 days. Histologic sections demonstrated transmural infarction, and thus immunohistochemistry was not performed because it was not possible to differentiate cell types. There were no deaths in the dopexamine-treated group. No significant association between grade of mucosal ischemic changes and sex, age, indication for surgery (AAA vs aortoiliac disease), clamp time and ligation or patency of the inferior mesenteric artery was found in this series. Also, there was no significant difference between the AAA and occlusive groups regarding fluid (3306 ± 1326 mL vs 3127 ± 765 mL, $P = .73$) or blood (481 ± 444 mL vs 379 ± 437 mL, $P = .60$) requirements. Although there was a greater perioperative blood requirement in the placebo group, this was not statistically significant and was not associated with the grading of mucosal ischemic changes. Furthermore, there was no significant difference in perioperative or postoperative cardiorespiratory parameters (Table IV) between the two groups. There was increased presence of both degranulated mast cells and neutrophils in those sections with evidence of mucosal ischemia ($P < .05$) (Fig 1). This was also associ-

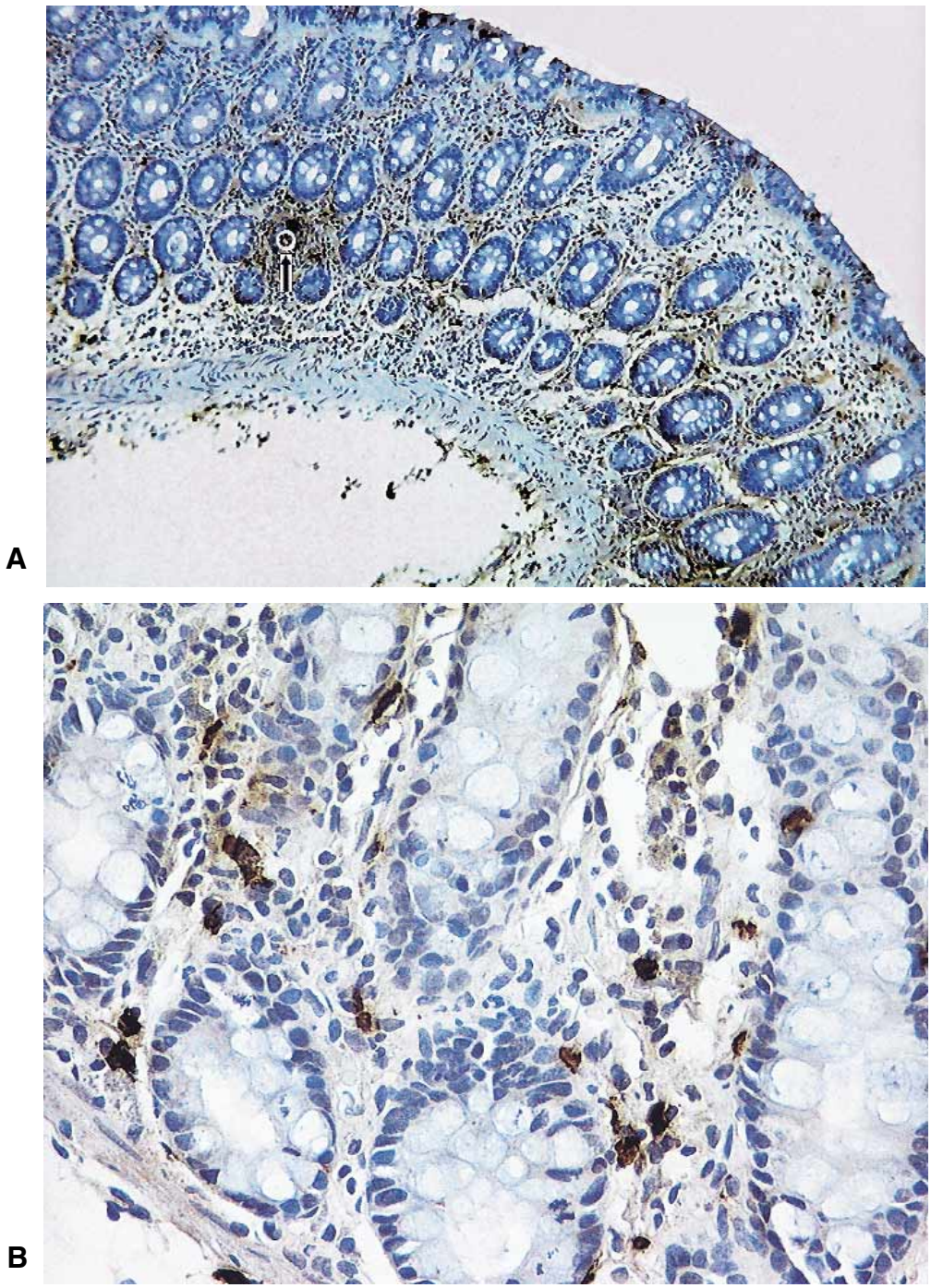

Fig 1. Immunohistochemical staining pattern in biopsy with colonic ischemia. **A,** Neutrophil infiltration within lamina propria (*brown staining*) as seen with myeloperoxidase staining. An early crypt abscess can be identified (*arrow*). Original magnification ×40. **B,** Mast cells identified within lamina propria by MCT (*brown staining*) Original magnification ×60.

ated with increased expression of iNOS (Fig 2) within the vascular ($P = .001$) and lamina propria elements ($P < .05$). However, no significant relationship was found with any of the immunohistochemical markers of inflammatory activation between treatment and placebo groups.

DISCUSSION

Optimization of cardiac performance by the use of invasive monitoring and fluid and inotrope administration for high-risk surgical patients has been shown to reduce morbidity and mortality rates.[21] In addition, this study has

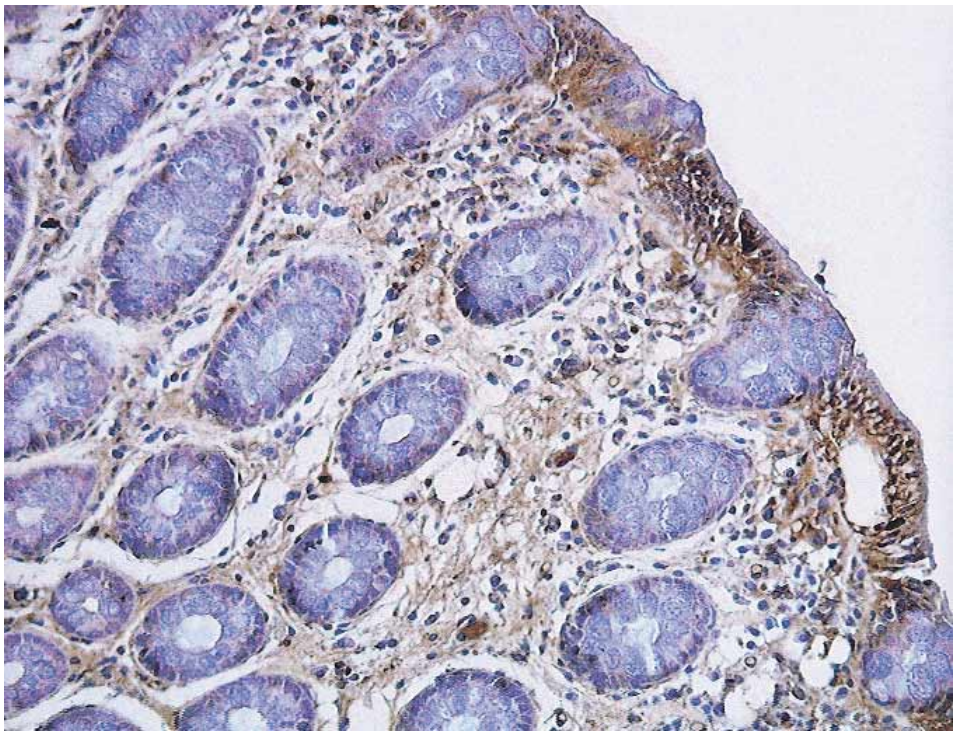

Fig 2. Marked iNOS expression within vascular, lamina propria, and epithelial components of ischemic colonic mucosa. Original magnification ×40.

demonstrated that a perioperative infusion of dopexamine hydrochloride can confer significant mucosal protection to the distal colon in patients undergoing infrarenal aortic surgery. In patients with histologic evidence of colonic ischemia, there was a typical pattern of increased iNOS expression, particularly within the vascular endothelium, and increased presence of both neutrophils (myeloperoxidase) and degranulated mast cells (MCT). The exact mechanism for this mucosal protection has not been identified in this study but may be due to either improved mucosal perfusion or a specific anti-inflammatory effect. The latter hypothesis has attracted more attention recently. Boyd et al[16] demonstrated a significant reduction of the mortality rate in a group of high-risk surgical patients receiving dopexamine when compared with those receiving placebo, despite an absence of increased oxygen consumption. Smithies et al[22] showed that dopexamine improved splanchnic oxygenation independent of its systemic effects. In a study with a porcine model of septic shock, where cardiac output and oxygen delivery were standardized, the β_2 effect of dopexamine was shown to maintain the histologic architecture of the liver when compared with dobutamine or fluids alone.[18] In fact, in this model the α_1 agonist properties of dobutamine were associated with more destruction to the liver than fluid alone. An anti-inflammatory action in humans has recently been shown in critically ill surgical patients.[17] These patients were all undergoing major abdominal surgery, excluding vascular surgery, and were randomly given dopexamine or placebo. There was a significant reduction in myeloperoxidase activity within the upper gastrointestinal mucosa 72 hours after surgery in patients treated with dopexamine. In this study we were unable to demonstrate any significant reduction in the expression of inflammatory markers in the dopexamine-treated group despite the clear reduction in histologic evidence of ischemic changes. One possible explanation could be that the protection afforded by dopexamine occurs early in the cascade of events that leads to structural damage, and therefore, a biopsy at 7 days may have missed these changes. However, the development of ischemic changes was associated with both increased mast cell and neutrophil activity. It has previously been demonstrated that degranulation of mast cells is responsible for the recruitment of neutrophils after intestinal IR injury in a rat model.[23] The finding of increased numbers of degranulated mast cells within the colonic mucosa in this study suggests that similar mechanisms exist for the development of colonic ischemia after aortic surgery. The significance of increased iNOS expression in both the vascular endothelium and lamina propria in these patients is less clear. Nitric oxide (NO) is generated in response to tissue reperfusion injury.[24] Studies with animal models of shock have reported both beneficial and detrimental effects of nitric oxide synthase inhibitors.[25-30] Kubes[31] has previously demonstrated that NO inhibition increased intestinal permeability after IR injury. In a rat model of endotoxic shock,

iNOS induction was noted in the mucosa of both the small and large intestines as well as in monocytes and macrophages in multiple organs.[32] Furthermore, there is evidence that iNOS in the lung is upregulated after intestinal IR injury.[33] It was suggested that this may be a compensatory protective response. However, the inappropriate overproduction of NO is also known to lead to loss of vascular vasomotor control and myocardial hypocontractility.[34-36] The mode of action of dopexamine, with respect to its anti-inflammatory properties, is far from clear, but light has recently been shed by Schmidt et al[20] using intravital microscopy in a rat endotoxemia model. Dopexamine administration significantly reduced leukocyte adherence to postcapillary venules in rat mesentery, and use of a β_2-adrenoreceptor antagonist did not attenuate this effect. However, an attenuating effect on vascular permeability was β_2-adrenoreceptor mediated. It is evident that the actions of dopexamine extend beyond a simple hemodynamic effect, and further work will need to focus on establishing the specific target of its anti-inflammatory effect.

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