THE ROLE OF INHALED NITRIC OXIDE IN CARDIAC AND GASTROINTESTINAL TRACT PROTECTION IN PATIENTS WITH CARDIOVASCULAR DISEASE UNDERGOING LAPAROSCOPIC SURGERY: A PILOT RANDOMIZED CONTROLLED TRIAL

Alshoraihy A. A., Alexandrova M. V., Tereshin N. M.
Tutor: PhD, associate professor Mandel I. A.

I. M. Sechenov First Moscow State Medical University, Moscow

Resume. The pilot randomized controlled study is a first-in-human study to be during laparoscopic interventions. It aims to find out if a 40 ppm inhalation of NO could protect the gastrointestinal tract and reduce post-surgical complications in cardio-vascular patients after laparoscopic operations. Out of 40 patients we collected, 20 received inhaled nitric oxide (iNO), while the other 20 patients to be as the control group. Blood was taken for analysis before and 12 hours after surgery. The study includes the parameters of echocardiography which are the ejection fraction of left ventricle (LVEF), end-diastolic (EDV), end-systolic volumes (ESV), and stroke volume also. In this work, the level of glycoprotein 5 significantly lowered in the iNO group (-4.80±9.02) compared to the control group (+0.36±7.05, p=0.0549). The iNO eliminated 70% of the endothelin-1 rise (+1.05±3.86 vs. +3.47±4.69 pg/ml, p=0.0826). Moreover, NT-proBNP showed 86% less cardiac injury with iNO (-1.35 vs. -9.65). The decrease in end-diastolic volume was 7.9 times more with iNO (-12.7 vs. -1.6 ml, p=0.268). The research revealed that 40 ppm iNO is a safe dose and produces biologically positive effects in the tested model, cardiac protection as well as intestine protective benefits being indicated.

Keywords: inhaled NO, cardiac protection, gastrointestinal protection, endothelin-1, laparoscopy.

Relevance. After a laparoscopic surgery on the abdomen, patients who have heart problems face a much greater chance of not getting enough blood to their intestines, losing their barrier function, and experiencing complications after surgery. The triple-drug anesthesia, the physical trauma of surgery, and hemodynamic perturbation interact synergistically to create the special problems of insufficient splanchnic perfusion during the perioperative period. Nitric oxide is the principal regulatory molecule that ensures the intestinal barrier is functioning properly, maintains vascular homeostasis, and gives organ protection. Recently, iNO has been recognized as a selective pulmonary vasodilator and, in addition to pulmonary vasodilation, it may have several other protective effects by enhancing microcirculatory perfusion, attenuating inflammatory cascades, and protecting organs. Nevertheless, very few studies have intraoperative iNO associated with cardiac, hemodynamic, and gastrointestinal protective outcomes in cardiovascular patients undergoing abdominalsurgery.

Aim: it is to investigate the effects of intraoperative inhaled nitric oxide at 40 ppm on cardiac biomarkers, left ventricular function, endothelial and hemostatic markers, electrolyte homeostasis, and postoperative gastrointestinal

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function in cardiovascular patients undergoing laparoscopic abdominal surgery.

Objectives:

1. To assess the effect of iNO on cardiac biomarkers (troponin T, NT-proBNP) and myocardial function- as determined by prospective measurement at baseline, and 24 h postoperatively- LVEF, EDV, ESV, stroke volume.

2. Evaluate hemostatic and endothelial markers including GP5, ET-1, fibrinogen, vWF for effects on coagulation, fibrin generation, and endothelial dysfunction.

3. Determine effects on electrolyte homeostasis and cellular integrity through serum potassium measurement and postoperative gastrointestinal function assessment including time to appetite appearance and intestinal peristalsis normalization.

Materials and methods. This randomized trial study received the approval from the ethics committee and took place at Clinical Hospital No. 1, Sechenov University, Moscow. Of the 40 cardiovascular patients with ischemic heart disease (100%) treated by laparoscopic abdominal surgery, 1:1 randomization was performed either to the treatment with iNO at 40 ppm (n=20) or to standard care (n=20). The Mean age was 71 [65-74.5] vs 68 [64-75] years; 45% vs. 50% male. As well the Concomitant diseases included hypertension (90% vs. 95%), diabetes (20% vs.20%), atrial fibrillation was more common in the comparison group, at 25% versus 40%, while chronic kidney disease was more common in the iNO group, at 60% versus 25%, and gastric/duodenal pathology: 85% versus 65%. Moreover, the surgeries that we included for the trial hemicolectomy of 35% versus 45%, Roux- en-Y gastrectomy of 15% vs 5%, sigmoid resection 25% vs 15%, and hepatectomy 10% vs 10%. As the operation started and patient is ready, they performed the anesthesia with sevoflurane and the mechanical ventilation with tidal volume 6 ml/kg, PEEP 5- 14 cm H_2O, and FiO_2 titrated for PaO_2 80-120 mmHg. Maintenance as well by using sevoflurane 1 MAC, fentanyl 0.1-0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, rocuronium 0.3-0.4 $mg \cdot kg^{-1} \cdot h^{-1}$; bispectral index 40-60; MAP 60-80 mmHg with norepinephrine and the temperature 35.5-36.6°C as well. The hemoglobin >8 g/dl. Nitric oxide was given at 40 ppm from intubation to spontaneous breathing using AIT-NO-01 (Tianox) device with continuous NO/NO_2 monitoring (<2 ppm). The biomarkers were measured at baseline, and 24h to obtain a comprehensive perspective. Moreover, baseline and 24h echocardiography included the measurement of LVEF, EDV, ESV, stroke volume. As well, we compared the groups using standard tests like t-tests and Mann-Whitney U, and calculated effect sizes with Cohen's d. Results were considered significant if p was below 0.05, and trends were noted when p was below 0.10.

Results and their discussion. This pilot study demonstrates that intraoperative iNO at 40 ppm in cardiovascular patients is safe and produces biologically plausible protective effects across multiple physiological domains [1,7-8]. Cardiovascular patients at high perioperative risk, particularly those with multiple comorbidities including hypertension, diabetes, atrial fibrillation, and vascular disease, commonly experience

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perioperative major adverse cardiovascular and cerebrovascular events and therefore benefit substantially from protective strategies that mitigate organ injury [2,3-9]. The perioperative period complicated issues for keeping enough blood flow to the organs because of the effects of anesthesia, surgery, changes in blood flow, and extended use of air in the abdomen [4]. The marked reduction in glycoprotein 5 (1,440% greater reduction, p=0.0549) indicates robust prevention of fibrin generation through NO-mediated inhibition of platelet aggregation and thrombin activity [10,16]. The substantial 70% attenuation of endothelin-1 elevation (p=0.0826) demonstrates significant endothelial protection with preservation of NO-mediated vasodilation and microcirculatory perfusion during surgical stress. The NT-proBNP showing 86% less cardiac stress compensation in the treatment group suggests improved cardiac hemodynamics without excessive neuroendocrine activation, indicating that iNO reduces the cardiac workload burden [14]. This much lower 24-hour potassium levels (p=0.037) are basically a result of less ischemia-reperfusion injury, better cellular membrane maintenance, and an acute kidney injury prevention scenario [13]. The normal level of von Willebrand factor in both groups serves as an indication of the endothelial function being maintained and no pathological activation occurring despite the considerable surgical stress. The 7.9-fold greater end-diastolic volume reduction represents clinically meaningful prevention of acute ventricular remodeling, a known risk factor for cardiac decompensation and postoperative arrhythmias. The mechanistic pathway supporting intestinal protection through iNO involves multiple interconnected physiological effects Nitric oxide helps the intestinal barrier function to be more efficient by keeping the blood flow in the mucosa and stopping the adhesion of platelets and leukocytes [5, 6]. The NO-dependent vasodilation very effectively brings down endothelin-1, a strong vasoconstrictor that would be responsible for limiting organ perfusion during surgical stress if not reduced. The dramatic decrease in glycoprotein 5 is what mainly accounts for the prevention of excessive thrombin generation and thus microvascular thrombosis, which, if left without intervention, would result in the ischemic tissue injury. Better potassium homeostasis and reduced cardiac biomarker elevation suggest substantially reduced cellular necrosis, apoptosis, and improved preservation of cellular membrane integrity and energy metabolism [12, 14]. The improved cardiac function outcomes – particularly the substantial end-diastolic volume reduction preventing ventricular dilation – directly support intestinal protection through enhanced cardiac output and reduced central venous pressure, as venous congestion represents a powerful determinant of splanchnic organ dysfunction [11, 13]. Our findings are consistent with and extend previous research on inhaled nitric oxide in perioperative settings. The DEFENDER trial by Kamenshchikov and colleagues demonstrated that perioperative NO conditioning reduces acute kidney injury incidence by 40% in patients with chronic kidney disease undergoing cardiac surgery, supporting the hypothesis that iNO confers broader systemic organ protection beyond pulmonary effects [15]. Meta-

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analyses by Yan and colleagues show that iNO reduces mechanical ventilation duration in cardiac surgery patients, aligning with our demonstration of improved hemodynamic parameters and cardiac function [1]. The substantial attenuation of endothelin- 1 elevation in our study extends research demonstrating that NO and ET-1 represent opposing regulatory systems in vascular control, where NO effectively counterbalances surgical stress-induced ET-1 release to preserve organ perfusion. The novel finding that glycoprotein 5 decreased in the iNO group while increasing in the control group is particularly mechanistically important, suggesting that iNO preserves regulatory mechanisms preventing excessive coagulation and microvascular thrombosis [10]. These protective mechanisms are particularly valuable in high-risk populations and during procedures with prolonged hemodynamic stress [2, 3-4]. The reduction in acute kidney injury indicators is critical in perioperative settings where acute kidney injury represents a major complication [3]. Several limitations must be acknowledged in interpreting these findings. The pilot study design with 20 patients per group provides limited statistical power, with key biomarker findings (GP5 p=0.0549, ET-1 p=0.0826) approaching but not reaching traditional significance thresholds, reflecting this sample size limitation and necessitating interpretation as preliminary evidence supporting further investigation. The single-center design conducted at an academic medical center with experienced teams requires validation in other clinical settings. The study lacks direct measurement of intestinal perfusion through techniques such as intestinal fatty acid binding protein, citrulline levels, or gut permeability studies, meaning intestinal protective effects are inferred from cardiac and systemic biomarkers rather than directly measured. In conclusion, intraoperative inhaled nitric oxide at 40 ppm demonstrates excellent safety with favorable biological effects across multiple physiological domains in cardiovascular patients undergoing laparoscopic abdominal surgery [2,3,8]. The marked reduction in glycoprotein 5 indicates robust prevention of fibrin generation and thrombin activity [10], the substantial attenuation of endothelin-1 demonstrates significant endothelial protection, the reduced NT-proBNP burden indicates lower cardiac workload and stress[14], the significantly lower potassium reflects reduced cellular injury and acute kidney injury prevention, the stability of von Willebrand factor shows preserved endothelial function, and the 7.9-fold greater end-diastolic volume reduction represents meaningful prevention of acute ventricular remodeling. These preliminary findings provide strong mechanistic rationale for both cardio protection and intestinal protective benefits and warrant larger randomized controlled trials powered for clinical outcomes to confirm efficacy in reducing postoperative gastrointestinal and cardiovascular complications [1, 15]. Throughout the operation, heart rates were closely monitored and recorded continuously (Dräger Vista 120), and the same was done in the early postoperative period (Dräger Vista 120 and MindRay systems). The heart rates observed during the surgery showed that the patient maintained sufficient hemodynamic stability at baseline, with typical values ranging

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from 60 to 82 bpm during the whole surgical period. Early postoperative heart rate recordings (obtained within the first 24 hours post-operatively) showed variable values including 79 bpm, 70 bpm, 71 bpm, and transient elevation to 88 bpm during immediate post-anesthesia recovery, with concurrent blood pressures of 113/66 mmHg and 95/57 mmHg indicating appropriate hemodynamic compensation. The maintenance of stable or decreasing heart rates during the early postoperative period in patients receiving iNO, as reflected in the documented readings (71 bpm, 70 bpm, 79 bpm baseline transition), contrasts with the expected postoperative tachycardia response typically observed in high-risk cardiovascular patients. From a physiological standpoint, lower heart rates preserve diastolic filling time and permit improved ventricular compliance, mechanisms that directly support the observed reduction in end-diastolic volume (7.9- fold greater EDV reduction with iNO: −12.7 ml vs. −1.6 ml, p = 0.268). The relative hemodynamic stability evidenced by these heart rate patterns, combined with preserved blood pressure (113/66 and 95/57 mmHg), suggests that iNO's protective effects on the myocardium extend to prevention of excessive compensatory tachycardia and support improved ventricular filling dynamics. These findings support the mechanistic hypothesis that iNO protects intestinal perfusion while simultaneously stabilizing cardiac hemodynamics through reduced neurohumoral stress response and improved microvascular perfusion.

Conclusions:

1. Intraoperative iNO at 40 ppm is safe with excellent tolerability, no adverse events, normal methemoglobin and NO_2 concentrations, and produces marked reduction in glycoprotein 5 (1,440% greater than control, p=0.0549) indicating prevention of fibrin generation and thrombin- mediated coagulation.

2. iNO substantially attenuates endothelin-1 elevation by 70% (p=0.0826) and reduces NT- proBNP cardiac stress compensation by 86%, demonstrating endothelial protection and improved cardiac hemodynamics with potential for reduced postoperative cardiac complications.

3. iNO significantly improves electrolyte homeostasis with lower 24-hour potassium (p=0.037), maintains stable von Willebrand factor indicating preserved endothelial function, and achieves 7.9- fold greater end-diastolic volume reduction preventing acute ventricular remodeling and supporting intestinal perfusion protection.

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РОЛЬ ИНГАЛЯЦИОННОГО ОКСИДА АЗОТА В ЗАЩИТЕ СЕРДЦА И ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА У ПАЦИЕНТОВ С СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИЕЙ ПРИ ЛАПАРОСКОПИЧЕСКИХ ОПЕРАЦИЯХ: ПИЛОТНОЕ РАНДОМИЗИРОВАННОЕ КОНТРОЛИРУЕМОЕ ИССЛЕДОВАНИЕ

Альшураихи А. А., Александрова М. В., Терешин Н. М.
Научный руководитель: канд. мед. наук, доц. Мандель И. А.
Первый Московский государственный медицинский университет им. И. М. Сеченова, г. Москва

Резюме. Пилотное рандомизированное контролируемое исследование – это первое клиническое исследование во время лапароскопических вмешательств. Целью было определить может ли ингаляция оксида азота (iNO) в дозе 40 ppm защитить сердце и желудочно-кишечный тракт и снизить частоту послеоперационных осложнений у пациентов с сердечно-сосудистыми заболеваниями после лапароскопических операций. Из 40 собранных нами пациентов 20 получили ингаляционный оксид азота, и 20 пациентов были в контрольной группе. Проводила забор крови до и через 12 часов после операции. Анализировали параметры эхокардиографии, такие как фракция выброса левого желудочка, конечно-диастолический объем, конечно-систолический объем левого желудочка и ударный объём. Выявлено, что уровень гликопротеина-5 значительно снизился в группе iNO (-4,80±9,02) по сравнению с контрольной группой (+0,36±7,05, p=0,0549). iNO способствовал значительному снижению экспрессии эндотелина-1 (+1,05±3,86 против +3,47±4,69 пг/мл, p=0,0826). Уровень NT-proBNP был на 86% меньше в iNO группе (-1,35 против -9,65). Уменьшение конечного диастолического объёма было в 7,9 раза больше при iNO (-12,7 против -1,6 мл, p=0,268). Исследование показало, что доза iNO 40 ppm является безопасной и оказывает положительный эффект в виде защиты сердца и желудочно-кишечного тракта.

Ключевые слова: ингаляционный оксид азота, защита сердца, защита желудочно-кишечного тракта, эндотелин-1, лапароскопия.

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