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Intermittent Remote Ischemia as a Perioperative Protective Factor in Abdominal Surgery

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Abstract

Introduction: Preconditioning therapy with intermittent Remote Ischemia (RII) has been shown to offer benefits in the event of a major ischemic event. Due to these encouraging results, studies have been carried out mainly in animals that demonstrate that conditioning with remote intermittent ischemia promotes angiogenesis and decreases the damage caused by ischemia-reperfusion.

Material and Methods: Longitudinal, prospective, experimental study randomized clinical trial type. All patients over 45 years of age were included, A blood pressure cuff with different time cut-offs was placed in the leg was to mimic RII.

Results: Fifty patients were included, with a mean age of 56.5 ± 12.2 years, 58% were women. Twenty-five patients per group were recruited. We did not find that the use of RII was significantly associated with shorter surgical time, or a lower incidence of intraoperative hypotension, vasopressor requirements, or lower intraoperative lactate levels. At follow-up at 12, 24, and 48 h, there was a greater elevation in blood troponin levels in the control group (5.2 *vs*. 3.6 ng/ml at 12 h and 5.8 *vs*. 3.4 ng/ml at 24 h and 8.9 and 5.2 ng/ml at 48 h), however, in the three times, it was not significantly different.

Conclusion: In our study, we did not find an associated benefit of the technique with respect to patient outcomes, quantifiable myocardial injury due to troponins, or 30-day mortality; however, it is possible that the benefit could be found in a cohort with much greater number of patients.

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Introduction

The 30-day mortality associated with noncardiac surgery, exceeds 2%, and exceeds 8% in patients with high cardiovascular risk. Cardiovascular complications are the most common causes of postoperative morbidity and mortality [1]. Major vascular complications include acute myocardial infarction, non-fatal cardiac arrest, and stroke, with Acute Myocardial Infarction (AMI) being the most frequent cause (5.7%) [2].

In the pathophysiology of perioperative myocardial infarction there are two potential mechanisms involved. The first of these is the formation of a thrombus in the coronary artery due to the inflammatory and hypercoagulable state induced by surgical stress and tissue damage. Recent studies show that patients with perioperative acute coronary syndrome have angiographic findings consistent with thrombotic complications, and the frequency of these findings is similar to that of patients presenting with non-surgical acute coronary syndrome. The second mechanism is the imbalance between myocardial oxygen supply and demand. On the one hand, the physiological response to surgical stress, which persists several days after the intervention, increases oxygen consumption and, on the other, multiple not infrequent circumstances during surgery and the postoperative period, such as hypotension, anemia, hypoxia or hypovolemia, decrease their contribution [2].

Perioperative myocardial infarction in patients who underwent non-cardiac surgery is an important clinical problem, due to the low prevalence of its diagnosis due to its low clinical suspicion. However, most of these occur in the first 48 h after the surgical procedure [3], which

makes it necessary to take paraclinical studies after surgery to obtain a timely diagnosis. Among these studies is the measurement of creatine phosphokinase and its MB fraction, cardiac troponins, as well as an electrocardiogram; however, these studies are not routinely performed in patients undergoing non-cardiac surgery, unless they present symptoms suggestive of an acute coronary syndrome [4,5].

The estimation of cardiovascular risk in the preoperative period improves the prognosis of patients with a higher probability of presenting a cardiovascular complication in the postoperative period [6]. However, the most widely used risk predictor models to date have limitations and tend to underestimate this risk. The main objective was to evaluate whether remote intermittent ischemia therapy offers a protective effect against cardiovascular complications when applied perioperatively in patients older than 45 years who will undergo major abdominal surgery.

Materials and Methods

A prospective and randomized study was carried out at the University Hospital "Dr. José Eleuterio González" from the Autonomous University of Nuevo León. All participants were previously informed of the procedures that will be carried out and will have to have signed an informed consent.

All patients over 45 years of age, regardless of gender, who underwent elective major abdominal surgery and who signed the informed consent were included. Pregnant patients with a history of deep vein thrombosis, Raynaud's disease and a history of severe respiratory condition were excluded. As well as patients who during their postoperative evolution presented a picture of severe abdominal sepsis.

A sample size calculation was made from a means calculation formula in two populations. Considering a cut-off point for high-sensitivity troponin T levels of 24 ± 15 ng/L after major abdominal surgery [7,8]. A halving of the mean high-sensitivity troponin T levels in the intervention group managed with remote intermittent ischemia (12 ± 15 ng/L), a power of 80% and a two-tailed significance level of 5%, at least 25 patients per group were required [9].

Therefore, it was decided to include 50 patients in the study, who were divided by means of simple randomization into two groups of 25 people each. Both groups underwent a clinical history, blood studies, electrocardiogram, preoperative assessment of surgical risk and their postoperative evolution will be evaluated during the first 30 days.

The randomization process was performed using, sequentially numbered envelopes, sealed and tamper-evident. They were carried out in blocks of 10 people (5 controls and 5 with preconditioning) to have a better control of the sample distribution. The envelope was opened until it was irreversibly assigned to one of the participants. Group 1 was made up of 25 people to whom a cuff was placed on the lower extremity at a pressure of 5 mmHg.

Group 2 was made up of 25 people in the same way, who were placed a blood pressure cuff and given a cycle of intermittent remote ischemia therapy with a pressure >200 mmHg in the operating room area after endotracheal intubation, before to start the surgical procedure.

Variables and units of measure

A database was created with information on the patients: Age, sex, history of chronic degenerative diseases (DM2, HAS), smoking, and BMI, as well as the already stipulated laboratory studies, which were: Hematic biometry, chemical blood, lipid profile and high-sensitivity cardiac troponins.

Vital signs were recorded during each of the six visits, and the presence of variation in these was evaluated before, during, and after the surgical intervention. In the same way, data of the surgical procedure such as duration, quantification of total bleeding, hypotension and use of vasopressors during the intraoperative period were obtained.

Information processing, analysis and interpretation

Upon enrollment in the study, participants were assigned by simple randomization into two groups. Both groups consisted of patients who underwent an elective major surgical procedure (major abdominal surgery). Both groups underwent a clinical history, EKG taking, and laboratory studies to perform a pre-surgical assessment. On the day of the scheduled surgery, in the operating room area after orotracheal intubation, the participants in group 1 (control) were placed a blood pressure cuff with a pressure of 5 mmHg on the left leg for 5 min with 10 min rest for 3 cycles. Group 2 was fitted with the same sphygmomanometer starting with intermittent remote ischemia therapy, which consisted of 3 cycles of 5 min of ischemia with a sphygmomanometer cuff placed on the left arm at 200 mmHg and later 10 min of reperfusion.

After the surgical procedure, both groups underwent serial measurement of cardiac troponins at 12, 24, and 48 h, a new electrocardiogram, and a complete blood count and blood chemistry at 24 and 48 h postoperatively. Based on the results, if data suggestive of myocardial injury was found, an evaluation by the cardiology service was requested.

At the end of the study, the clinical information obtained was analyzed, as well as the comparison of laboratory results and physical measurements. Descriptive and inferential statistical analysis was performed, and it was evaluated whether there was any significant difference between the groups in terms of the clinical and laboratory parameters described above. The analysis was carried out using the IBM SPSS Statistics program.

It was reported in case of withdrawal from the study or exclusion of participants during the study and the reasons for leaving the study. In addition to notifying complications or serious adverse effects that occurred during the study to the committees involved. Until now, only transient pain at the site of intermittent ischemia has been reported in the literature, so the patient was informed that he should notify in case of presenting symptoms such as pain, color changes, lower limb edema, or paresthesia's [10].

In case of presenting this, medical attention would be provided. Or if during the conduct of the study the participant presented any other symptom or complication of his underlying conditions, he was referred for timely attention.

Results

A total of 50 patients were included in the study. The mean age was 56.5 ± 12.2 years; the majority was women (58%). Table 1 describes their baseline characteristics. Twenty-five patients underwent the intervention with remote Intermittent Ischemia (RII) preconditioning and included 25 controls.

Of the total number of patients, 14 (28%) had a history of

Table 1: Baseline characteristics of the patients.

Variable	Global	Control	RII	P
Age	56.5 ± 12.2	58.2 ± 11.4	54.8 ± 12.9	0.318
Gender				0.39
Female	29 (58%)	16 (64%)	13 (52%)	
Male	21 (42%)	9 (36%)	12 (48%)	
Weight (kg)	74.4 ± 13.3	74.9 ± 14.0	75.9 ± 12.9	0.787
Height (m)	1.63 ± 0.07	1.62 ± 0.07	1.65 ± 0.07	0.141
BMI (kg/m2)	28.1 ± 4.7	28.5 ± 5.1	27.7 ± 4.2	0.585
Alcoholism	14 (28%)	6 (24%)	8 (32%)	0.529
Smoking	16 (32%)	5 (20%)	11 (44%)	0.069
Type 2 Diabetes Mellitus	10 (20%)	5 (20%)	5 (20%)	0.999
Arterial Hypertension	21 (42%)	9 (36%)	12 (48%)	0.39
Heart Disease	4 (8%)	3 (12%)	1 (4%)	0.297
Oncologic Surgery	19 (38%)	9 (36%)	10 (40%)	0.771

Table 2: Preoperative assessment of patients: Cardiac risk, anesthetic and vital signs.

Variable	Total	Control	RII	P
Lee				0.551
1	21 (42%)	10 (40%)	11 (44%)	
2	28 (56%)	15 (60%)	13 (52%)	
3	1 (2%)	0 (0%)	1 (4%)	
ASA				0.131
I	8 (16%)	2 (8%)	6 (24%)	
II	20 (40%)	10 (40%)	10 (40%)	
III	15 (30%)	7 (28%)	8 (32%)	
IV	7 (14%)	6 (24%)	1 (4%)	
Respiratory Breathing	17 (15-20)	18 (15-20)	17 (15-20)	0.945
Heart Rate	83 (75-93)	84 (69-100)	81 (75-90)	0.443
Systolic Blood Pressure	120 (110-130)	120 (110-130)	120 (115-130)	0.494
Diastolic Blood Pressure	70 (60-80)	70 (60-80)	70 (65-80)	0.616
EKG				0.203
BRD	1 (2%)	1 (4%)	0 (0%)	
FA	2 (4%)	2 (8%)	0 (0%)	
S/A	47 (94%)	22 (88%)	25 (100%)	

alcoholism, 16 (32%) smoking, 10 (20%) diabetes mellitus, 21 (42%) arterial hypertension, 4 (8%) heart disease, and 19 (38 %) were operated due to oncological surgery.

We did not find significant differences in the baseline characteristics of the patients. Patients are classified according to the Lee Cardiac Risk Index with 1 point for 21 (42%) patients, 2 points for 28 (56%), and 3 points for 1 (2%). They were classified according to the ASA classification as I to 8 (16%), II to 20 (40%), III to 15 (30%) and IV to 7 (14%).

Median heart and respiratory rates were 17 (15-20) breaths per minute and 83 (75-93) beats per minute. Median systolic and diastolic blood pressures were 120 (110-130) mmHg and 70 (60-80) mmHg, respectively. Based on the baseline electrocardiogram, two patients with atrial fibrillation and one patient with right bundle branch block were identified (all of them from the control group). We found no

Table 3: Preoperative laboratory parameters of patients.

Variable	Global	Control	RII	P
Hemoglobin (g/dL)	12.8 (10.9-14.6)	12.7 (11.3-14.5)	12.9 (9.7-15)	0.869
Leukocytes	10.1 (7-13.2)	9.7 (5.9-12.8)	10.8 (7.8-14.4)	0.352
Platelets (× 10^6)	268 (188-305)	256 (183-296)	272 (210-336)	0.56
Glucose	110 (93-142)	114 (87-152)	109 (103-130)	0.6
BUN	14 (10.7-24.7)	13 (8-26.5)	15 (12-23.5)	0.22
Creatinine	0.9 (0.7-1.3)	0.9 (0.6-1.2)	0.9 (0.7-1.3)	0.741
High Cholesterol	7 (14.3%)	2 (8.3%)	5 (20%)	0.226
Hypertriglyceridemia	11 (22.4%)	6 (25%)	5 (20%)	0.675
High LDL	3 (6.1%)	1 (4.2%)	2 (8%)	0.516
Cholesterol/High HDL	39 (79.6%)	17 (70.8%)	22 (88%)	0.128

Table 4: Vital signs, troponin levels a level of pain reported by the patients at 12 hours of postoperative follow up.

Variable	Global	Control	RII	P
Respiratory breathing	16 (15-19)	17 (15-19)	16 (14-18.5)	0.446
Heart rate	87 (76-95)	90 (75-98)	86 (76.5-90)	0.496
Systolic Blood Pressure	120 (110-132)	115 (105-135)	120 (110-135)	0.575
Diastolic Blood Pressure	70 (68-80)	70 (70-80)	80 (60-80)	0.602
Troponins 12 hours	4.25 (1.97-12.85)	5.2 (2.25-16.55)	3.6 (1.55-9.4)	0.473
Pain (EVA)	4 (2-4)	3 (2-4)	4 (2.5-5)	0.38

significant differences in cardiac risk, anesthetic risk, preoperative vital signs, or the presence of electrocardiographic changes in the patients (Table 2). No acute myocardial infarction was found in our groups.

Table 3 describes the baseline laboratories of the patients before surgery. We also found no significant differences in the preoperative laboratory parameters of the patients in both groups.

At 12-h follow-up, we found no differences in the vital signs of the patients. Although troponin levels were lower in the RII intervention group (3.6 *vs.* 5.2 ng/ml, P=0.473), it was not significantly higher. The level of pain between patients in both groups was equally comparable (3 *vs.* 4 points, P=0.038) (Table 4).

Regarding interleukin levels before and after surgery, we found no significant differences, evaluating each group separately (Table 5).

Analysis was performed to determine if there was a difference in interleukin levels between the postoperative and baseline measurements between one group and another. We observed in the control group a decrease of 1.95 pg/ml of IL-1b postoperatively, while in the group with RII there was no change (0 pg/ml) (P=0.039). We found no differences in the changes in the levels of the rest of the interleukins between groups (Table 6).

Discussion

While restoration of blood flow to the ischemic heart is important to improve clinical outcome, the reperfusion process itself can paradoxically induce irreversible cell damage, referred to as cardiac reperfusion injury [11].

Many of the published clinical trials have shown that ischemic postconditioning can mitigate infarct size [12]. However, both ischemic preconditioning and postconditioning require invasive

Table 5: Comparison of interleukin level changes by group before and after.

Variable	RII			Control		
	Basal	Post Op	P	Basal	Post Op	P
IL1b	0.01 (0.01-0.01)	0.01 (0.01-4.4)	0.214	1.96 (0.01-7.94)	0.01 (0.01-4.48)	0.248
TNF	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.686	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.465
IL10	0.01 (0.01-229.5)	0.01 (0.01-340.4)	0.753	0.01 (0.01-327)	0.01 (0.01-306.8)	0.31
IL6	11.03(0.01-23.29)	9.95 (0.01-28.62)	0.753	6.22 (0.01-42.29)	14.37 (0.01-61.54)	0.959

Table 6: Comparison of interleukin level changes between groups.

Variable	RII	Control	P
Δ IL 1b	0 (0 a 4.05)	-1.95 (-6.94 a 0)	0.039
Δ TNF	0 (0 a 0)	0 (0 a 0)	0.653
Δ IL 10	0 (-165.45 a 0)	0 (0 a 176.36)	0.452
Δ IL 6	0 (-15.01 a 8.47)	0 (-15.69 a 5.77)	0.886

procedures that can present high risk in a clinical setting [13-18].

Given the increased risk of cardiovascular complications, and the increase in postoperative mortality due to cardiovascular disease after surgery, it was decided to address the issue of cardioprotection of RII in abdominal surgeries [19,20].

We did not find that the use of RII was significantly associated with less intraoperative bleeding, shorter surgical time, or a lower incidence of intraoperative hypotension. Neither was it associated with a lower requirement for vasopressors or lower intraoperative lactate levels.

At follow-up at 12 and 24 h, there was a greater elevation in blood troponin levels in the control group (5.2 *vs.* 3.6 ng/ml at 12 h and 5.8 *vs.* 3.4 ng/ml at 24 h), and a general increase in troponin levels was identified at 48 h, of 8.9 and 5.2 ng/ml in the control group and RII group, respectively, however, in the three times, it was not significantly different.

In addition, there was no alteration in the other laboratory parameters or in the vital signs of the patients during the 48-h follow-up. After hospital discharge, the patients were followed up for 30 days. It was found that 2 (4%) patients died, corresponding to 8% of the control group and 0% of the RII group. Despite this null 30-day mortality in the RII group, no significant difference was observed in this variable.

This technique has been widely studied for different surgeries associated with cardiovascular protection; however, to our knowledge, it is the first study that addresses cardioprotection of the patient associated with non-cardiac surgery. The first attempt was made by Gunayidin et al. in coronary bypass surgery, however, the results found could be related to the lower power of the study [21], which could also have been associated in our work.

Similar to our study, Zhang et al. they did not find an impact of the technique on 30-day mortality in 8 studies evaluated by coronary bypass grafting [22]. However, Thielmann et al. found in their clinical trial that the technique has an impact on mortality at one year, as well as adverse cerebrovascular and cardiac events at one year, after the administration of the remote ischemic post-conditioning technique after anesthesia induction [23].

In patients undergoing valve replacement surgery with or without coronary bypass, no differences have been found in the application of preconditioning with or without remote postconditioning [24], nor has an alteration in cardiac biomarkers been seen in patients at risk [25].

So far, the technique appears to be beneficial, although there is some controversy regarding its use, which could have had an impact on our findings, as well.

First, it is possible that most of the studies, including ours, have had little representativeness of the impact that it may have, or that the impact may be beneficial in a certain number of patients from a high group of patients, raising the number needed to try intervention.

Second, it is possible that the lack of representativeness of patients with properly defined cardiovascular risk, or that the study was not carried out exclusively in patients with cardiovascular risk or comorbidity, may have had an effect by underestimating the impact of the technique, since it included to a proportion of patients without cardiovascular risk that could have masked the benefits of the intervention.

Lastly, this technique seems to be more appropriate for certain specific populations, with cardiovascular risk, or who are at risk for other organs that could also benefit, such as the kidney, 32 brain, 32, 33 transplanted solid organs, 34 livers, among others.

That is why it would be worth detailing in a certain sub-analysis of a larger cohort of patients to verify the factors associated with receiving a benefit in the intervention. This is because it is an accessible, free intervention that can reduce the risk of complications and cardiovascular morbidity and mortality after any type of surgery.

Conclusion

This study details the first results obtained from a protocol where RII was intervened in patients undergoing non-cardiac surgery, exclusively abdominal, after the controversial evidence about the benefit of this technique in patients with cardiovascular risk or undergoing cardiac surgery. We did not find an associated benefit of the technique with respect to patient outcomes, quantifiable myocardial injury due to troponins, or 30-day mortality, however, it is possible that the benefit could be found specifically in those in whom the evidence dictates that they may benefit more from the technique due to their cardiovascular risk.

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