Long-Term Results of One Cycle Of Remote Ischemic Preconditioning Applied Before Elective Percutaneous Coronary Intervention

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ABSTRACT

Introduction: Myocardial injury after percutaneous coronary intervention (PCI) is frequently seen. Ischemia/reperfusion injury, side branch occlusion and distal embolisation of atherothrombotic debris are the main causes of myocardial injury. Remote ischemic preconditioning (RIPC) is a promising technique for protection from ischemia/reperfusion injury, but there isn't sufficient data of long-term clinical outcomes. In this study we planned to investigate the effect of one cycle of RIPC on major cardiovascular events one year after elective PCI.

Materials and Method: 102 patients, undergoing elective PCI, with normal baseline cTroponin-I (cTn-I) values, were randomized equally into two groups .5 minute of ischemic preconditioning was applied before the intervention to the preconditioning group, by inflating blood pressure cuff up-to 200mmHg on non-dominant arm. After 1 year, the clinical outcomes of these patients (angina, heart failure, death, myocardial infarction, repeat revascularisation) were questioned.

Results: 90 of these 102 patients could be reached after 1 year. The mean duration of follow-up was 432 vs 423.5 days (p=0.793). Post-PCI 16th hour cTn-I was insignificantly lower in the preconditioning arm (0.079 µg/L vs 0.069 µg/L, p=0.074). The incidence of cTn-I elevation 5 fold above the URL (>0.115 µg/L) was lower in the preconditioning group, but it was also insignificant (24.4 % vs 13.3 %, p=0.301). Death, MI or repeat revascularisation rates did not differ between groups.

Conclusion: One cycle of RIPC had no effect on MACE after elective percutaneous coronary intervention.

Keywords: Remote ischemic preconditioning; percutaneous coronary intervention.

Elektif Perkütan Koroner Girişim Öncesi Uygulanan Uzaktan İskemik Önkoşullanmanın Uzun Dönem Sonuçları

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ÖZET

Giriş: Perkütan koroner girişim sonrası miyokard hasarı sıklıkla görülmektedir. Miyokard hasrarı iskemi/reperfüzyon hasarına, yan dal tıkanmasına ve aterotrombotik debrisi distal embolizasyonuna bağlı gelişmektedir. Uzaktan iskemik önkoşullanma iskemi reperfüzyon hasarından korunmada ümit verici tekniklerdendir ancak uzun dönem sonuçları ile ilgili yeterli veri henüz bulunmamaktadır. Biz bu çalışmada perkütan koroner girişim öncesi uygulanan tek sefer uzaktan önkoşullanmanın 1 yıl sonunda majör kardiyovasküler olaylar üzerine etkisini araştırmayı planladık.

Hastalar ve Metod: Elektif perkütan koroner girişim planlanan 102 hasta çalışmaya alındı ve hastalar 2 gruba randomize edildi. Önkoşullanma grubundaki hastalara girişimden önce, kan basıncı manşonu 5 dakika

boyunca 200 mmHg'da şişirilerek, önkoşullanma uygulandı.İşlem öncesi ve sonrası cTroponin-I değerlerine bakıldı. Birinci yıl sonunda hastaların klinik durumları sorgulandı (angina, kalp yetersizliği,ölüm, miyokard enfarktüsü, tekrar revaskülarizasyon).

Bulgular: Yüz iki hastanın 90'ına ulaşılabildi. Ortalama takip süresi 432 vs 423.5 gün (p=0.793). Ön koşullanma grubunda koroner girişim sonrası 16. saat c-Troponin –I dereğeri kontrol grubuna göre daha düşük bulunda ancak istatistiksel analamlılık saptanmadı (0.079 µg/L vs 0.069 µg/L, p=0.074). C-Troponin-I 5 kat arttığı hasta oranı da önkoşullanma grubunda daha azdı ancak bu fark da istatistiksel olarak anlamlı saptanmadı (24.4 % vs 13.3 %, p=0.301).Ölüm, miyokard enfarktüsü ve tekrar revaskülarizasyon açısından gruplar arasında fark saptanmadı.

Sonuç: Tek sefer uzaktan iskemik önkoşullanmanın elektif perkütan koroner girişim sonrası majör kardiyovasküler olaylar üzerine etkisi saptanmamıştır.

Anahtar Kelimeler: İskemik önkoşullanma; perkütan koroner girişim.

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Introduction

Myocardial injury after percutaneous coronary intervention (PCI) is frequently observed. Although the prognostic importance of troponin elevation after PCI is under debate (1-3), there are studies reporting that even minor elevations are significant (4). Ischemic pre- or post-conditioning to protect the myocardium from ischemia/reperfusion injury has been investigated in various trials. Remote ischemic preconditioning (RIPC) before elective PCI has been demonstrated as beneficial in protecting the heart from post–PCI myocardial injury (5-7), but there is not sufficient data about its effect on major cardiovascular events (MACE). In remote ischemic preconditioning (RIPC), brief episodes of sublethal ischemia, followed by reperfusion, is applied to decrease myocardial injury. However, the best timing and protocol has not been yet determined. In one study, it has been demonstrated that one cycle of RIPC is also effective in reducing post-PCI myocardial injury (7), whereas in our study with a similar study population, we could not demonstrate cardioprotection with one cycle of RIPC (8). Most of the studies about RIPC evaluated myocardial injury by post-PCI cardiac enzyme elevation, there are a few studies with clinical end-points. Long term effects of RIPC has been investigated in CRISP stent trial and they were able to show a decrease

in MACE ratio (9). Our aim in this study was to evaluate the long term effects of one cycle RIPC on major cardiovascular events.

Methods

We previously conducted a study to assess the effect of one cycle of RIPC after elective PCI, on myocardial injury. This study was a single center randomized study and approved by local ethical committee and registered to clinicaltrials.gov. The details and results of this study were recently published (8). Patients with stable angina pectoris and undergoing elective PCI were randomized into two groups. Exclusion criteria were presence of 1) acute coronary syndrome, 2) left main disease, 3) baseline cardiac Troponin-I (cTn-I) elevation (>0,023ng/ml), 4) hemodynamically instability 5) renal failure (a glomerular filtration rate (GFR) below or equals a threshold value of 60 ml/min/1,73m^2), 6) glibenclamide or nicorandil usage 7) contraindication to cuff inflation in upper extremities (lymphoedema, fistula) 8) suspicion of pregnancy. Patients not giving written informed consent were not enrolled to the study.

Follow-up data of the patients were gathered from outpatient clinic files or by phone call. Eventually 90 of the 102 patients could be reached. Recurrent angina, stent restenosis, thrombosis, revascularization of any lesion, heart failure symptoms, myocardial infarction, death and cerebrovascular incidents were recorded.

Statistical Methods

Statistical analysis was performed using IBM SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY,IBM Corp). Continous variables (heart rate, systolic and diastolic blood pressure etc.) were summarized as mean, standart deviation, minimum, maximum, median and compared by use of Student's t test or Mann-Whitney U test when appropriate. Categorical data (target vessel, lesion type etc.) were expressed as numbers, percentages and compared by use of chi square test. A value of $p<0.05$ was accepted significant.

Results

Ninety of the 102 patients could be reached. Forty-five patients in each group were analyzed.

The demographic data of the patients were listed in table 1. There were no significant differences between the groups in terms of risk factors. The lesion type, target vessel, stenosis severity and Approoach score also did not differ between groups (Table 2). Likewise, there were no procedural differences between two groups regarding the procedural data such as predilatation, postdilatation and total dilatation durations and counts (Table 2).

Post-PCI 16th hour cTn-I values and the cTn-I change (difference between 16th hour and baseline cTn-I values) were also compared in these 90 patients. There were no significant differences between the control group and preconditioning group (0.079 vs 0.069, p=0.074 and 0.073 vs 0.06, p=0.051 consecutively).

The incidence of patients with troponin above the upper reference limit (URL) (>0.023 µg/L) was insignificantly lower in the preconditioning group. (77.7% vs 66.6 % , p=0.101). The incidence of cTn-I elevation 5 fold above the URL (>0.115 µg/L) was lower in the preconditioning group, but it was also insignificant (24.4% vs 13.3 %, p=0.301).

The follow-up data is presented in Table 3. The mean duration of follow-up was 432 (404.8-459.7) days in the control group and 423.5 (406.2-441) days in the preconditioning group (p=0.793). MACE ratio, death, MI, revascularization, angina, heart failure also did not differ between groups. One patient in each group died from subacute stent thrombosis /MI. One patient in the preconditiong group died from acute cerebrovascular incident.

Discussion

The present study demonstrated that one cycle of RIPC just before elective PCI had no effect on long-term cardiac events.

Periprocedural myocardial injury is frequently observed after elective PCI. With the ongoing developments in interventional techniques and stent technology, major complications like death and extensive myocardial infarctions have decreased. Although the prognostic importance of troponin elevation after PCI is under debate (1-3), guidelines recommended troponin measurement to detect myocardial injury (10-12). Particularly pre-procedural troponin elevation is linked to poorer prognosis (13), besides there are studies indicating even minor troponin elevations after PCI have worse prognosis (4).

Side branch occlusion, atherosclerotic debris embolization and ischemia/reperfusion injury are the main reasons of PCI-related myocardial injury. Various adjunctive pharmacological agents and methods have been tried to reduce ischemia reperfusion injury but none of them have been proven (14-16). Remote ischemic preconditioning is an easy, cheap, and practical method. The basics underlying remote ischemic preconditioning is that brief sublethal episodes of ischemia followed by reperfusion in another organ can reduce the hazardous effects of the subsequent ischemia. The whole process of ischemic preconditioning has not yet been understood. Neural pathways, cellular mechanisms and circulating mediators such as adenosine, aldehyde dehydrogenase-2, apolipoprotein A1, nitrite, stromal cell derived factor-1æi, have a role in the potential mechanisms of RIPC (17-21). The earlier animal studies confer a more evident beneficial

effect, whereas clinical studies have conflicting results. Recently published trials of RIPC in CABG surgery could not reveal effective myocardial protection (22, 23), whereas in the acute myocardial infarction setting, the application of remote ischemic conditioning before primary PCI reduced the infact size (24).

Majority of the studies investigating the effect of RIPC before elective PCI, used 3 cycles of 5 minutes ischemia/reperfusion and the results were mostly favourable. CRISP stent trial was the first and largest study demonstrating that 3 cycles of RIPC was successful in reducing myocardial injury (5) Nevertheless not all of the studies supported this conclusion. Prasad et al. (25) used a different protocol with 3 minutes of RIPC instead of 5 minutes. They implied that shorter time of RIPC could be an insufficient stimulant, resulting neutral outcome. Differently, Zografos et al. (7), demonstrated reduced type 4a MI after elective PCI with one cycle of RIPC, whereas in our study we could not demonstrate a significant reduction (8). 6 year clinical outcomes of the patients enrolled in CRISP trial, were also published and the results were coherent with the CRISP trial with lower MACE in the RIPC group(5, 9). Miyoshi et al.(26) recently published a study comparing the effects of RIPC and nicorandil, although postprocedural myocardial injury was lesser than the control group in either treatment group, the results were not statistically significant. Several meta-analysis (27) have been published so far, despite the beneficial effects demonstrated in these articles, the insufficient data about the long term outcomes prevented the translation into daily clinical practice.

In the present study we could not demonstrate any difference between the control group and the RIPC group, in terms of one year clinical outcomes. The study population, method of RIPC, follow-up period and size of the study, are the main potential factors that might cause lack of effect on clinical outcomes. We have recently published the effect of one cycle of RIPC on post-PCI myocardial injury in the same patient population. Failure to achieve significant reduction in myocardial injury with one cycle of RIPC might also be the reason of lack of benefit in the long-term, we might not reach the acquired treshold of preconditioning. The treshold and the effect of RIPC can be affected by numerous factors such as, age, sex, comedications, and comorbidities, but the study was not powerful enough to analyse all the possible confounding factors (28-30). The size of the study could also explain the neutral results, it could be underpowered to demonstrate the moderate differences in post-PCI myocardial injury, leading to a type II error. Another possible reason is that the follow-up period is just about 1 year. In this period, lower rates of MACE have occurred, with longer time of follow-up, the difference in adverse events might be meaningful .

In conclusion, one cycle of RIPC did not have an effect on long term- outcomes after elective PCI. Remote ischemic preconditioning is a promising technique, but still the opitmal protocol and the patients who will have the most benefit have not been determined. Further multicenter studies with large populations

targeting high risk patients are needed to overcome these limitations and evaluate the effects of confounding factors.

Conflict of Interest

The authors declare no potential conflicts of interest.

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Table 1. Demographic and Clinical Data of the Patients

Variable	Controls (n=45)	Preconditioning (n=45)	P
Demographics			
Age, years	60.7 (38-79)	57.4 (39-76)	0.126
Male/Female	37/8	34/11	0.438
Risk Factors			
Hypertension, n (%)	37 (82.2%)	42 (93.3%)	0,102
Hyperlipidemia, n (%)	38(84.4 %)	40 (88.9%)	0,534
Family history, n (%)	7(15.6%)	12(26.7%)	0.194
Smoker, n (%)	33(73.4%)	30(66.7%)	0.490
Diabetes Mellitus, n (%)	13(28.9%)	15(33.3%)	0.649
BMI, kg/m^2	28.4 (26.8 – 29.9)	28,83 (27.5 – 30.2)	0.626
Clinical Features			
LVEF (%)	58 (55.3 – 60.9)	58.3(56 – 59)	0,869
GFR, mL/min/1.73m2	92.6 (86.7 – 98.5)	90.2 (85.1– 95.3)	0.529
CCS 2/3 n/n	29(64.4%)	19(42.2%)	0.035
Previous MI, n (%)	9(20%)	10(2.2%)	0.796
Previous CABG-O, n (%)	3(6.7%)	2(4.4%)	1
Last 24 hour angina, n (%)	6(13.3%)	3(6.7%)	0.485
Medications, n (%)			
β-blockers	43(95.6%)	43(95.6%)	1
ACEI /ARB	33(73.3%)	36(80%)	0.454
Ca-channel Blocker	9(20%)	10(22.2%)	0.796
Statins	32(71.1%)	34(75.6%)	0.633

ACEI, angiotensin- converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCS, Canadian Cardiology Society; CABG-O, coronary artery bypass graft operation; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Table 2. Angiographic and Procedural Data of the Patients.

Variable	Controls (n=45)	Precondtioning (n=45)	P
Angiographic Parameters			
Target vessel, n (%)			0.515
LAD	13(28.89%)	%35.56 (16)	
LCx	5(11.11%)	8(17.78%)	
RCA	18(40.00%)	16(35.56%)	
Combined/other	9(20.00%)	5(11.11%)	
Lesion AHA/ACC, n (%)			0.955
Type A	8(17,78%)	9(20,00%)	
Type B	21(46,67 %)	21(46.67%)	
Type C	16(35,56%)	15(33,33%)	
Approach Score,	27.57 (23.45 – 31.71)	25.07 (21.34 – 28.81)	0.455
Stenosis severity	82.3 (79.51 – 85.1)	82 (79.1 – 84.7)	0.842
TIMI flow 0-2, n (%)	33(73.33%)	38(84.44%)	0.194
Procedural Data			
Heart rate, beats/min	77.5 (74.2 – 76)	74.22 (71.4 – 77.05)	0,134
Systolic blood pressure ,mmHg	138.7 (134.3 – 143.1)	141 (135 – 147)	0,548
Diastolic blood pressure ,mmHg	77.7 (75.3 – 80)	75.38 (73-78)	0.356
Procedural angina, n (%)	23(51.11%)	22(48.89%)	0.833
Procedural ST deviation, n (%)	15(33.33%)	10(22.22%)	0.238
Bifurcation procedure, n (%)	3(6.67%)	4(8.89%)	0.693
DES/BMS/Balloon ,n/n/n	40/5/0	43/0/2	0.007
Stent length ,mm	27.1 (23 – 31.16)	26.14 (22.7 – 29.7)	0.973
Stent number (n)	1.31 (1.16 – 1.47)	1.16 (1.01 – 1.3)	0.185

Table 2 Angiographic and Procedural Data of the Patients (continued)

Variables	Control (n=45)	Preconditioning (n=45)	P
Stent diameter, mm	2.87 (2.75 – 3)	2.81 (2.7 – 2.92)	0,614
Total Dilatation time, s	76 (59.02 – 93)	80,17 (68 – 92.36)	0,686
Predilatation , n (%)	19(42.22%)	20(44.44%)	0,832
Postdilatation , n (%)	28(62.22%)	29(64.44%)	0,827
Predilatation time, s	34.25 (17.91- 50.6)	22.2 (17.15 – 27.2)	0.443
Postdilatation time, s	45.07 (34 – 56.16)	47.6 (38.4 – 56.85)	0.436
Total dilatation count (n)	3.66 (2.85 – 4.50)	3.62 (3.05 – 4.20)	0.472
Post-PCI Results			
TIMI flow 2/3	0 / 45	2 / 43	0.093
cTn-I Values			
Bazal cTn-I	0,006 (0.004 – 0,009)	0.009 (0,007 – 0,011)	0.139
cTn-I rise, median, µg/L (16.saat- bazal)	0,073 (0,051 – 0,094)	0.060 (0.029 – 0.092)	0.051
cTn-I 16.h, median, µg/L	0.079 (0.058 - 0,100)	0,069 (0.036 – 0.101)	0.074
cTn-I > 5 x URL , n (%)	11 (24.4%)	6 (13.3%)	0.301
cTn-I> URL, n (%)	35 (77.7%)	30 (66.6%)	0.101

BMS, bare metal stent; cTn-I, cardiac troponin-I; DES, drug eluting stent; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction, URL; upper reference limit.

Table 3. Follow-up data of the patients

Variable	Controls (n=45)	Preconditioning (n=45)	P
Follow-up duration	432.2(404.8 – 459.7)	423.5(406.2 – 441)	0.793
Angina	10 (22.2%)	10 (22.2%)	1
Revascularization	6 (13.3%)	5(11.1%)	0.748
Heart Failure	0	2(4.4%)	0.494
Death	1(2.2%)	2(4.4%)	0.553
MI	2(4.4%)	1(2.22)	0.553
Stent Restenosis/Thrombosis	1/2	2/1	1
MACE, (%)	2(4.4%)	2(4,4%)	1
Any event	10(22.2%)	10(22.2%)	1

MACE; Major cardiovascular events, MI; Myocardial Infarction