Remote Ischemic Preconditioning and Diabetic Macular Edema

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Received: 01 January 2019

Accepted: 21 February 2019

Published in May 2019

Abstract

Objective: Remote Ischemic Preconditioning (RIPC) as the transient ischemia and reperfusion of the arm is a promising method for protecting different tissue from future ischemia. These effects might be mediated through vascular and endothelial growth factor (VEGF) pathway. We investigated the influence of RIPC on diabetic macular edema (DME) as a chronic ischemic condition in patients who were candidate to receive anti-VEGF therapy.

Materials and Methods: In this Single blinded, randomized controlled trial, 40 eligible type 2 diabetes mellitus (T2DM) patients with macular edema who were candidate to receive anti-VEGF therapy randomized into intervention (CP) and sham controlling (SP). The CP received RIPC in three consecutive days before anti-VEGF injection. Data of optical cochrane tomography (OPC) before and 10 days after procedure were compared as outcomes.

Results: Central foveal volume and visual acuity mean difference before and after intra-vitral anti-VEGF injection in both groups was significant. There were no significant mean differences in central macular thickness in case groups. Comparing the mean between two groups did not show a significant difference in visual acuity, central foveal volume (*P*-value: 0.69) and central macular thickness (*P*-value: 0.62). There were no significant differences in the desired changes pattern of DME between two groups (*P*-value: 1.00).

Conclusion: This pilot study did not show any additive positive effect of RIPC on retinal outcomes especially visual acuity in T2DM patients with DME who were received anti-VEGF treatment.

Keywords: Ischemic preconditioning, Type 2 diabetes mellitus, Macular edema, anti-VEGF

Introduction

Ischemic preconditioning (IPC) is the phenomenon which the short and transient periods of ischemia result in protection against subsequent long-term hazardous ischemic events. When the stimulus applied to a tissue or organ, exerts its beneficial protective effects for ischemia on a remote organ, the phenomenon is called remote ischemic preconditioning (RIPC) (1,2).

Murry et al (1) described RIPC for the first time. They reduced the infarct area size by induction of ischemia on canine circumflex artery after clamping it for a long time (1). Finding showed that RIPC may be activated only short periods of ischemia at extremities, simplified the induction of IPC in experimental studies. Since RIPC causes protective effects at vital organs via induction of ischemia in non-vital organs, it is clinically more practical than direct ischemic preconditioning (3). The RIPC which is induced by this method prevents ischemia-reperfusion injury in human.

Several clinical trials have been conducted regarding the effects of RIPC on ischemic heart diseases, but its beneficial effects have also been evaluated for acute kidney injury (4). Brain and neurologic injuries (5,6), and solid organs (kidney, pancreas, liver, etc.) transplantation (7). In most of these studies, leg or arm has been compressed by an inflated cuff five minutes three times with 200 mmHg pressure, and deflating the cuff at 5 minute intervals.

A systematic review showed that from 2000 to 2011, twenty-two clinical trials have been done for evaluating the effects of RIPC (7).

IPC shows diminished efficacy in animal models of type 2 diabetes mellitus (T2DM) while the efficacy is inconclusive in diabetic humans (8-11). This is attributed to reduced humoral cardio-protective factor release or decreased target tissue response to this factor (12).

IPC causes a protective effect which is transient and lasts 24-72 hours after the stimulation (13,14).

A survey in 2004 showed that IPC attenuated the ischemia-reperfusion injury in retina of rats (15). Chronic ischemia is a principal hallmark of diabetic retinopathy and ischemic pulses antagonize the vascular endothelial growth factor (VEGF) increase in diabetic retinopathy. Indeed, animal studies have shown that injection of VEGF into a healthy eye may cause ophthalmic diseases resembling what occurs during diabetes mellitus. So, it seems that induction of IPC may act as an anti-VEGF treatment (16). In a study on streptozocin-induced diabetic rats, with retinal ischemia induced by increasing intraocular pressure, brief pulses of ischemia reduced the incidence of retinal edema as well as VEGF increment (16).

Diabetic retinopathy is a main etiology of blindness and visual disturbance worldwide (17). There are growing evidence of advantageous effects of anti-VEGF medications in the management of diabetic retinopathy and especially for diabetic macular edema (17,18). Also RIPC through using a simple, noninvasive technique, composing three cycles of 5 min‑ischemia of both upper arms, showing a significant increase in Ankle Brachial Index (ABI) level in diabetic patients (19). The aim of this study was to evaluate the effects of RIPC on diabetic patients who were eligible for intravitreal injection of bevacizumab for the management of macular edema due to diabetic retinopathy.

Materials and Methods

This was a pilot single-blinded randomized controlled trial (RCT) to determine the effect of IPC on diabetic macular edema in patients referring to Yazd Diabetes Research Center.

Inclusion criteria: age between 30-60 years old, at least five years of diabetes history, candidate for anti-VEGF therapy. Exclusion criteria: blood pressure≥160/90 mmHg, triglyceride≥400 mg/dl, total cholesterol≥500 mg/d, previous coronary bypass surgery, severe heart failure requiring percutaneous cardiopulmonary support. This study was a pilot study and therefore we didn't determine sample size for it. Forty patients were selected and put into two groups randomly. Simple randomization was done. The written and oral consent was received from all of the participants. This research was presented to the ethics committee of Shahid Sadoughi University of Medical Sciences and approved by the internal medicine department. The ethics committee approved the study with the number 17/138561 on October 1, 2014. The intervention group (CP) received RIPC on three consecutive days before intra vitrous anti-VEGF injection according to the following protocol:

A standard blood pressure cuff was fastened on the patients' arm and inflated up to 200 mmHg and left inflated for five minutes. Then the cuff was deflated completely for five minutes and this cycle was repeated three times in each day for 3 consecutive days before injection.

In the control group (SP) the mentioned procedure was done through sham treatment, in which the pressure does not cause ischemic conditions for the arm (60 mmHg, two min for each time). In each group, before intervention and ten days after Anti-VEGF (avastin) injection, the OCT (Optical Coherence Tomography) image was provided for patients and its indices (ie, central macular thickness, central foveal volume, visual acuity and also pattern of DME) were compared before and after the procedure and between groups at the end of study.

The trial was registered at the Iranian Registry of Clinical Trials (http://www.irct.ir) with the IRCT ID: IRCT2016080118858N4.

Parametric statistical tests (paired samples T-test and independent samples T-test) were used in the normal variable distribution and in cases where the variables distribution was not normal the non-parametric tests (two independent samples test and two-related samples test) were used. Analysis of data was performed by spss 20 statistical software.

Results

A flow diagram is shown in Figure 1. Forty patients who met the inclusion criteria were selected among 200 patients referred to Yazd Diabetes Research Center for DME. Patient characteristics were similar between the groups, except total and LDL-cholesterol (Table 1). The mean changes of three variables were compared between the two groups (Table 2).

Significant improvement in visual acuity and central foveal volume were observed in both groups after the interventions however comparing the mean between two groups did

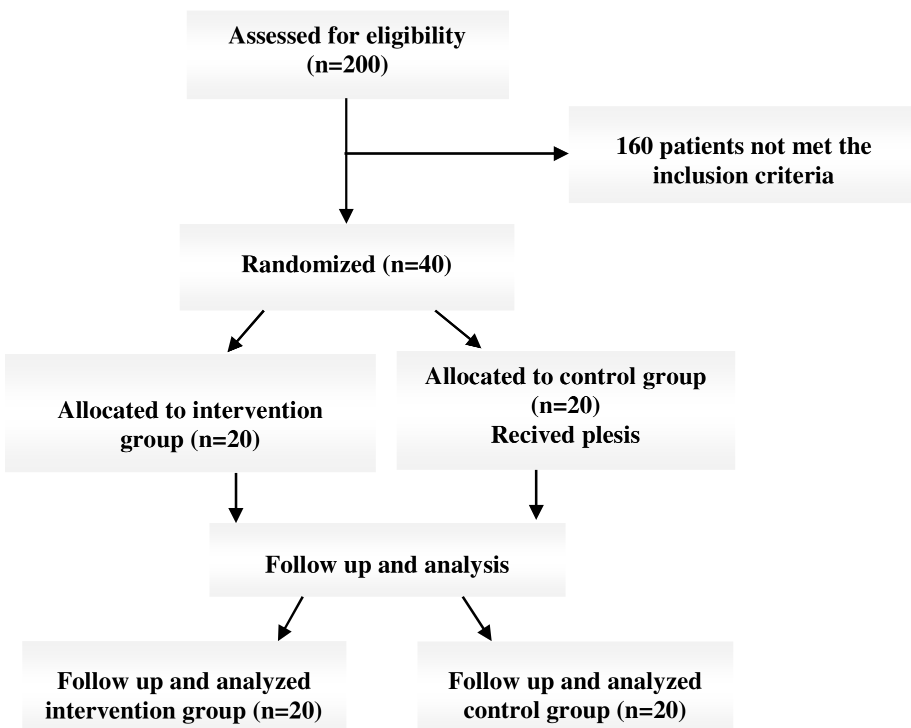

Figure 1. Study flow diagram

not show any significant difference in visual acuity, central foveal volume and central macular thickness before and after the intervention (*P*-value:0.96; 0.69; and 0.62, respectively). It is also found no significant mean differences between groups in central macular thickness (*P*-value: 0.62) and central foveal volume (*P*-value:0.69). Desirable changes in each of the 4 macular edema pattern was attributed to there was a pattern in pre-intervention and did not exist in post-intervention.

As well, desired changes pattern of DME compared between two groups. Desirable change pattern of sponge like retinal swelling had taken in 2 patients in CP (10%) and 3 patients in SP (15%). There were no significant differences in the desired changes pattern of DME between groups throughout the study period (*P*-value: 1.00).

Desirable change pattern of cystoid macular edema was observed in 6 patients in CP (30%) and 6 patients in SP (30%) (*P*-value: 1.00).

Desirable change pattern of sub-retinal fluid was observed in 4 patients in CP (20%) and 5 patients in SP (25%) (*P*-value: 1.00).

In this study, none of the patients had posterior hyaloidal traction pattern so desirable change in the pattern was meaningless.

Discussion

This study showed that in T2DM patients with macular edema undergoing anti-VEGF intra-vitrous injection, RIPC did not alter central macular thickness, central foveal volume, visual acuity and macular edema pattern, as compared to sham preconditioning group. With our best knowledge; this is the first study that evaluates the effect of RIPC on diabetic macular edema and assesses additive effect on anit-VEGF therapy in human. Previous studies showed promising role of RIPC in improvement of macrovascular complication of diabetes mellitus (10,20). Another study assessed RIPC on nondiabetic rats with optic nerve injury and showed beneficial effect on ganglian cell survival (21). In two recent studies the beneficial effect of RIPC on retinal cells in nondiabetic rats were showed (22,23). Retinal ischemia induced by increasing

Table 1. Patient characteristics at the baseline

Variable	Mean ± SD (Frequency)		*P*-value
	Intervention group	Control group	
Age(years)	51.55 (± 8.1)	52.20 ± 5.7	0.772
Sex (male)	10 (25%)	10 (25%)	1.00
Disease duration (years)	15.70 (± 6.2)	14.95 (± 7.4)	0.732
HbA1c (%)	7.83 (± 1.2)	8.29 (± 1.1)	0.230
TG (mg/dl)	162.75 (± 83.2)	148.95 (± 74.2)	0.585
HDL (mg/dl)	42.05 (± 12.7)	42.25 (± 6.4)	0.950
LDL (mg/dl)	109.09 (± 30.1)	70.05 (± 24.6)	< 0.001
TC (mg/dl)	193.95 (± 51.0)	150.75 (± 31.7)	0.003
SBP* (mm Hg)	138.00 (± 19.8)	138.50 (± 14.9)	0.929
DBP° (mm Hg)	81.00 (± 6.9)	71.5 (± 28.3)	0.160
Thickness (µm)	527.25 (± 156.2)	502.15 (± 187.1)	0.648
Volume (mm3)	0.40 (± 0.1)	0.39 (± 0.1)	0.689
Acuity (logMAR)	18.50 (± 5.6)	18.39 (± 6.0)	0.897
Sponge like retinal swelling (%)	19 (47.5%)	19 (47.5%)	1.00
Cystoid macular edema (%)	14 (35%)	14 (35%)	1.00
Sub-retinal fluid (%)	11 (27.5%)	8 (20%)	0.34
Posterior hyaloid traction (%)	0 (0%)	0 (0%)	-

*systolic blood pressure
°diastolic blood pressure

Table 2. Comparison of test results between the two groups

Variable	Mean diffrences ± SD		*P*-value
	Intervention group	Control group	
Thickness	-75.15 (± 167.5)	-101.05 (± 145.4)	0.62
Volume	-0.05 (± 0.11)	-0.07(± 0.11)	0.69
Acuity	-0.11 (± 0.15)	-0.17 (± 0.44)	0.96

intraocular pressure in diabetic rats can protect against diabetic retinopathy with VEGF-correlated mechanism (16). Retinal changes are mediated by increased endothelial permeability secondary to increased VEGF production and based on this study inducible mild ischemia in retina might have anti-VEGF effects. However our study that assessed the effect of RIPC on macular edema in T2DM patients who receive anti-VEGF therapy could not show any additive positive effect on outcomes such as visual acuity. There are some evidences that VEGF pathway is one of the most important mechanisms leading to cell protection in RIPC.(24) In another study RIPC effectively inhibited neurodegeneration and bevacizumab (a VEGF inhibitor) effectively inhibited vascular permeability in response to retinal ischemia. It means that RIPC protective effect for retinal cells in response to ischemia is distinct from bevacizumab (25). Our study was a pilot for evaluating effect of RIPC on macular edema in T2DM patients. Our trial was not able to answer to all questions in this field, definitely. There are needs to do larger studies with more participants and also different protocols of RIPC for evaluating the effect on macular edema.

Conclusions

Pilot study did not show any additive positive effect of RIPC on retinal outcomes especially visual acuity in T2DM patients with macular edema who were received anti-VEGF treatment.

Acknowledgments

This paper was extracted from research project (17/138561) in Yazd Diabetes Research Center, Iran. Special thanks are given to all investigators of Yazd Diabetes Research Center.

Funding

The authors received no financial support for the research or publication of this article.

Conflict of Interest

There is no conflict of interest to be declared.

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