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In: Clinical Hemorheology and Microcirculation (2016) IOS Press

DOI: 10.3233/CH-168101

Effect of Ioxaglate on the cutaneous microcirculation in patients with coronary artery disease: randomized, double blind, placebo-controlled study

U. Gerk[1], C. Mrowietz[2], R. Sternitzky[3], R.P. Franke[4], S.G. Spitzer[3], F. Jung[5]

1: Krankenhaus Dresden-Friedrichstadt, II. Medizinische Klinik, Dresden, Germany
2: Institute for Heart and Circulation Research, Eißendorfer Pferdeweg, Hamburg-Harburg, Germany
3: Praxisklinik Herz und Gefäße, Dresden, and Brandenburgische Technische Universität (BTU), Cottbus-Senftenberg, Germany
4: Department of Biomaterials, Central Institute for Biomedical Engineering, University of Ulm, Ulm, Germany
5: Institute of Biomaterial Science and Berlin-Brandenburg Centre for Regenerative Therapies, Helmholtz-Zentrum Geesthacht, Teltow, Germany

Corresponding author: F. Jung, friedrich.jung@hzg.de

Abstract

Radiographic contrast media (RCM) can initiate microcirculatory disorders. This study was performed to investigate effects of Ioxaglate on the cutaneous microcirculation. The investigation was carried out on two groups of n=10 patients each who had to undergo a diagnostic coronary angiography.

The confirmatory parameter of the study was mean erythrocyte capillary velocity [v_{RBC} in mm/sec]. $\mathbf{V}_{RBC}$ in the ipsilateral nail-fold capillaries was recorded continuously for 3 min before and 6 min after injection of RCM or isotonic saline solution respectively, and was evaluated off-line.

$\mathbf{V}_{RBC}$ in nailfold capillares was found to be decreased by Ioxaglate by 34% 150 seconds after injection, while isotonic NaCl solution immediately induced a slight increase of 14%.

Key words: Cutaneous microcirculation, Ioxaglate, coronary artery disease

Introduction

Radiographic contrast media are widely used to visualize blood vessels in clinical medicine. Ideally, RCM should not affect diameters of the blood vessel lumen [4]. However, all RCMs exhibit a more or less strong effect on endothelial cells [14, 15, 31, 33] as well as on erythrocytes. Three minutes after injection of RCM red blood cells have transformed to echinocytes depending on the type of RCM administered [3, 16, 18, 20, 25]. Concomitantly, a buckling of endothelial cells into the vascular lumen up to the double of height of the endothelial cell and interendothelial fenestrations develops after administration of RCM in different extent [14].

It is very probable that capillary perfusion is deteriorated by echinocytic transformation which leads to a reduction of deformability [26] and buckling of endothelial cells [14].

Indeed, a decline of velocity of RBCs in nailfold capillaries occurred in patients with coronary artery disease after injection of RCM in the supplying artery [5,6]. RCM showing the strongest morphological effects in erythrocytes [18] as well in endothelial cells [15] induced stasis of blood flow in capillaries in some patients up to three minutes [6]. Such microcirculatory disorders after injection of RCM have been shown in animal models as well [23, 24, 28, 35].

In this study the influence of Ioxaglate on the cutaneous capillaries in patients with coronary artery disease when injected into the ipsilateral axillary artery was investigated.

Material and Methods

Study design

The present study was carried out as a single-centre prospective randomized double-blind comparison in parallel-group design with n=10 patients in both groups. The injected medium was assigned at random, using the random permuted blocks procedure. This ensured that 10 patients each would receive one of the two media. The confirmatory variable was mean capillary erythrocyte velocity [mm/sec] in the ipsilateral nail-fold capillaries before and after injection of a bolus of 20 ml Ioxaglate or isotonic NaCl solution respectively into the axillary artery. Blood pressure, heart rate, and skin temperature at the nail fold were recorded during the investigation.

Pharmaceuticals

Both products (see Table 1) are registered at the Federal Institute for Drugs and Medical Devices in this form are available on open market under the names Hexabrix® (Guerbet, Frankfurt) and isotonic sodium chloride solution 0.9% (Fresenius Kabi Deutschland, Bad Homburg).

Table 1

Shows iodine content, osmolality, and viscosity of the media investigated

	Iodine content [mg/ml]	Osmolality [mOsmol/kg]	Viscosity [mPa.sec] at 37°C
Ioxaglate 320	320	580	7.5
NaCl solution	0	310	0.7

Implementation of the study

Directly before the start of each diagnostic cardiac catheter examination a diagnostoc catheter (Judkins right 4, 5 French) was inserted into the left axillary artery distally of the origin of the vertebral artery. Continuous video-recording of blood flow through the nail-fold capillaries of the left hand with intravital capillary microscopy was started 3 min before administration of the investigatory medium.

Customarily measurements were carried out on the 4th finger of the left hand. Merely in injuries of the nail fold the 5th finger was examined. Capillary blood flow was recorded for 3 min then a bolus of 20 ml of the investigational medium was injected. The temperature of the medium was 37°C. The diagnostic catheter

was withdrawn of the axillary artery immediately after injection in order to not influence the perfusion of the arm. Capillary blood flow was recorded continuously for 6 min after administration of the medium. Skin temperature, blood pressure and heart rate were recorded before and once a minute during examination.

Every patient was informed that participation in this study was voluntary and that he could drop out at any time without giving any reasons. The patients were also told about the test substances and their possible side effects. The study was carried out in accordance with the principles of the Declaration of Helsinki/Somerset West 1996, the GCP guidelines. Ethical approval was received from the Ethics Committee of the Medical Council of the State of Saxony. The manuscript complies with the ethical guidelines of Clinical Hemorheology and Microcirculation [1].

All sensations and subjective or objective symptoms observed in the context of the study, regardless of whether or not they were connected with the test substance, were recorded as adverse reactions.

Capillary Microscopy

Video capillary microscopy was done with an optical system consisting of a reflected-light microscope connected to a video recorder system [13, 17]. The whole system comprised a reflected-light microscope with an ACM stage (C. Zeiss, Oberkochen) and a coarse and fine drive, an objective (Neofluar 6.3/0.20), an Optovar 1.0-2.0 (to allow a quick change of post-objective magnification), a cold light source (Schott KL 1500) with a green filter (in the wavelength range of haemoglobin absorption at about 560 nm to ensure good contrast between erythrocytes and tissue) and a heat filter (to minimize heating of the area being recorded), a video camera with a Newvicon tube, a video timer, a 3/4“ video-recorder, and a black-and-white monitor. Depending on the setting of the Optovar, the final magnification was 285-570.

Velocity measurements were made interactively using „Cap-Image“ software (Zeintl, Heidelberg, Germany) [22].

Due to vasomotion, erythrocyte velocity in the capillaries changes between 6 to 10 times per minute [12]. For this reason, erythrocyte velocity was recorded over three minutes, or six minutes respectively, and velocity calculations were done at least 10 times per minute. Highlighted mean erythrocyte velocity given in this manuscript is therefore an average obtained from at least 10 measurements in 2 to 4 capillaries.

Intraindividual variability of $\mathbf{v}_{RBC}$ under resting conditions over one day was examined in 8 apparently healthy subjects [19]. The coefficient of variation (CV) of $\mathbf{v}_{RBC}$ in nailfold capillaries under resting conditions was CV = 23.4% ± 7.8%. There were no significant differences between the four samples ($p > 0.05$).
The intraindividual variability of $\mathbf{v}_{RBC}$ under resting conditions from day to day was examined in nine apparently healthy subjects [19]. $\mathbf{v}_{RBC}$ was measured on five consecutive days in one week at the same time [8 a.m.]. The coefficient of variation CV of $\mathbf{v}_{RBC}$ in nail-fold capillaries under resting conditions was CV = 23.8% ± 9.5%. There were no significant differences between the five samples ($p > 0.05$).
The intraindividual variability of $\mathbf{v}_{RBC}$ under resting conditions over one year was examined in eleven apparently healthy subjects [19]. $\mathbf{v}_{RBC}$ was measured every month for one year at the same time every 1st Monday (8 a.m.). The coefficient of variation CV of $\mathbf{v}_{RBC}$ in nail-fold capillaries under resting conditions was CV = 21.1% ± 7.9%. There were no significant differences between the twelve samples ($p > 0.05$).

Statistics

The estimate of the required number of patients, made in accordance with the principles of Good Clinical Practice, was based on the following assumptions: expected erythrocyte velocity before injection of the medium $\mathbf{v}_{RBC}$ =0.76±0.27 [mm/sec], expected change in erythrocyte velocity after injection of the medium (Δ $\mathbf{v}_{RBC}$ =0.25 [mm/sec], type 1 error 0.05, type 2 error 0.02, power 0.80, correlation coefficient 0.80. The required number of patients was n=2 x 10.
For all samples arithmetic mean and standard deviation are given. The test for normal distribution was carried out as per Kolmogoroff and Smirnow. The significance level was p=0.10.
To check structural similarity of the two groups, homogeneity of the baseline parameters was tested using Student's t-test for continuous variables, the Wilcoxon pair-difference test for not normally distributed random samples, and the χ2-homogeneity test for classified variables.
The statistical analysis was carried out by analysis of variance (model: repeated measurements: 1 within, 1 between). A difference was considered to be significant if $p < 0.05$.

Results

Study group

The study included n=20 patients in whom elective diagnostic cardiac catheterization was to be carried out. The patients recruited were over 18 years of age and their serum creatinine was in normal range. The exclusion criteria were manifest hyperthyroidism, allergy to contrast media, pregnancy or breastfeeding, patients with pathologically increased serum creatinine (> 1.3 mg/dl), and patients in whom, in the opinion of the investigator, the examination would constitute a clinically unacceptable risk.

10 men were included in the Ioxaglate group, and 10 men in the NaCl group. Distributions of pathological somatic cardiovascular risk factors and of the degrees of severity of coronary artery disease (CAD) were comparable in the two groups (see Table 2). Mean age of the patients in the Ioxaglate group was 61.9±10.7 years, in the NaCl group 60.2±12.8 years. Height of the patients was 178.4 ± 6.3 cm and 173.6 ± 6.2 cm respectively. Mean body weight was 91.3±11.9 kg and 84.7±10.8 kg respectively.

Distributions of pathological somatic cardiovascular risk factors and of degree of severity of CAD were comparable in both groups.

Table 2: Risk factors and angiographic results
(HYP: hypertension; DM: diabetes mellitus; DLM: disturbed lipid metabolism; CAD0: no coronary artery disease; CAD1: 1-vessel disease; CAD2: 2-vessel disease; CAD3: 3-vessel disease)

PN	risk factors	diagnosis	artery	age [years]	height [cm]	weight [kg]	sex
1	Hyp DLM	CAD3	RCA,LAD,LCA	59	180	87	m
2	DLM	CAD3	RCA, LAD, CX	36	182	94	m
3	Hyp, DLM	CAD0	LAD	52	164	80	m
4	Hyp DLM DM	CAD3	RCA,LAD,CX	61	180	106	m
5	DLM	CAD2	RCA,LAD	70	168	69	m
6	Hyp Dm DLM	CAD1	RCA	62	174	94	m
7	Hyp	CAD1	LAD	64	172	106	m
8	Hyp	CAD3	RCA, LAD,CX	71	178	74	m
9	Hyp, DLM	CAD0	LAD	58	180	95	m
10	Hyp, DLM	CAD3	RCA, LAD, CX	74	176	81	m
11	-	CAD0	-	48	159	62	m
12	Hyp	CAD0	-	70	178	102	m
13	DLM Hyp	CAD0	-	45	187	96	m
14	DLM	CAD0	-	67	162	67	m
15	DLM	CAD3	RCA, LAD, CX	56	173	79	m
16	Hyp	CAD2	LAD, CX	53	170	90	m
17	Hyp Dm	CAD0	-	57	183	94	m
18	Hyp DLM	CAD1	LAD	71	186	101	m
19	Hyp	CAD2	RCA, CX	78	170	81	m
20	Hyp	CAD3	LCA, LAD, CX	69	168	72	m

Confirmatory variable "Mean erythrocyte velocity $\mathbf{v}_{RBC}$*"*

Figure 1 shows the time course of $\mathbf{v}_{RBC}$ before and after administration of Ioxaglate or NaCl solution, respectively. Immediately after injection of 20 ml Ioxaglate into the axillary artery $\mathbf{v}_{RBC}$ in the ipsilateral capillaries at the nailfold started to decrease. 150 sec after injection the decrease of $\mathbf{v}_{RBC}$ was most pronounced with 35%. Until 180 sec $\mathbf{v}_{RBC}$ was significantly lowered in comparison to the baseline value (non-Bonferoni-adjusted: $p<0.05$ compared with the time-points before infusion; at all later times $p>0.05$). Thereafter $\mathbf{v}_{RBC}$ recovered, reaching baseline values after 360 sec. Overall, however, $\mathbf{v}_{RBC}$ was not significantly affected (ANOVA for repeated measures, $p=0.2759$).

Injection of 20 ml of isotonic NaCl solution, however, led to a slight but significant increase in $\mathbf{v}_{RBC}$ of 14% 10 sec after injection ($p<0.05$). Thereafter $\mathbf{v}_{RBC}$ returned to baseline values.

Time course of $\mathbf{v}_{RBC}$ after injection of both media differed between Ioxaglate and NaCl solution significantly (ANOVA, model 1 within, 1 between: $p=0.002$).

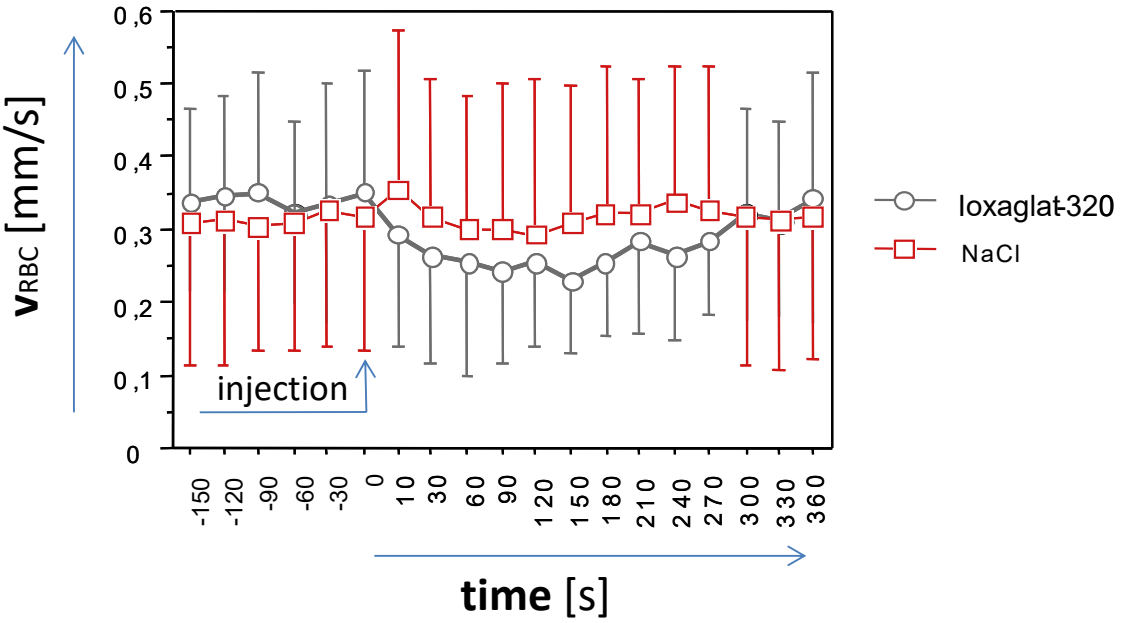

Figure 1: Mean erythrocyte velocity v_{RBC} in [mm/s] in nailfold capillaries of patients with coronary artery disease prior and after a bolus of 20 ml each of Ioxaglate or NaCl solution into the A. axillaris
(Arithmetic mean ± standard deviation)

Relevance of the results

Standard difference „SD“ according to Cohen [11] was calculated to assess whether reduction in velocity should be regarded as relevant. This is a measure of velocity difference produced by the injected media in relation to the variability of capillary erythrocyte velocity. Values greater than 0.8 should be considered as biometrically relevant.

Ioxaglate 320: SD = (0,352 mm/s - 0,230 mm/s) / 0,160 mm/s = 0.76

NaCl: SD = (0,318 mm/s - 0,362 mm/s) / 0,160 mm/s = 0.28

The study revealed that the decrease of velocity of red blood cells after injection of Ioxaglate can be assessed as biometrically weak, the increase after injection of NaCl solution as very weak.

The skin temperature on the nail fold, the heart rate, and the systolic and diastolic blood pressure were recorded exploratively at 6 time-points. There was no influence on systolic and diastolic blood pressure, heart rate, or skin temperature during the examinations in both groups.

A sensation of pressure and warmth in the arm was to be expected after injection of 20 ml of solution warmed up to 37 degree C (using Ioxaglate 5 patients, using NaCl 7 patients). Pain was recorded as well (using Ioxaglate 3 patients, using NaCl 1 patient). There were no serious adverse events.

Discussion

The study revealed a significant decrease of the mean erythrocyte velocity in cutaneous capillaries after injection of Ioxaglate 320 into the ipsilateral axillary artery, while isotonic NaCl solution induced a very slight increase. However, both patient groups differed significantly in the response to the injections ($p=0.002$).

At baseline, both patient groups were comparable, as there were no significant differences between the groups in any of the parameters measured at the start of the study.

Because of the strong temperature-dependence of skin microcirculation [30], RCM and NaCl solution were warmed up to 37°C before injection. The constancy of skin surface temperature during the entire measurement period showed that any substantial influence of temperature effects on capillary blood flow could be ruled out.

The catheter was slowly pushed forward into the axillary artery, avoiding irritations of the vessel wall. During manipulation, the ipsilateral capillary erythrocyte velocity was recorded and no effects on capillary blood flow were observed. Hence, a vasoconstriction due to the catheter manipulation can be largely excluded. Pull back of the catheter immediately after injection of the medium also did not have any effect on capillary erythrocyte velocity.

No effect of the catheter itself on capillary blood flow was observed, and no such effect was expected in respect of the size of the catheter (diameter 1.6 mm) in relation to the diameter of the vascular lumen (approx. 7 mm).

Since skin temperature as well as blood pressure and heart rate remained unchanged, and no medication was administered before or during the procedure [30]. Therefore, it can be assumed that the observed effects are due primarily to the injection of the RCM or the NaCl solution respectively.

There were no cases of temporarily cessation of capillary blood flow, which has been observed after injection of Ultravist 370 [6]. Only a slight, weakly relevant reduction in erythrocyte velocity 150 sec after injection of Ioxaglate was detected. This suggests that the increase in viscosity of the Ioxaglate-plasma mixture was nearly compensated by vasodilation [7, 10, 21, 32]. Also, echinocyte formation,

which is induced by most of the RCM [3, 16, 18, 20, 25] and which also could cause a microcirculatory disorder, was reported not to occur [16].
Other possible factors which might contribute to a decrease in microcirculatory blood flow in response to administration of RCM are increases in calcium, adenosine, prostacyclin and endothelin, stress hormones and decreased production of nitric oxide [2, 8, 27, 29, 34, 35]. These parameters were not measured in the present study and, thus, the extent to which these mechanisms might have influenced the results cannot be determined.

Conclusion

Ioxaglate-320 induced a significant decrease of erythrocyte velocity in nailfold capillaries of patients with coronary artery disease after injection of 20 ml in the axillary artery by about 34%, while in contrary after a bolus of 20 ml isotonic NaCl solution a slight increase of about 14% occurred. In patients with severe CAD and a myocardial perfusion at its limits, the injection of radiographic contrast media could induce massive perturbations in the microcirculation and even ischemia [9].

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