Local paclitaxel delivery as a treatment of persistent, recurrent in-stent restenosis – safety assessment

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Abstract

Introduction: In-stent restenosis still remains a serious clinical problem. Local intramural drug delivery (LDD – *Local Drug Delivery*) seems to be an interesting alternative to drug-eluting stents (DES).

Aim: The aim of the study was to assess the safety and effectiveness of local intramural paclitaxel administration in the treatment of recurrent in-stent restenosis (ISR).

Methods: Five patients were enrolled in the study (3 men, mean age 50±7 years) with at least a second episode of ISR within the same stent. Percutaneous coronary angioplasty was performed on a total of 11 vessel segments. Remedy delivery catheters (Boston Scientific) were used for balloon angioplasty. Inflation pressure was calibrated to obtain a balloon/vessel lumen ratio of 1.1:1. Then the pressure was lowered to 3 atmospheres and 100 µg of paclitaxel diluted in 2 ml of 0.9% NaCl was given over 60 seconds under the pressure of 2-3 atmospheres. This dose was used for each 10 mm of lesions. Control coronary angiography was performed six months after the procedure.

Results: In all patients effective target vessel revascularisation was achieved. No adverse events were observed in the periprocedural period or during the 6-month follow-up period. Control angiography revealed ISR in three segments (27.2%) and in-stent late lumen loss of 0.21±0.93 mm.

Conclusions: Local intramural paclitaxel delivery is a safe and effective method of ISR treatment. The optimal paclitaxel dose should be established in further studies.

Key words: in-stent restenosis, local intramural drug delivery, paclitaxel

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Introduction

Coronary angioplasty with drug-eluting stent implantation (DES) is an efficient method of treatment of symptomatic angina, caused by significant coronary artery stenosis. Significant reduction of the risk of in-stent restenosis (ISR) was achieved by the use of local delivery of cytotoxic drugs which limit excessive neointima proliferation within stents. The rate of ISR was reduced from 30-40% with bare metal stents [1, 2] to 3-5% in the case of DES [3, 4]. Despite these encouraging results, there is still a population of patients in whom DES implantation is associated with a 15-20% risk of restenosis. These are patients with diabetes mellitus as well as with bifurcation stenosis and restenosis.

The treatment of restenosis remains a major clinical problem. The most effective methods of ISR treatment include brachytherapy and another DES implantation [5, 6]. Low availability, as well as an increased risk of late in-stent thrombosis, are the main limitations of brachytherapy, while the implantation of another DES

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seems to be ineffective in the following situations: bifurcation restenosis (incomplete lesion coverage by the initial stent), narrow vessels (significant reduction of vessel lumen by another endoprosthesis) and multilevel lesions.

Therefore, the use of local drug delivery (LDD), which limits excessive neointima proliferation, seems to be an attractive method of management of such lesions. This method enables the administration of antimitotics to the area outside stent coverage. A greater flexibility and smaller size of the balloon catheter in comparison with coronary stents allows in some cases a successful application of the drug in arterial segments where endoprosthesis implantation is difficult or undesirable for other reasons (for example, high costs of more than one stent).

The aim of this study was to assess the safety of local cytotoxic drug administration – paclitaxel, in patients with recurrent (at least second episode) restenosis within previously implanted coronary stents. The protocol of the study was approved by the local Ethics Committee.

Methods

Five patients were enrolled into the study (3 men, mean age 50.7 years) with at least a second episode of ISR within the same stent. Percutaneous coronary angioplasty was performed on a total of 11 vessel segments, including:

– left anterior descending artery in the medial segment in one patient; in the distal segment in two patients;
– left main coronary artery in three patients;
– right coronary artery in the proximal segment in one patient, in the medial segment in two patients and in the distal segment in three patients.

The mean lesion length was 16.5±7.0 mm; stenosis degree – 67±15% and reference segment diameter – 2.70±0.75 mm. All treated lesions were characterised by recurrent ISR. In three segments second restenosis was observed; in four segments third, and in another four a fourth restenosis episode occurred.

Percutaneous coronary angioplasty with local drug delivery

Patients received a bolus of unfractioned heparin at a dose of 100 j/kg of body weight during the angioplasty procedure. The dose was adjusted to maintain activated clotting time (ACT) above 300 seconds. Remedy delivery catheters (Boston Scientific) were used for balloon angioplasty. Inflation pressure was calibrated to gain a balloon/vessel lumen ratio of 1.1:1. Then the pressure was lowered to 3 atmospheres and 100 µg of paclitaxel diluted in 2 ml of 0.9% NaCl was given over 60 seconds under the pressure of 2-3 atmospheres. Such a dose was used for each 10 mm of lesions.

In all patients combined antiplatelet therapy was initiated at least one day before the procedure: oral 150 mg Aspirin and 2x250 mg ticlopidine. Ticlopidine in this dose was administered for one month after the procedure. Other drugs were used at the physician's discretion.

According to the study protocol, control coronary angiography was to be performed six months after the procedure. In the case of clinical symptoms of angina and compelling indications, angiography was performed before 6 months and the data were used for further analysis.

Angiographic analysis

Three angiograms of the target lesion were obtained in each patient: the first directly before the intervention, the second after the procedure, and the third at six months.

All angiograms were analysed by an independent investigator, based on a digital automatic quantitative analysis by Medis software. Calculations were performed based on calibration to the catheter filled with the contrast. A reference diameter (RD) was calculated as the arithmetic mean of vessel diameter proximal and distal to the target lesion. A diameter stenosis (DS) was defined as the minimal lumen diameter (MLD) divided by RD. Late lumen loss (LL) was defined as the difference between MLD assessed after stent implantation and at six-month follow-up. In-stent restenosis was defined as a recurrence of luminal narrowing of more than 50% of the reference diameter (>50% DS).

Statistical analysis

The results are presented as a mean ± standard deviation. The differences in the angiographic parameters were compared using the Wilcoxon test. A p value <0.05 was considered significant.

Results

In all patients successful target vessel revascularisation was achieved (PTCA+LDD). A significant MLD increase within target lesion was reached (Table I). No cases of wall dissection or the necessity of additional stent implantation were noted. No adverse events were observed in the periprocedural period and during the 6-month follow-up. Laboratory tests (blood morphology and transaminase levels) performed directly after the procedure and at a control visit after one month did not reveal any toxic effect of paclitaxel.

According to the study protocol, control angiography was performed six months after paclitaxel

Table I. Comparison of quantitative digital angiography parameters obtained before (1) immediately after the procedure (2), and during control coronary angiography (3)

	n	prox. RD [mm]	MLD [mm]	dist. RD [mm]	Percent of stenosis %DS [%]	LL [mm]
1. Initial values	11	2.70±0.84	0.95±0,75	2.64±0.85	67±15	–
2. After LDD procedure and POBA	11	2.83±0.89	2.22±0.58	2.74±0.79	20±16	–
3. Control coronary angiography	11	2.90±0.84	2.00±1.09	2.53±0.77	26±29	0.21±0.93
1 *vs* 2		ns	<0.001	ns	<0.001	–
2 *vs* 3		ns	ns	ns	ns	–

Abbreviations: RD – reference diameter, MLD – minimal lumen diameter, DS – diameter stenosis, LL – late lumen loss, LDD – local drug delivery, POBA – percutaneous balloon angioplasty, n – number of treated segments

injection. It revealed ISR in three segments (27.2%). Late lumen loss was assessed to be 0.21±0.93 mm. The results of control digital quantitative angiography are given in Table I.

Discussion

The implantation of DES is currently a routine method of LDD. Paclitaxel is an acknowledged antiproliferative drug, currently used as a cytotoxic agent in DES. Hydrophobic properties of taxanes allow their direct deposition on the metal surface of stents (e.g. Supra-G Stent, V-Flex stent), as well as their release from the stent-covering polymer (Taxus stent) [4, 7, 8].

Direct balloon catheter coating with paclitaxel is an interesting alternative to DES. The results of such ISR treatment indicate its high effectiveness (LL 0.13 mm *vs* 0.82 mm) [9]. Interestingly, the amount of drug (3.1 μg/mm^2) covering the balloon was close to the doses used in several DES (Supra-G Stent – 3.1 μg/mm^2; V-Flex stent – 2.7 μg/mm^2) [7-9]. Despite theoretically less effective drug application using a paclitaxel-coated balloon catheter (application time about 60 sec), the results of 6-month follow-up demonstrate very similar effectiveness of both methods (LL 0.11-0.29 mm – DES *vs* 0.13 mm – POBA) [7-9]. The use of paclitaxel-coated catheters appeared to be also effective in the prevention of primary ISR.

Animal model experiments revealed more than 60% reduction in the neointima area in stents after the use of taxane-coated balloon catheters [10]. In another study, paclitaxel solution added to the contrast agent used during PTCA was also effective in reducing the excessive proliferation of neointima [11]. These encouraging results are due to the unique properties of paclitaxel [12], such as hydrophobicity and perfect transmural distribution. *In vitro* experiments on isolated blood vessel wall revealed that in the case of endovascular application, the tissue drug concentration was 100 times higher than in the perfusion solution and the mean permeation depth was about 0.7 mm [12]. These properties result not only from the poor water-solubility of the agent; apart from diffusion and convection in the hydrophobic environment of the vessel wall, the active binding of paclitaxel with structures of the intima and media plays an important role. These properties of taxanes theoretically make them ideal drugs for local delivery using the transport balloon catheter.

The effectiveness and safety of LDD was confirmed in our previous studies [13]. For example, intramural enoxaparin application significantly reduced the risk of ISR [14].

In the present study, a relatively high efficacy of LDD with paclitaxel in the treatment of recurrent persistent ISR was demonstrated. Taking into consideration the fact that the risk of restenosis after ISR treatment with balloon angioplasty equals 45% [4, 5], the 45% recurrence rate achieved in our study should be considered satisfactory. Also, small in-stent LL (0.21 mm *vs* 0.55mm in the case of POBA in other studies [4, 5]) suggests the potential efficacy of local paclitaxel delivery. Other advantages include the simplicity of the method and its low periprocedural risk. The low cost of the procedure is of great importance, especially in the case of ISR in several vascular segments in the same patient.

The dose of the drug used in the study (100 μg) corresponds to the amount of drug released by stents coated with paclitaxel (e.g. Supra-G Stent); however, there are no data on the amount of the drug absorbed by the dilated vessel segment.

Optimal dosing, time of application, as well as the volume and the level of pressure remain to be clarified. An increased amount of intramuraly administered paclitaxel seems to be safe and a more effective dose. The risk of general toxicity still remains minimal, but a higher drug dose can increase the local intramural drug bioavailability. However, it was decided not to apply higher doses because of the safety of the study.

In summary, it seems that further studies are warranted to establish the safest and most effective paclitaxel dose, enabling results comparable with DES to

be achieved. It could result in the optimisation of procedures in which the use of DES is limited due to various causes, thus increasing the efficacy of coronary angioplasty.

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Miejscowe śródścienne podawanie paklitakselu w celu leczenia uporczywej, nawrotowej restenozy w stencie – ocena bezpieczeństwa metody

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Streszczenie

Restenoza w stencie pozostaje nadal poważnym problemem klinicznym. Miejscowe, śródścienne podawanie leków cytotoksycznych (*Local Drug Delivery*, LDD) może stanowić interesującą alternatywną metodę w stosunku do stosowania stentów typu DES.

Cel: Celem badania była ocena bezpieczeństwa i skuteczności śródściennego, miejscowego podawania paklitakselu w leczeniu nawrotowej restenozy w stencie (ISR).

Metoda: Do badania włączono 5 chorych (3 mężczyzn, średni wiek 50±7 lat), z co najmniej drugim epizodem ISR w obrębie tego samego stentu. Zabiegom PTCA poddano łącznie 11 segmentów naczyniowych. Do angioplastyki balonowej użyto cewników transportowych Remedy (Boston Scientific). Ciśnienie inflacji dobierano tak, aby uzyskać stosunek średnicy balon/naczynie 1.1:1. Następnie zmniejszano ciśnienie do 3 atm. i przez około 60 s podawano 100 µg paklitakselu rozpuszczonego w 2 ml 0,9% NaCl pod ciśnieniem 2–3 atm. Powyższą dawkę stosowano na każde 10 mm długości docelowej zmiany. Kontrolne badanie angiograficznie wykonano po upływie 6 miesięcy u wszystkich chorych.

Wyniki: U wszystkich chorych uzyskano skuteczne poszerzenia zmian docelowych. W okresie okołozabiegowym oraz podczas 6-mies. okresu obserwacji nie zanotowano zdarzeń niepożądanych. Kontrolna koronarografia ujawniła ISR w trzech segmentach (27,2%) oraz średnią późną utratę światła w obrębie stentu 0,21±0,93 mm.

Wnioski: Zabiegi LDD z użyciem paklitakselu są bezpieczną i skuteczną metodą leczenia ISR. Ostateczna wielkość dawki paklitakselu powinna być określona w następnych badaniach.

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