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Original article

Drug-eluting balloons in patients with non-ST elevation acute coronary syndrome

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ABSTRACT

Background: We compared efficacy of bare-metal stent (BMS) and drug-eluting balloon (DEB) combination vs BMS alone, in patients with non-ST elevation acute coronary syndrome treated with percutaneous coronary intervention (PCI).
Methods: Patients with non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) were randomized to BMS only or BMS + DEB group. Angiographic follow-up was performed after 6 months. The primary endpoints were binary in-stent restenosis (ISR) and late lumen loss (LLL) and the secondary endpoints were target lesion revascularization (TLR), stent thrombosis (ST), and new acute coronary syndrome (ACS).
Results: A total of 85 patients were enrolled, 44 (BMS) and 41 (BMS + DEB). The median age was 67 (36–84) years and 68 (80%) were male. Fifty-two patients (61.2%) had NSTEMI and 33 patients (38.8%) UA. There was no difference in patient demographics, risk factors, and clinical characteristics, except for more smokers in the BMS + DEB group 18/41 (43.9%) vs 9/44 (20.5%). At follow-up, no significant difference in binary ISR was found; $p = 0.593$, but LLL was significantly lower in the BMS + DEB group 0.68 (0.00–2.15) mm vs 0.22 (0.00–2.35) mm; $p = 0.002$. The difference in major adverse cardiac events (MACE) rate combining TLR, ST, and ACS, between the groups was also non-significant, 29.5% (BMS) vs 24.4% (BMS + DEB); $p = 0.835$. One patient had a subacute ST (BMS + DEB) due to clopidogrel resistance.
Conclusion: Patients treated with BMS + DEB combination for non-ST elevation acute coronary syndrome had significantly less LLL in comparison to patients treated with BMS alone but without an impact on patient clinical outcomes.

Introduction

Drug-eluting balloons (DEBs) are coated with paclitaxel, a potent cell inhibitor which irreversibly inhibits arterial smooth muscle cell proliferation. They can be used in combination with bare metal stent (BMS) or alone (DEB only). The usage of DEB in BMS and drug-eluting stent (DES) restenosis showed good clinical results [1–4] and therefore they have a class IIA, level of evidence B indication for in-stent restenosis (ISR) in the European guidelines [5]. Their effect in de novo coronary lesions is controversial and there are several studies and trials with conflicting results in patients with stable coronary artery disease. Good results are achieved in small vessel disease, long lesions, and bifurcations especially without concomitant BMS implantation. There are few data about DEB in acute coronary syndromes. The only large trial was the DEB-AMI trial in ST-elevation myocardial infarction (STEMI) patients [6], but randomized trials in non-ST elevation coronary syndromes (±BMS) are missing. The only data are from small studies or registers. There are some randomized trials currently being conducted (DEBUT – DEB vs BMS, DEB first – DEB + BMS vs DES, PEPCADNSTEMI – BMS vs DEB with provisional stenting).

Patients with non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) are usually older then STEMI patients with more comorbidity and multivessel disease. Complications during and after percutaneous coronary intervention (PCI) are not rare and they have a higher incidence of stent thrombosis and restenosis than patients with stable coronary artery disease. The purpose of this study was to evaluate the angiographic and clinical outcomes of BMS + DEB in patients with non-ST elevation acute coronary syndrome.

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Methods

This is a single-center, randomized, prospective study of patients with non-ST elevation acute coronary syndrome (NSTEMI and UA) treated in University Hospital Center Zagreb, Zagreb, Croatia, from February 2011 to June 2013. The University Hospital Center Ethics Committee approved the study.

Patients

Patients with NSTEMI or UA with signed informed consent for coronary angiography and participation in this investigation were included. The patient exclusion criteria were informed consent not signed, STEMI, cardiogenic shock, hemorrhagic diathesis or major bleeding within 2 weeks, and contraindication for dual antiplatelet therapy. Angiographic inclusion criteria were de novo coronary lesions and exclusion criteria: ISR and left main disease.

Study procedure

Coronary angiography was performed in all patients in the first 48 h. The lesions were classified according to the American College of Cardiology/American Heart Association classification [7]. The patients were randomized into two groups: BMS only – PCI of the target lesion with BMS and BMS + DEB combination – PCI of the target lesion with BMS followed by post-dilatation with DEB. All patients received 600 mg of clopidogrel and 300 mg of aspirin with unfractionated heparin during the procedure. The use of glycoprotein (GP) IIb/IIIa inhibitors (eptifibatide) during and after PCI was optional. Lesion pre-dilatation with plain balloons was also optional. We used two different DEBs: Elutax (Aachen Resonance GmbH, Aachen, Germany) and SeQuent Please (B. Braun AG, Melsungen, Germany). They were inflated during 30–45 s at 8–10 atm and a 1:1 balloon to artery ratio was used. We decided to implant the BMS first and then post-dilate with DEB to avoid geographic mismatch. All patients received dual antiplatlet therapy during 12 months according to guidelines for acute coronary syndromes without ST elevation [8]. Baseline, post-procedure, and follow-up coronary angiographies were analyzed by quantitative coronary angiography (QCA). We measured the reference vessel diameter (RVD), minimal lumen diameter (MLD), and lesion length before PCI and in-stent MLD after PCI. At follow-up in-stent MLD, late lumen loss (LLL – difference between the post-procedural and follow-up MLD), and binary in-stent restenosis (defined as 50% or more at follow-up) were measured. No patient was lost during the follow-up.

Study endpoints

The primary endpoints of interest were binary ISR and late lumen loss (LLL) and the secondary endpoints were target lesion revascularization (TLR), stent thrombosis (ST), and new acute coronary syndrome at 6 months. Angiographic follow-up was performed after 6 months, except in five patients who because of a new acute coronary syndrome were admitted earlier. The main reason for TLR at follow-up was binary in-stent restenosis $\geq$50% by QCA.

Statistics

The statistical analysis was performed using software STATA/IC ver.11.1 (StataCorp LP, College Station, TX, USA). Comparisons between the two groups were performed using the Mann–Whitney *U* test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. The level of statistical significance was set at $p = 0.05$.

Table 1
Baseline characteristics of the study population.

	BMS 44 patients	BMS + DEB 41 patients
Age (years)	68 (36–84)	63 (41–79)
Male	35/44 (79.5%)	33/41 (80.5%)
UA	17/44 (38.6%)	16/41 (39.0%)
NSTEMI	27/44 (61.4%)	25/41 (61.0%)
GRACE SCORE	126 (66–176)	131 (60–186)
BMI	28.1 (22.1–37.3)	29.0 (22.0–36.4)
Hypertension	44/44 (100%)	41/41 (100%)
Diabetes mellitus	12/44 (27.3%)	13/41 (31.7%)
Hyperlipidemia	39/44 (88.6%)	36/41 (87.8%)
Smoking	9/44 (20.5%)	18/41 (43.9%)
Chronic kidney disease	3/44 (6.8%)	6/41 (14.6%)
Prior myocardial infarction	6/44 (13.6%)	4/41 (9.8%)
Prior PCI	3/6 (50%)	2/2 (50%)
LVEF (%)	60 (35–74)	60 (35–70)

Values are presented as median and range or number (%).
BMS, bare-metal stent; DEB, drug-eluting balloon; UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events score; BMI, body mass index; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

Results

Patient demographics

A total of 85 patients were included, 44 in the BMS group and 41 in the BMS + DEB group. The median age was 67 (36–84) years, and there were 68 (80%) males. Fifty-two patients (61.2%) had NSTEMI and 33 (38.8%) had UA. There was no significant difference in patient demographics, risk factors, and clinical characteristics between the two groups [age, sex, body mass index (BMI), NSTEMI or UA, Global Registry of Acute Coronary Events (GRACE) score, prior myocardial infarction and revascularization, left ventricular ejection fraction (LVEF), and risk factors] except there were more smokers in the BMS + DEB group 18/41 (43.9%) vs 9/44 (20.5%). Patients' demographics are shown in Table 1.

Angiographic findings and procedural characteristics

A total of 23 patients (27.1%) had 1-vessel disease, 38 (44.7%) 2-vessel disease, and 24 (28.2%) 3-vessel disease. The left anterior descending artery (LAD) was the most common target vessel in both groups: BMS 16/44 (36.4%) and BMS + DEB 22/41 (53.7%), and B1 the most common lesion type: BMS 31/43 (72.1%) and BMS + DEB 32/41 (78%). There was no difference in median stent diameter between the two groups: BMS 3.0 (2.5–4.0) mm vs BMS + DEB 3.0 (2.5–3.5) mm, but there was a difference in median stent length: BMS 18 (12–26) mm vs BMS + DEB 18 (13–24) mm. However, the median total stent length was the same: 18 (12–62) mm in the BMS group and 18 (13–63) mm in the BMS + DEB group. The median number of DEB implanted per patient was 1 (1–3), diameter 3 (2.5–3.5) mm, length 24 (17–30) mm. Pre-dilatation of the target lesion was equal in both groups: BMS 19/44 (20.5%) and BMS + DEB 16/41 (39%), GP IIb/IIIa inhibitors were used rarely BMS 9/44 (20.5%) vs BMS + DEB 4/41 (9.8%). Procedural success was achieved in 100% of lesions with thrombolysis in myocardial infarction 3 flow. Data are presented in Tables 2 and 3.

QCA data and follow-up

There was no significant difference between the two groups in RVD: BMS 3.08 (2.22–4.33) mm vs BMS + DEB 3.01 (3.30–4.05) mm; lesion length: BMS 15.8 (9.3–45.2) mm vs BMS + DEB 15.7 (9.0–48.5) mm; baseline MLD: BMS 0.99 (0.01–1.77) mm vs

Table 2
Basic angiographic data.

	BMS 44 patients	BMS + DEB 41 patients
Number of diseased vessels	2 (1–4)	2 (1–3)
Treated vessel		
RCA	15/44 (34.1%)	14/41 (34.1%)
LAD	16/44 (36.4%)	22/41 (53.7%)
LCX	6/44 (13.6%)	2/41 (4.9%)
D1	1/44 (2.3%)	0/41 (0%)
OM1	4/44 (9.1%)	1/41 (2.4%)
OM2	1/44 (2.3%)	1/41 (2.4%)
RIM	1/44 (2.3%)	1/41 (2.4%)
Lesion type		
A	4/43 (9.3%)	3/41 (7.3%)
B1	31/43 (72.1%)	32/41 (78%)
B2	5/43 (11.6%)	5/41 (12.2%)
C	3/43 (7%)	1/41 (2.4%)
Reference vessel diameter (mm)	3.08 (2.22–4.33)	3.01 (3.30–4.05)
Lesion length (mm)	15.8 (9.3–45.2)	15.7 (9.0–48.5)
MLD before PCI (mm)	0.99 (0.01–1.77)	1.18 (0.25–2.24)

Values are presented as median and range or number (%).
BMS, bare-metal stent; DEB, drug-eluting balloon; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; D1, first diagonal; OM1, first obtuse marginal; OM2, second obtuse marginal; RIM, ramus intermedius; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention.

Table 3
Procedural characteristics.

	BMS 44 patients	BMS + DEB 41 patients
Number of stents implanted per patient	1 (1–3)	1 (1–3)
Stent length (mm)	18 (12–26)	18 (13–24)
Stent diameter (mm)	3.0 (2.5–4.0)	3.0 (2.5–3.5)
Total stent length (mm)	18 (12–62)	18 (13–63)
Pre-dilatation	19/44 (43.2%)	16/41 (39.0%)
Glycoprotein IIb/IIIa inhibitors	9/44 (20.5%)	4/41 (9.8%)
DEB		
Number of DEB per patient	–	1 (1–3)
DEB length (mm)	–	24 (17–30)
DEB diameter (mm)	–	3 (2.5–3.5)
Total DEB length (mm)	–	24 (17–66)

Values are presented as median and range or number (%).
BMS, bare-metal stent; DEB, drug-eluting balloon.

BMS + DEB 1.18 (0.25–2.24) mm; and post-procedure in-stent MLD: BMS 2.72 (1.66–3.80) mm vs BMS + DEB 2.65 (2.05–3.64) mm. Eighty (94.1%) patients had a follow-up angiography at 6 months and five (5.9%) patients earlier because of NSTEMI or UA. The incidence of binary ISR was 10/44 (22.7%) in the BMS group and 7/41 (17.1%) in the BMS + DEB group. All patients were revascularized percutaneously except one patient from the BMS + DEB group who was sent to surgery due to in-stent LAD occlusion. There was a significant difference at 6 months follow-up between the two groups in in-stent MLD: BMS 2.0 (0.65–2.91) mm vs BMS + DEB 2.31 (0.3–3.64) mm; $p = 0.015$ and therefore in LLL: BMS 0.68 (0.00–2.15) mm vs BMS + DEB 0.22 (0.00–2.35) mm; $p = 0.002$, but without a difference in major adverse cardiac events (MACE) (ST, TLR, and new acute coronary syndrome) 13/44 (29.5%) BMS vs 11/41 (24.4%) BMS + DEB. The incidence of TLR was 10/44 (22.7%) in the BMS group and 8/41 (19.5%) in the BMS + DEB group. There was one subacute ST in the BMS + DEB group because of clopidogrel resistance. No deaths occurred (Table 4).

Discussion

The aim of this prospective study was to evaluate the efficacy of BMS + DEB combination in patients with non-ST elevation acute coronary syndrome. DEB trials and studies in stable coronary artery disease have been published with good angiographic and clinical results. The results in small vessel disease (PEPCAD I, BELLO) in comparison to paclitaxel DES are encouraging, especially without concomitant BMS implantation [9,10]. In bifurcation lesions the results are also promising (PEPCAD V, DEBUIT) even with BMS use, nevertheless BMS + DEB in the DEBUIT trial was not superior to BMS alone [11,12]. However, the results in trials comparing BMS + DEB and DES (PEPCAD III, OCTOPUS) in de novo coronary lesions were disappointing [13,14] except if it was a paclitaxel DES (PEPCAD IV, PEPCAD CTO, LOCAL TAX) [15–17]. Trials in acute coronary syndromes are rare. The only trial with published results is the DEB-AMI trial comparing DEB + BMS, BMS and DES (Taxus, Boston Scientific, Natick, MA, USA) in STEMI patients [6]. The results showed that DEB + BMS were not superior to BMS only and that both groups were inferior to DES in terms of binary restenosis, LLL, and MACE after 6 months.

Table 4
Quantitative coronary angiographic data: immediate results and after 6 months follow-up.

	BMS 44 patients	BMS + DEB 41 patients	*p*-value
In-stent MLD post-PCI (mm)	2.72 (1.66–3.80)	2.65 (2.05–3.64)	0.899
In-stent MLD (mm) at 6 months	2.0 (0.65–2.91)	2.31 (0.3–3.64)	**0.015**
Binary (≥50%) in-stent restenosis	10/44 (22.7%)	7/41 (17.1%)	0.593
% in-stent restenosis	30% (0–99%)	20% (0–100%)	**0.007**
LLL (mm)	0.68 (0.00–2.15)	0.22 (0.00–2.35)	**0.002**
TLR	10/44 (22.7%)	8/41 (19.5%)	0.770
ST	0/44 (0%)	1/41 (2.4%)	0.488
ACS	3/44 (6.8%)	2/41 (4.8%)	0.720
MACE	13/44 (29.5%)	11/41 (24.4%)	0.835

Values are presented as median and range or number (%).
BMS, bare-metal stent; DEB, drug-eluting balloon; MLD, minimal lumen diameter; PCI, percutaneous coronary intervention; LLL, late lumen loss; TLR, target lesion revascularization; ST, stent thrombosis; ACS, acute coronary syndrome; MACE, major adverse cardiac events.

We can conclude that there is strong evidence of DES (limus) superiority to BMS + DEB in stable coronary artery disease and STEMI, but data in NSTEMI and UA are missing (trials being conducted). In Croatia, because of high prices of DES, patients in acute coronary syndromes are receiving BMS. DES are used in specific indications: BMS in-stent restenosis, diabetic patients with small vessel disease and long lesions, bifurcations, and left main disease. Therefore, we conducted this study to evaluate the potential benefit of BMS + DEB in these patients. There are two studies in favor of BMS + DEB vs BMS. The first is the Local Tax study comparing Genie (fluid paclitaxel) +BMS, BMS and DES (Taxus). The results were as follows: LLL 0.61 vs 0.99 vs 0.44; ($p = 0.006$ Genie + BMS vs BMS). The cumulative overall rate of MACE was 13.4% vs 26.8% vs 14.9%, $p = 0.078$. TLR was 13.4% vs 22.1% vs 13.4%; $p = 0.23$. Compared with BMS-only patients, patients randomized to receive a BMS plus local paclitaxel demonstrated superior angiographic results and showed no inferiority compared with paclitaxel-eluting stents [17].

The second was the Perfect study comparing [endothelial progenitor capturing (EPC) stent] + DEB with BMS (EPC stent). This study showed even better results: LLL 0.34 vs 0.88, total segment binary restenosis 5.1% vs 23.2% ($p = 0.005$). TLR rates were 4.8% and 15.5%, respectively ($p = 0.05$). Total major cardiovascular events (TLR, non-target vessel MI, and cardiac death) rates were 4.8% and 17.2%, respectively. They concluded that EPC stent implantation followed by DEB post-dilation demonstrated superior LLL and markedly reduced restenosis rates with no ST events in either group [18].

In this study, BMS + DEB in NSTEMI and UA showed significantly less LLL in comparison to BMS alone, BMS 0.68 (0.00–2.15) mm vs BMS + DEB 0.22 (0.00–2.35) mm; $p = 0.002$ at 6-month angiographic follow-up, but no significant difference in binary ISR and MACE (TLR, ST, and new acute coronary syndrome). The results are comparable with DEB results in stable coronary artery disease. Although the overall TLR rates were relatively high 22.7% BMS vs 19.5% BMS + DEB, the clinically driven TLR rates were 6.8% BMS vs 4.8% BMS + DEB. These data are similar with data from studies where routine angiographic follow-up increased oculostenotic revascularization of nonischemic intermediate lesions [19]. One patient from the DEB + BMS group with three implanted BMS (lesion length 63 mm) had an asymptomatic in-stent occlusion with collaterals and was deferred to bypass surgery. There was one subacute ST in the BMS + DEB group because of clopidogrel resistance. The dose was doubled and the patient was not excluded from the study with good angiographic follow-up results.

In this study significant reduction in LLL did not translate into significant reduction in binary ISR and TLR. This was also observed in studies comparing BMS and DES, especially comparing the efficacy of different DES. The possible explanation is the stability of LLL due to its direct measurement of narrowing and lack of influence of other factors in its calculation, in contrast to the dependency of TLR rate estimation on RVD. Therefore in-stent LLL provides a more reliable measure of anti-restenosis propensity than TLR or binary restenosis rates [20,21].

Nevertheless, despite less LLL, there was no impact on the clinical outcomes of the patients. This was also noted in most studies comparing DES and BMS, but PCI procedures had been predominantly performed on a single vessel, as was the case in our study. However, data from the Frankfurt multivessel PCI registry showed that the use of DES vs BMS in stable patients with multivessel PCI was associated with improved survival [22]. In a retrospective study with acute coronary syndrome patients and multivessel disease, a difference was observed between STEMI and NSTEMI patients in terms of type of revascularization and clinical outcome. Patients with STEMI had a similar risk of mortality if treated with DES in comparison to coronary artery bypass graft, but a higher MACE because of repeat revascularizations, whereas in NSTEMI patients the MACE and mortality were the same [23]. According to this, patients with non-ST elevation acute coronary syndrome and multivessel disease can be treated with multivessel PCI. Therefore, a larger sample size of patients with BMS + DEB multivessel PCI is needed to evaluate this method in terms of clinical outcome.

There is also the question of DEB only in patients with non-ST elevation acute coronary syndrome. The data from clinical trials in stable coronary artery disease demonstrate superiority in LLL of DEB only vs BMS + DEB. In the Valentines II trial the MACE at 8 months was 8.7%; TLR was 6.9%, cardiac death and myocardial infarction were 2%, with LLL of 0.30 mm and a 10.7% binary restenosis rate [24]. Trials in acute coronary syndromes are needed to evaluate these results.

Study limitations

This study enrolled a relatively small number of patients with a small percentage of diabetics (29.4%) and patients with renal insufficiency (10.6%), and those are the patients of special interest due to higher rates of restenosis and reinterventions. The other limitation is the usage of two different DEB. The Elutax DEB has no excipient and a paclitaxel concentration of 2 $\mu g/mm^2$ while the SeQuent Please has iopromide as an excipient and a paclitaxel concentration of 3 $\mu g/mm^2$. In our study we used Elutax DEB in 31/41 (76%) patients vs SeQuent Please in 10/41 (24%) patients. There are some data from an observational study in Sweden (report from the SCAAR registry) in patients with stable coronary artery disease and acute coronary syndromes (NSTEMI and STEMI) that show that the restenosis rate with Elutax DEB was 12.5% and with SeQuent Please 3.4% [25]. These results suggest that there is no class effect for DEB. Therefore, we can only speculate what the results of this study would be if we had used only SeQuent Please DEB and how it would reflect on the angiographic and clinical outcomes of the patients.

Conclusions

There was significantly less LLL in BMS + DEB in comparison to BMS alone, but without an impact on patient clinical outcomes. The performance of DEB appears to be between DES and BMS, but studies with larger sample sizes are needed to evaluate the potential benefit of BMS + DEB combination in this particular group of patients. We have also recently started a DEB only study in patients with acute coronary syndromes with promising immediate and follow-up results. Nevertheless, until more data from ongoing studies are attainable, DEB may be considered in patients with contraindications for DES or if DES are not available.

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