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ORIGINAL ARTICLE

The Effects of Dextromethorphan on the Outcome of Percutaneous Coronary Intervention with Bare-metal Stent Implantation

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Background: In the era of drug-eluting stents, although bare-metal stent (BMS) remains an option for percutaneous coronary intervention (PCI), restenosis remains the Achilles' heel of BMS implantation. A recent study demonstrated several pleiotropic anti-inflammatory effects of dextromethorphan (DXM). This study aims to evaluate the effects of DXM on the outcome of PCI with BMS implantation. **Methods:** In this prospective, double-blind, randomized trial, we enrolled 55 patients who underwent PCI with BMS implantation from May 2006 to February 2009. The patients were divided into DXM (60 mg once daily) and placebo groups. We compared mortality rates, myocardial infarction (MI), target lesion revascularization (TLR), restenosis, stent thrombosis, and plasma levels of high-sensitivity C-reactive protein (hs-CRP) with repeated coronary angiography 6 months after the initial procedure. **Results:** During the 6-month follow-up period, no events of death, MI and stent thrombosis were reported in both groups. The TLR rate was 16.7% in patients receiving DXM compared to 24% receiving a placebo ($P = 0.521$). The restenosis rate was 30% in patients receiving DXM as compared to 40% receiving the placebo ($P = 0.571$). Although nonsignificant, the percentage of hs-CRP elevation was lower in the DXM group (20%) compared to the placebo group 32%; $P = 0.363$). **Conclusions:** DXM is safe to use in patients who underwent PCI. Although DXM therapy following BMS implantation did not significantly reduce the TLR and restenosis rates, it implied a trend toward a lower TLR and restenosis and reduced inflammation in the DXM group compared to the placebo group. Nonetheless, further extensive studies are warranted to elucidate the anti-restenosis effects of DXM.

Key words: Dextromethorphan, restenosis, bare-metal stent implantation

INTRODUCTION

Although percutaneous coronary intervention (PCI) revolutionized the management of coronary artery disease (CAD),[1] restenosis after a successful balloon coronary angioplasty or intracoronary stent placement remains the Achilles' heel of PCI. Restenosis, defined as a ≥50% diameter stenosis within the treatment site at follow-up, is associated with the increased rates of reintervention and major adverse clinical events, including myocardial infarction (MI) and death.[2]

The primary mechanism of restenosis in a stented coronary artery is neointimal hyperplasia after intimal injury with inflammatory reaction.[3-5] Reportedly, the drug-eluting stent (DES) can significantly reduce restenosis as compared to bare-metal stent (BMS) implantation.[6] Even in the era of second- and third-generation DES, BMS plays a role in PCI, especially in patients who cannot tolerate the recommended duration of dual antiplatelet therapy due to noncompliance, the need for noncardiac surgery, or increased risk for bleeding.[7]

Dextromethorphan (DXM) is a dextrorotatory morphinan that is widely used as a nonopioid cough suppressant in

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several over-the-counter remedies.[8] Lately, the potential anti-inflammatory effects of antitussives have been explored, in addition to their clinical application. A recent study demonstrated that DXM reduced the inflammation-mediated degeneration of dopaminergic neurons by inhibiting microglial activation.[9] Moreover, the neuroprotective activity was proved through animal models of cerebral ischemia and hypoglycemic neural injuries.[8,10,11] However, the anti-inflammatory activity of DXM on CAD remains unclear.

Therefore, this study tested the hypothesis that the potential anti-inflammatory effect of DXM therapy might prevent restenosis and improve clinical outcome after PCI with BMS implantation.

METHODS

Patient population

We conducted this double-blind, randomized trial at Tri-Service General Hospital, National Defense Medical Center (Taipei, Taiwan) from May 2006 to February 2009. We enrolled patients with stable angina and objective evidence of myocardial ischemia who were admitted for coronary angiography and completed PCI with BMS implantation. This study adhered to the ethical principles in clinical research and was approved by the Institutional Review Board of the center (IRB 094-05-0035). We obtained informed consent from all patients enrolled in this study.

The inclusion criteria included ages between 20 and 80 years, stable angina with objective evidence of myocardial ischemia, significant CAD, and patients who underwent PCI and BMS implantation. In contrast, the exclusion criteria included acute MI <3 months; restenotic lesions; vein graft lesions; patients who received primary PCI; and allergy to DXM, contrast media, or antiplatelet agents.

We performed BMS deployment according to the standard practice. The degree of coronary artery stenosis was assessed by visual estimation and quantitative coronary angiography analysis. Patients with stenosis ≥70%, requiring PCI and BMS implantation, were eligible candidates for this study. Dual antiplatelet therapy (aspirin + clopidogrel) was provided at least 1 month after PCI.

Randomization was performed in a double-blind manner with the use of sealed envelopes containing the block randomization sequence. The treatment protocol is summarized in Figure 1. Double-blinding was achieved by the use of similar-appearing capsule containing either 60 mg of DXM or placebo per day for the respective treatment groups for 6 months after PCI.

Follow-up

We executed a clinical follow-up in the following 1, 3, and 6 months after the procedures by telephone contact or office visits. In addition, a follow-up coronary angiography was performed in all patients 6 months after PCI as per the protocol.

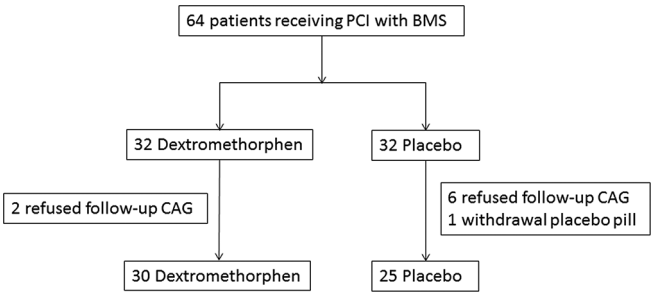

Figure 1: Flow chart of randomization in patients with stable coronary artery disease receiving percutaneous coronary intervention with bare-metal stent implantation

Study end points and definitions

The study end point was the 6-month mortality rate, MI, and target lesion revascularization (TLR). Stent thrombosis was defined on the basis of the Academic Research Consortium definitions for definite or probable stent thrombosis and further categorized as follows: acute <1 day; subacute as 1–30 days, and late >30 days. Angiographic restenosis was defined as ≥50% in-stent stenosis (reference vessel diameter – minimum luminal diameter)/reference vessel diameter ≥50%. The level of high-sensitivity C-reactive protein (hs-CRP) was detected before and 6 months after PCI.

Statistical analyses

Statistical analyses were performed using the SPSS software package (version 21.0; SPSS, Chicago, IL, USA), and $P < 0.05$ was considered as statistically significant. While continuous variables are presented as mean ± standard deviation, categorical variables are presented as the number of patients and the corresponding percentage. The differences in the characteristics of groups were assessed using an unpaired two-tailed Student's *t*-test or one-way analysis of variance for continuous variables and Chi-square and Fisher's exact tests for nominal variables.

RESULTS

Of 64 patients initially enrolled in this study, 9 withdrew consent after randomization. At the end of the study, thirty patients were in the DXM group and 25 in the placebo group [Figure 1]. No statistically significant difference was observed in the baseline characteristics of these two groups [Tables 1 and 2].

TLR rates 6 months after PCI were 16.7% in the DXM group and 24% in the placebo group ($P = 0.521$). Angiographic

Table 1: Baseline characteristics

Characteristics	Dextromethorphan (*n*=30)	Placebo (*n*=25)	*P*
Age, years (mean±SD)	62.6±8.21	59.8±7.21	0.476
Male, %	63.3 (19/30)	64 (16/25)	1.000
Body weight, kg (mean±SD)	69.8±12.3	70.0±15.6	0.956
Comorbidities, %			
Diabetes mellitus	33 (10/30)	44 (11/25)	0.577
Hypertension	70 (21/30)	68 (17/25)	1.000
Hyperlipidemia	73 (22/30)	68 (17/25)	0.768
Congestive heart failure	7 (2/30)	12 (3/25)	0.649
Tobacco use, %	30 (9/30)	36 (9/25)	0.774
Alcohol, %	3 (1/30)	16 (4/25)	0.165
Concomitant medication, %			
Bokey	80 (24/30)	92 (23/25)	0.269
Plavix	97 (29/30)	88 (22/25)	0.320
ACEI/ARB	57 (17/30)	52 (13/25)	0.790
Beta-blockers	70 (21/30)	72 (18/25)	1.000
Statins	80 (24/30)	84 (21/25)	0.741

ACEI=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin receptor blockers; SD=Standard deviation

Table 2: Baseline angiographic and procedural characteristics

Characteristics	Dextromethorphan (*n*=30)	Placebo (*n*=25)	*P*
Target lesion location, %			
LAD	27 (8/30)	44 (11/25)	0.256
LCx	17 (5/30)	20 (5/25)	1.000
RCA	57 (17/30)	36 (9/25)	0.177
ACC/AHA lesion type			
A	30 (9/30)	32 (8/25)	1.000
B	56.7 (17/30)	52 (13/25)	0.790
C	13.3 (4/30)	16 (4/25)	1.000
Bifurcation lesions, %	23.3 (8/30)	20 (6/25)	1.000
Ostial lesions, %	16.7 (5/30)	16 (4/25)	1.000
Heavy calcification, %	26.7 (7/30)	24 (5/25)	1.000
Stent size <3 mm, %	43.3 (13/30)	52 (13/25)	0.593
Stent length, mm (mean±SD)	16.0±5.81	17.0±4.43	0.498
Procedural success, %	100	100	1.000

LAD=Left ascending artery; LCx=Left circumflex artery; RCA=Right coronary artery; SD=Standard deviation; AHA=American Heart Association; ACC=American College of Cardiology

restenosis 6 months after PCI was reduced 10% in the DXM group (30%) compared to the placebo group (40%; $P = 0.571$). In comparison with the baseline, the percentage of hs-CRP elevation was 32% in the placebo group higher than 20% in the DXM group ($P = 0.363$) [Table 3]. Although all study end points were not statistically significant, it revealed a trend toward a lower TLR and restenosis rate in the DXM group compared to the placebo group. No death, MI, and stent thrombosis were reported in both groups. Only one serious adverse event occurred in this study; a patient with a history of peptic ulcer disease in the DXM group developed upper gastrointestinal bleeding.

DISCUSSION

This study investigated the effects of DXM on PCI with BMS implantation. Although DXM therapy following BMS implantation did not significantly reduce the death, MI, TLR, and restenosis rate, it exhibited a trend toward a lower TLR and restenosis rate compared to the placebo group. Moreover, DXM administration was safe without any side effect and did not lead to treatment withdrawal in this study.

Increased knowledge of pathophysiology of restenosis after BMS implantation has facilitated the recognition of event prevention. Neointimal hyperplasia is the primary component of restenosis after BMS deployment. The prevalence of angiographic restenosis after BMS deployment is up to 40%–60%. Despite several attempts to reduce restenosis rates, only reduction of the stent structure thickness resulted in reduced restenosis.[2]

Several interventional devices, including laser excimer atherectomy, directional atherectomy, rotational atherectomy, and cutting balloon angioplasty, have been applied to prevent restenosis; however, the results have been discouraging. Although intracoronary radiotherapy using beta and gamma emitters promises the prevention of restenosis, the unresolved issues for intracoronary radiotherapy include cost, logistics, long-term safety, and late-stent thrombosis.[12] Reportedly, pharmacological approaches have not consistently reduced the frequency of angiographic or clinical restenosis after PCI despite trying several agents.[13]

Furthermore, the reduction of restenosis was essayed by oral drug administration. However, the results of the drugs attempted were not convincing to warrant their introduction into clinical practice.[14] Previous investigations, including the oral sirolimus to inhibit recurrent in-stent stenosis, oral rapamune to inhibit restenosis, and oral rapamycin to prevent restenosis in Argentina and other studies, evaluated the oral use of sirolimus and reported an average efficacy. Unfortunately, these drugs brought about several major adverse effects, which might have contributed to their lack of interest in Phase III clinical trials.[15-17] On the contrary, DXM had no major side effects and was safe and well tolerance.

In the early phase of stent implantation leading to endothelium injury, inflammatory process progressed.

Table 3: Clinical outcomes

Characteristics	Dextromethorphan (*n*=30)	Placebo (*n*=25)	*P*
Death, %	0	0	
MI, %	0	0	
TLR, %	16.7 (5/30)	24 (6/25)	
Restenosis, %	30 (9/30)	40 (10/25)	0.521
Stent thrombosis, %	0	0	0.571
hs-CRP elevation, %	20 (6/30)	32 (8/25)	0.363

MI=Myocardial infarction; TLR=Target lesion revascularization; hs-CRP=High-sensitivity C-reactive protein

Several studies have highlighted the significance of inflammation as an early event after stenting in different animal models using specific antibodies to leukocytes (CD45), macrophages (CD14), and monocytes (CD115).[18] The anti-inflammatory effect of DXM was by inhibiting lipopolysaccharide (LPS)-induced superoxide production than the production of nitric oxide and tumor necrosis factor-α (TNF-α). A previous study demonstrated protective effects of DXM against LPS-mediated neurodegeneration in neuron–glia cultures or against endotoxic shock in mice by inhibiting the inflammation reaction, not potential antagonistic effect on the N-methyl-D-aspartate receptor complex.[9] The DXM-induced reduction in superoxide was attributed to the inhibition of production, but not scavenging of the superoxide free radical. Current studies have proved that the protective mechanism of DXM is reducing the LPS-induced production of superoxides, free radicals, and TNF-α through the inhibition of nicotinamide adenine dinucleotide phosphate oxidase.[19,20] The anti-inflammatory effect of DXM not only relates to the reduction of reactive oxygen species but also with the reduction of TNF-α secretion. Such evidence suggested the anti-inflammatory effects of DXM, which might reduce neointimal hyperplasia of stented coronary arteries.

DES was an expandable framework, used as a platform to carry and release drugs at the site of coronary lesions. The drugs most commonly administrated in the current clinical practice are from limus family and paclitaxel, which markedly reduce the chance of restenosis compared to BMS.[21,22] DESs with some cell mitosis inhibitors, such as dexamethasone and tacrolimus, have not demonstrated sufficiently positive effects in preclinical and clinical studies to allow their use in clinical practice.[23,24] The improvements in newer-generation DESs have translated into better safety and efficacy compared to the earlier generation DESs and BMS. However, high costs have hindered the introduction of this material on a large scale in underdeveloped or developing countries, despite the long-term cost-benefit that seems to be better in DES.[25,26] Therefore, searching for a low-cost treatment with a protective effect on restenosis is imperative for patients with limited financial resources. Furthermore, the feasibility of effective and safe treatment, which was not used in the population due to its high cost, should be addressed.

Study limitations

This study has several limitations. First, the sample size is small. Second, 6-month follow-up might not be adequate to assess the late benefit or evaluate events. Finally, the evaluation of an intracoronary image was not performed in this study.

CONCLUSIONS

In summary, despite high restenosis rate, BMS plays a role in the era of DES. DXM is an old and safe medication with high anti-inflammatory properties. This study suggests that DXM exhibits a lower trend toward TLR and restenosis rate compared to placebo. Nonetheless, further extensive studies are warranted to elucidate the anti-restenosis and beneficial clinical effects of DXM on atherosclerotic cardiovascular disease.

Consent for publication

All the authors confirmed the manuscript and approved the publication. The corresponding author had completed the "consent for publication."

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Conflicts of interest

There are no conflicts of interest.

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