CRT-504

A Pilot Study of the Effect of Niacin on Pulmonary Arterial Pressure

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Background: Niacin, a compound primarily used for its lipid altering properties, has been shown to improve endothelial function with short term administration, via the release of prostaglandins. We hypothesized that via these effects, niacin could lead to reductions in pulmonary artery pressures.
Methods: Pilot study involving 32 subjects with known tricuspid regurgitation (TR) and a Doppler jet velocity of 2.7 m/s or greater. Subjects were randomized in a 1:2:2 ratio to receive a single dose of either placebo, niacin 100mg or niacin 500mg respectively in a double blinded, acute provocation study. Following baseline assessment of TR jet velocity, blinded study drug was administered. At peak absorption of niacin and maximal flushing triggered by prostaglandin release (1 hour post-administration), TR jet velocity was re-assessed. The study was powered to detect a difference of 0.2 ± 0.2 m/s in TR jet velocity between groups.
Results: Baseline TR jet velocity was 2.89 ± 0.30 m/s. The mean change in Doppler jet velocity was -0.024 ± 0.15 m/s in the placebo group, compared to -0.041 ± 0.27 m/s with niacin 100 mg, and -0.065 ± 0.17 m/s with niacin 500 mg. This trend was not statistically significant (ANOVA). The overall reduction in TR jet velocity observed with niacin, (2.93 ± 0.32 m/s to 2.87 ± 0.42 m/s) was small and not statistically significant (P = 0.26). There was no observed effect among subgroups with above or below median baseline TR Doppler jet velocities.
Conclusion: Single dose administration of immediate-release niacin 100 mg or 500 mg has no significant effect on PA pressures at 1 hour post administration.

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Impact of Hyperuricemia on Development of New-Onset Diabetes Mellitus in Asian Population: Five-Year Clinical Outcomes

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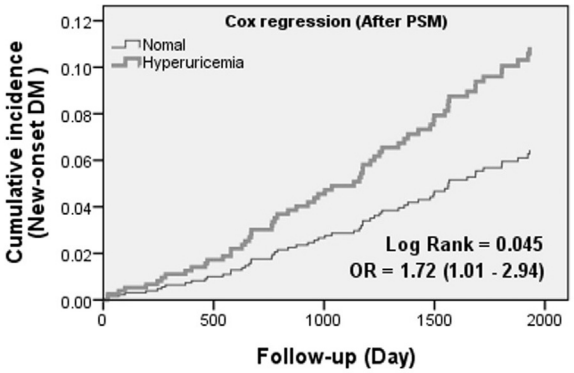
Background: Hyperuricemia is a well-known risk factor for diabetes mellitus (DM) and other cardiovascular diseases, but the relationship between hyperuricemia and the development of new-onset DM is not clear. We evaluated the impact of hyperuricemia on the development of new-onset DM based on 5-year cumulative clinical outcomes in Asian patients.
Methods: A total of 3,274 patients who did not have DM were enrolled. New-onset DM was defined as having a fasting blood glucose ≥126mg/dL or HbA1c ≥6.5%. Hyperuricemia was defined as uric acid ≥7.0 mg/dL. Baseline characteristics between the hyperuricemia and control groups were matched with propensity score matching (PSM, C-statistics=0.731). 5-year cumulative incidence of new-onset DM was compared between the two groups.
Results: At baseline, patients in the hyperuricemia group showed a higher prevalence of male gender, hypertension and dyslipidemia. The hyperuricemia group had higher levels of basal insulin, HOMA-IR, triglyceride and lower levels of HDL-C. Development of new-onset DM was higher in the hyperuricemia group (13.5% vs. 7.9%, p<0.001). After PSM, baseline characteristics were well balanced (C-statics=0.731). After adjustment with cox-regression analysis, hyperuricemia remained to be an independent predictor of new-onset DM (OR 1.72, 95% CI 1.01 - 2.94, p=0.045, figure).
Conclusions: Hyperuricemia was shown to be an independent predictor of new-onset DM. Therefore it may be suggested that uric acid levels should be included in the prediction of DM and patients with hyperuricemia may benefit from measures to reduce the uric acid.

Figure. Impact of hyperuricemia on new-onset DM following PSM analysis



Thrombosis

CRT-506

Endothelial Biocompatibility of Biodegradable Polymers

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Background: The concept of biodegradable polymer-based scaffolds has emerged as an alternative to the permanent metallic device implants to treat a transient vascular healing problem. The development of a suitable polymer has been challenging because it must exhibit vascular biocompatibility while allowing time- and dose-controlled antiproliferative drug release such that complete healing is achieved. The aims of this study were to characterize intimal biocompatibility of biodegradable polymers and drugs using screening assays of apoptosis, oxidative stress, proinflammatory mediators, adhesion molecules, prothrombotic and antithrombotic mediators in endothelial cells.
Methods: Endothelial cell line EAHy926 were cultured in chamber slides coated with poly-DL-lactide (PDLA) and paciltaxel for seven days. Flow cytometric analysis was used to measure cytotoxicity, apoptosis (annexin V and 7-amino-actinomycin D staining, 7-AAD), nitrotyrosine expression, thrombomodulin, tissue factor, cell adhesion molecules (PECAM-1, P-selectin and PSGL-1), activated protein C receptor and co-stimulation modulators (CD40L, TNF receptor).
Results: Treatment of endothelial cells with PDLA and paclitaxel induced increase in annexin V expression (4.4%) compared to control (0.3%), but not 7-AAD stained dead cells, indicating enhanced apoptosis. Paciltaxel alone and in combination with PDLA showed upregulation of tissue factor (38.8% vs control 7.3%) and down-regulation of thrombomodulin (86.8% vs control 98.5%). Endothelial cells incubated in PDLA and paciltaxel showed a marked increase in nitrotyrosine expression and exhibited an apparent cell death compared to the negative control. Paciltaxel alone or in combination with PDLA showed upregulation of microtubule-associated protein 1A/1B-light chain 3 (31.3% vs. control 5.0%) and p62 protein (56.4% vs. control 7.2%) indicating stimulation of autophagy. PDLA and paciltaxel had minimal effect on the expression of cell adhesion molecules, activated protein C receptor, or co-stimulation modulators.
Conclusion: The results indicate that PDLA and paciltaxel induce nitrative oxidative stress, stimulate autophagy, promote prothrombotic mediators, and cytotoxicity in endothelial cells. The study emphasizes endothelial biocompatibility screening of newly evolving biodegradable polymers as drug carriers and bioresorbable vascular scaffolds.