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Letter to the Editor

# Use of Warfarin as a Component of Melbourne Cocktail in Chronic Kidney Disease and the Association with Acute Kidney Injury - A Historical Perspective

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## DEAR EDITOR,

In the 1970's and early eighties, the combination therapy of cyclophosphamide, dipyridamole and warfarin known as the Melbourne Cocktail was introduced and popularized by Professor Priscilla Kincaid Smith from the Royal Melbourne Hospital. Professor Kincaid Smith's focus on the role of platelets in Glomerulonephritis (GN) found evidence to support the use of dipyridamole (antiplatelet agent) in GN. She discovered a supporting role of platelet involvement in GN through her work on Beta-Thromboglobulin, Platelet Factor 4 and other renal histological studies in Membranoproliferative GN and Focal and Segmental Glomerulosclerosis. These two types of GN including IgA nephritis were treated with the above triple therapy of the Melbourne Cocktail where warfarin was given in anticoagulant doses to reduce thrombotest to between 7% to 15% together with dipyridamole and cyclophosphamide. In the treatment group, though patients improved their renal function, there was more glomerular bleeding as evidenced by urinary RBC counts compared to the control group [1].

When we devised our own studies in Singapore [2], because our Asian patients had a tendency to take traditional herbal medicine, we had to be cautious with the use of warfarin. So we employed an antithrombotic dose of warfarin to keep thrombotest not lower than 30% in the triple regime for the treatment of our patients with IgA nephritis.

Our paper [2] on the effects of a 3 year triple therapy (modified Melbourne Cocktail) in patients with IgA nephritis was published in 1987. Those patients in the treatment group had delayed progression to end stage renal disease compared to the control group. We did not notice the problem of haematuria in the treatment group. In fact, the treatment group showed a reduction of proteinuria and preservation of renal function compared to the control group. We had postulated then that anticoagulant doses of warfarin was deleterious and could cause glomerular haemorrhage with renal deterioration. Our earlier observation on warfarin therapy [3,4] is in agreement with Brodsky's postulate [4] that warfarin- related nephropathy is simply a reflection of AKI (acute kidney injury) due to warfarin induced glomerular haemorrhage when warfarin is prescribed in anticoagulant doses.

The modified Melbourne Cocktail trial in IgA nephritis was successfully repeated using only dipyridamole and low- dose warfarin by Lee et al. [5], in 1989. The evidence for therapy was provided from further work by Liem and Choong [6] from their work on mesangial cells and umbilical cord endothelial cells. Both showed the effects of dipyridamole and warfarin on the suppression of cell proliferation through cytokine inhibition. Today the above combination of drugs have given way to newer drugs like Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARB) as these drugs are more effective in reducing proteinuria and retarding the progression of GN [7].

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