The effect of ex-vivo rotenone intoxication on dopamine re-uptake of *LRRK2*-R1441G mutant mouse

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Introduction: Mutations in *LRRK2* are strongly associated with Parkinson's disease, and R1441G is the second most common mutation of *LRRK2*. In order to develop a mouse model for Parkinson's disease, we have generated a knock-in mouse carrying this mutation. However, the mutant mice remain healthy and do not demonstrate any behavioural or histological abnormalities until 18 months old. Since an important neurochemical defect in Parkinson's disease is decreased dopamine content in the striatum, and both genetic background and environmental stress make contribution to the disease progression, we investigated the effect of *LRRK2*-R1441G mutation and ex-vivo rotenone treatment on the ability of dopamine re-uptake.

Methods: Synaptosomes were isolated from mouse striatum and incubated with 3H-labelled dopamine with or without low-dose rotenone pre-treatment, and the radioactivity of synaptosomes was measured to assess the ability of dopamine re-uptake by dopaminergic neurons. Wild type and *LRRK2*$^{R1441G/R1441G}$ mutant mice at both 3 months and 18 months old were compared.

Results: There was no significant difference in the ability of dopamine re-uptake between wild type and mutant mice in either young (3 months old) or aged (18 months old) groups without rotenone treatment. However, dopamine re-uptake is significantly compromised in the mutant mice at 3 months old under rotenone treatment.

Conclusions: *LRRK2*-R1441G alone may not be sufficient to affect dopamine transmission even in aged mice, but the synergetic effect of *LRRK2* mutation and rotenone stimulus can lead to impaired dopamine uptake. Therefore, this study implies the importance of interaction between genetic and environmental factors in Parkinson's disease.

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A pilot study on the efficacy and safety of Prismocitrate 18/0 replacement solution in continuous venovenous haemodiafiltration (CVVHDF)

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Introduction: Regional citrate anticoagulation is efficacious for prolonging filter function, and confers less risk of bleeding and mortality compared to systemic anticoagulation. However, technical complexity, risks of sodium disturbance and citrate toxicity related to older citrate formulation limit its widespread use. Primocitrate 18/0 (Gambro), a new formulation of citrate with modified sodium content, could potentially ameliorate these side-effects. We aimed to develop a feasible protocol using this solution coupled with calcium-free dialysate (Prism0cal B22) for CVVHDF, and to determine its safety and efficacy for local critical care setting.

Methods: Asian medical patients admitted to the adult Intensive Care Unit (AICU) of Queen Mary Hospital who are indicated for continuous renal replacement therapy, without a history of advanced cirrhosis, or shock on high dose vasopressor, are recruited. The protocol adopts fixed flow rates of blood and Primocitrate 18/0 as pre-dilution at 120 mL/min and 1000 mL/min, respectively. Dialysate (Prism0cal B22) flow rate was adjusted according to body weight to achieve the ultrafiltration dose of 30-35 mL/kg/hour. CVVHDF is performed using Prismaflex® machine with high-flux filter (ST100, Gambro). Pre-filter and post-filter calcium levels target between 0.3 and 0.5 mmol/L. Calcium was replaced systemically via a separate central venous access. Systemic total calcium to ionised calcium ratio (target <2.5) was monitored for potential citrate toxicity.

Results: Fifteen eligible subjects (10 males, 5 females; age 49-85 years) were recruited so far. All of them fulfilled the AKIN definition of acute kidney injury and two of them were diagnosed metformin-associated-lactic-acidosis. Nine of them completed the CVVHDF therapy without filter clotting, and CVVHDF therapy last 12 to 72 hours. No electrolytes disturbance, citrate toxicity, or bleeding episode was reported after starting on the protocol. Filter clotting was reported in three subjects, after CVVHDF for 26, 38, 53 hours. Among the three subjects with filter clotted, catheter malfunction requiring A-V swapping was reported in two, which was believed to be a major reason predisposing to clotting of filter. The remaining subject had venous thrombosis elsewhere and required investigations for systemic thrombotic tendency. Three subjects were withdrawn from the study after CVVHDF for 5, 12 and 21 hours, subsequent to clinical deterioration with the development of contra-indications for citrate infusion. All subjects achieved pre-filter and post-filter calcium level within the targeted range. Systemic ionised calcium level was maintained within safe range (1.0-1.2 mmol/L) using the current protocol.

Conclusion: The current CVVHDF protocol using Prismocitrate 18/0 as replacement solution is feasible and no adverse events were reported so far. Safety profile is to be observed further upon ongoing recruitment.

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