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Xeno-free autologous platelet rich plasma for chronic wound management – Case series

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ABSTRACT

Background: In chronic wounds, healing process gets halted in inflammatory phase owing to lack of growth factors (GF). The concept of exogenous delivery of such GF as platelet rich plasma (PRP)/fibrin (PRF) could be logical strategy for their management. We evaluated efficacy of single dose of non-activated PRP and self-polymerized platelet rich fibrin (PRF) in subjects with chronic wounds.

Methods: 35 Subjects with wounds of different depths and etiologies were administered with PRP or PRP + PRF and assessed with Bates-Jensen Wound Assessment Tool (BWAT).

Results: Majority of subjects in PRP group responded well and entered into regenerative zone. In PRP + PRF group, 36% subjects benefitted from this treatment.

Conclusion: Our study demonstrates that single dose of non-activated PRP is an efficacious treatment regime for chronic wounds. Further, it eliminates need for multiple doses due to continual release of growth factor over a long period of time, thus considerably reducing effective cost of procedure.

1. Introduction

Chronic wounds are a growing public health concern affecting patients' health, emotional state and quality of life [1]. They represent a major burden to healthcare system, costing an estimated 2–3% of healthcare budgets in developing countries [2]. With increasing incidence of diabetes and trauma related injury, care of these wounds is fast becoming a billion-dollar business.

Wound healing is a complex process where platelets play a crucial role. In chronic wounds, healing process gets halted indefinitely in inflammatory phase owing to lack of growth factors (GFs) and/or consistently high levels of matrix metalloproteinases and proinflammatory cytokines [3,4]. Concept of exogenous delivery of such GFs seems a logical strategy. An increased understanding of physiological roles of platelets has advanced their use as a novel therapeutics in wounds [5].

Platelet rich plasma (PRP) contains high level of platelets which release cocktail of GFs from α-granules upon activation. They possess mitogenic and chemotactic properties and curb release of inflammatory cytokines and interact with macrophages to improve tissue healing and regeneration, angiogenesis and augment epithelialization in chronic wounds [6]. PRP is mixed with bovine-derived thrombin before application with intention to generate fibrin gel and platelet GF-rich exudates [7]. Several trials and retrospective reviews substantiated potential efficacy of autologous thrombin/CaCl2-activated PRP in expediting healing of chronic wound [8,9]. Studies have demonstrated significant increase in limb salvage rate/amputation prevention among high-risk diabetes patients when combined with comprehensive local wound care [10].

Platelet-Rich Fibrin (PRF) has been shown to be of better-quality than traditionally prepared PRP, due to its ease of preparation and lack of biochemical handling [11]. It removes superfluous process of anticoagulant addition and conversion of fibrinogen to fibrin, thus making this preparation strictly autologous.

Activating platelets through thrombin would allow them to degranulate rapidly which eventually lose 90% of their payload within 60 min [12]. Our intention was to have good quality xeno-free platelets that will continue to live for several days secreting small but significant platelet factors that are short-lived once secreted. Hence this study was initiated to evaluate efficacy of subcutaneous injection of single dose of non-activated PRP in patients with chronic wounds of different

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RESEARCH ARTICLE

Efficacy of Intra-Articular Injection of Platelet Rich Plasma and Hyaluronic Acid in Early Knee Osteoarthritis – Case Series

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Higher prevalence and growing burden of knee Osteoarthritis (OA) combined with recent safety concerns about pharmacological interventions has increased demand for new effective technologies for its management. Need of the hour is an innovative treatment alternative which may repair cartilage damage rather than just reduce symptoms of pain. Hyaluronic acid (HA) and PRP has been shown to relieve pain and symptoms as well as slow the progression of disease as stand-alone therapy. Treatment combining these modalities could be particularly hopeful owing to their positive and diverse interaction among themselves.

Combinational treatment using both PRP and HA was performed on a series of 12 patients with early stage primary knee OA who fulfilled all the designated inclusion and exclusion criteria. All the patients were evaluated before and after treatment (1, 3, 6 and 12 months) by physical examination, assessment of VAS for pain, WOMAC, IKDC, KOOS and OKS to record the patient-reported improvement in pain, functionality and quality of life (QOL). 2-tailed Mann Whitney U Test was performed to assess the effect of treatment at different follow-up times of all the clinical scores. Whereas, Pearson correlation coefficient was done to evaluate the correlation between different clinical scores. For all tests, $p < 0.05$ was considered significant.

All patients showed statistically significant improvement in all orthopedics scores evaluated. VAS score was improved significantly from 3.00 ± 0.49 at baseline to 1.57 ± 0.41 ($p = 0.031$) in Grade I and 3.60 ± 0.51 at baseline to 2.10 ± 0.29 ($p = 0.031$) in Grade II patients at 6 months' follow-up respectively. Other scores followed similar trends with statistically significant improvement at 6 months' follow-up which maintained throughout till end of the study period.

All patients treated experienced strong functional improvement and substantial gains in pain relief, functionality and QOL. Hence our preliminary findings suggest that combined PRP and HA procedure is safe and potentially efficacious, which merits further investigation in large clinical settings and also in controlled clinical trials with long-term follow-ups.

Focal Points

Bench side: Platelet Rich Plasma (PRP) deliver a large pool of signalling proteins including growth factors and cytokines to the local milieu driving the tissue regeneration and repair mechanisms which when combined with high molecular weight cross-linked hyaluronan could bestow greater viscoelastic properties and alleviate the symptoms of osteoarthritis.

Bedside: Osteoarthritis (OA) is a chronic degenerative disease and there is no cure for OA except medical management and partial/total knee replacement in advanced stage. PRP along with HA could have the therapeutic potential to promote cartilage regeneration and inhibit inflammation synergistically by decreasing the friction coefficient and minimizing wear.

Community: The burden of OA on quality of life, disability and health care utilization is quite high. Combined PRP and HA could be an effective single-dose treatment modality restoring the functional activities and considerably reducing effective cost of the treatment.

Governments and regulatory agencies: The technology to obtain PRP is FDA-approved and its safety and efficacy has been well established through several clinical studies. Regulatory agencies should consider the evidences put forth by the researchers and sanction grants to investigate in larger clinical settings and also in controlled trials with different ethnicities with long-term follow-ups.

Keywords: Platelet rich plasma; Hyaluronic acid; Knee osteoarthritis; WOMAC; pain scale

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ARTICLE

Environmental impact on the onset of hypertension-induced end-stage renal disease

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ABSTRACT

This study intends to assess the impact of environmental factors on the onset of hypertension-induced end-stage renal disease (ESRD) and to compare the level of oxidative stress with nonhypertensive diabetic ESRD.

ESRD patients were evaluated along with healthy controls through questionnaire for demographic, nutritional and lifestyle variables. Oxidants were measured along with antioxidants. Multiple linear regression (MLR) models were applied to analyze association of studied variables with oxidants and antioxidants.

Most of the hypertensive nephrosclerotic patients were residing in locality that was either closer to industrial belt or polluting water bodies, belonging to low socioeconomic status that invariably affected their lifestyle and nutritional status. Hypertensive ESRD patients showed more pronounced oxidative stress than diabetic ESRD. Several of the studied variables were significantly associated with oxidants and antioxidants.

Demographic, nutritional and lifestyle variables appeared to have suggestive effect on the onset of hypertensive nephrosclerosis.

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Hypertension; renal disease; dialysis; environmental exposure; nutritional status; oxidative stress

Introduction

Hypertensive nephrosclerosis is a chronic renal disease associated with indispensable hypertension. A population-based study calculated end-stage renal disease (ESRD) incidence at 152 per million populations and diabetic kidney disease as the most common cause of ESRD (Jha 2013). However, according to the latest report, hypertensive nephrosclerosis has moved up to the fourth position in terms of diagnostic frequency cited as causing ESRD in chronic dialysis patients (Rajapurkar et al. 2012). Renal damage represents a common event in the course of hypertensive nephrosclerosis, and the relative risk of developing ESRD is increased up to 20 times in hypertensive patients (Klag et al. 1996). However, the lack of association between hypertension control and progression to ESRD suggests that mechanisms responsible for varied susceptibility among human population could be pointed toward complex interaction among elevated blood pressure (BP), altered paracrine and endocrine factors, genetic factors or the presence of underlying renal disease (Luft 2000). Involvement of environmental factors in the pathogenesis of hypertensive nephrosclerosis has also been proposed (Luke 1999).

A definite association exists between oxidative stress within the kidney and development of hypertension. However, it is still a debate whether oxidative stress is a cause or a result of hypertension (Grossman 2008). Reactive oxygen species (ROS) are potent modulator of vascular contraction and

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Genetic variants in post myocardial infarction patients presenting with electrical storm of unstable ventricular tachycardia

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ABSTRACT

Electrical storm (ES) is a life threatening clinical situation. Though a few clinical pointers exist, the occurrence of ES in a patient with remote myocardial infarction (MI) is generally unpredictable. Genetic markers for this entity have not been studied. In the present study, we carried out genetic screening in patients with remote myocardial infarction presenting with ES by next generation sequencing and identified 25 rare variants in 19 genes predominantly in RYR2, SCN5A, KCNJ11, KCNE1 and KCNH2, CACNA1B, CACNA1C, CACNA1D and desmosomal genes - DSP and DSG2 that could potentially be implicated in electrical storm. These genes have been previously reported to be associated with inherited syndromes of Sudden Cardiac Death. The present study suggests that the genetic architecture in patients with remote MI and ES of unstable ventricular tachycardia may be similar to that of Ion channelopathies. Identification of these variants may identify post MI patients who are predisposed to develop electrical storm and help in risk stratification.

1. Introduction

Sudden Cardiac Death (SCD) in patients with remote myocardial Infarction (MI) is due to the occurrence of malignant ventricular arrhythmias, the most common being 'Ventricular Tachycardia' (VT). Few patients in this subset during their natural history develop Electrical storm (ES) which is defined as "Three or more distinct episodes of ventricular tachycardia (VT)/ventricular fibrillation (VF) within 24 h, requiring the intervention of the defibrillator (anti-tachycardia pacing or shock)" [1]. The timing and occurrence of ES is unpredictable. It is a life threatening cardiac emergency with a reported incidence of 10–28% and an in-hospital mortality of 60–70% [2]. Current knowledge on genetic markers related to ventricular arrhythmias in post MI patients with LV dysfunction is very limited. This paper summarizes the genetic variations identified in patients with remote myocardial infarction presenting with ES of unstable VT by next generation sequencing.

2. Material and methods

2.1. Patient population

Consecutive patients with Left ventricular dysfunction (LVEF≤ 35%), underlying remote myocardial infarction (>1 year), presented to our institute with electrical storm and hemodynamically unstable monomorphic VT, were included in the study. Patients with ES and other underlying substrates and those with stable VT or VF were not included. Study patients were managed by standard institutional protocol involving mechanical ventilation, hemodynamic support, anti-arrhythmic medications, radiofrequency ablation and stellate ganglionectomy as indicated. The management protocol and clinical outcomes of these patients have been detailed in a separate manuscript [3].

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Novel mutations of *ATP7B* gene in Wilson's disease patients of South Indian cohort

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ABSTRACT

Wilson Disease is an autosomal recessive inherited disorder caused by abnormal copper metabolism. Mutations in P-type adenosine triphosphatase -*ATP7B* gene are known to result in excessive copper deposition in liver, brain and cornea leading to hepatic, and neuropsychiatric manifestations. Wide clinical and genetic heterogeneity is observed despite being a monogenic condition, making diagnosis difficult. Unlike other populations where a common causal mutation has been established, Indian population has revealed heterogeneous data attributing to its genetic diversity. Therefore we considered screening of ATP7B gene to identify any novel disease causing mutation and establish genotype-phenotype correlation.

Genetic screening of the entire coding region of *ATP7B* gene was carried out in thirteen WD patients and nine of available family members by PCR based direct sequencing for hotspot exons 8, 13, 14, 15 and 18 and PCR based SSCP analysis for the rest of 16 exons.

We report five novel mutations (3 missense, 1 frameshift and 1 intronic) and five reported mutations (2 missense, 1 silent, 1 intronic and 1 in 5′UTR). Mutations were mostly observed in hotspot exons 8, 13 and 18. Genotype-phenotype correlation revealed predominance of mutations in certain clinical subtype along with regional variation. Molecular genetic analysis has proved to be the most reliable method for confirmation of clinical diagnosis and identification of pre-symptomatic individuals, however screening of the entire gene can be time consuming and an expensive method. Since the hotspot exons: 8, 13, 14, 15, and 18 constitute for nearly 85% of the mutations, screening of these exons can be an efficient and an economical option.

1. Introduction

Wilson disease (WD-MIM#277900) is an autosomal recessive disorder of copper metabolism resulting in excessive copper deposition, primarily in the liver and the brain, leading to hepatic and neuropsychiatric manifestations (Ferenci et al., 2003). The copper is also deposited as rings in the cornea of the eye called 'Keyser-Fleisher ring' (KF). Mutations in ATPase copper transporting beta gene (*ATP7B*) are known to cause a defective copper transporting copper-transporting ATPase 2 protein resulting in copper accumulation. *ATP7B* gene is comprised of 21 exons, 80 kb in length and code for a 1465 amino acid protein (Bull et al., 1993; Tanzi et al., 1993). Although it's a monogenetic disease, varied clinical heterogeneity is observed in patients with hepatic, neurological and corneal manifestations in variable combinations (Dastur et al., 1968; Pfeiffer, 2007; Aggarwal et al., 2009), making clinical diagnosis difficult.

More than 500 mutations in *ATP7B* have been documented from various countries available on Wilson disease database (www.wilsondisease.med.ualberta.ca/). Genetic studies from India have been reported mainly from three centres: Chandigarh, Kolkata and Vellore (Gupta et al., 2005; Kumar et al., 2005; Santhosh et al., 2006) wherein, a total of 51 mutations of *ATP7B* have been documented. There is no single predominant mutation noted in the Indian population unlike in other countries wherein H1069Q is observed in 60% of central European population and R778L in 45% of Chinese population, (Gromadzka et al., 2006) thus suggesting wide genetic heterogeneity in Indians.

In the present study, mutational analysis of entire *ATP7B* gene was carried out in thirteen patients and their available family members (n = 9), to identify any common mutation and establish genotype-phenotype correlation. We identified five novel mutations (3 missense, 1 frameshift, and 1 intronic) and five reported mutations (2 missense, 1

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THERAPEUTIC HOTLINE

Clinical efficacy of platelet rich plasma in combination with methotrexate in chronic plaque psoriatic patients

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ABSTRACT: Psoriasis affects up to 3% of the world's population or more than 125 million people. There is an urgent need for new treatment strategy, as up to 50% of patients are not satisfied with current therapies. We evaluated the combined efficiency of platelet rich plasma (PRP) and methotrexate (MTX) in the management of patients with plaque psoriasis. Twenty-one patients with chronic plaque psoriasis were recruited in the study. Sixteen patients were assigned into combinational treatment group (PRP + MTX) and monotherapy group (MTX alone) consisted of five patients. All patients in combinational therapy received autologous PRP in their first sitting and subsequently followed with folitrax-15 for 4 weeks, while patients in monotherapy group received only folitrax-15, all patients received intra-lesional injections. Digital photograph, Psoriasis Area Severity Index (PASI) score and adverse events were recorded at weeks 0, 4, 8, 12 and 16 and were evaluated by three investigators independently. Patients treated with PRP/MTX showed substantial improvement in term of reduction in erythema, induration and desquamation at each visit and was effectively cleared off psoriasis at week 16. Combination treatment of PRP with MTX was well tolerated by all patients without any serious adverse events.

KEYWORDS: anti-inflammatory, combinational therapy, PASI, PRP, Psoriasis

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CYP2C9, *VKORC1*, *CYP4F2*, *ABCB1* and *F5* variants: Influence on quality of long-term anticoagulation

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ABSTRACT

Aims: The study aims to evaluate the impact of genetic, demographic and clinical data on various measures of outcome of anticoagulation quality in patients.
Patients and methods: The study consisted of 310 patients receiving long-term oral anticoagulation therapy in our hospital. Apart from demographic and clinical variables, 21 SNPs (in 7 genes) were analyzed and compared with the outcomes of anticoagulation therapy. Various outcomes that were measured are; supra therapeutic INRs (INR >3, >6), anticoagulation stabilization, time taken to stabilize and proportion of INRs within (2–3), above (>3) and below (<2) therapeutic range.
Results: Supra therapeutic INRs were influenced by *CYP2C9**2, *3, *CYP4F2* rs2108622, *VKORC1*-1639G>A, 1173C>T, rs55894764 along with concomitant drugs, smoking, body weight and height. Persistently fluctuating INRs/absolute instability correlated with *VKORC1*-1639G>A, gender, height and body mass index. The time taken to stabilize was associated with *CYP4F2* rs2108622, *CYP2C9**14, smoking, clinical indication and concomitant drugs. The overall distribution of INR was influenced by variants in *CYP4F2* rs2108622, *CYP2C9**3, rs9332230, *VKORC1* 1173C>T, −1639G>A, rs55894764, *ABCB1* rs2032582, rs1128503, rs1045642 and *F5* rs6025, age, smoking and concomitant drugs.
Conclusions: Knowledge of factors influencing the quality of long term anticoagulation can help clinicians to customize therapy either by dose variation, therapy with alternate choice of drug, concurrent heparin therapy and/or frequent INR monitoring.

Introduction

The quality of anticoagulation therapy and drug toxicity in patients may be measured by different means. The most commonly studied parameters for drug response are the stabilized dose and occurrence of bleeding events. Apart from these, the anticoagulant efficiency and risk of toxicity may be calculated by the length of time taken to stabilize, time spent (or percent) within and outside the therapeutic international normalized ratio (INR) range, over anticoagulation (elevated INRs > 3.0 or 4.0), severe over anticoagulation (elevated INRs > 5.0 or 6.0), absolute instability or persistently fluctuating INRs. A wide range of therapy-related clinical factors such as the initiation dose, scheme of dose titration, target INR range, quality and frequency of anticoagulation monitoring and concurrent therapy with interacting drugs can contribute to variations in any of the above quality measures. Environmental and demographic causes of variation may be attributed to food intake, body weight and height, age, smoking and alcohol abuse, clinical indication and comorbidities. Most important are the inherent and unvarying variable, i.e.

Abbreviations: OAC, oral anticoagulant; ADR, adverse drug reaction; BMI, body mass index; SD, standard deviation; CI, confidence interval; BSA, body surface area; INR, international normalized ratio; AOD, arterial occlusive disease; CAD, coronary artery disease; AVR, aortic valve regurgitation; FVL, factor V Leiden; ACE, angiotensin converting enzyme.

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