Tibial Fracture – Platelet Rich Plasma and Bone Marrow Aspirate Concentrate (T-PAC): A Randomized Controlled Feasibility Study

James Shen Hwa Vun[1], Michalis Panteli, Anthony Howard[2], Paul Harwood, Nikolaos K Kanakaris[3], Jehan El-Jawhari, Elena Jones[4], Peter Giannoudis[5]
[1]Academic Department of Trauma and Orthopaedics, [2]Academic Dept of Trauma and Orthopaedics, University of Leeds, [3]Academic Dept of Trauma and Orthopaedics, [4]University of Leeds, [5]Leeds Gen.L Infirm/Dept of Trauma & Ortho

INTRODUCTION:
We aim to assess the feasibility of conducting a randomized clinical trial (RCT) evaluating the effect of augmenting acute fracture healing with autologous bone marrow aspirate concentrate (BMAC) and platelet rich plasma (PRP) in addition to standard care in patients with acute, unilateral tibial diaphyseal fractures.
METHODS:
This was a prospective single, patient-blinded randomized controlled trial based in a single major trauma center which has gained ethical approval. Patients were randomized at a 2:1 ratio (treatment: control arm) using an online randomization platform. Patients were eligible if they were aged 18-65, sustained an acute unilateral closed tibial diaphyseal fracture, able to provide consent, and definitive fixation with statically locked, reamed intramedullary nail or fine wire ring fixator within 14 days of injury. Autologous BMAC and PRP prepared following centrifugation of bone marrow aspirate harvested from iliac crest and peripheral blood respectively were injected percutaneously into fracture site under fluoroscopic guidance on the day of surgery. We assessed the safety profile of BMAC-PRP injection. Primary outcomes were time to painless weight bearing (clinical union); radiological union assessed using the radiological union score in tibial fractures (RUST) at weeks 2,8,12,16,20,26,39; and patient reported outcome measure (PROM) using the lower extremity functional scale (LEFS) at weeks 0, 12, 26, 39.
Main study variables were assessed and found not the meet the assumptions for parametric analysis, including examination of data distribution ($p < 0.05$, Shapiro-Wilk test). Summary data were therefore presented as median, interquartile range (IQR), and absolute range and non-parametric analyses were used throughout. Quantitative variables were compared using the Mann-Whitney U test and Wilcoxon signed-rank test as appropriate. Qualitative data were presented as number and percentages, with chi-squared test used when comparing between groups. Statistical significance was assumed at the $p<0.05$ level.
RESULTS:
Of the 54 patients who met the inclusion criteria, 45 patients were recruited and randomized. Two patients were withdrawn before surgery (1 compartment syndrome, 1 delay to operation beyond 14 days). Majority of the tibial fractures were distal 1/3rd diaphyseal fractures (84%). Commonest fracture patterns were AO42A1 (47%) and AO42A3 (21%). There were no nonunion, delayed union, deaths reported. No adverse effects, serious adverse effects, or complications observed with BMAC-PRP injection.
A larger proportion of patients in the treatment arm achieved radiological union (RUST≥10) earlier at weeks 12 (23% vs. Control: 0%) and 16 (73% vs. Control:31%). RUST scores in the treatment arm were significantly higher compared to control arm at weeks 8, 12, 16, 20 ($p<0.05$). Reflecting the quicker time to radiological union observed, a larger proportion of patients from the treatment arm achieved clinical union earlier at weeks 8 (40% vs. Control: 31%); 12 (67% vs. Control: 38%); and 16 (77% vs. Control 69%). This was further confirmed by the shorter time to painless full weight bearing observed in the treatment arm, albeit not reaching statistical significance (Treatment: median 60.5 days [IQr:40-114; Range:20- 258]; Control: median 107 days [IQr: 40 -114; Range: 31-287]). No clinically significant difference (Difference in LEFS score of >9 points) was observed at all timepoints when comparing the median LEFS score between the two groups.
To account for the confounding effect of different fracture patterns, we further categorized fractures according to three main groups (AO42A, AO42B, AO42C), and analyzed the largest fracture group (AO42A: control n=10; treatment n=23). A greater proportion of patients from the treatment arm achieved radiological at weeks 12 (26% vs. Control: 0%) and 16 (74% vs. Control: 20%). The RUST scores were statistically significant in the treatment arm at weeks 8, 12, 16, 20 reflecting quicker radiological union. A similar improvement in clinical union was observed in this subgroup. A larger proportion of patients from the treatment arm achieved earlier clinical union at weeks 8 (47% vs. Control: 31%); 12 (70% vs. Control: 40%); and 16 (74% vs. Control 69%), further reflected by the shorter time to painless full weight bearing, although not significantly different (Treatment: median 51 days [IQr:39-113; Range:20- 198]; Control: median 108 days [IQr: 37 -132; Range: 31-287]). No clinically significant difference was observed when comparing the median LEFS scores between the two groups at all timepoints.
DISCUSSION AND CONCLUSION:

This study demonstrated the feasibility of conducting a full scale RCT, with a high recruitment rate. Furthermore, BMAC-PRP injection has a good safety profile. Augmenting acute fracture healing with BMAC-PRP was found to improved radiological union, mirrored by the trend toward shorter clinical union time observed in this study.