The thrombogenic risk induced by intraportal infusion of Adult Derived Human Liver Stem/ Mesenchymal Cells in Wistar rats can be controlled with a combination of anticoagulant drugs, heparin and bivalirudin.

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Background:

Mesenchymal stem cell (MSC) infusions are currently tested in numerous clinical trials, but therapy-induced thrombi have been described in several patients. Most MSCs, like Adult Derived Human Liver Stem Cells (ADHLSCs), in fact express a procoagulant activity (PCA) linked to tissue factor (TF) expression, which is the fuse that ignites the coagulation cascade leading to coagulation factors consumption.

The aim was to study *in vivo*, the effect of anticoagulant drugs, combining an antithrombin activator, heparin and a thrombin inhibitor, bivalirudin and the effect of cell doses on the thrombogenic risk induced by intraportal infusion of ADHLSCs.

Methods

Wistar rats (n=6/group) were infused with 3 different cell dosages (50 (High), 12.5 (High) and 5 (Low) million ADHLSCs/kg), with or without anticoagulant therapy through an intraportal catheter. Control group was infused with PBS. Blood samples were collected before and 1 hour after cell infusion (Total blood count, coagulation factors and thrombin-antithrombin (TAT) complexes). Rats were sacrificed and liver tissue was collected 1 hour after cell infusion. Serial slides were performed to analyze the localization of AHDLSCs and fibrin.

Results

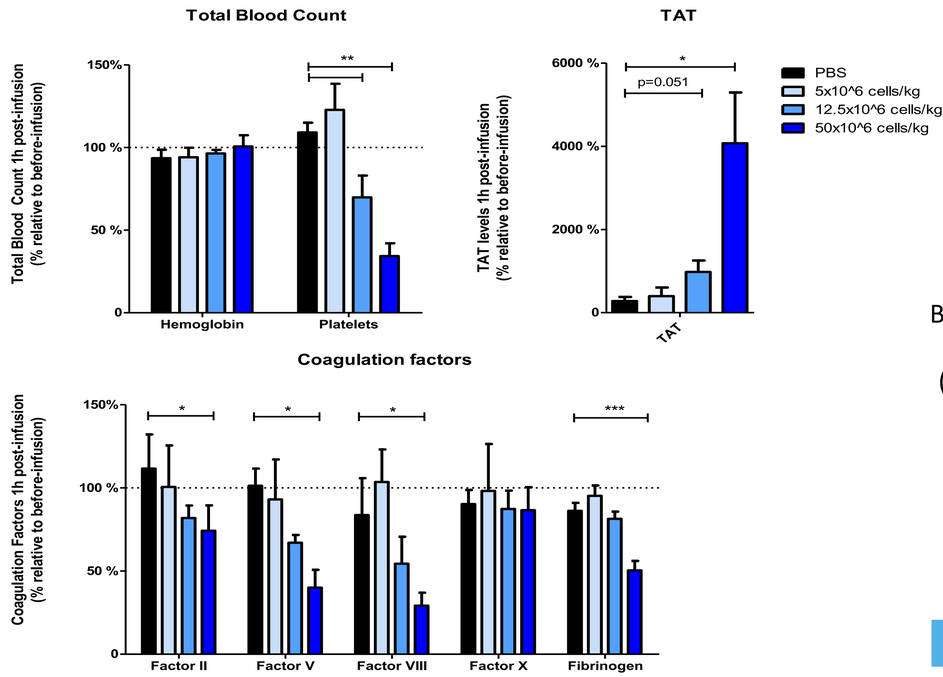
ADHLSCS intraportal infusion influences after 1h platelet count levels and coagulation factors in a cell dose dependant manner (Fig.1). Infusion of high cell dosage of ADHSLCs, 12.5 - 50x10^6 cells/kg, induced a significant decrease in platelets ($p<0.01$) without inducing a drop in haemoglobin levels. When 50x10^6 cells/kg are infused, fibrinogen ($p<0.001$), coagulation factors II, V and VIII ($p<0.01$) levels decrease and Thrombin-Antithrombin (TAT) complex levels increase significantly ($p<0.05$).

Adding anticoagulants prevented significantly the decrease in platelet counts ($p<0.01$, Fig.2) and factor II, V and VIII ($p<0.05$). . Fibrin production around the infused cells localized in Portal Veins (PV) was significantly ($p < 0.001$) reduced, from 86.6% ± 6.4 to 26.4% ± 13.8 in the anticoagulated group. Nevertheless, TAT complex levels increased significantly ($p<0.01$) showing the activation of coagulation is limited but not completely prevented.

Conclusion

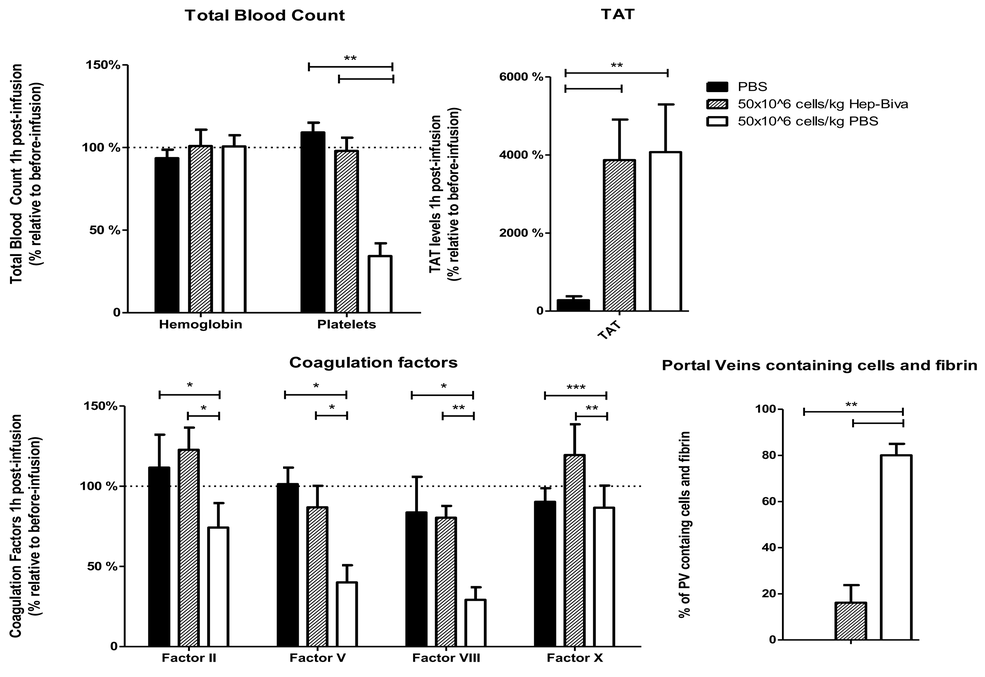
Infusion of low doses, such as 5x10^{6}cells/kg is safe, and infusion of high doses, such as 50x10^{6}cells/kg can be controlled when anticoagulant drugs, heparin and bivalirudin are added.

Fig. 1 Effect of cell doses on activation of coagulation by ADHLSCs



Bar graph (mean with SEM). Mann-Whitney test
(*$p<0.05$, ** $p<0.01$,*** $p<0,001$).

Fig. 2 Effect of anticoagulant drugs on the thrombogenic risk induced by ADHLSCs



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