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Intravenous administration of synthetic platelets (SynthoPlate™) in a mouse liver injury model of uncontrolled hemorrhage improves hemostasis

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Abstract

Background—Clinical resuscitative treatment of traumatic hemorrhage involves transfusion of RBC, platelets and plasma in controlled ratios. However, use of such blood components, especially platelets, present many challenges including availability, portability, contamination risks, and short shelf-life, which limit the use of platelet transfusions outside of large trauma centers such as remote civilian hospitals and austere pre-hospital settings. This has prompted significant research in platelet substitutes that may resolve the above issues while providing platelet-mimetic hemostatic action. In this framework, we have developed a synthetic platelet surrogate, SynthoPlate™, by integrative decoration of platelet function mimetic peptides on a biocompatible lipid nanovesicle platform. We have previously demonstrated hemostatic capability of SynthoPlate™ in correcting tail-bleeding time in thrombocytopenic mice. Building on this, we hypothesized that SynthoPlate™ transfusion would decrease bleeding in a murine model of acute hemorrhagic shock.

Methods—A validated model of uncontrolled intraperitoneal hemorrhage, via liver laceration was utilized to induce hemorrhagic shock in mice. SynthoPlate™, control (unmodified) particles,

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Disclosure of Conflicts of Interest

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Author Contributions

M.R. Dyer, D. Hickman, N. Luc, S. Haldeman, C. Pawlowski, A. Sen Gupta, and M.D. Neal designed the research study. D. Hickman, N. Luc, C. Pawlowski, and A. Sen Gupta fabricated the SynthoPlate™ particles. M.R. Dyer, D. Hickman, and S. Haldeman conducted the experiments. M.R. Dyer, D. Hickman, S. Haldeman, and P. Loughran acquired data. M.R. Dyer, D. Hickman, P. Loughran, A. Sen Gupta, and M.D. Neal analyzed the data. M.R. Dyer, A. Sen Gupta, and M.D. Neal wrote the manuscript.

and normal saline were administered as pre-treatment and rescue infusions to mice undergoing liver laceration and evaluated for hemostatic benefit by determining differences in blood loss and monitoring real-time hemodynamic data.

Results—Pre-treatment SynthoPlate™ transfusion resulted in significant reduction of blood loss following hemorrhage, compared to control particles or normal saline treatment (0.86 ± 0.16 g CP vs. 0.84 ± 0.13 g NS vs. 0.68 ± 0.09 g SynthoPlate™, $p < 0.005$). SynthoPlate™ transfused mice demonstrated improved hemodynamics taking significantly longer to develop post-injury hypotension (168.3 ± 106.6 seconds CP vs. 137 ± 58 seconds NS vs. 546.7 ± 329.8 seconds SynthoPlate™, $p < 0.05$). SynthoPlate™ infusion following liver laceration, i.e. rescue transfusion, also resulted in a significant decrease in blood loss (0.89 ± 0.17 g CP vs. 0.92 ± 0.19 g NS vs. 0.69 ± 0.18 g SynthoPlate™, $p < 0.05$).

Conclusions—Transfusion of SynthoPlate™ particles reduces blood loss in a murine model of liver injury, and SynthoPlates™ may represent a viable transfusion product for the mitigation of blood loss in acute, severe hemorrhagic shock.

Keywords

Platelets; Hemorrhage; Synthetic Platelet; Shock; Trauma

Background

Traumatic hemorrhage continues to be a leading cause of preventable death in civilian and battlefield scenarios. In such situations, prompt resuscitation and point-of-injury treatment of ongoing hemorrhage is of upmost importance to improve survival.^{1,2} In recent years, resuscitation of bleeding trauma patients has shifted away from crystalloid fluids to balanced blood product transfusion.^{3–5} Important in the current resuscitation strategies is the transfusion of pooled platelets, which have been shown to be a critical component of modern hemostatic resuscitation strategies.^{6,7} However, platelet transfusions are fraught with several challenges including increased risk of bacterial contamination in storage, platelet activation/degranulation during storage and a limited shelf life of only 5–7 days.^{8,9,10} As well, platelet transfusions account for 25–30% of all transfusion reactions while only accounting for around 10% of blood product transfusions.^{8,11} Finally, given the challenging requirements for storage of pooled platelets, there is very limited availability of platelets outside of large central blood banks, which presents a major problem for hemorrhage resuscitation in remote civilian locations and austere battlefield conditions.^{8,11}

Given these challenges associated with platelet transfusions, there is significant clinical interest in extending the shelf-life and hemostatic viability of platelets via cold-storage and lyophilization^{12,13}, as well as, in developing transfusable synthetic platelet substitutes that allow long-term storage and platelet-mimetic hemostatic action.^{10,14,15} To this end, we have developed a synthetic platelet nanotechnology, namely SynthoPlate™, that incorporates the pro-adhesive and pro-aggregatory properties of native platelets by virtue of decorating a combination of platelet function-mimicking peptides (vWF-binding peptides or VBP, collagen binding peptides or CBP and active platelet GPIIb-IIIa-binding fibrinogen-mimetic peptides or FMP) on a biocompatible lipid vesicle platform.¹⁶ SynthoPlate™ is shelf-stable,

portable, and easily administered, addressing many of the challenges and limitations of human platelet usage in remote and pre-hospital settings. Detailed chemistry of these peptide decorations and functions, in vitro characterization of the resultant SynthoPlate™ technology and its promising hemostatic effect in correcting tail bleeding time in normal as well as thrombocytopenic mice, have been reported previously.^{17,18} Building on these findings, we hypothesized that SynthoPlate™ treatment would result in decreased blood loss in acute, hemorrhagic shock. To test this, we utilized a validated, reproducible and high-throughput model of murine liver injury that results in uncontrolled intraperitoneal haemorrhage and severe shock.¹⁹

Materials and Methods

Animals

C57BL/6 WT mice (8–12 weeks, male) were purchased from the Jackson Laboratories (Bar Harbor, ME). Mice were housed in accordance with University of Pittsburgh (Pittsburgh, PA, USA) and National Institutes of Health (NIH; Bethesda, MD, USA) animal care guidelines in specific pathogen-free conditions with 12-hr light-dark cycles and free access to standard feed and water. All animal experiments were approved conducted in accordance with the guidelines set forth by the Animal Research and Care Committee at the University of Pittsburgh.

SynthoPlate™ manufacture

SynthoPlate™ is made of multiple lipid, lipid-peptide and cholesterol components, as has been described previously.^{17,18} 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-1000] (DSPE-mPEG₁₀₀₀), 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000] (DSPE-PEG₂₀₀₀-Mal) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[azido(polyethylene glycol)-2000] (DSPE-PEG₂₀₀₀-Azide) were purchased from Avanti Polar Lipids (Alabaster, AL, USA). Rhodamine B-dihexadecanoyl-sn-glycero-3-phosphoethanolamine (DHPE-RhB) was purchased from Invitrogen (Carlsbad, CA, USA). The peptides VBP (sequence CTRYLRHPQSWVHQI), CBP (sequence C[GPO]₇) and FMP (sequence cyclo-{Pra}CNPRGD{Tyr(OEt)}RC) were custom-synthesized by GeScript (Piscataway, NJ, USA). VBP and CBP were conjugated to DSPE-PEG₂₀₀₀-Mal using thiol-maleimide coupling²⁰ and FMP was conjugated to DSPE-PEG₂₀₀₀-azide via copper-catalyzed alkyne-azide cycloaddition ‘click’ chemistry (CuCAAC)²¹. The conjugates were purified by dialysis and characterized by MALDI-TOF mass spectrometry. Cholesterol was purchased from Sigma-Aldrich (Saint Louis, MO, USA). The lipid vesicle fabrication technique of ‘film rehydration and extrusion’ was used to manufacture SynthoPlate™ as described previously.^{13,14} Heteromultivalently decorated SynthoPlate™ vesicles were produced and dynamic light scattering (DLS) and electron microscopy characterization indicated fresh-made vesicles were ~200nm in diameter as we have previously reported.¹⁷

Liver laceration model of uncontrolled hemorrhage and SynthoPlate™ evaluation

We developed and validated a murine model of uncontrolled hemorrhage using a liver laceration.¹⁹ A schematic and timeline of the experimental design is presented in Figure 1. Briefly, mice were anesthetized with sodium pentobarbital (70mg/kg) via intraperitoneal injection and real-time hemodynamic monitoring is achieved through femoral arterial cannulation. A midline laparotomy is performed, pre-weighed absorption triangles are inserted away from the liver, and 75% of the left middle lobe of the liver is lacerated. Mice were treated via tail-vein injection with SynthoPlate™ particles (30mg/kg), control particles (unmodified particles, 30mg/kg), or normal saline (0.9%) either 30 minutes' prior (pre-treatment) to or 1 minute after (rescue) performing the liver laceration. Animal surgeons were blinded to treatment groups. For rescue strategy experiments the tail vein was cannulated with a mouse tail vein catheter (SAI Infusion Technologies) and the treatment was administered through the catheter. The dose for SynthoPlate™ infusion was determined from prior work in tail transection bleeding models, with final infusion volumes of 250–300µl.¹⁷ When administered in the rescue setting, the SynthoPlate™ infusion was followed by a flush of normal saline, equal volume, to ensure particles were infused into the circulation. To determine the effect of SynthoPlate™ on acute blood loss mitigation mice were sacrificed 20 minutes following liver laceration. Blood loss was calculated by assessing the difference in the weight of absorption triangles pre- and post-liver laceration. The weight of the resected liver was determined immediately following sacrifice. Hemodynamic data was collected using DMSI-400 (Micro-Med) software.

In vivo Biodistribution of SynthoPlate™ particles

In consideration of a theoretical risk of systemic off-target sequestration of SynthoPlate™ resulting in microvascular complications, we sought to evaluate the biodistribution and determine clearance of SynthoPlate™ following hemorrhagic shock in mice subjected to liver laceration as described above. Tissue homogenates were analyzed using ultra high-performance liquid chromatography (UPLC). For this, organs (brain, heart, lung, liver, injured liver, kidney, and spleen) were harvested at the time of sacrifice, snap-frozen in liquid nitrogen, dried in a lyophilizer and dry weight was recorded. The organs were homogenized at 4000 rpm for 2 cycles of 25 seconds using a BeadBug Microtube Homogenizer (Benchmark Scientific, Edison, NJ) with 3.0 mm high impact zirconium beads. Samples were shaken overnight at 750rpm at 37°C in a 1:1 solution of methanol/chloroform to extract the RhB-conjugated lipids. These samples were centrifuged at 12,000g for 20 minutes and the supernatant, containing RhB-labeled lipids from SynthoPlate™, was collected. The RhB-labeled lipids were resolved using Waters Acquity UPLC system (column: Waters BEH C8 1.7µm) and analyzed with a fluorescence detector (Waters Corporation, Milford, MA, USA) using excitation wavelength 560nm and emission wavelength of 580nm. The uptake of SynthoPlate™ in the organs was determined using an RhB-fluorescence based calibration curve for SynthoPlate™ and reported as the percent of injected dose as per calibration curve.

Statistics

The primary objective for this study was to determine the efficacy of SynthoPlate™ transfusion to reduce blood loss in acute, hemorrhagic shock compared to control particles and normal saline (0.9%). Secondary endpoints were hemodynamic analysis and biodistribution. Based on pilot data, to detect a decrease in blood loss of 20% resulting in a treatment effect size of 1.5, at 80% power, and a significance level of 0.05, we determined 8 mice per group would be needed for the primary endpoint analysis. All data are presented as mean $\pm$ SD for $n = 3$ unless stated otherwise in the figure legends. Statistical significance was determined with the 2-tailed Student's *t* test or 1-way ANOVA with Bonferroni post-hoc test using Graph Pad Prism software (GraphPad). A *p* value of less than 0.05 was considered significant.

Results

Pre-treatment SynthoPlate™ transfusion results in decreased blood loss and improved hemodynamics during acute, severe hemorrhagic shock

We evaluated the capability of SynthoPlate™ to improve hemostasis, as determined by blood loss, in a severe model of trauma and hemorrhagic shock, utilizing a validated murine model of uncontrolled hemorrhage induced by liver laceration (Fig. 1).¹⁹ As demonstrated in Figure 2A, mice pretreated 30 minutes prior to liver laceration with SynthoPlate™ showed a significant decrease in acute blood loss following liver laceration, compared to mice treated with control particles or normal saline (0.86 $\pm$ 0.16g CP vs. 0.84 $\pm$ 0.13g NS vs. 0.68 $\pm$ 0.09g SynthoPlate™). To ensure the differences in blood loss between treatment groups was due to SynthoPlate™ transfusion and not secondary to differences in levels of severity of liver injury, the weight of the segment of liver resected during the laceration was determined. There were no significant differences between treatment groups with regards to the weight of the resected liver (Figure 2B, 0.32 $\pm$ 0.05g CP vs. 0.33 $\pm$ 0.03g NS vs. 0.30 $\pm$ 0.04g SynthoPlate™). All animals had femoral arterial lines placed for real-time hemodynamic monitoring and as a secondary endpoint, we compared the time elapsed following liver laceration to development of hypotension, defined as a mean arterial pressure less than 40mmHg. As shown in Figure 2C–D, the time to develop hypotension, is significantly prolonged in mice pretreated with SynthoPlate™ and hypotension was prevented in some mice pretreated with SynthoPlate™ compared to mice treated with control particles or normal saline (168.3 $\pm$ 106.6 seconds CP vs. 137 $\pm$ 58 seconds NS vs. 546.7 $\pm$ 329.8 seconds SynthoPlate™).

Systemic Biodistribution SynthoPlate™ particles following liver laceration

We sought to evaluate the biodistribution-organ distribution, particle clearance, and off-target sequestration of SynthoPlate™ particles in the setting of our hemorrhagic shock model. Ultra high-performance liquid chromatography (UPLC) was performed to determine the percent of injected SynthoPlate™ particle extracted from an organ harvested following liver laceration. We found that in the acute hemorrhagic shock setting SynthoPlate™ particles are distributed most frequently in the lung, liver, and in the injured liver site (Fig. 3), although the overall sequestration of these particles in uninjured sites was low. As inferred from Figure 3, immediately following hemorrhage, only ~25% of the injected

SynthoPlate™ particles are cleared into the various organs, suggesting that most of the transfused SynthoPlate™ particles remain in circulation and available for continued assistance in hemorrhage control over time, if needed.

SynthoPlate™ particles reduce blood loss and improve hemodynamics in mice in hemorrhagic shock

After determining efficacy in reducing blood loss and improving hemodynamics in a pretreatment setting, we next sought to evaluate efficacy in a rescue model where SynthoPlate™ transfusion was performed after liver laceration in order to more accurately model traumatic hemorrhage (Fig. 1). Mice transfused with SynthoPlate™ following liver laceration experienced significantly less blood loss compared to either CP or NS treated mice (Figure 4A, 0.89 ± 0.17 g CP vs. 0.92 ± 0.19 g NS vs. 0.69 ± 0.18 g SynthoPlate™). The weights of the resected livers were determined to control for model severity. Consistent with the findings in the pre-treatment experiments, there were no significant differences in the weight of the resected liver between the treatment groups (Figure 4B, 0.33 ± 0.05 g CP vs. 0.31 ± 0.05 g NS vs. 0.30 ± 0.06 g SynthoPlate™). In contrast to the pre-treatment experiments, SynthoPlate™ transfusion following liver laceration did not result in any hemodynamic differences between the SynthoPlate™ group compared to control particles or normal saline (Figure 4C, 543 ± 208 seconds CP vs. 486 ± 127 seconds NS vs. 510 ± 202 SynthoPlate™).

Discussion

We present here the potential applicability of an intravenous synthetic platelet nanotechnology (SynthoPlate™) as a primary resuscitative agent in mitigating traumatic hemorrhage in a murine model of uncontrolled hemorrhage. Our data demonstrate the ability of SynthoPlate™ particles to assist in primary hemorrhage control in a setting of severe bleeding, in a pre-treatment setting as well as a rescue strategy. This data is particularly striking when it is considered that the SynthoPlate™ particles are administered as a single-dose injection without other sources of fluid resuscitation during the hemorrhage period.

SynthoPlate™ particles can improve hemostasis by direct mimicry and amplification of platelet's primary hemostatic mechanisms of injury site-specific *adhesion* and *aggregation* resulting in 'in effect' enhancement of available platelet pro-coagulant surface to also amplify secondary hemostasis (Fig. 1). While SynthoPlate™ has been evaluated previously, both via in vitro characterization and in vivo via tail vein bleeding assays, we sought to evaluate the hemostatic capabilities in a more severe model of bleeding with resultant shock physiology. We initially chose to evaluate the effects of SynthoPlate™ transfusion in a pre-treatment setting in the severe hemorrhage model in mice because our previous studies had shown hemostatic benefit of SynthoPlate™ pre-treatment in murine models of sub-acute bleeding (tail transection) and we hypothesized that this benefit is conserved when bleeding became more acute (hemorrhagic trauma).^{17,18} After seeing promising results of hemostatic and hemodynamic benefit in pre-treatment evaluation, we moved to evaluation in a model more reflective of rescuing from traumatic hemorrhage, i.e. transfusion *after* the liver injury was performed. Again, in this setting we noted improved blood loss in mice transfused with

SynthoPlate™. In parallel, our group has investigated the hemostatic effects of SynthoPlate™ transfusion in model of swine femoral arterial hemorrhage and demonstrated reduced blood loss and stabilization of hemodynamics following injury to the femoral artery; however, the present manuscript is directed at intrabdominal, non-compressible hemorrhage and currently is being investigated in higher animal studies.²⁶ Together, our collective results from these studies provide complimentary evidence toward the effectiveness of SynthoPlate™ in providing hemostasis in situations of hemorrhage and together move forward to evaluations in polytrauma.

SynthoPlate™ transfusion in the pre-treatment setting resulted in improved hemodynamics, as measure by the time elapsed from liver laceration to a drop to a mean arterial pressure below 40mmHg. In contrast to pre-treatment transfusion, the hemodynamic effects of SynthoPlate™ transfusion following liver laceration did not result in a different hemodynamic profile compared to either control particles or saline. In fact, the hemodynamic profiles between the two experimental strategies are quite different as all treatment groups in rescue experiments took longer to develop hypotension. We rationalize this difference between experiments may be due to delivery of the particles. To ensure the particles, either SynthoPlate™ or control, are delivered and completely removed from the catheter a saline flush is performed immediately after injecting the particle dose. This is in effect a secondary fluid bolus delivered to the mouse which may alter the time to hypotension as compared to the pre-treatment strategy.

We also emphasize here that several ‘synthetic platelet’ designs have been developed and reported in the past few decades, but these designs have been very rarely evaluated in an in vivo model of traumatic uncontrolled hemorrhage. The majority of past studies with synthetic platelet designs have involved particles that only bear the aggregatory function of platelets (e.g. liposomal, albumin or polymeric particles coated with fibrinogen or fibrinogen-relevant RGD peptides) and these have been evaluated mostly as pre-treatment in platelet dysfunction (e.g. thrombocytopenia) models utilizing tail-bleeding and ear-punch injuries in mice, rats or rabbits.^{5,22} Only one specific design made from polymeric nanoparticles decorated with a generic RGD peptide (GRGDS) has been studied in a more severe injury (femoral artery bleed) as a pre-treatment (administered 5 min before injury) and a rescue treatment in blast trauma (administered 5 min after blast injury), in mice, showing promising results.^{23,24} Therefore, our current studies with SynthoPlate™ administered intravenously as pre-treatment (30 min before injury) as well as a rescue treatment in a mouse model of uncontrolled liver hemorrhage, are essentially one of the very few to show the feasibility and potential of such a technology in mitigating severe hemorrhage in both prophylactic (e.g. in elective surgery) and emergency (e.g. trauma) framework.

Previous work has demonstrated that intravenous injection of SynthoPlate™ particles in uninjured mice does not lead to systemic pro-thrombotic risks, as evidenced by a lack of generation of pro-thrombin fragments or D-dimer fragments in circulation.¹⁸ Also, two hours following injection in uninjured mice, clearance of SynthoPlate™ particles from circulation was found to be ~ 15%, with the liver and spleen being primarily responsible for clearance.¹⁸ Analysis of systemic biodistribution of SynthoPlate™ particles during

hemorrhage showed the liver as the major clearing site for circulating SynthoPlate™ particles consistent with the prior studies in uninjured mice. Finally, we quantified the clearance of SynthoPlate™ from circulation in the setting of acute hemorrhage and found that only ~25% of injected particle dose was cleared at the time of sacrifice. This suggests that most the SynthoPlate™ transfused remains in circulation and can provide hemostatic assistance in areas with ongoing bleeding.

While our findings certainly present evidence for the beneficial effects of SynthoPlate™ transfusion on reducing blood loss in severe, hemorrhagic shock our work is not without limitations. First, our study was powered to detect differences in blood loss and therefore other important endpoints in hemorrhagic shock such as survival could not be adequately addressed in this current study. Second, our comparison groups were control particles and normal saline. More evidence is suggesting early administration of blood products, including packed red blood cells, fresh frozen plasma, and platelets have benefits over crystalloid administration. Future studies that compare SynthoPlate™ transfusion against platelet transfusion and in conjunction with platelet transfusion are needed and a planned area of work.

Despite these limitations, we present evidence for the effectiveness in two different strategies, pre-treatment and rescue strategies. Pre-treatment effectiveness presents the potential for use of SynthoPlate™ in the setting of thrombocytopenia and platelet dysfunction (e.g. uremia) to reduce blood loss during planned procedures. Rescue therapy effectiveness highlights an exciting potential for the use of SynthoPlate™ as part of a resuscitation protocol, in conjunction with platelets or as a substitute, in acute bleeding.

In conclusion, this data shows great promise for the use of SynthoPlate™ as a viable intravenous resuscitative product for resuscitative mitigation of hemorrhagic shock by decreasing blood loss.

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Figure 1. Experimental Timeline, Liver laceration model, and SynthoPlate™ mechanism
 (A) Experimental design and timeline for pre-treatment studies. (B) Experimental Design and timeline for rescue studies. (C) The liver laceration procedure is performed through a midline laparotomy and 75% of the left middle lobe is lacerated. This results in uncontrolled intraperitoneal hemorrhage and associated hemorrhagic shock. SynthoPlate™ particles, a novel synthetic platelet nanotechnology, mimic the adhesion and aggregatory properties of native platelets by decorating lipid vesicles with platelet functioning-mimicking peptides including include a vWF-binding peptide (VBP), a collagen binding peptide (CBP) and an active platelet GPIIb-IIIa-binding fibrinogen-mimetic peptide (FMP). These peptides are those able to bind to sites of haemorrhage and other activated platelets to assist and amplify hemostasis.

Figure 2. Analysis of SynthoPlate™ pre-treatment on blood loss and hemodynamics during hemorrhagic shock

Mice were pre-treated 30 minutes prior to liver laceration with either control particles (CP), SynthoPlate™, or 0.9% normal saline (NS). Pre-treatment with SynthoPlate™ results in a significant reduction in blood loss acutely (20 minutes) after liver laceration (n=12 CP, n=14 SP and NS) (A). As a measure of control for degree of hemorrhage between the different treatment groups the weight of the resected liver was weighed to ensure the same degree of liver injury, as demonstrated in (B) no significant difference between the liver injury between any treatment group was identified. All mice underwent arterial cannulation and real-time hemodynamic monitoring, shown in (C) mice that received SynthoPlate™ took significantly longer to develop hypotension (defined as <40 mmHg) compared to mice treated with control particles or saline (n=8 per group). Representative tracings of the mean arterial pressure (MAP) between mice treated with SynthoPlate™ particles compared to control particles demonstrating the improved hemodynamics and delay to develop hypotension (D). No difference in time to hypotension was noted between SynthoPlate™ or control particle treated mice (n=11 CP, n=12 SP, n=11 NS) (F). *p<0.005 **p<0.01 ***p<0.05

Figure 3. In vivo Biodistribution of SynthoPlate™ Particles

The systemic biodistribution of SynthoPlate™ particles following liver laceration and hemorrhagic shock was assessed utilizing two different methods. SynthoPlate™ particle concentration in each organ was determined with ultra-performance liquid chromatograph (UPLC) and then expressed as a percent of the overall dose that was injected prior to liver laceration. As shown, the liver is most common organ the SynthoPlate™ particles are found, which is consistent with prior data the demonstrated in uninjured mice the liver and spleen were the major organs for SynthoPlate™ clearance (n=6).

Figure 4. Analysis of SynthoPlate™ transfusion on blood loss and hemodynamics as a rescue strategy in acute, hemorrhagic shock

Mice underwent liver laceration and were transfused either control particles (CP), SynthoPlate™, or 0.9% normal saline (NS) following the liver laceration. Administration of SynthoPlate™ following liver laceration led a significant reduction in blood loss compared to control particles or saline (n=11 CP, n=12 SP, n=11 NS) (A). As a control for the degree of hemorrhage, the weight of the resected liver was determined and as demonstrated in (B) there were no significant differences between the treatment groups. Finally, hemodynamic monitoring did not reveal any significant differences in the hemodynamic profiles between the treatment groups, as assessed by time to develop hypotension (C). *p<0.05