A pilot study on relationship between quantity of growth factors and cytokines to blood groups in umbilical cord blood-derived PRP

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Summary

Objective: Umbilical cord blood-derived platelet-rich plasma (UCB-PRP) contains essential growth factors and cytokines that play a crucial role in tissue regeneration and immune modulation. This study aims to investigate several growth factors and cytokines in UCB-PRP related to ABO blood types. *Subject and method:* UCB was collected in the delivery room and transferred to the laboratory for PRP preparation. Subsequently, the Luminex assay was used to analyze the expression of four growth factors, including fibroblast growth factor 2 (FGF-2), platelet-derived growth factor BB (PDGF-BB), vascular endothelial growth factor A (VEGF-A), and hepatocyte growth factor (HGF), as well as three cytokines, including interleukin 6 (IL-6), IL-7, and IL-8. *Result:* Results showed that B blood type UCB-PRP exhibited the highest total factor concentration (3708.515 pg/mL), followed by UCB-PRP O blood type (830.531 pg/mL), and UCB-PRP A blood type (455.01 pg/mL). PDGF-BB, FGF-2, and VEGF-A were highly expressed in the UCB-PRP B blood type, while HGF was more abundant in the UCB-PRP O blood type. Additionally, IL-6, IL-7, and IL-8 were more prevalent in the B blood type-UCB-PRP, with IL-7 being the only cytokine detected across all blood types. However, regression analysis indicated weak correlations between growth factor and cytokine levels with ABO blood groups, suggesting that additional factors influence PRP composition. *Conclusion:* These findings highlight differential expression of several growth factors and cytokines in UCB-PRP and indicate the potential correlation of these factor expression with a particular UCB group for PRP. These data have potentials for the utilization of blood group-specific PRP applications.

Keywords: Umbilical cord blood, blood type, PRP, growth factors, cytokines.

I. BACKGROUND

Platelet-rich plasma (PRP) is a regenerative treatment that utilizes the patient's own blood to accelerate healing in various medical and cosmetic applications [1, 2]. PRP is derived by centrifuging blood to concentrate platelets, which are rich in growth factors that promote tissue repair, reduce inflammation, and stimulate collagen production [3-5]. In medicine, PRP is widely used in orthopedics to treat joint injuries, tendonitis, and osteoarthritis by enhancing tissue regeneration [6-9]. It is also popular in dermatology and aesthetics for hair restoration and skin rejuvenation, helping to combat hair loss and improve skin texture. Additionally, PRP is applied in dentistry for bone healing and in sports medicine to speed up recovery from injuries. Due to its natural approach and minimal side effects, PRP is gaining popularity as an effective treatment across various fields of healthcare.

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PRP derived from umbilical cord blood (UCB) is emerging as a promising new resource in regenerative medicine. Unlike traditional PRP, which is obtained from a patient's own peripheral blood, UCB-derived PRP is collected from the donated umbilical cord tissue at birth and provides a rich source of growth factors, cytokines, and regenerative proteins [3, 10]. This new approach provides several advantages, including higher concentration of platelets and bioactive factors, making it more potent for tissue healing and regeneration. Additionally, because umbilical cord blood is young and free of age-related deterioration, it may offer stronger anti-inflammatory and regenerative properties compared to autologous PRP [4, 10, 11]. This innovation is particularly beneficial for individuals with low platelet counts or chronic conditions that limit their ability to generate high-quality PRP.

Additionally, recent studies suggest that blood type may innfluence various biochemical and immunological characteristics of plasma, including the concentration of growth factors and interleukins [12, 13]. Since PRP therapy relies on these bioactive molecules to promote tisue repair and regeneration, variations among diferent blood groups could affects ít therapeutic potential. Thus, studying the expression of molecules in PRP associated with blood type is crucial for understanding variability in PRP effectiveness and optimizing personalized treatments. Research has shown that blood types can affect the immune response, thereby increasing or decreasing the risk of diseases [14, 15]. However, we did not find any investigation on the relationship between growth factor and cytokine expression level in PRP with ABO blood groups, including UCB. Thus, we hypothesize that ABO blood groups may affect the amount of growth factors and cytokines in UCB-derived PRP. By analyzing these molecular levels, scientists can determine whether certain blood types produce PRP with higher regenerative potential or whether specific blood groups are more effective for treating conditions, such as wound healing, osteoarthritis, or hair loss. This approach could lead to improved clinical outcomes, making PRP treatments more precise and effective. In this investigation, we pilot the expression of several growth factors and cytokines in UCB-PRP in different blood types.

II. SUBJECT AND METHOD

Research site

Experiments of this study have been performed at Vinmec Hi-Tech Center.

Umbilical cord blood (UCB) collection

UCB collection ($n \geq 3$) was performed immediately after the baby was safely delivered, and the umbilical cord was clamped and cut. A sterile collection bag containing an anticoagulant (such as citrate-phosphate-dextrose) is used to prevent clotting. The healthcare provider inserts a needle into the umbilical vein of the clamped cord, allowing gravity to facilitate blood flow into the collection bag. Typically, 40 to 150mL of cord blood is collected within a few minutes. UBC units were stored at 20 - 25 °C for a maximum of eight hours and transferred to the laboratory

PRP preparation

UCB was divided into 15 mL centrifuge tubes and centrifuged at 3000 RPM for 20 minutes (80-2B Centrifuge, Jangsu Xinkang Medical, China) to separate three layers: Top plasma, intermediate buffy coat, and bottom red blood cells. The middle layer, considered inactivated PRP, was collected (2 mL from 10 mL UCB) and transferred into a new tube before being supplemented with $CaCl_2$ (10%) and thrombin (8%) to activate platelets. The mixture was then incubated at 4 °C for 30 minutes. During this time, platelets in inactivated PRP were activated and gradually transformed from liquid to gel. Using an 18G needle to extract UCB-PRP liquids for storage and remove the remaining gels. UCP-PRP liquids were stored at 4 °C for up-to 2 hours or at -80 °C for a longer time for further evaluation.

Quantification of growth factors and cytokines

The amount of seven growth factors and cytokines, including FGF-2, HGF, PDGF-BB, VEGF-A,

IL-6, IL-7, and IL-8, in UCB-PRP was measured by Luminex assay using ProcartaPlex™ Multiplex Immunoassays (Human Custom ProcartaPlex 7-Plex Kit, ThermoFisher, Massachusetts, US). Briefly, a total of 50 µL of Magnetic Beads was added to each well and subsequently washed using Wash Buffer. Following this, 50 µL of Antigen Standard, blank, and PrP samples were introduced and incubated for two hours. After incubation, the wells were washed with Wash Buffer to eliminate any unbound reagents. Reagent preparation and experimental procedures were conducted according to the manufacturer's instructions. The luminescent signal, indicative of growth factor concentrations, was measured using the Luminex™ 100/200™ system equipped with xPONENT 3.1 software.

Statistical analysis

Statistical analysis and graph generation were performed using GraphPad Prism (v10; GraphPad Software, San Diego, California) and Microsoft Excel for Mac (v16.92). Data are presented as the mean ± SD and analyzed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Regression anlysis was performed using Microsoft® Excel for Mac (Version 16.101.3 (25100321). A p-value of < 0.05 was considered statistically significant.

III. RESULT

Factors expressed more in PRP derived from the B blood type

When analyzing the total amount of factors, including four growth factors and three cytokines, in UCB-PRP, results showed that B blood type-derived UCB-PRP had the highest total amount, significantly exceeding UCB-PRP derived from A and O blood types, which have similar and much lower levels. In detail, a total of seven factors were 3708.515 ± 702.9pg/mL, 830.531 ± 253.872pg/mL, and 455.01 ± 128.191pg/mL, and in UCB-PRP derived from B blood type, O blood type, and A blood type, respectively (Figure 1).

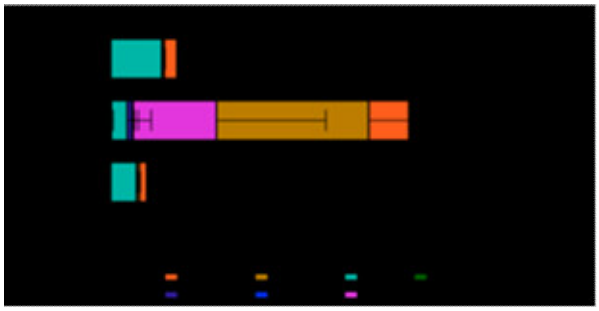

Figure 1. Total amount of seven factors in PRP derived from different blood type ($n \geq 3$).

Differential expression of growth factors in PRP derived from different UCB blood type

Four growth factors that play important roles in wound healing and regeneration were expressed differently in PRP (Figure 2). Regarding UCB type, higher amounts of FGF-2, PDGF-BB, and VEGF-A were detected in PRP derived from the B UCB (FGF-2: 16.12 ± 13.48 pg/mL, PDGF-BB: 1888.86 ± 1499.0 pg/mL, and VEGF-A: 498.046 ± 374.14 pg/mL) type compared to the A (FGF-2: 0.63 ± 0.09 pg/mL, PDGF-BB: 31.97 ± 0.97 pg/mL, and VEGF-A: 88.22 ± 1.23 pg/mL) and O UCB (FGF-2: 0.27 ± 0.28 pg/mL, PDGF-BB: 23.81 ± 1.28 pg/mL, and VEGF-A: 155.63 ± 5.38 pg/mL) types, but the differences are not statistically significant.

Additionally, the details of the analyzed factors showed that HGF was detected in the highest amounts in A and O UCB types (642.17 ± 8.62 pg/mL). Compared to A and B UCB types (328.4 ± 2.49 pg/mL and 197.18 ± 287.78 pg/mL, respectively), ($p < 0.05$ and $p<0.0001$).

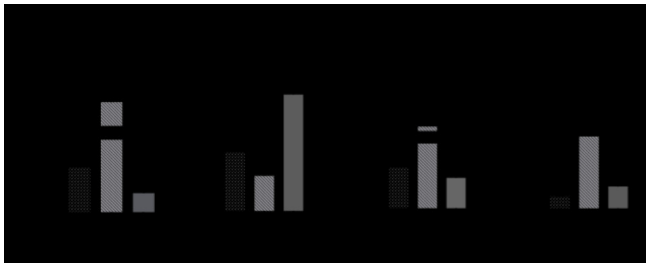

Figure 2. Different expression of growth factors, including FGF-2, HGF, PDGF-BB, and VEGF-A, in UCB-derived PRP. * indicates p-value <0.05, *** indicates p-value < 0.001, **** indicates p-value < 0.0001.

Differential expression of cytokines in PRP derived from different UCB blood types

Similar to the growth factor analysis, Figure 3 indicates that IL-6, IL-7, and IL-8 were detected at higher levels in PRP derived from the B UCB (IL-6: 62.41 ± 63.73pg/mL, IL-7: 11.41 ± 6.36pg/mL, and IL-8: 1034.49 ± 1348.49pg/mL)_type than in those derived from A (IL-6: 3.66 ± 2.11pg/mL, IL-7: 2.13 ± 0.15pg/mL, and IL-8: 0pg/mL) and O UCB (IL-6: 2.66 ± 0.13pg/mL, IL-7: 2.66 ± 0.13pg/mL, and IL-8: 2.66 ± 0.13pg/mL) types. Additionally, only IL-7 was detected in all three blood type-derived PRP samples, while IL-6 was not detected in PRP derived from the O UCB type, and IL-8 was not detected in PRP derived from the A UCB type.

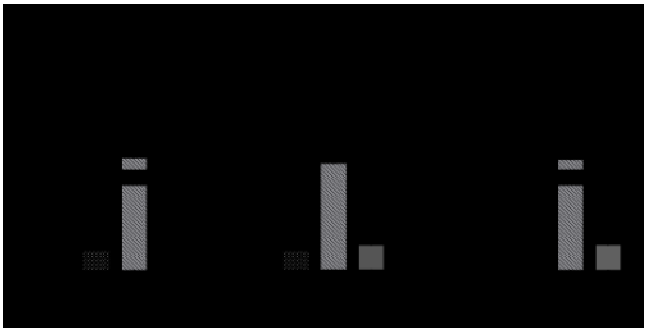

Figure 3. Different expression of cytokines, including IL-6, IL-7, and IL-8, in UCB-derived PRP. * indicates p-value <0.05, ** indicates p-value < 0.01.

Regression analysis reveals a weak relation between the expression of factors and blood group

Table 1 presents the results of regression analysis for ABO blood groups and the levels of analyzed factors, along with the coefficient of determination (r^2) values for various growth factors and cytokines, indicating the correlation among them. Higher r^2 values indicate a stronger relationship between the factor and the model, meaning that variations in IL-7, PDGF-BB, and FGF-2 are more predictable than those in HGF and IL-8, which have weaker associations. However, all r^2 values are small, which may indicate a weak correlation between growth factors and cytokines and ABO blood groups.

Table 1. Regression analysis of the amount of growth factors and cytokines in PRP with UCB groups

Factors	r^2
FGF-2	0.343
HGF	0.135
PDGF-BB	0.372
VEGF-A	0.316
IL-6	0.271
IL-7	0.436
IL-8	0.198

IV. DISCUSSION

This is the preliminary study (with a small number of samples) on the association of several growth factors and cytokines with ABO blood types. The analysis indicates that PRP derived from the B blood group contains the highest total amount of some growth factors and cytokines, far exceeding those in PRP from A and O blood groups, which showed similar but much lower concentrations. This may indicate that the expression of these factors depends on the blood type**.**

Among the four key growth factors investigated, FGF-2, PDGF-BB, and VEGF-A were detected in higher amounts, but not in statistically significant differences, in PRP derived from the UCB B blood type than in PRP from UCB A and O blood types. These factors play critical roles in wound healing, tissue regeneration, and angiogenesis [1, 16, 17]. In contrast, HGF, which plays a crucial role in cell proliferation, tissue repair, and anti-fibrotic activity [18], was found in higher concentrations in PRP derived from the O UCB group compared to the A and B UCB groups. This suggests that O blood type-UCB-PRP might have specific advantages in reducing fibrosis and promoting soft tissue healing, although it generally has lower total growth factor levels compared to B UCB-PRP.

Similar to the pattern observed in growth factors, cytokines IL-6, IL-7, and IL-8 were detected at significantly higher levels in B UCB group-PRP compared to PRP derived from A and O blood

groups. This suggests that B UCB group-PRP has a stronger immune-modulating and inflammatory response, which could be beneficial in certain wound healing and regenerative applications.

Further cytokine analysis revealed additional blood group-specific differences. For example, IL-7 was the only cytokine detected in all three blood type-derived PRP samples, suggesting it plays a fundamental role in all UCB-derived PRP regardless of blood group. Additionally, IL-6 was absent in PRP derived from O UCB group, indicating a potential variation in its inflammatory response [19]. Finally, IL-8 was not detected in PRP derived from the A UCB group, which may impact its ability to recruit immune cells during tissue repair [20]. These differences suggest that PRP from different blood types may have unique clinical applications based on their cytokine composition, influencing their role in inflammatory regulation, immune response, and healing efficiency.

The differences in growth factor and cytokine expression across UCB-derived PRP from different blood types highlight the potential for personalized regenerative therapies. However, the correlation between growth factor and cytokine levels with UCB groups was not strongly established. It is important to note that this study is a pilot investigation with a small sample size, and the variation among single samples is large, as indicated by the standard deviation. This may be due to the nature of the samples or a technical issue that we need to re-evaluate in the next investigations. Additionally, AB UCB blood groups were not included in the analysis due to unavailability during the study period. Therefore, further researches are required, including (1) increasing number of samples to show the real value; (2) investigating the mechanisms behind blood type-related differences in PRP-derived bioactive molecules; (3) determining the functional impact of these variations in clinical applications, including tissue repair, orthopedic interventions, and immune therapies; and (4) optimizing PRP formulations based on blood group, potentially leading to more targeted and effective regenerative medicine protocols.

V. CONCLUSION

This preliminary study highlights significant differences in the expression of growth factors and cytokines in UCB-derived PRP across different blood types. The findings indicate that B UCB-PRP contains the highest total levels of bioactive factors, significantly exceeding those in PRP derived from A and O blood types. Notably, FGF-2, PDGF-BB, and VEGF-A were highly expressed in B UCB-PRP, while HGF was more abundant in O UCB-PRP, suggesting possible blood type-specific regenerative properties. Additionally, IL-6, IL-7, and IL-8 were detected in higher concentrations in B UCB-PRP, indicating potential immunomodulatory advantages. However, regression analysis showed weak correlations between growth factors, cytokines, and ABO blood groups, suggesting that additional factors may influence PRP composition. These findings emphasize the need for further research with larger sample sizes to better understand blood group-related variations in PRP and their implications for personalized regenerative medicine.

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