Original Article

Mechanical Cold Stimulus Helps Release of PDGF from Platelet Granules: A Pilot Study

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Abstract

Background: Platelets are produced and released into the bloodstream by megakaryocytes, which reside within the bone marrow. It is pivotal in healing, hemostasis, and inducing inflammatory responses. Platelet-derived growth factor (PDGF), a critical cytokine, is released from the alpha granules of platelets and plays a significant role as a stimulator of cell division, blood vessel proliferation, and the proliferation of mesenchymal cells, including fibroblasts, osteoblasts, and vascular smooth muscle cells. PDGF also plays a role in inducing inflammation and promoting wound healing.
Aims and Objectives: The study aimed to assess the PDGF concentration in PRP at 24°C and 4°C following cold stimulation.
Methods: A total of 24 healthy volunteers participated in this study. A 10 mL blood sample was collected from their antecubital vein using a citrated Vacutainer in an aseptic manner. Four samples were discarded due to hemolysis, and six due to a low platelet count. Fourteen PRP samples were aliquoted into two parts for PDGF estimation at room temperature ($22 \pm 2\,^{\circ}$C) and after cold stimulation at $4\,^{\circ}$C for 10 min using the sandwich ELISA method.
Results: Semi-quantitative estimation of PDGF in normal (room temperature) and at $4\,^{\circ}$C shows a significant difference in OD value ($P < 0.001$). PDGF value showed a moderate, positive correlation with the platelet number in PRP.
Conclusion: The study concluded that cold exposure was strongly correlated with an increase in platelet count and PDGF concentration, which may explain the initiation of growth factor-induced rapid wound healing in cold-compressed traumatic injuries in local areas.

Keywords: Platelet-rich plasma; Platelet-derived growth Factors; cold stimulus

Introduction

Increasing experimental and clinical evidence has revealed platelets as key modulators of critical pathological processes, including inflammation, wound healing, and cellular and tissue regeneration. Platelets also release growth factors, cytokines, and extracellular matrix modulators that promote angiogenesis, tissue hemostasis, and repair of damaged connective tissue, as well as the proliferation and differentiation of mesenchymal stem cells into specific cells [1, 2, 3, 4, 5]. Giulio Bizzozero, an Italian physician, first identified these anuclear cellular fragments circulating in the peripheral blood in 1881 and demonstrated their key role in the haemostatic process [5]. Max Schultze (1865) described platelets as the smallest human blood cells, with a diameter of around 2 μm [5, 6].

During cellular injury, the release of various factors from platelet granules helps wound healing [7, 8]. In addition to growth factors, platelets contain more than 30 bioactive proteins [9]. Platelet granules and their contents play a crucial role in

maintaining the balance between hemostasis and thrombosis [10]. Platelet granules are unique in their content and life cycle, containing three primary granules: i. dense granules, ii. α-granules, and iii. Lysosomes. The presence of other granule types in the platelet has also been reported [11].

α-Granules are the most abundant of all the platelet granules. They number around 50–80 per platelet and usually measure 200–500 nm in diameter. α-Granules account for about 10% of the platelet volume. There are more than 300 soluble proteins that are involved in a wide variety of functions, including hemostasis (e.g., von Willebrand factor [VWF] and factor V) and inflammation (involving chemokines like CXCL1 and IL-8). In wound healing, α-granules help in the secretion of vascular endothelial growth factor [VEGF] and fibroblast growth factor [FGF] [12, 13].

The second most abundant type of platelet granules is dense granules (also known as δ-granules), which have 3–8 counts per platelet and are typically approximately 150 nm in diameter [14]. Dense granules contain bioactive amines (like serotonin and histamine), adenine nucleotides, polyphosphates, and pyrophosphates, as well as high concentrations of cations, particularly calcium [15].

The third main granular component of platelets is lysosomes. Platelets contain approximately 1–3 lysosomes per platelet and peroxisomes; their function is unclear [16].

PDGFs are essential growth factors, and the active form has a half-life of less than 2 minutes after being released from platelets [17]. These are also potent mitogens and are chemical adsorbents for fibroblasts and mesenchymal cells [18]. PDGF is crucial in various wound healing processes, including cellular proliferation, differentiation, embryonic development, inflammation, survival, and migration [19]. PDGFs are dimeric glycoproteins and exist in four isoforms: i. PDGF-A, ii. PDGF-B, iii. PDGF-C, and iv. PDGF-D [20]. PDGF-BB homodimer is the most abundant in the human body

Aims and Objectives of the Study

To assess the semi-quantitative PDGF concentration in platelet-rich plasma in healthy volunteers by ELISA reading [optical density (OD)]. Whether a mechanical cold stimulus increases PDGF release from platelet granules. PRP platelet count was relevant to PRP's PDGF concentration.

Materials and Methods

Methodology of Blood Collection

The study was conducted on a pilot basis from March 1st to May 31st, 2024, after approval from the institutional ethics committee (MC/KOL/IEC/NON-SPON/2648/12/2024, dated December 20, 2024) at the Department of Immunohematology and Blood Transfusion, Medical College Hospital, Kolkata.

In this study, 24 healthy volunteers weighing more than 45 kg were selected according to the guidelines of voluntary blood donation, as revised and published by the Ministry of Health and Family Welfare, Government of India, in 2024. A 10 mL whole blood sample was collected aseptically from the antecubital vein using a 19-G needle in a citrate-containing Vacutainer (Haemochek, Polymed) with a BP cuff, maintaining pressure at 40–60 mmHg and normal room temperature [24].

Sample preparation

All collected samples were centrifuged at room temperature at 2500 rpm/800 RCF using a tabletop centrifuge (REMI) for 10 minutes [25]. The supernatant PRP was separated using 19-G needles with a 5-mL syringe in a labelled dry tube. Counting platelets from the PRP was conducted using a three-part cell counter (Sysmex XP-100), and the results were recorded in a master chart. Four samples were discarded from these 24 sets due to red cell contamination, and six samples with a low platelet count ($\leq 150 \times 10^9/\mu$L) could only be processed for incubation at 24°C.

Quality control of the PRP samples

The PRP samples with visible red cell contamination and platelet counts $< 150 \times 10^9/\mu$L were excluded from analysis.

The supernatant PRP was separated into two aliquots in sterile EDTA vacutainers, one for cold incubation for 10 minutes and another at 24°C for 10 minutes. All the samples were tested for semi-quantitative PDGF estimation using ELISA methods (ELK Biotechnology, human PDGF (platelet-derived Growth Factor AB), Cat No: ELK1089, Lot No: 17417261), [Table 1].

Test Principle

The test principle applied for this method was the sandwich enzyme immunoassay. The microtiter plate provided in the ELISA kit was pre-coated with an antibody specific to human platelet-derived growth factor-AB (hPDGF-AB). Standards or samples added to the appropriate microtiter plate wells were conjugated with a biotin-conjugated antibody specific to human plate-derived growth factor (hPDGF-AB). Avidin was conjugated to Horseradish Peroxidase (HRP) and added to each microplate well, then incubated according to the protocol requirements. After adding the TMB substrate solution, only those wells containing hPDGF-AB, biotin-conjugated antibody, and enzyme-conjugated avidin exhibited a colour change. The addition of sulphuric acid solution terminated the enzyme-substrate reaction. The colour change was measured spectrophotometrically at a wavelength of 450 ± 10 nm. The concentration of hPDGF-AB in the samples was then determined by comparing the samples' optical density (OD) to the standard curve.

Parameters of the sample studied

1. Platelet count of the sample (PRP) at normal temperature. 2. PDGF estimation by ELISA.

Initial procedure for PDGF estimation by ELISA

All the kit components and samples were brought to room temperature (24°C) before the test.

All components were dissolved and mixed well before using the kit. The 25× wash buffer was diluted into 1× wash buffer with double-distilled water.

To prepare the standard working Solution, the Standard was centrifuged at $1000 \times g$ for 1 minute. It was then reconstituted with 1.0 ml of Standard Diluent Buffer and kept for 10 minutes at room temperature with gentle shaking. The Standard was dissolved within 15 minutes before the test.

The standard concentration in the stock solution is 5000 pg/ml, and seven tubes containing 0.5 ml standard diluent buffer were prepared. To mix each tube thoroughly before the next transfer, the solution was pipetted up and down several times. Seven points of Diluted Standard, such as 5000 pg/ml, 2500 pg/ml, 1250 pg/ml, 625 pg/ml, 312.5 pg/ml, 156.25 pg/ml, and 78.13 pg/ml, were set up [Table 2, Figure 1]. The last tube with Standard Diluent was the Blank, as zero pg/mL was added from the former tube, and no pipette solution was added.

1× Biotinylated Antibody and 1× Streptavidin-HRP: The stock Biotinylated Antibody and Streptavidin-HRP were briefly centrifuged ($1000 \times g$ for 1 minute) before use and were diluted to the working concentration 100-fold with Biotinylated Antibody Diluent and HRP Diluent, respectively.

TMB Substrate Solution: The needed solution dosage was aspirated with sterilised tips. The TMB Substrate Solution was dispensed within 15 minutes after the microtiter plate was washed. TMB is contaminated if it turns blue before use and should be discarded.

Assay Procedure

Seven wells for standard and one for blank were prepared, to which 100 μL each of standard working solution or 100 μL of samples were added to the appropriate wells. The plates were covered and incubated for 80 minutes at 37°C.

The solution was aspirated and washed by adding 200 μL of 1x wash solution to each well and letting it sit for 1-2 minutes. The remaining liquid from all the wells was removed completely by snapping the plate onto absorbent paper. The washing was done three times. After the last wash, any remaining wash buffer was removed by aspirating or decanting. Invert the plate and blot it against absorbent paper.

100 μL of Biotinylated antibody working solution was added to each well, and the plates were covered and incubated for 50 minutes at 37°C. The wash process was repeated three times.

Next, 100 μL of Streptavidin-HRP Working Solution was added to each well, which was covered with plates and incubated for 50 minutes at 37°C. The aspiration was repeated, and the wash process was conducted five times. In the next step, 90 μL of TMB Substrate Solution was added to each well, which was covered with a new plate cover. The plates were incubated for 20 minutes at 37°C in the dark.

The liquid changed to blue by adding TMB Substrate Solution. 50 μL of stop reagent was added to each well, and the liquid turned yellow by the addition of stop reagent. Any drop of water was wiped off, and the absence of any bubbles on the

surface of the liquid was confirmed. The microplate reader was run, and the measurement was conducted immediately at 450 nm.

Corrected OD values were calculated as per the kit literature by subtracting the blank values given in Table 2. The standard curve is represented by a scatter diagram, as shown in Figure 1.

The quantitative estimation of PDGF (pg/ml) was calculated from the standard calculation of PDGF concentration vs the OD values as per the kit literature. For example, the 0.0902 OD value corresponds to 78.13 pg/ml of PDGF, and the 0.1 OD value corresponds to 86.61 pg/ml [Table 3].

Results

All data were assessed [Table 3] using online DATATab software to identify the OD values of PDGF-AB kept at room temperature and cold stimulus, along with the platelet count in PRP. Correlation significance was set at a P value of < 0.05. The median OD value of 20 samples at room temperature was 0.1078 (mean = 0.1074); the remaining 14 samples were 0.1153 (mean = 0.1129) and 0.17115 (mean = 0.2032) at normal room temperature and after cold stimulus, respectively. The mean PDGF value among the RT and CRT groups was 98 pg/ml and 176 pg/ml [Table 4]. The study discarded six samples due to low platelet count ($< 150 \times 10^9/\mu$L) [Table 3].

Statistical analysis of the semi-quantitative value of PDGF by calculating the OD of PRP at 24°C (Room temperature) and 4°C (Cold exposure)

The OD of the PRP group at 24°C had lower values (M = 0.1129, SD = 0.0052) than the cold 4°C stimulant group (M = 0.2032, SD = 0.0591). A paired t-test showed that this difference was statistically significant, t(13) = -5, $P < 0.001$, 95% Confidence interval. The t-test result was therefore significant for the present data, and the null hypothesis was rejected. It confirms that cold temperature increases the quantity of PDGF [Figure 2].

Correlation between platelet count and PDGF concentration at room temperature

Kendall's tau correlation showed a moderate, negative correlation between the OD of PRP concentration and platelet count. The correlation between OD of PRP and Platelet count was not statistically significant, r(12) = 0, $p = 0.125$ [Table 5, Figure 3].

Correlation between the number of platelets and PDGF after a cold stimulus

The result of Kendall's tau correlation showed that there was a very high, positive correlation between OD with cold stimulant and Platelet count. The correlation between OD with cold stimulant and Platelet count was statistically significant, r(12) = 1, $p < 0.001$ in 14 samples $> 150 \times 10^9$/mL [Table 5, Figure 3].

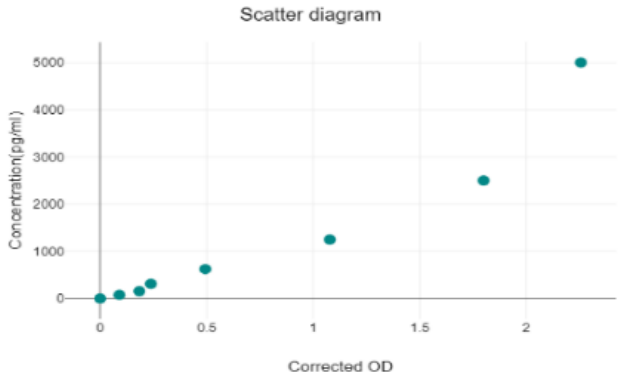

Figure 1: OD value of standards concerning PDGF in the scattered diagram

Discussion

Platelet-rich plasma (PRP) is a promising substance applied in tissue healing and regeneration. It contains a high concentration of platelets, which release growth factors such as PDGF, VEGF, and TGF-β. These factors promote tissue repair, angiogenesis,

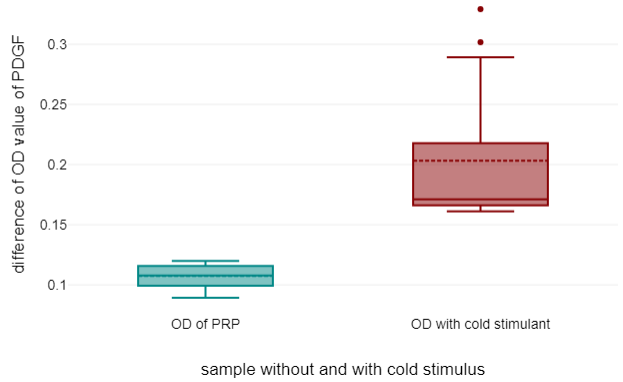

Figure 2: Box plot represents the Changes of OD in 24°C (green box) and 4°C (red box)

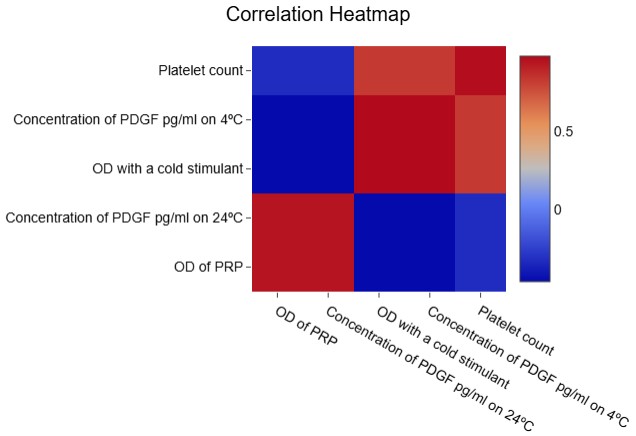

Figure 3: Correlation heat map showing positive and negative correlations with platelet count, OD values at 24°C and 4°C, and with PDGF concentration at 24°C and 4°C

Table 1: KIT components

Reagents	**Quantity (48 test)**	**Storage condition**
Pre-coated Microplate	6 strips X 8 wells	4°C / -20°C
Standard (Lyophilised)	1 vial	4°C / -20°C
Biotinylated Antibody (100x)	60 μl	4°C / -20°C
Streptavidin-HRP (100x)	60 μl	4°C / -20°C
Standard/sample diluent buffer	10 ml	4°C / -20°C
Biotinylated Antibody Diluent	6 ml	4°C / -20°C
HRP Diluent	6 ml	4°C / -20°C
Wash Buffer (25x)	10 ml	4°C / -20°C
TMB Substrate Solution	6 ml	4°C / -20°C (store in dark)
Stop Reagent	3 ml	4°C / -20°C
Platelet Covers	1 piece	4°C / -20°C

and cell proliferation, making PRP a valuable adjunct in regenerative therapies. While promising, standardisation in PRP protocols remains challenging, and further research is needed to optimise its clinical use. However, the effectiveness of PRP depends on factors such as platelet concentration and preparation methods, which can influence its regenerative potential. PDGF is a potent mitogenic and regenerative signal-producing activity [26]. PDGF induces the proliferation of mesenchymal stem cells, which facilitates tissue reconstruction and regeneration without the need for traditional healing processes [27]. The USA FDA-approved PDGF formulation is used for the topical application of chronic ulcers, in periodontal and orthopaedic surgery, and various aspects of aesthetic medicine [28]. Naturally activated PDGF from PRP, following cold exposure, may potentiate tissue regeneration, thereby eliminating the need for healing and restoration of normal tissue function [29].

In this study, PRP was separated by simple centrifugation from anticoagulated whole human blood at 20–24°C (RT) at 2500 rpm for 10 minutes. There were no changes in the platelet counts of these PRP after cold incubation (4°C) for 10

Table 2: OD value of standards concerning PDGF concentrations

Concentration (pg/ml)	OD	Corrected OD
5000	2.4482	2.2562
2500	1.9897	1.7995
1250	1.2682	1.078
625	0.6836	0.4934
312.5	0.4291	0.2383
156.25	0.3741	0.1839
78.13	0.2804	0.0902
0	0.1902	0.000

Table 3: OD values of PDGF in PRP samples at 24°C and 4°C vs the platelet count/μL

Sample ID	OD at 24°C	Conc. at 24°C (pg/ml)	OD at 4°C	Conc. at 4°C (pg/ml)	Platelet count
1	0.1157	100.20	0.17	147.23	158
2	0.1049	90.85	0.3292	285.12	357
3	0.1199	103.84	0.1612	139.61	168
4	0.1069	92.58	0.1654	143.25	155
5	0.1162	100.64	0.1687	146.11	158
6	0.1157	100.20	0.1723	149.22	189
7	0.1149	99.51	0.3018	261.38	286
8	0.1179	102.11	0.1622	140.48	152
9	0.1069	92.58	0.1654	143.25	155
10	0.1167	101.07	0.1787	154.77	178
11	0.1049	90.85	0.2892	250.47	280
12	0.1162	100.64	0.1687	146.11	168
13	0.1149	99.51	0.2292	198.51	258
14	0.1088	94.23	0.1832	163.10	245
15	0.0967	83.75	Not done	Not done	109
16	0.0978	84.70	Not done	Not done	108
17	0.0893	77.34	Not done	Not done	118
18	0.0947	82.02	Not done	Not done	110
19	0.0911	78.90	Not done	Not done	74
20	0.0998	86.43	Not done	Not done	78

Table 4: Descriptive analysis of RT and CRT groups with the same Platelet counts

	Conc. at 24°C (pg/ml)	Conc. at 4°C (pg/ml)	Platelet count
Mean	98	176	208
Std. Deviation	4	51	65
Minimum	91	140	152
Maximum	104	285	357

Table 5: Correlation and significance

Variable 1	Variable 2	Correlation	p-value
OD at 24°C	Conc. at 24°C (pg/ml)	1	<0.001
OD at 24°C	OD at 4°C	0	0.028
OD at 24°C	Platelet count	0	0.125
OD at 4°C	Conc. at 4°C (pg/ml)	1	<0.001
OD at 4°C	Platelet count	1	<0.001

minutes. The fresh platelet-formed clots, they started to retract in less than 10 min, followed by morphological changes [30]. The final platelet count was recorded in the master chart in an MS Excel data sheet. The study's objective was to quantify the growth factor (PDGF-AB) between the OD value of PRP at room temperature and after cold mechanical stimulus.

a. Statistical analysis of PDGF value between OD of PRP at room temperature and after Cold exposure

In the present study, the semi-quantitative estimation of growth factors and heterodimer PDGF-AB concentrations in inactivated PRP and PRP activated by a cold stimulus was analysed.

Our study reveals a significant difference in OD values for PDGF-AB at room temperature and after exposure to a cold stimulus. After cold incubation, the OD value increases from a median of 0.1153 to 0.1711, and $P < 0.001$, which is significant. From the above result, it can be inferred that a simple mechanical cold stimulus may help to release more PDGF-AB from alpha granules of platelets. A study by Tablin et al. (2000) demonstrated that when PRP is frozen at -20°C, human platelets become activated, and growth factors are released from alpha granules [31]. Franklin et al. (2017) studied canine platelet-rich plasma (PRP) in animal models and compared the activation protocols on platelets and the release of growth factors from these platelets

b & c. Correlation between several platelet counts and PDGF before and after the cold stimulus

In the above study, the concentration of PDGF-AB was assessed by Kendall's tau correlation, which showed a moderate, positive correlation between OD of PRP and platelet count in the group without cold stimulus ($P < 0.06$, which is insignificant). Kendall's tau correlation showed that there was a very high, positive correlation between OD with cold stimulant and platelet count, $P < 0.001$. Franklin et al. (2019) further demonstrated a positive correlation between platelet and PDGF concentrations in canine PRPs [34]. Castillo et al. (2011) also showed a positive correlation between the growth factors and platelet concentration

Conclusion

PDGF-like platelets are also present in other tissues, such as WBCs. PDGF estimation by sandwich ELISA from PRP stored at normal room temperature reveals a moderate association between PDGF and platelet concentrations. Secondly, PDGF concentration was also high in the sample platelet concentration after incubation at cold temperature ($4 \pm 2\,^{\circ}$C) for 10 minutes, which was statistically significant. Therefore, this suggests a strong association between PDGF concentration and platelet count. The study concludes that cold stimulus and the number of platelets are directly associated with PDGF concentration, and the activation of growth factors may be upregulated in patients with traumatic injury, particularly when cold compression is applied locally, which may further initiate growth factor-induced healing.

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