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The impact of mean platelet volume on post-dural puncture headaches

Post-dural başağrısı üzerine ortalama trombosit hacminin etkisi

HakanTapar

Department of Anesthesiology and Reanimation, Medical Faculty, Gaziosmanpasa University, Tokat, Turkey
Corresponding author: Hakan Tapar, MD, Department of Anesthesiology and Reanimation, Medical Faculty, Gaziosmanpasa University, Tokat, Turkey
E-mail: hakantapar@hotmail.com
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SUMMARY

Objective: Post-dural puncture headache (PDPH) is a major complication associated with loss of cerebrospinal fluid (CSF), which occurs due to dural defect. Platelets play an important role in tissue healing and homeostasis. Mean platelet volume (MPV) is an indication of platelet function. In this study we wanted to investigate the relationship between MPV and PDPH.

Method: Between January 2016 and January 2018, 182 patients who had a caesarean using spinal anaesthesia were included in this study. Patients were divided into two groups as PDPH (+) and PDPH (-). The preoperative and postoperative haemoglobin (HGB), haematocrit (HCT), platelet (PLT), MPV, white blood cell (WBC), neutrophil (NEUT) and lymphocyte (LYMPH) levels of the patients according to PDPH were evaluated.

Results: There was no difference between preoperative and postoperative MPV values of PDPH (+) patients (respectively 10.77±1.17, 10.83±1.04, p=0.483) but there was a significant difference between MPV values of PDPH (-) patients (respectively 10.94±1.20, 11.10±1.11, p<0.001).

Conclusions: There are a number of reasons that affect and predict the occurrence of PDPH. According to this study, postoperative MPV levels (high or low) could cause a prediction for PDPH.
Keywords: Post-dural puncture headache, Mean platelet volume, Neutrophil

ÖZET

Amaç: Post-dural ponksiyon baş ağrısı (PDPH) dural defekten dolayı meydana gelen serobrospinal sıvı kaybı ile ilişkili major bir komplikasyondur. Trombositler doku iyileşmesi ve homeostasis'te önemli rol oynarlar. Ortalama trombosit hacmi (MPV) trombosit fonksiyonunun bir göstergesidir. Bu çalışmada PDPH ve MPV arasındaki ilişkiyi araştırmak istedik.

Yöntem: Ocak 2016 ile Ocak 2018 arasında, spinal anestezi ile sezaryen geçiren 182 hasta bu çalışmaya dahil edildi. Hastalar PDPH (+) ve PDPH (-) olmak üzere iki gruba ayrıldı. PDPH'ye göre hastaların preoperatif ve postoperatif hemoglobin (HGB), hematokrit (HCT), trombosit (PLT), MPV, beyaz kan hücresi (WBC), nötrofil (NEUT) ve lenfosit (LYMPH) düzeyleri değerlendirildi.

Bulgular: PDPH (+) hastalarının preoperatif ve postoperatif MPV değerleri arasında fark yoktu (sırasıyla 10.77±1.17, 10.83±1.04, p =0.483) ama PDPH (-) hastalarının MPV değerleri arasında anlamlı fark vardı (sırasıyla 10.94±1.20, 11.10±1.11, p <0.001).

Sonuç: PDPH'nin oluşumunu etkileyen ve tahmin eden birçok sebep vardır. Bu çalışmaya göre, postoperatif MPV düzeyleri (yüksek veya düşük) PDPH için bir öngörüye neden olabilir.
Anahtar sözcükler: Post-dural ponksiyon baş ağrısı, Ortalama trombosit hacmi, Nötrofil

INTRODUCTION

Post-dural puncture headache (PDPH) is a major complication associated with dural damage and loss of cerebrospinal fluid (CSF) depending on dural damage. According to the International Headache Society, PDPH is a headache type that occurs less than seven days after spinal puncture, increases when sitting (less than five minutes), decreases when lying (less than thirty minutes) and is accompanied by at least one of the following symptoms: nausea, photophobia, tinnitus, stiffness in the neck or hyperacusis [1].

The first of two theories explaining the PDPH mechanism describes it as the loss of more CSF from the dural tear than production and reflex vasodilatation in the cerebral vessels due to low CSF pressure [2]. The second theory states reduced CSF pressure causes the reduction of the cushioning effect provided by the intracranial fluid. Especially in a sitting position, traction occurs in pain sensitive intracranial structures, and this leads to neck, shoulder and frontal headache [1].

A large dural hole and healing delay after spinal anaesthesia causes more CSF loss, and this is an increased risk for PDPH development [3].The incidence of PDPH in smokers is lower than in non-smokers. This is due to the tendency of smokers to clot and the closure of the dural defect with blood clotting, although the exact mechanism is not clear [4].

When the tissues are damaged, the healing process is as follows: clotting (haemostasis) phase, inflammation phase, tissue growth phase (proliferation) and remodelling phase (maturation) [5]. Indication of platelet function is mean platelet volume (MPV) and is inversely related to the number of the thrombocyte. Mean MPV is 8.9±1.4 fL [6]. Platelet granules contain 30 different growth factors and cytokines such as clotting, wound healing, collagen as well as platelet-derived growth factor (PGDF), which plays a role in fibroblast proliferation and transforming growth factor beta (TGF - ß). This is especially important in wound healing and regeneration [7]. In contrast to this positive effect, platelets play a role in the formation of atheromatous plaques leading to peripheral and coronary artery disease [8].Therefore, with these two different effects, platelets can be effective on PDPH.

The inflammation phase of wound healing is important. Neutrophils have an important role in wound healing and maturation. And even the neutrophil lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are suggested in screening and following systemic inflammation [9].These values may be used to assess inflammation in patients with and without PDPH.

According to this information, platelets may play a role in healing of dural defect and haemostasis. The primary goal of this study is to assess the relationship between the MPV value, which is the indication of the platelet function, and PDPH. The second goal is to assess the relationship between peripheral blood parameters (such as white blood cell, neutrophil, NLR) and PDPH.

MATERIAL AND METHODS

After study approval was obtained from the Gaziosmanpasa University Clinical Research Ethics Committee (18-KAEK-102), between January 2016 and January 2018, 182 patients who had a caesarean using spinal anaesthesia at Gaziosmanpasa University Medical Faculty Hospital were included in this retrospective study. These patients were divided into two groups with PDPH (+), n = 91 and without PDPH (-), n= 91 after spinal anaesthesia. Patients who underwent spinal anaesthesia under elective conditions as ASA 2 over 18 years of age were included in the study. Patients with headache, migraine, chronic pain, platelet dysfunction, blood disease and analgesic use were excluded. Patients were called by phone and asked whether they have PDPH symptoms (increases when sitting (less than five minutes), decreases when lying (less than thirty minutes) and is accompanied by at least one of the following symptoms: nausea, photophobia, tinnitus, stiffness in the neck or hyperacusis) or not and they separated into two groups in order to have PDPH or not.

Spinal anaesthesia applied to caesarean patients during the study by different anaesthesiologists, experienced at the specialist level, who used a 12.5 mg bupivacaine (Marcaine heavy) 25 G cutting spinal needle.

In this study, the preoperative and postoperative haemoglobin (HGB), haematocrit (HCT), platelet (PLT), MPV, white blood cell (WBC), Neutrophil (NEUT) and Lymphocytes (LYMPH) levels of the patients with and without PDPH were evaluated according to the blood samples taken from the patients. In addition, the NEUT / LYMPH ratio (NLR), MPV / PLT ratio (MPR) and PLT / LYMPH ratio (PLR) of the patients was calculated. Preoperative blood values were recorded according to blood values during the surgical preparation period. Postoperative blood values were recorded according to blood values taken immediately after the surgery.

Statistical Analysis

A pilot study revealed a PI value of 9±2 fL, and assuming a change by 10% on this value in patients with PDPH (accepting type I error of 0.05 and a power of 0.80) showed that a total of 126 patients were required to find a statistically significant difference.

The normal distribution coherence of the data was evaluated by the single sample Kolmogorov-Smirnov test. Qualitative data will be expressed as number and percentage, quantitative data as mean ± standard deviation. The relationship between OTH of PSBA patients and non-PSBA patients was assessed by an independent sample t-test analysis. Statistical Package for Social Sciences (SPSS, IL) version 20.0 was used for evaluation of all data. A value of $p < 0.05$ was considered significant.

RESULTS

The main demographic features, such as age, height, weight and body mass index (BMI) are shown in Table 1. While there was no statistically significant difference between preoperative and postoperative HCT, PLT, MPV, WBC and LYMPH values of patients with PDPH (-) and PDPH (+), there was a statistically significant difference at NEUT values (Table 2). Although there was no statistically significant difference between the MPV values of patients with PDPH (+) and PDPH (-), the MPV values of patients with PDPH (-) was numerically higher than PDPH (-) patients.

Table 1. Demographic characteristics

	PDPH(+)	PDPH(-)	p
Age[a] (years)	27.86±5.12	28.67±4.54	0.717
Weight (kg)	74.18±8.53	76.27±9.12	0.397
Height (cm)	161.17±5.19	162.56±6.23	0.872
BMI[b] (kg/m^2)	28.64±3.56	29.11±5.98	0.119

BMI,Body mass index

[a]Values are given as mean ± SD unless indicated otherwise.

[b]Calculated as weight in kilograms divided by the square of height in meters

Table 2. Comparison of PDPH groups

	PDPH(+)	PDPH(-)	p
Preoperative			
Hb(g/dL)	10.47±2.29	10.15±2.45	0.135
Hct(%)	35.21±3.23	34.55±2.84	0.144
WBC(10^3/mm^3)	10.47±2.29	10.15±2.45	0.379
NEUT(10^3/mm^3)	7.64±1.99	7.43±2.11	0.484
LYMPH(10^3/mm^3)	2.02±0.49	1.94±0.53	0.331
PLT(fL)	236±12	220±66	0.084
MPV(fL)	10.77±1.17	10.94±1.20	0.353
Postoperative			
Hb(g/dL)	10.50±1.35	10.78±1.37	0.161
Hct(%)	31.22±3.52	32.02±3.66	0.135
WBC(10^3/mm^3)	13.36±3.19	14.38±4.00	0.061
NEUT(10^3/mm^3)	10.96±2.93	12.00±3.77	**0.039**
LYMPH(10^3/mm^3)	1.60±0.49	1.52±0.54	0.310
PLT(fL)	201.85±49.11	188.58±56.47	0.092
MPV(fL)	10.83±1.04	11.10±1.11	0.092

Hb,Hemoglobin;Htc,Hematocrit;WBC,White Blood Cells;NEUT,Neutrophils

LYMPH,Lymphocytes;PLT,Platelets;MPV,Mean Platelet Volume

When the groups are evaluated within themselves, although there was no difference between preoperative and postoperative MPV values of PDPH (+) patients (respectively 10.77±1.17, 10.83±1.04, p=0.483) (Table 3), there was a significant difference between preoperative and postoperative MPV values of PDPH (-) patients (respectively 10.94, 11.10, p<0.001) (Table 4).

Table 3. Comparison preoperative and postoperative of PDPH(+) group

	Preoperative	**Postoperative**	**p**
Hb(g/dL)	10.15±2.45	10.78±1.37	**<0.001**
Hct(%)	34.55±2.84	32.02±3.66	**<0.001**
WBC(10^3/mm^3)	10.15±2.45	14.38±4.00	**<0.001**
NEUT(10^3/mm^3)	7.43±2.11	12.00±3.77	**<0.001**
LYMPH(10^3/mm^3)	1.94±0.53	1.52±0.54	**<0.001**
PLT(fL)	220±66	188.58±56.47	**<0.001**
MPV(fL)	10.94±1.20	11.10±1.11	**<0.001**

Hb,Hemoglobin;Htc,Hematocrit;WBC,White Blood Cells;NEUT,Neutrophils
LYMPH,Lymphocytes;PLT,Platelets;MPV,Mean Platelet Volume

Table 4.

	Preoperative	**Postoperative**	**p**
Hb(g/dL)	10.47±2.29	10.50±1.35	**<0.001**
Hct(%)	35.21±3.23	31.22±3.52	**<0.001**
WBC(10^3/mm^3)	10.47±2.29	13.36±3.19	**<0.001**
NEUT(10^3/mm^3)	7.64±1.99	10.96±2.93	**<0.001**
LYMPH(10^3/mm^3)	2.02±0.49	1.60±0.49	**<0.001**
PLT(fL)	236±12	201.85±49.11	**<0.001**
MPV(fL)	10.77±1.17	10.83±1.04	0.483

Comparison preoperative and postoperative of PDPH(-) group

Hb,Hemoglobin;Htc,Hematocrit;WBC,White Blood Cells;NEUT,Neutrophils
LYMPH,Lymphocytes;PLT,Platelets;MPV,Mean Platelet Volume

There was a significant difference when the percent change in WBC and NEUT (preoperative and postoperative) of patients PDPH (+) and PDPH (-) were compared (respectively 29.65±25.70, 43.01±25.23, p=0.001; 47.66±36.33, 64.51±33.46, p=0.001). While a significant difference was found according to postoperative NEUTL / LYMPH (NLR) and MPV / PLT (MPR) ratio of the patients, the difference was insignificant according to a PLT / LYMPH (PLR) ratio of PDPH (-) patients (respectively 7.43±2.90, 8.89±4.27, p=0.008; 0.05±0.01, 0.06±0.02, p=0.018; 137.11±59.06, 137.89±58.08, p=0.928) (Table 5).

	PDPH(+)	PDPH(-)	p
NLR	7.43±2.90	8.89±4.27	**0.008**
MPR	0.05±0.01	0.06±0.02	**0.018**
PLR	137.11±59.06	137.89±58.08	0.928
WBC Exchange Ratio	29.65±25.70	43.01±25.23	**0.001**
NEUT Exchange Ratio	47.66±36.33	64.51±33.46	**0.001**

Table 5. Comparison of NLR, MPR, PLR and percent change (WBC and NEUT) of PDPH groups.

NLR,Neutrophil/Lymphocytes Ratio;MPR,Mean Platelet Volume/Platelet Ratio
PLR,Platelet/ Lymphocytes Ratio

There was a low correlation between the preoperative and postoperative PLT and MPV values of those with PDPH (+) (r:-0.493, p<0.001; r:-0.469, p<0.001) (Figure 1). There was a negative moderate correlation between preoperative and postoperative PLT and MPV values of PDPH (-) patients (r:-0.569, p<0.001; r:-0.604, p<0.001) (Figure 2).

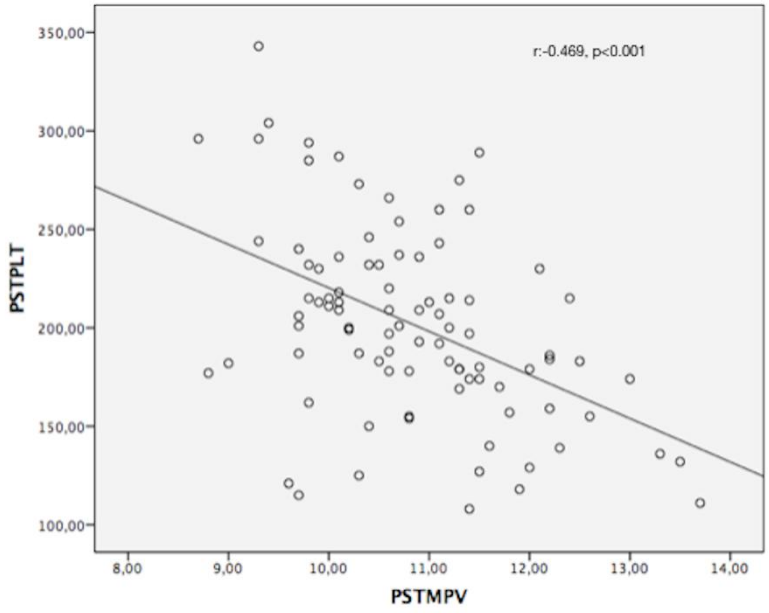

Figure 1. Assessment of the correlation between PSTPLT and PSTMPV in the PDPH (+) group. PSTPLT, postoperative platelet;PSTMPV, postoperative mean platelet volume

Respectively r:-0.493,p<0.001;r:-0.469,p<0.001

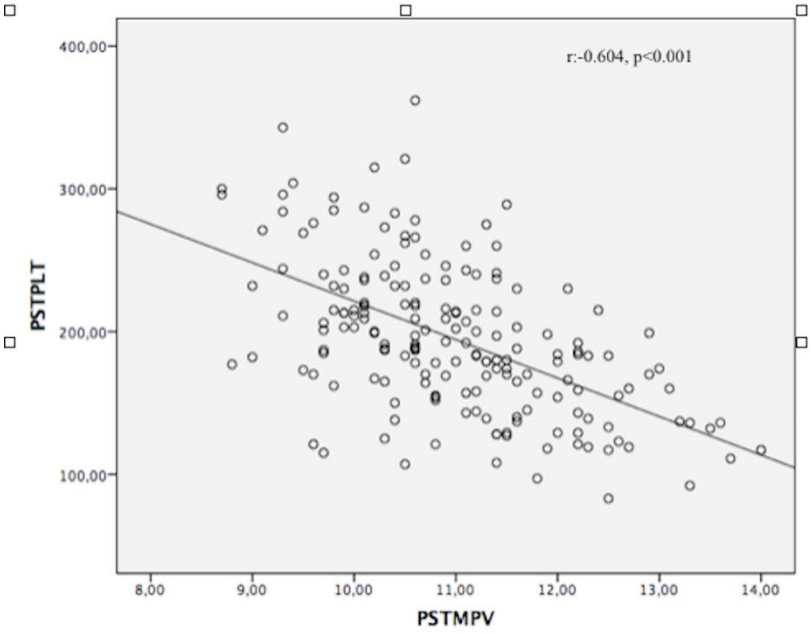

Figure 2. Assessment of the correlation between PSTPLT and PSTMPV in the PDPH (-) group. PSTPLT, postoperative platelet;PSTMPV, postoperative mean platelet volume

Resectively r:-0.569,p<0.001;r:-0.604,p<0.001

DISCUSSION

In this study, there was a significant difference between preoperative and postoperative MPV values of PDPH (-) patients. The postoperative NLR, MPR values of PDPH (-) patients and WBC, percent change in NEUT were significantly higher than PDPH (+) patients.

Closure speed of the dural defect reduces the frequency and severity of PDPH. For example, obese individuals are less likely to have PDPH than thin ones. The reason is that increased intraabdominal pressure in obese individuals has been seen as a binding task for closure of the dural defect and loss of CSF [10]. It is known that epidural blood patches continue to be used as the gold standard method in the treatment of long-lasting and lingering PDPH. As an alternative to the epidural blood patch, local usage of fibrin glue containing thrombin and fibrinogen has been suggested and has been used effectively in a PDPH case where the epidural blood patch failed [11]. The cause of this effect is thrombin as it is converts fibrinogen into fibrin monomers [12]. According to the literature mentioned above, removal of the defect, whether mechanically or in the direction of healing, treats PDPH and reduces its frequency.

This study has shown two positive effects on the PDPH of the MPV value. The first is the faster recovery of the dural defect and thus less loss of CSF. The spinal dura mater is a vascularized connective tissue consisting of dense collagen and elastic fibres extending longitudinally from the foraminal magnum to the second segment of the sacrum [13]. PDPH occurs due to damage of this structure, which is rich in vascular structure and its severity and its duration change due to loss of CSF. At tissue healing, the haemostasis phase occurs several minutes after tissue damage and involves the accumulation of platelets in the damaged area. Platelets include PDGF, which accelerates wound healing, epidermal growth factor (EGF), fibroblast growth factor (FGF) and cytokines besides clotting and haemostasis [14]. Platelets increase tissue vasculature, collagen synthesis and tissue granulation through increased angiogenesis [15]. So, platelets play an important role in tissue healing and regeneration [16]. Today, platelet rich plasma (PRP) obtained by centrifugation of the patient's own blood is used in wound healing and chronic skin ulcers [17]. In this study, it has been seen that while the change between preoperative and postoperative MPV values of patients without PDPH was significant, there was no significant difference in patients with PDPH. This situation may be a consequence of both the faster haemodilution of the dural defect and the positive effects of platelets on tissue and

wound healing in proportion to the MPV value, which is indicative of platelet activity.

The second positive effect of MPV on PDPH is the reduction of blood flow in proportion to the MPV value. In one of the mechanisms that explain PDPH, vasodilation occurs in the cerebral vessels in order to keep the intracranial pressure constant due to loss of CSF. This situation causes tension in the pain sensitive cranial structures [18].This theory is supported by transcranial Doppler ultrasound scanning [19], as well as increased cerebral vasodilatation due to higher levels of oestrogen that causes more PDPH in the pregnant women [20]. Another reason to support this theory is that the use of caffeine and aminophylline have vasoconstrictor effects in PDPH treatment. Aminophylline increases vasoconstriction by blocking adenosine receptors that cause venous and arterial vasodilatation and is therefore used in PDPH treatment [21].The platelet size, MPV, is an indication of platelet function. The accepted view is that large platelets are both more enzymatically active and more thrombotic than small platelets [22].That is why MPV is important. Ranjith's work showed that patients with acute coronary syndromes have a lower number of platelets and larger volume than stable angina patients [23]. High MPV value is associated with restenosis after coronary angio and non-ST acute coronary syndrome. This has been linked to value and a shrink in coronary vessels and a decrease in blood flow with an increase in MPV [24]. The MPV is positively associated with thromboxane A2, platelet factor 4 and beta-thromboglobulin, which are indicators of platelet activity. Thromboxane A2 is a potent vasoconstrictor; therefore, it causes coronary and cerebral ischemia [25]. According to this study, another positive effect of high MPV value on PDPH is due to the effect of decreasing cerebral vasodilatation, which develops as a compensator due to CSF loss and increases cerebral blood flow.

The second aim of this study was to investigate the impact of WBC and NEUT on PDPH. WBC and NEUT are effective in wound healing and in the formation of granulation tissue when the tissue is damaged. Neutrophils, monocytes / macrophages migrate to that part to prevent wound infection, and macrophages especially improves the growth of fibroblasts that help repair damaged tissue and shape the granulation tissue [26]. In the inflammation phase of wound healing, dead cells and bacteria are cleared by neutrophils through phagocytosis [27]. Cantürk et al. gave a granulocyte-macrophage colony-stimulating factor (GM-CSF) to some of the rats and the number of neutrophils in the rats increased. The phagocytosis and wound scoring of the rats in this group were significantly different in both the saline control group and the cyclophosphamide treated group, and this result was linked to the increased number of neutrophils [28].When patients who underwent head and neck reconstruction were seen to have two groups of patients with and without wound healing failure were separated into two groups, it was seen that there is a significant relationship between wound healing and the value of NLR, and low NLR causes failure in wound healing [29]. According to our study, the percentage of WBC and NEUT change in patients without PDPH was significantly higher than those with PDPH. In this case, we think that the healing of the dural defect in particular has a positive effect on the inflammation phase.

CONCLUSION

There are many reasons that affect the formation of PDPH, and we know these all. According to this study, we believe that the MPV value, which is indicative of platelet activity, are predictive factor for PDPH.

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