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Impact of Parathormone Hormone on Platelet Count and Mean Volume in End-stage Renal Failure Patients on Regular Hemodialysis

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The increased bleeding tendency of end-stage renal failure patients under hemodialysis (HD) has been attributed to platelet dysfunction. We sought to conduct a study to consider the effect of parathormone on mean platelet volume and count in chronic hemodialysis patients. Complete blood count containing platelet count and Mean Platelet Volume (MPV) and levels of serum calcium, phosphorus, alkaline phosphatase and Intact serum PTH (iPTH) were measured. Total patients were 36 (F = 14, m = 22), consisting of 26 non-diabetic HD patients and 10 diabetic HD patients. Findings were a near significant difference of PLT count between diabetic and non-diabetic HD patients with more values in diabetic population, a significant inverse correlation PLT count and MPV and a near significant positive correlation of MPV with serum iPTH. A significant inverse correlation of PLT count with serum iPTH was seen too. The inverse correlation of serum parathormone with platelet count and the positive correlation of serum parathormone with MPV shows the role of secondary hyperparathyroidism in PLT dysfunction regarding the bleeding tendency of uremic patients, which implies to better control of PTH over secretion in these patients.

Key words: Platelet counts, hemodialysis, secondary hyperparathyroidism, parathormone, end-stage renal failure, Mean Platelet Volume (MPV), age, dialysis dosage

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INTRODUCTION

Patients with end-stage renal disease suffer from complex hemostatic disorders. Uremic patients show a bleeding diathesis that is mainly due to abnormalities of primary hemostasis[1,2]. The increased bleeding tendency of chronic renal failure patients has been attributed to platelet dysfunction[1,3]. The most common abnormalities are defective platelet aggregation, decreased platelet adhesiveness, decreased platelet factor-3 availability and prolongation of the bleeding time[4]. Some of the pathophysiologic mechanisms which have been implicated include platelet inhibition by plasma metabolites, eg, urea, guanidinosuccinic acid, phenolic acid; increased vessel wall prostacyclin; abnormal platelet arachidonic acid metabolism and increased levels of parathyroid hormone[4]. Secondary hyperparathyroidism (SHPT) is a common occurrence in patients with chronic renal failure and is characterized by excessive serum parathyroid hormone (PTH) levels and an imbalance in calcium and phosphorus metabolism[5]. PTH acts as an uremic toxin and may be responsible for many complications which frequently seen in hemodialysis patients[5-7]. In uremia the platelet count is usually normal, but platelet function is impaired. The platelet granule content is decreased, a reduction in the storage pool of ADP and serotonin is present. Calcium content is increased in uremic patients (generally due to secondary hyperparathyroidism) and this increase in serum calcium cause an abnormality in the mobilization of Ca^{++} in response to stimulation[8,9]. This observation, coupled with the fact that PTH inhibits platelet function in vitro led to the speculation that PTH might play a role in the genesis of such defects[8]. Recently, an indice related to platelet count has been provided by hematologic analyzers. Concerning the platelet parameter, the Mean Platelet Volume (MPV) has been described[10]. Platelet volume is a marker and possibly a determinant of platelet function in that large platelets are more active than normal sized platelets. MPV a measure of platelet size, reflects changes in either the level of platelet stimulation or the rate of platelet production[11]. Increased MPV may reflect increased platelet activation or increased numbers of large, hyperaggregable platelets and is accepted as an independent coronary risk factor[12] and mean platelet volume could be an independent risk factor for myocardial infarction in the general population and also CHD in hemodialysis patients[13]. Regarding the above mentioned data, studies concerning the factors affects the MPV regulation, specially serum PTH in hemodialysis is quiet scarce and we therefore sought to conduct a study to consider the association of serum parathormone on mean platelet volume and count in chronic hemodialysis patients containing diabetics and nondiabetic patients due to end-stage renal failure.

MATERIALS AND METHODS

Patients: This cross-sectional study was conducted on patients with End-stage Renal Disease (ESRD), who were undergoing maintenance hemodialysis treatment with acetate basis dialysate and polysulfone membranes. According to the severity of secondary hyperparathyroidism, each patient being treated for secondary hyperparathyroidism was given oral active vitamin D3 (Rocaltrol), calcium carbonate and Rena-Gel capsules at various doses. According to the severity of anemia, patients were under IV iron therapy with Iron sucrose (Venofer) at various doses after each dialysis session, all patients were under treatments of 6 mg folic acid daily, 500 mg L-Carnitine daily, oral Vitamin B-complex tablet daily and also 2000 U IV Eprex (recombinant human erythropoietin (rHuEPO) unique for each patient after each dialysis session routinely. Exclusion criteria were active or chronic infection and using NSAID or ACE inhibitor drugs and also using the other drugs had adverse effects on platelet production or function. The study was done in Hemodialysis Section of Hajar Medical Educational and Therapeutic Center of Shahrekord University of Medical Sciences in Shahrekord of Iran.

Laboratory methods: Blood samples were collected after an overnight fast. For patients, complete blood counts containing platelet counts and (MPV) (fl) were measured using Sysmex-KX-21N cell counter (Ref. range 7.5 - 11.5). Levels of serum Calcium (Ca), Phosphorus (P) and also Alkaline Phosphatase (ALP) were measured using standard kits. Intact serum PTH (iPTH) was measured by the radioimmunoassay (RIA) method using DSL-8000 of USA (normal range of values are 10-65 pg mL^{-1}). Duration and dosages of hemodialysis treatment were calculated from the patients' records. The duration of each hemodialysis session was 4 h.

Statistical analysis: Results are expressed as the mean±SD and median values. Comparison between the groups was done using Student's t-test. Statistical correlations were assessed using partial correlation test. Statistical analysis was performed on total hemodialysis (HD), females, males, diabetics and non diabetics populations separately. All statistical analyses were performed using SPSS (version 11.5.00). Statistical significance was determined at a $p \leq 0.05$.

Table 1: Mean±SD, minimum and maximum of age, duration and dose of hemodialysis and also laboratory results of total, non-diabetic and diabetic hemodialyzed patients

Total patients (n = 36)	Minimum	Maximum	Mean±SD	Median
Age (years)	16	80	46 ±16.5	43.0
DH* (months)	2	156	30±36.0	17.5
Dialysis dose (sessions)	18	1584	285±396.0	144.0
iPTH (Pg mL^{-1})	16	1980	435±454.0	309.0
Ca (mg dL^{-1})	5	10	7.7±0.9	8.0
P (mg dL^{-1})	3.4	10	6.4±1.8	6.2
Alp (IU L^{-1})	150	5487	533±890.0	444.0
PLT [x10^3 μL^{-1}]	99	396	162±75.0	163.0
MPV (fl)	7.2	11.5	9±1.0	9.2
Non diabetics n = 26				
Age (years)	18	80	43.6±16.5	41.5
DH* (months)	2	156	37±41.0	20.5
Dialysis dose (sessions)	18	1584	348±451.0	154.5
iPTH (pg mL^{-1})	22	1980	519±482.0	335.0
Ca (mg dL^{-1})	6	9	7.8±0.7	8.0
P (mg dL^{-1})	3	10	6.5±1.8	6.5
Alp (IU L^{-1})	150	5487	750±1025.0	479.0
PLT [x10^3 μL^{-1}]	11	396	148±7.0	143.0
MPV (fl)	7.2	11.5	9.2±1.0	9.2
Diabetics n = 10				
Age (years)	27	75	51±16.0	55.0
DH* (months)	6	24	14±6.0	12.0
Dialysis dose (sessions)	54	316	119±55.5	99.0
iPTH (Pg mL^{-1})	16	860	218±287.0	43.0
Ca (mg dL^{-1})	5	10	7.5±1.0	7.5
P (mg dL^{-1})	4	10	6.2±2.0	6.0
AlP (IU L^{-1})	175	584	330±155.0	289.0
PLT [x10^3 μL^{-1}]	99	320	198±87.0	188.0
MPV (fl)	7.5	9.9	8.7±0.8	8.8

*Duration of hemodialysis

RESULTS

Total patients were 36 (F = 14, M = 22), consisting of 26 non-diabetic HD patients (F = 10, M = 16) and 10 diabetic HD patients (F = 4, M = 6). The mean patient's age was 46±16.5 years Table 1. The mean length of the time patients had received hemodialysis was 30±36 (median = 17.5) months. The mean PLT counts was 162±75 [10^3 μL^{-1}]. The mean PLT counts within the diabetic and non-diabetic groups were 198±78 and 148±67 [10^3 μL^{-1}], respectively. The mean MPV of total patients was 9±1 fl. The mean of MPV within the diabetic and non-diabetic groups were 8.7±0.80 and 9.2±1 fl, respectively. The mean serum iPTH was 435±454 (median = 309) pg mL^{-1}. The mean iPTH values within the diabetic and non-diabetic groups were 218±287 (median = 43) and 519±482 (median = 335) pg mL^{-1}, respectively. In this study, no significant differences was foung between PLT count and MPV in males and females respectively. No significant differences of MPV between diabetic and non-diabetic HD patients was found, however, a near significant difference of PLT count between diabetic and non-diabetic HD patients (p = 0.078; Fig. 1) was existed. In total patients, a significant inverse correlation of PLT count and MPV (r = -0.39, p = 0.018; Fig. 2) was

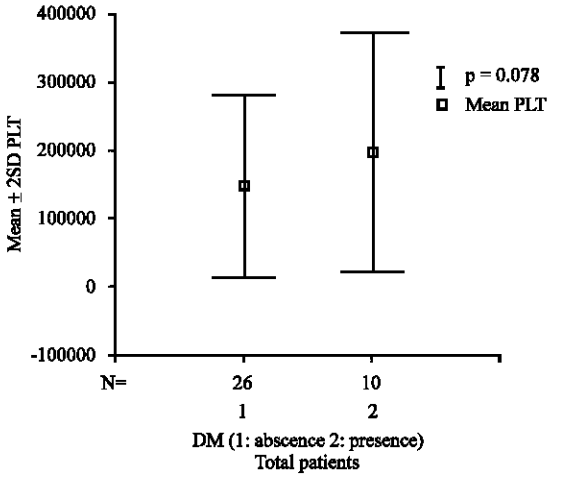

Fig. 1: Near significant difference of PLT count between diabetic and non-diabetic HD patients

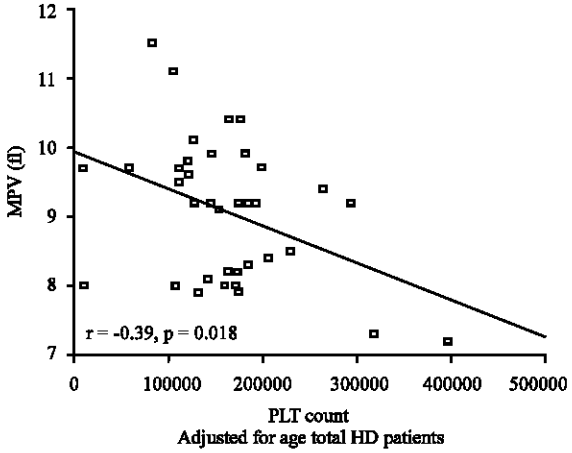

Fig. 2: Significant inverse correlation of PLT count and MPV

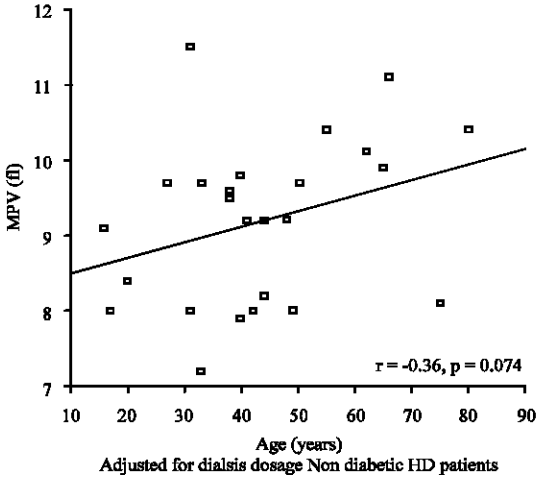

Fig. 3: Near significant positive correlation of MPV with age

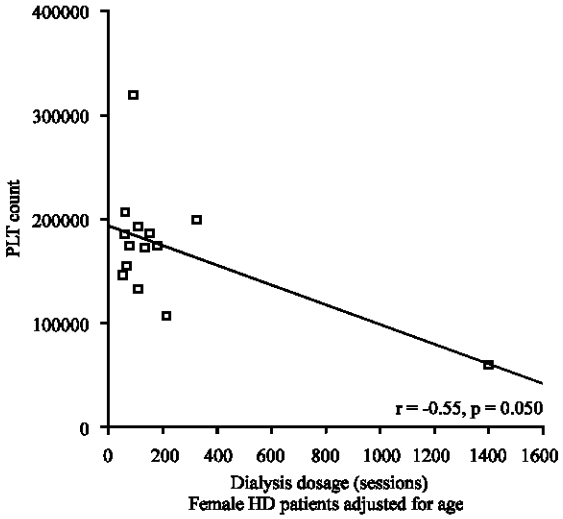

Fig. 4: Significant inverse correlation of PLT count with dialysis dosage

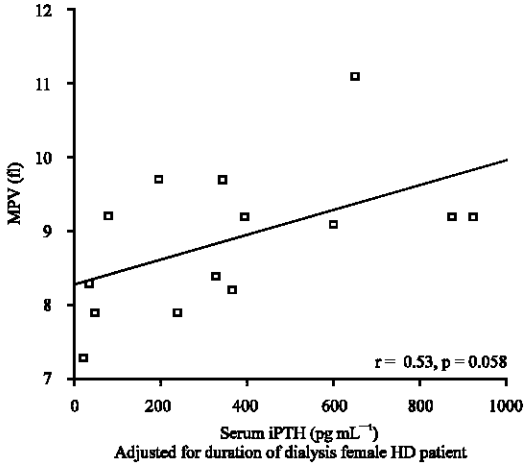

Fig. 5: Near significant positive correlation of MPV with serum iPTH

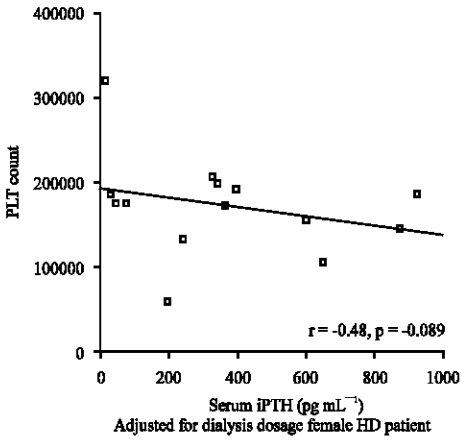

Fig. 6: Near significant inverse correlation of PLT count with serum IPTH

seen. In non diabetic HD patients a near significant positive correlation of MPV with age(r = 0.36, p = 0.074; Fig. 3) (adjusted for dialysis dosage)was found. In female HD patients a significant inverse correlation of PLT count with dialysis dosage (r = 0.55, p = 0.050; Fig. 4) (adjusted for age) and a near significant positive correlation of MPV with serum iPTH (r = 0.53, p = 0.058; Fig. 5) (adjusted for dialysis duration) were found too. Moreover in this group a near significant inverse correlation of PLT count with serum iPTH (r = -0.48, p = 0.089; Fig. 6) (adjusted for dialysis dosage) and a near significant positive correlation of MPV with serum phosphorus(r = 0.49, p = 0.085) (adjusted for dialysis duration) were seen and also a near significant inverse correlation of PLT count with serum ALP (r = -0.48, p = 0.090) (adjusted for dialysis dosage) was found too. In diabetic HD patients a significant inverse correlation of PLT count with serum iPTH (r = -0.76, p = 0.017) and also a near significant positive correlation of PLT count with ages of this group were found (r = 0.59, p = 0.096 (adjusted for dialysis dosage for above two correlations).

DISCUSSION

In this study the important findings were, a near significant difference of PLT count between diabetic and non-diabetic HD patients with more values in diabetic population, a significant inverse correlation of PLT count and MPV and a near significant positive correlation of MPV with age and also a significant inverse correlation of PLT count with dialysis dosage were found. A near significant positive correlation of MPV with serum iPTH and a significant inverse correlation of PLT count with serum iPTH were existed too. Although the platelet parameter, mean platelet volume have been routinely available to clinicians for some time, its role in the diagnosis and management of patients remains unclear. While factors affect PLT count and volume during hemodialysis is under investigation, it is believed that platelet activation and aggregation and coagulative activation are the earliest and most important phenomena that occur after contact between blood and artificial membranes[14]. It was concluded that an increase in cytosolic calcium in uremia which could explain some platelets dysfunction may be at least in part induced by PTH[9]. In an agreement with the present finding, Grzegorzewska and Mariak[15] study on seven diabetic patients and 16 non diabetic patients treated with continuous ambulatory peritoneal dialysis, showed a significantly higher numbers of PLTs in patients with diabetes as compared with patients without diabetes, also platelets had an inverse correlation with serum PTH.

Papanas *et al.*[16] in a study on 416 type2 diabetic patients, found that MPV is higher in type 2 diabetic patients than in non-diabetic patients and among type 2 diabetic patients, MPV is higher in those who have microvascular complications. Mean platelet volume is a physiological variable of hemostatic importance[17]. Large platelets are more reactive, produce more prothrombotic factors[17-19] and aggregate more easily. They also contain more dense granules and release more serotonin and ß-thromboglobulin than do small platelets[19,20]. Platelets have no nuclei and their characteristics are determined by their progenitor cell, the bone marrow megakaryocyte, it is generally accepted that platelet volume and density are determined at thrombopoiesis and that, once in the circulation, platelets do not change in size[21-23]. The mechanisms controlling platelet production are obscure, although it has been suggested that both MPV and platelet count are under independent hormonal control[23-25], however Larger platelets are more reactive and may contribute to the increased risk of thrombosis associated with r-HuEPO[26]. Adverse effects of high serum PTH on RBC production and intensification of anemia in hemodialysis patients was shown in our previous study and also by others too[27,28]. Possible pathogenic links between anemia and parathyroid hormone (PTH) include reduced erythropoiesis due to calcitrol deficiency and direct or indirect effects of PTH on erythropoietin release, red blood cell production, survival and loss[29]. As the bovine parathyroid-gland extracts inhibited platelet aggregation in a dose-dependent manner[30] and as parathyroid hormone raises intracellular cyclic AMP (cAMP) levels via adenyl cyclase activation and stimulates Ca^{2+} transport across cell membranes, it is unlikely that PTH inhibits platelet aggregation through an adenyl cyclase stimulated increase of cAMP[31]. Since PTH levels are markedly increased in uremic plasma, it might contribute to the defective platelet function and the bleeding tendency frequently occurring in uremic patients[31].Takan together, we showed inverse correlation of secondary hyperparathyroidism (serum iPTH and ALP) with platelet counts and positive correlation of MPV with serum iPTH, which to our knowledge is the first report about this correlation which needs to more attention in hemodialysis patients.

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REFERENCES

1. Boccardo, P., G. Remuzzi and M. Galbusera, 2004. Platelet Dysfunction in Renal Failure. Semin Thromb Hemost., 30: 579-589
2. Moal, V., P. Brunet, L. Dou, S. Morange, J. Sampol and Y. Berland, 2003. Impaired expression of glycoproteins on resting and stimulated platelets in uraemic patients. Nephrol Dial Transplant., 18: 1834-1841.
3. Krawczyk, W., A. Dmoszynska and B. Sokolowska, 1994. Evaluation of platelet hemostasis in patients with chronic renal failure. Wiad Lek., 47: 93-99.
4. Jubelirer, S.J., 1985. Hemeostatic abnormalities in renal disease. Am. J. Kidney Dis., 5: 219-225.
5. Hörl, W.H., 2000. Secondary hyperparathyroidism: Present and future therapeutic implications. Nephrol. Dial Transplant., 17: 732-733.
6. Moe, S.M. and T.B. Drüeke, 2003. Management of Secondary Hyperparathyroidism: The Importance and the Challenge of Controlling Parathyroid Hormone Levels without Elevating Calcium, Phosphorus and Calcium-Phosphorus Product. Am. J. Nephrol., 23: 369-379.
7. Okuno, S., 2004. Extraskeletal actions of parathyroid hormone in hemodialysis patients. Clin. Calcium, 14: 27-31.
8. Liberato, B.B., Hemostasis in Chronic Renal Failure. Nephrology. http://www.medstudents.com.br
9. Lin, S.H., S.D. Shieh, S.H. Chyr, K.C. Lu, Y.F. Lin, L.K. Diang, T.C. Chou and Y.A. Ding, 1994. Effect of intravenous calcitriol on platelet intracellular calcium in uremic hemodialysis patients with secondary hyperparathyroidism. Zhonghua Yi Xue Za Zhi (Taipei), 54: 240-245.
10. Wiwanitkit, V., 2004. Plateletcrit, mean platelet volume, platelet distribution width: its expected values and correlation with parallel red blood cell parameters. Clin. Applied Thromb. Hemost.,10: 175-478.
11. Bancroft, A.J., E.W. Abel, M. Mclaren and J.J. Belch, 2000. Mean platelet volume is a useful parameter: A reproducible routine method using a modified Coulter thrombocytometer. Platelets, 11: 379-387.
12. Ozdemir, O., M. Soylu and O. Alyan, 2004. Association between mean platelet volume and autonomic nervous system functions: Increased mean platelet volume reflects sympathetic overactivity. Clin. Cardiol., 9: 243-247.
13. Henning, B.F., W. Zidek, B. Linder and M. Tepel, 2002. Mean platelet volume and coronary heart disease in hemodialysis patients. Kidney Blood Press Res., 25: 103-108.

14. Coli, L., LB.De Sanctis, G. Feliciangeli *et al*. Dialysis membrane biocompatibility: effects on cellular elements. Nephrol Dial Transplant., 10: 27-32
15. Grzegorzewska, A.E., I. Mariak, 2001. Parathyroid hormone contributes to variations in blood morphology in diabetic and non diabetic patients treated with continuous ambulatory peritoneal dialysis. Adv. Perit Dial., 17: 5-9.
16. Papanas, N., G. Symeonidis, E. Maltezos, G. Mavridis, E. Karavageli, T. Vosnakidis and G. Lakasas, 1990. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets, 15: 475-478.
17. Martin, J.F., A. Trowbridge, 1990. Platelet Heterogeneity: Biology and Pathology. London, UK, Springer-Verlag, 1990.
18. Jakubowski, J.A., C.B. Thomson, R. Vaillancourt, C.R. Valeri and D. Deykin, 1983. Arachidonic acid metabolism by platelets of differing size. Br. J. Haematol., 53: 503-511.
19. Martin, J.F., E.A. Trowbridge, G. Salmon and J. Plumb, 1983. The biological significance of platelet volume: Its relationship to bleeding time, platelet thromboxane B_2 production and megakaryocyte nuclear DNA concentration. Thromb. Res., 32: 443-460.
20. Haver, V.M. and A.R.L. Gear, 1981. Functional fractionation of platelets. J. Lab. Clin. Med., 97: 187-204.
21. Thompson, C.B., K.A. Eaton, S.M. Princiotta, C.A. Kushkin and CR. Valeri, 1982. Size dependent platelet subpopulations: Relationship of platelet volume to ultrastructure, enzymatic activity and function. Br. J. Haematol., 50: 509-519.
22. Thompson, C.B., J.A. Jakubowski, P.G. Quinn, D. Deykin and C.R. Valeri, 1983. Platelet size as a determinant of platelet function. J. Lab. Clin. Med., 101: 205-213.
23. Thomson, C.B., D.G. Love, P.G. Quinn and C.R. Valeri, 1983. Platelet size does not correlate with platelet age. Blood, 62: 487-494.
24. Martin, J.F., 1989. The relationship between megakaryocyte ploidy and platelet volume. Blood Cells, 15: 108-117.
25. Martin, J.F., J. Plumb, R.S. Kilby and Y.T. Kishk, 1983. Changes in platelet volume and density in myocardial infarction. Br. Med. J., 287: 456-459.
26. Sharpe, P.C., Z.R. Desai and T.C. Morris, 1994. Increase in mean platelet volume in patients with chronic renal failure treated with erythropoietin. J. Clin. Pathol., 47: 159-61.
27. Nasri, H., 2003. Intensification of anemia by secondary hyperparathyroidism in hemodialysis patients. Iran J. Med. Sci., 28: 195-197.
28. Brancaccio, D., M. Cozzolino and M. Gallieni, 2004. Hyperparathyroidism and anemia in uremic subjects: A combined therapeutic approach. J. Am. Soc. Nephrol., 1: S21-S24.
29. Drueke, T.B. and K.U. Eckardt, 2002. Role of secondary hyperparathyroidism in erythropoietin resistance of chronic renal failure patients. Nephrol Dial Transplant., 5: 28-31.
30. Leithner, C., J. Kovarik, H. Sinzinger and W. Woloszczuk, 1984. Parathyroid hormone does not inhibit platelet aggregation. Lancet, pp: 367-368.
31. Benigni, A., M. Livio, P. Dodesini, A. Schieppati, M. Panigada, G. Mecca, G. de Gaetano and G. Remuzzi, 1985. Inhibition of human platelet aggregation by parathyroid hormone. Is cyclic AMP implicated? Am. J. Nephrol., 5: 243-247.