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Research Article

# ASYMPTOMATIC PROLONGED APTT IN PATIENTS WITH MULTIPLE MYELOMA

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**ABSTRACT**

Multiple myeloma (MM) is the most common plasma cell dyscrasia and accounts for approximately 10-13% of haematological malignancies. We studied tests of hemostasis including platelet count, Prothrombin time, Activated Partial Thromboplastin time, Thrombin time and plasma fibrinogen in 30 patients of multiple myeloma and 30 age matched controls. Prolongation of APTT was the most common screening test which was abnormal. One or more laboratory parameter of hemostasis was abnormal in all 30 (100%) patients. It has been reported that bleeding may occur as a late manifestation in these patients. Screening for these abnormalities and close follow up can help reduce morbidity and mortality and improve prognosis in these patients.

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## INTRODUCTION

Multiple myeloma (MM) is the most common plasma cell dyscrasia and accounts for approximately 10-13% of haematological malignancies and 1% of all cancer deaths every year worldwide (Saraf *et al*, 2012).The exact incidence of MM in India is not known but is reported to be approximately 0.3 to 1.9 per 1,00,000 for men and 0.4 to 1.3 per 1,00,000 for women (Kumar *et al*, 2006).

Both bleeding and thrombotic abnormalities have been reported inpatients with MM (Coppola *et al* 2011, Kristinsson *et al* 2008). Bleeding manifestations include asymptomatic prolongation of screening tests of hemostasis (Gupta *et al*, 2000), overt haemorrhagic manifestations (Saif *et al* 2001, Glaspy *et al*,1992) and life threatening DIC(Usheva *et al*,1986).

Prolongation of screening tests of hemostasis without evidence of clinical bleeding has been frequently reported in patients with MM (EbyC, 2009; Eby CS, 2007). In a study of 252 patients of MM, abnormality in screening coagulation tests was observed in 31% patients, of which an isolated prolonged PT was the most common (Pandey *et al*, 2013). Saif *et al* observed an increase in TT and PT in a patient with MM (Saif *et al*, 2001).

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Patients with asymptomatic prolongation of screening tests of hemostasis are at increased risk of late bleeding (Eby, 2007). Prolongation of screening hemostatic tests has been correlated with a poor outcome in some studies (Teng *et al*, 2007). Early demonstration of an abnormality in these tests will help in identification of patients at risk of bleeding and adverse outcome. This study estimated screening tests (platelet count, PT, APTT, TT and plasma fibrinogen) of hemostasis in patients with MM at admission.

## MATERIAL AND METHODS

Thirty patients of MM diagnosed as per standard criteria (Dispenzieri *et al*., 2009) and thirty age matched controls were included in the study. Written informed consent was obtained from all patients before their inclusion in the study. The study received clearance from the Institutional Ethics Committee for human research.

The following tests were done on all subjects: Complete blood counts (Automated hematology analyser LH500), tests of hemostatsis including Prothrombin time (PT; Dade Behring Thromborel S), Activated Partial Thromboplastin Time (APTT; Dade Behring Actin FS), Thrombin time (TT; Sigma Aldrich) and plasma fibrinogen (Quantia, Tulip diagnostics). Results of biochemical parameters including serum calcium, creatinine, total proteins and β-2 microglobulin were noted from the records.

***Statistical analysis:*** The data was subjected to statistical analysis using IBM SPSS software statistics 20 package. Mean value of continuous variables was compared using unpaired t-test. Level of significance and level of confidence were 5% and 95% respectively

## RESULTS

The results of screening tests of hemostasis and the abnormality therein are shown in Table 1.

**Table 1** Tests of hemostasis in patients and controls and abnormality in each

| Parameter | Mean±SD | | Abnormal results | |
|---|---|---|---|---|
| | Patients | Controls | Cut off values | Number of patients (%) |
| Platelet count($x10^9$/L) | 211±127 | 246±75 | <150 | 5(16.7) |
| PT(secs) | 14.1±3.3 | 12.4±0.9* | >14 | 14(46.7) |
| APTT(secs) | 39.6±10.1 | 29.6±1.3* | >32 | 20(66.7) |
| TT(secs) | 11.3±2.7 | 9.8±0.5* | >11 | 10(33.3) |
| Plasma fibrinogen (mg/dl) | 272.9±185.6 | 225.0±58.7 | <150 | 11(36.7) |

*p<0.01

***Platelet count:*** There was no significant difference in the platelet count of patients and controls. Thrombocytopenia was identified in 5(16.7%) patients, the count being normal in all controls.

***Screening tests of hemostasis:*** The reference value of PT, APTT and TT of laboratory controls was 11 secs, 26 secs and 9 secs respectively. PT, APTT and TT were significantly ($p<0.01$) higher in patients as compared to controls. Prolonged PT, APTT and TT were observed in 46.7%, 66.7% and 33.3% patients respectively and were normal in all controls.

***Plasma fibrinogen:*** There was no significant difference in the level of plasma fibrinogen of patients (Mean±SD: 272.9±185.6mg/dl) and controls (Mean±SD:225.0±58.7mg/dl). Reduced plasma fibrinogen (<150mg/dl) was observed in 11 (36.7%) patients; being within the reference range in controls.

One or more laboratory parameter of hemostasis was abnormal in all 30 (100%) patients.

Prolongation of APTT was the most common screening test which was abnormal, being present in 20 (66.7%) patients. An isolated prolonged APTT was seen in 4(13.3%) patients. Prolonged PT and APTT together were seen in 10 (33.3%) patients.

On logistic regression analysis, no statistically significant correlation was observed between any of the abnormal tests of hemostasis and other prognostic factors i.e. elevated urea, creatinine, total protein, serum albumin, $\beta_2$-microglobulin, stage of the disease and percentage of plasma cell in bone marrow.

## DISCUSSION

This study evaluated the prevalence of thrombocytopenia and prolonged screening hemostatic tests in patients with MM at admission. Thrombocytopenia was identified in 5(16.7%) patients. Similar findings have been reported by other authors (Kyle *et al*, 2002). Gupta *et al* reported three cases who presented initially with features of ITP but were subsequently found to have multiple myeloma (Gupta *et al*, 2000). Perkin *et al* reported thrombocytopenia in 30%, 20% and 0% patients of IgG, IgA and free light chain only myeloma respectively (Perkin *et al*, 1970).

Hemostatic abnormalities were observed in all patients in this study. The frequency is higher than that observed by other authors (Teng *et al*, 2007). The most frequent abnormal screening test was APTT seen in 66.7% patients. Elice *et al* reported prolonged APTT in 11% of newly diagnosed and 16% of previously treated myeloma patients (Elice *et al*, 2006). In contrast, prolonged APTT was seen in <1% and 9.5% patients of MM in other studies (Pandey *et al*, 2013;Teng *et al*,2007).

This study did not observe any correlation between prolonged APTT and other prognostic factors. Similarly, in a study on 101 newly diagnosed patients of MM, no correlation was observed between APTT and stage of MM or type of M protein (Huang *et al*,2015). Teng *et al* reported prolonged APTT to be an independent prognostic factor in IgA myeloma(Teng *et al*,2007).Similar findings were reported by Perkin *et al* in 40% patients of IgA myeloma in their study(Perkin *et al*,1970). However, this characterization was not done in this study.

In this study, prolonged PT was present in 14 (46.7%) patients. No correlation was observed between prolonged PT and other prognostic factors. These results are consistent with those reported by other authors (Teng *et al*,2007; Perkin *et al*,1970; Kyle *et al*,2002). Pandey *et al* reported an isolated prolonged PT to be the most frequent abnormal coagulation test (Pandey *et al*, 2013).They also did not observe any correlation between prolonged PT and other prognostic markers (Pandey *et al*,2013).

In this study, prolonged PT and APTT together were observed in 10(33.3%) patients. Pandey *et al* reported prolonged PT and APTT in 10(4%) patients (Pandey *et al*,2013). Teng *et al* reported prolonged PT and APTT in 12(5.4%) patients (Teng *et al*,2007).

In this study, TT was prolonged in 10 (33.3%) patients.No correlation was seen between prolonged TT and other prognostic factors. Pandey *et al* reported prolonged TT in 44% patients (Pandey *et al*,2013). In contrast, Perkin *et al* observed prolonged TT in 71%, 57% and 15% patients of IgG,IgA myeloma and in macroglobulinemias (Perkin *et al*,1970). Robert *et al* reported prolonged TT as the most frequent abnormal screening test which was seen in 64% patients. They observed a correlation between prolonged TT and increased serum viscosity and circulating monoclonal proteins (Robert *et al*,1993).

There was no difference in the level of plasma fibrinogen of patients and controls.Plasma fibrinogen did not show any correlation with other prognostic markers.

None of the patients in the present study had any clinical evidence of bleeding. Similar results have been reported by other authors (Perkin *et al*,1970; Robert *et al*,1993). However, few case reports of MM patient presenting with bleeding diathesis have also been reported (Hasnain *et al*,2007; Botin *et al*,2015; Colwell *et al*, 1997).

It has been reported that bleeding may occur as a late manifestation in these patients. Their presence also correlates

with an adverse outcome. Screening for these abnormalities hence assumes importance in these patients at diagnosis. Close follow up can help reduce morbidity and mortality and improve prognosis.

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