

Midazolam-induced platelet inhibition on thromboelastography in a trauma patient

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Abstract

We present a trauma patient with no history of anticoagulant use who demonstrated evidence of platelet inhibition on thromboelastography with platelet mapping presumably due to midazolam and associated clinical bleeding. After cessation of midazolam and no other changes in clinical treatment, his platelet inhibition resolved.

Keywords

thromboelastography; trauma; platelet inhibition

Introduction

Thromboelastography (TEG) is used to detect disorders orders of coagulation, often in hemorrhaging trauma patients and during cardiovascular surgery. Patients taking anticoagulants have altered TEG results dependent on the medication. We present a case of a trauma patient with no anticoagulant use who demonstrated platelet inhibition on TEG with platelet mapping presumably due to midazolam and associated clinical bleeding. Although previous studies have demonstrated that midazolam impairs platelet aggregation [1,2], this is the first report to our knowledge of this finding being detected by TEG with platelet mapping in a clinical setting.

Case Presentation

A 41 y/o male suffered a self-inflicted gunshot to the left chest. Prior to arrival at our facility, he was intubated for respiratory insufficiency, underwent tube thoracostomy, and blood product transfusion. His pre-arrival transfusion consisted of 5 units of red blood cells. He arrived at our institution hypotensive, hypothermic, and hypoxemic. There was a 3 cm circular wound just medial to the left nipple. There was a 10 x 4 cm complex wound in the left axilla with a large air leak. His 20-French chest tube was exchanged for a 36-French tube with the evacuation of copious amounts of blood. He was taken emergently to the OR for thoracotomy and left upper lobectomy. On laboratory analysis, he was noted to be thrombocytopenic with a platelet count of $75 \times 10^9/L$. Coagulation profile studies were slightly elevated but within normal range. Massive transfusion protocol was initiated and after administration of 8 units of packed red blood cells, 4 units of platelets, and 5 units of plasma, a TEG performed showed no evidence of clotting abnormalities (Table 1, Admission). Ketamine and midazolam were used for sedation

management. Due to ongoing transfusion requirements and failure to correct his coagulopathy, a repeat TEG with platelet mapping was performed (Table 1, Repeat) at 24 hours after his admission TEG and within 6 hours of receiving midazolam. This TEG showed evidence of 84.5% arachidonic acid (AA) inhibition and 77.3% adenosine diphosphate (ADP) inhibition. Concurrently with this TEG the patient's CBC demonstrated a hemoglobin of 10.8 g/dL and a hematocrit of 29.9%. His platelet count was $71 \times 10^9/L$. At that time, he was receiving intermittent parenteral midazolam at usual doses which were suspected as the etiology of his TEG platelet inhibition and possibly of his ongoing hemorrhage. The midazolam was discontinued and a final TEG with platelet mapping (Table 1, Final) was performed at 48 hours from his admission TEG and 30 hours from the last administration of midazolam. The TEG analysis demonstrated correction of this previous platelet inhibition. Simultaneously, he required no further platelet transfusions and remained hemodynamically stable.

Discussion

TEG is a technique utilized to detect functional disorders in clotting and platelet function. It was initially described in 1948 and provides a real-time assessment of viscoelastic clot strength in whole blood. These tests allow visual assessment of blood coagulation from clot formation, through propagation, and stabilization, until clot dissolution [3]. TEG is used often in the bleeding patient to determine how to best correct their coagulopathy, whether it be to replace factors with plasma or cryoprecipitate or platelet replacement. The platelet mapping function of TEG allows assessment of drugs that inhibit AA and ADP-stimulated aggregation. Abnormalities on TEG are commonly seen in those taking oral anticoagulants for heart arrhythmias, mechanical heart valves, various vasculature stents, or those who are pre-disposed to form clot due to a systemic disease process. Platelet inhibition has also been previously demonstrated after midazolam administration. *Sheu et al.* demonstrated that midazolam inhibits agonist-induced human platelet aggregation in-vitro. This inhibitory effect was postulated to be caused by the induction of conformational changes in platelet membrane, with a resulting influence on membrane fluidity. This is followed by inhibition of the activation of phospholipase C and subsequent inhibition of phosphoinositide breakdown and thromboxane A₂ formation, thereby leading to inhibition of both intracellular calcium mobilization and phosphorylation of P47 [1]. These findings were further confirmed by *Hsaio et al.* [11] Their demonstration of platelet inhibition was at doses equivalent to those used during intermittent and ICU sedation. ADP is present in dense granules and is released by platelet stimulating agents, such as thrombin and collagen. ADP induces platelet aggregation and stabilization of aggregates through the P-selectin adhesion molecule. *Tsai et al.* demonstrated that midazolam significantly inhibited ADP-induced platelet P-selectin expression and further platelet aggregation [2]. Postoperatively, our patient was sedated with expected doses of midazolam. Also, he continued to require product transfusion. On repeat TEG analysis, he demonstrated significant platelet inhibition that had been absent on admission. His midazolam therapy was terminated and there were no significant changes in other clinical therapies. He had a significantly reduced need for product transfusion. Specifically, he required no subsequent platelet transfusions after midazolam was terminated. On follow-up TEG analysis, his platelet function had returned to normal. The platelet inhibition was transient and appears directly related to midazolam.

TEG is useful for the rapid evaluation of trauma induced coagulopathy (TIC) which could also explain an abnormal admission tracing. The phenomenon of TIC has been extensively described [8]. Platelet dysfunction in trauma is one arm of TIC and is a known entity reflecting a global process rather than isolated AA or ADP inhibition [5, 9, 10] *Wolhauer et al.* showed evidence that within 30 minutes of injury, trauma patients exhibit signs early platelet dysfunction on TEG analysis in response to agonists (AA and ADP) when compared to a healthy cohort [5]. Our patient arrived at our facility 2 hours post-injury having already received a significant product transfusion. At admission, he was not noted to be coagulopathic on coagulation profile studies. As stated, he continued to receive massive transfusion after admission. His initial TEG, performed after he had already received significant component therapy, did not show evidence of platelet inhibition and he was not coagulopathic. Clot formation and platelet function abnormalities can also be seen in those who have disease processes that makes them inherently coagulopathic, i.e. liver cirrhosis [6]. Thrombocytopenia alone has been shown to contribute to platelet dysfunction [7]. Our patient had no known history of disease processes that would explain a coagulopathy of systemic illness. In our opinion, his thrombocytopenia on admission was most likely due to consumption as he had no known history of thrombocytopenia and had not received platelet transfusion before arrival. While we cannot fully rule out the possibility of TIC as a cause of his platelet dysfunction, he had normal coagulation profiles and normal TEG parameters at admission. One would expect that if our patient was coagulopathic due to TIC, this would have been demonstrated on his admission coagulation profile studies and his initial TEG because it is seen acutely and has a later presentation if there is a new hemorrhage. *Castellino et al.* demonstrated that patients who suffer traumatic brain injuries show evidence of inhibition of platelets through the AA and ADP pathways [4]. This was seen in the absence of anticoagulant use and was seen very early on after injury. However, our patient did not suffer a TBI and had an admission TEG with platelet mapping that was without signs of platelet inhibition.

Table

Table 1: Repeat TEG was performed 24 hours after admission TEG. Final TEG was performed 48 hours after admission TEG.

Function	Admission	Repeat	Final	Ref
R (Reaction time)	6.6 minutes	6.9 minutes	6.7 minutes	5-10
K (Kinetics)	3.3 minutes	1.7 minutes	1.6 minutes	1-3
Angle	49.8 degrees	66.2 degrees	67.3 degrees	53-72
MA (max amplitude)	51.0 mm	61.3 mm	67.4 mm	50-70
G (Clot firmness)	5.2 dynes/cm ²	7.9 dynes/cm ²	10.9 dynes/cm ²	4.5-11
EPL (Est. % lysis)	0%	.4%	.3%	0-15
Ly30 (% lysis @ 30 min)	0%	.4%	.3%	0-8
AA	Less than 20%	84.5 % inhibition	Less than 20%	<=20
ADP	Less than 20%	77.3% inhibition	Less than 20%	<=20

Conclusion

Our patient demonstrated platelet inhibition with no known use of platelet inhibitors, no evidence of coagulopathy or platelet inhibition at admission, and no evidence of further injury outside of his gunshot wound. We believe that his platelet inhibition was caused by midazolam use for sedation in the ICU. After discontinuing midazolam, a repeat TEG with platelet mapping showed complete resolution of the platelet inhibition. This is the first known report of apparent midazolam-induced platelet inhibition in a clinical setting. In those patients who demonstrate platelet inhibition and ongoing bleeding who are also receiving midazolam, one may consider the inhibitory effect and decreased aggregation that midazolam has on platelets.

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