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Topical Review

Valproic Acid–Induced Coagulopathy

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ABSTRACT

Background: Valproic acid is one of the most commonly used antiseizure medications. Multiple hematologic abnormalities have been reported with the use of valproic acid, which may be particularly relevant in the perioperative surgical setting. The incidence of these abnormalities and prevalence of periprocedural hemorrhage vary significantly in the published literature. In this article we analyze the prevalence and possible etiology of coagulopathy and hemorrhage in patients receiving valproic acid.
Methods: A literature search was completed using "VPA," "coagulopathy," and "surgery." The available published data from case reports to large case series were reviewed.
Results: Thrombocytopenia was noted to be the most common laboratory abnormality associated with valproic acid. An association between valproic acid and acquired von Willebrand disease has also been suggested. There are case reports describing bleeding in the setting of hypofibrinogenemia and factor XIII deficiency. Perioperative hemorrhage was reported in pediatric studies of orthopedic procedures, but not in adult cohorts undergoing neurosurgical interventions.
Conclusions: VPA use can cause thrombocytopenia and other coagulation abnormalities. Rigorous, prospective trials are needed to better assess the association between valproic acid and clinically significant coagulopathy. Until such data are available, physicians need to be aware of the potential risk of bleeding in patients receiving valproic acid. A hemostatic evaluation should be considered in symptomatic patients, and may be considered for patients taking VPA who are scheduled for surgery. If an abnormality is detected, hematologists should be involved to make recommendation on perioperative hemostatic strategy.

Introduction

Valproic acid (VPA), a derivative of valeric acid and component of the plant *Valeriana officinalis*, is widely used for epilepsy treatment. Since the first description by Meunier et al. on the successful use of VPA for the management of childhood seizures,[1] it has rapidly evolved into a front line antiepileptic agent for the management of generalized tonic-clonic seizures and focal seizures.[2,3] VPA is also used to treat specific epilepsy syndromes such as Lennox-Gastaut encephalopathy with status epilepticus during slow wave sleep and Dravet syndrome.[2,4-6] VPA is predominantly metabolized by the liver with a small amount excreted unchanged in urine.[7,8] Metabolism involves cytochrome P450 enzymes, glucuronide conjugation, and β-oxidation in mitochondria.[9,10] VPA is highly protein bound with about 95% of the drug bound to albumin. The binding sites saturate with concentrations greater than 50 mg/L, resulting in a disproportionate increase in unbound concentration.[11] Half-life is variable between four and 17 hours, with shorter half-life reported in children and a steady state reached in around 24 to 48 hours. The mechanism of action for its antiepileptic drug effect includes γ-aminobutyric acid potentiation, inhibition of *N*-methyl-D-aspartate receptor-mediated transmission, sodium and calcium channel blockage, and inhibition of histone deacetylases.[12]

VPA has multiple side effects, which may either be dose dependent or part of an idiosyncratic reaction. Herein, we review the existing literature on coagulation abnormalities associated with VPA use, and the potential implications for patients undergoing surgery. Several coagulation abnormalities, namely thrombocytopenia, platelet functional defects, hypofibrinogenemia, factor XIII

Conflicts of Interest: None.

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TABLE 1.
Selected studies investigating the impact of valproic acid on laboratory markers of hemostasis

Author/Year	Study Design	Sample size	Principal Findings
Thrombocytopenia/platelet dysfunction			
Zighetti et al./2015[13]	Case-control	12 cases-8 controls	No significantly different results were appreciated between cases and controls with regards to (i) platelet count, (ii) PFA-100 CT, (iii) platelet aggregation,
Koenig et al./2008[14]	Prospective cohort	23 subjects	• 9% subjects developed platelet counts <150,000/ cu mm • 35% subjects had prolongation of Col/Epi PFA-100 closure time
Nasreddine and Beydoun/2008[16]	Prospective cohort	265 subjects	• 18% subjects were noted to have a platelet count <100,000/ cu mm. • Thrombocytopenia developed a median of 82 days after starting VPA. • Platelet counts were negatively correlated with serum VPA concentration
De Berardis et al./2002[17]	Case-control	25 cases-20 controls	While a significant drop in platelet count was appreciated after 10 months of VPA therapy, no patient was noted to have a platelet count <150,000/ cu mm.
Conley et al./2001[18]	Case series	264 subjects	• 12% of subjects were noted to have thrombocytopenia. • Older age (>65 years; $P = 0.002$) and higher dose of VPA ($P < 0.0001$) were associated with thrombocytopenia.
Serdaroglu et al./2001[19]	Cross-sectional	29 subjects	3% subjects had thrombocytopenia
Allarakhia et al./1996[20]	Retrospective cohort	167 cases	• 22% of subjects were noted to have platelet counts <200,000/ cu mm. • Platelet counts were negatively correlated with serum VPA concentration. • Older age was predictive of developing thrombocytopenia
Delgado et al./1994[30]	Case-control	306 cases-91 controls	• 21% of cases were noted to have platelet counts <150,000/ cu mm • 10.5% of cases were noted to have platelet counts <100,000/ cu mm • Platelet counts were negatively correlated with serum VPA concentration ($P < 0.001$)
Hypofibrinogenemia			
Karakayah et al./2016[21]	Case report	1 subject	Right knee hemarthrosis and severe hypofibrinogenemia after 2-years of VPA therapy. Fibrinogen levels increased after stopping VPA therapy.
Chen et al./2013[22]	Case report	1 subject	Hypofibrinogenemia and cerebral bleeding 12 days after starting VPA. Fibrinogen levels increased after stopping VPA, and decreased with re-exposure to VPA.
Koenig et al./2008[14]	Prospective cohort	23 subjects	57% subjects had fibrinogen levels <150 mg/dL.
Serdaroglu et al./2001[19]	Cross-sectional	29 subjects	28% subjects had hypofibrinogenemia
Factor XIII deficiency			
Koenig et al./2008[14]	Prospective cohort	23 subjects	13% subjects had FXIII levels < 70%
Teich et al./2004[15]	Case series	2 subjects	Both subjects developed bleeding and low FXIII activity shortly after starting VPA. FXIII activity returned to normal after discontinuation/dose reduction of VPA.
Pohlmann-Eden et al./2003[23]	Case report	1 subject	Intracranial hemorrhage and low FXIII activity appreciated shortly after starting VPA.
Acquired Von Willebrand Syndrome			
Zighetti et al./2015[13]	Case-control	12 cases-8 controls	No significantly different results were appreciated between cases and controls with regards to VWF:RCo
Eberl et al./2009[24]	Prospective cohort	40 subjects	• No alterations appreciated in FVIII activity and VWF:RCo • There was a statistically significant decrease in VWF:Ag; though no patient developed pathological levels.
Koenig et al./2008[14]	Prospective cohort	23 subjects	35% subjects developed acquired von Willebrand syndrome
Serdaroglu et al./2001[19]	Cross-sectional	29 subjects	21% of subjects had low VWF:RCo
Kreuz et al./1992[25]	Case-control	30 cases-43 controls	67% subjects had type 1 von Willebrand disease

Abbreviations:
Col/Epi = collagen epinephrine
FXIII = factor 13
PFA = platelet function analysis
VPA = valproic acid
VWF:Ag = von Willebrand factor antigen
VWF:RCo = von Willebrand ristocetin cofactor activity

(FXIII) deficiency, and acquired von Willebrand syndrome have been associated with the use of VPA. The incidence on these abnormalities has varied significantly in the published literature[13-15] (see Table 1 for details). Furthermore, the exact clinical impact of these coagulation abnormalities remains unclear, with some but not all studies documenting an association with increased bleeding symptoms including perioperative hemorrhage.

Overview of hemostasis

Hemostasis refers to the arrest of bleeding at the site of vessel wall injury and is traditionally divided into primary and secondary hemostasis (see Fig 1 for details).[26] Primary hemostasis initiates immediately after endothelial damage and comprises four sequential but overlapping phases, namely (1) vasospasm, (2) platelet adhesion to the underlying collagen mediated by the large multimeric glycoprotein—von Willebrand factor (VWF), (3) platelet activation, and (4) platelet aggregation.[26] The final end product of primary hemostasis is the formation of a platelet plug. A quantitative deficiency or qualitative defect in either platelets or VWF may result in a bleeding disorder. Disorders of primary hemostasis are typically characterized by mucocutaneous bleeding symptoms—epistaxis, easy bruising, petechiae, menorrhagia, and bleeding after surgical or dental interventions. Congenital von Willebrand disease (VWD) is the most common bleeding diathesis with an estimated prevalence of 1:1000 individuals.[27] Common laboratory tests used to investigate the primary hemostatic pathway include complete blood count (to evaluate platelet count), platelet function analysis closure times (PFA-100 CT), platelet aggregation and von Willebrand panel (including von Willebrand antigen [VWF:Ag], von Willebrand ristocetin cofactor function [VWF:RCo], factor VIII [FVIII] activity, and VWF multimer analysis).

Secondary hemostasis involves the sequential interaction of serine protease zymogens and their cofactors via the coagulation pathway and comprises three overlapping phases: initiation, amplification, and propagation. Secondary hemostasis results in the formation of covalently cross-linked fibrin that stabilizes the primary platelet plug.[26] Details of the coagulation pathway are elaborated elsewhere.[26] Disorders of secondary hemostasis are less common—hemophilia A (X-linked congenital deficiency of FVIII) has an

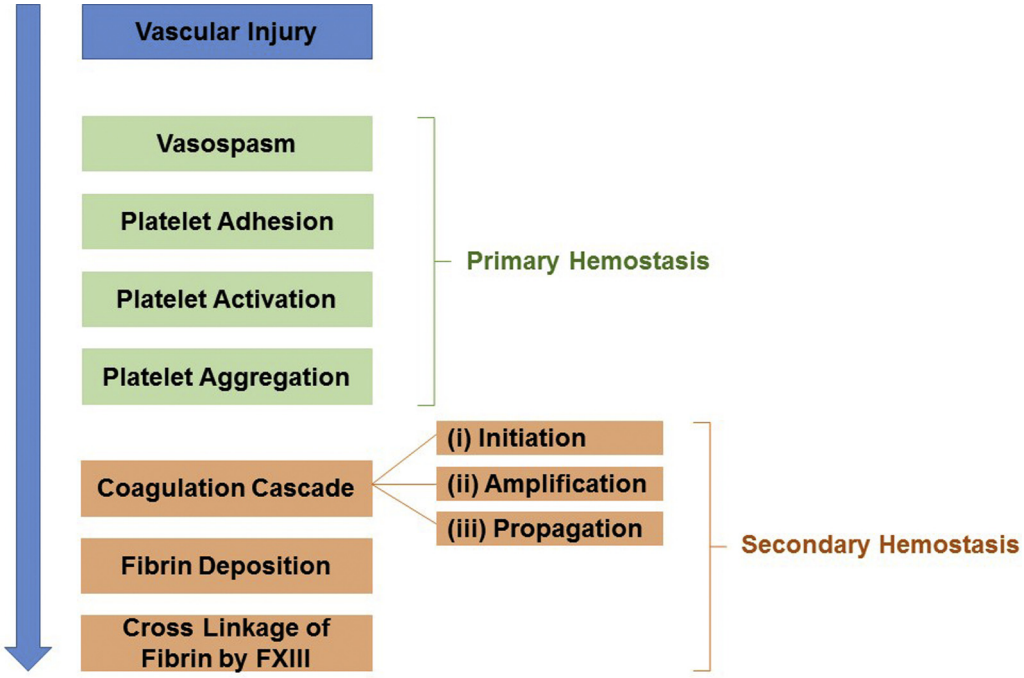

FIGURE 1. Overview of coagulation.

estimated prevalence of 1:5000 males,[27] whereas congenital FXIII deficiency has an estimated prevalence of 1:2,000,000 individuals.[28] Disorders of secondary hemostasis typically present with deep bleeds into muscles, hemarthrosis, and intracranial hemorrhage. The prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time are commonly used to screen for disorders of secondary hemostasis (see Fig 2 for details). When the results are abnormal, individual levels of clotting proteins (e.g., FVIII, FIX and so forth) can be obtained to help identify the exact disorder.

Impact of valproic acid on laboratory markers of coagulation

In a cohort of 385 pediatric patients treated with VPA, Gerstner et al. identified clinically significant coagulopathies in eight patients; seven additional patients were found to have a coagulopathy based on preoperative testing.[29] They estimated the cumulative incidence of coagulation abnormalities associated with VPA to be 4%, which likely represents an underestimation as all patients were not screened.

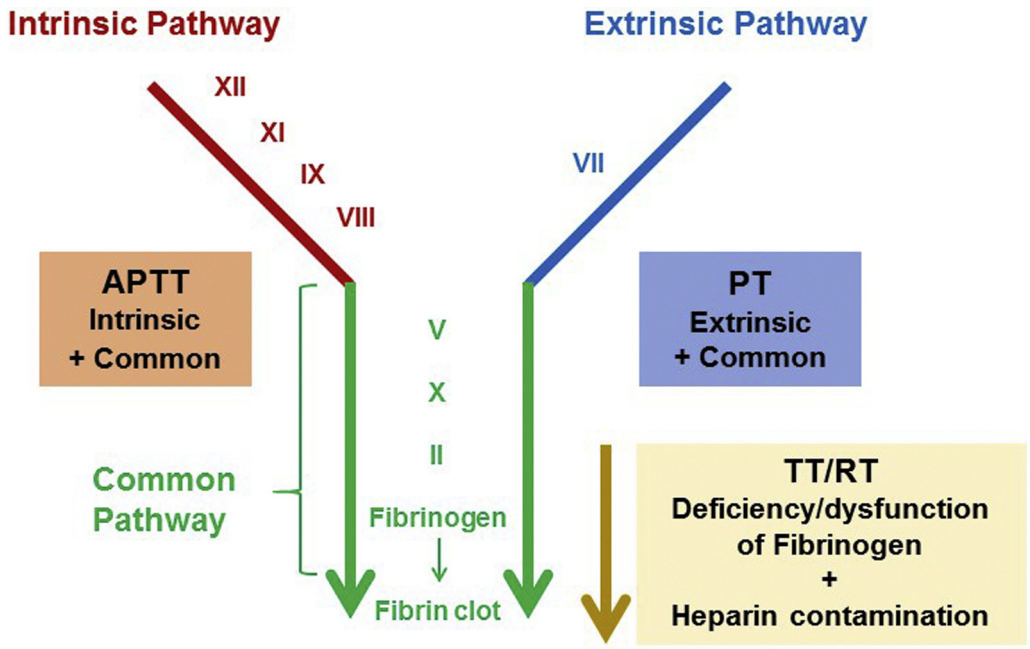

FIGURE 2. Schematic representation of the coagulation cascade *in vitro*. APTT, activated partial thromboplastin time; PT, prothrombin time; RT, reptilase time; TT, thrombin time. Modified with permission from Kumar et al.[26]

TABLE 2.
Association of Valproic Acid and Perioperative Hemorrhage With Orthopedic Interventions

Author/Year	Study Design	Sample Size	Age of Cohort	Indication for Surgery	Excessive Bleeding Noted
Kumar/2005[33]	Case series	2 Subjects	Pediatric	Orthopedic surgery	Yes
Carney and Minter/2005[34]	Retrospective	29 Subjects	Pediatric	Femoral osteotomy in children with cerebral palsy	Yes
Chambers et al./1999[35]	Retrospective	114 Subjects	Pediatric	Spinal fusion for progressive scoliosis	Yes
Winter/et al.1996[36]	Retrospective	139 Subjects	Pediatric	Spinal fusion for progressive scoliosis	Yes

Thrombocytopenia is the most common laboratory abnormality associated with VPA use, with most, but not all studies demonstrating this association.[13,17] In general, the incidence of VPA-associated thrombocytopenia in the published literature has ranged from 3% to 40%, with clinically significant thrombocytopenia developing in about 10%.[16-18,20,29-31] Although the exact mechanism of VPA-mediated thrombocytopenia remains unclear, immune-mediated destruction of platelets and direct toxicity to the bone marrow have both been hypothesized as possible etiologies. Studies have also demonstrated a negative correlation between VPA serum concentration and platelet count.[16,18,20] The largest pediatric study investigating the association between VPA and thrombocytopenia was reported by Delgado et al.[30] Of the 306 children investigated, 64 (21%) developed thrombocytopenia and 21 (10.5%) developed clinically significant thrombocytopenia, defined as a platelet count less than 100,000/mm^3. Average time for thrombocytopenia to develop was 7.5 months. Of note, only eight patients (2.6%) had bleeding symptoms. Their median platelet count was 50,000/mm^3 (range: 19,000 to 68,000/mm^3). Most patients had prompt improvement of their platelet count within one week of lowering the VPA dose, and only one patient required discontinuation of VPA. In addition, platelet functional abnormalities independent of thrombocytopenia, including impaired platelet aggregation with agonists like collagen and adenosine diphosphate, have also been described.[13,14]

The association between VPA and VWD is less clear. In a case-control study of 30 children on VPA and 43 children with congenital type 1 VWD, Kreuz et al.[25] classified 67% of the children receiving VPA as having type I VWD. However, the exact cutoff of VWF:Ag or VWF:RCo used for making the diagnosis was not elaborated. In another retrospective analysis of 29 children receiving VPA for at least 6 months, six (21%) developed low VWF:RCo levels (median, 33.05%; range, 11.5% to 39.7%). In a prospective trial of 23 children, coagulation parameters were obtained at baseline, 6 weeks and 6 months after starting VPA. A significant decrease was appreciated in both VWF:Ag and VWF:RCo, with eight patients (35%) developing clinical VWD.[14] These initial observations, however, were not confirmed in a recently published, prospective multicenter trial.[24] Eberl et al. investigated 40 consecutive patients and obtained coagulation specimens before one week, two, three, and six months after starting VPA. No significant alterations were appreciated in either VWF:RCo or FVIII activity. Although a slight decrease was seen in the VWF:Ag results, no patient developed pathologic levels (defined as less than 50% VWF:Ag; Dr. Wolfgang Eberl, Klinikum Braunschweig, Germany, personal communication, January 10, 2019). Several case reports of bleeding in the setting of hypofibrinogenemia have been described in patients receiving VPA.[21,22] Causality between hypofibrinogenemia and VPA therapy was suggested based on the fact that fibrinogen levels rapidly corrected after cessation of therapy. In the previously mentioned prospective study by Koenig et al.,[14] 12 of 23 patients (57%) developed hypofibrinogenemia, defined as a fibrinogen level less than 150 mg/dL. Similarly, in the prospective multicenter trial reported by Eberl et al.,[24] 9 of 40 (23%) developed pathologic fibrinogen concentrations within 6 months of starting therapy with VPA (defined as less than 180 mg/dL fibrinogen level; Dr. Wolfgang Eberl, Klinikum Braunschweig, Germany, personal communication). There are case reports documenting FXIII deficiency associated with VPA therapy.[15,23] Although the exact etiology is unclear, VPA-mediated hepatotoxicity (fibrinogen and FXIII are both synthesized in the liver) is postulated to be responsible for these specific deficiencies.

Perioperative hemorrhage in the setting of valproic acid use

Bleeding complications in the operating room can impose major challenges for surgeons. At this time, there are no published guidelines regarding monitoring of potential coagulation abnormalities in patients on VPA scheduled to undergo surgical interventions. Although there are several publications investigating the impact of VPA on platelet count and platelet function (Table 1),[32] there are few case reports or case series reporting the hemorrhagic side effects of VPA on patients undergoing surgery (Tables 2 and 3). Interestingly, despite the high incidence of reported abnormalities in the coagulation system, the risk of perisurgical bleeding, particularly in adults undergoing neurosurgical interventions, appears to be low.[33,37]

Winter et al. first published the impact of VPA on postoperative bleeding in 139 children undergoing posterior spinal fusion. At the time of surgery 22 subjects were receiving VPA. Use of VPA was associated with increased need for perioperative blood transfusion.[36] In a subsequent study from the Children's Hospital of San Diego, Chambers et al. investigated 114 patients with cerebral palsy undergoing spine surgery for progressive paralytic scoliosis. Of these 114 patients, 18 were receiving VPA monotherapy and 44% of patients on VPA had prolonged bleeding times. Patients on VPA had increased blood loss and required more red blood cell infusions compared with patients on other antiepileptic agents.[35] These initial observations were confirmed in a recent retrospective study of 29 children undergoing bilateral femoral osteotomy. VPA use was associated with increased perioperative blood loss and need for transfusion.[34]

TABLE 3.
Association of Valproic Acid and Perioperative Hemorrhage With Neurosurgical Interventions

Author/Year	Study Design	Sample Size	Age of Cohort	Indication for Surgery	Excessive Bleeding Noted
Kurwale et al./2016[37]	Retrospective	169	Both	Medically intractable epilepsy	No
Manohar et al./2011[38]	Retrospective	84	Pediatric	Medically intractable epilepsy	No
Psaras et al./2008[39]	Retrospective	85	Adult	Brain tumor	Excessive bleeding was associated with tumor size but not VPA use
Ward et al./1996[40]	Retrospective	87	Adult	Medically intractable epilepsy	No

In stark contrast to these observations in children undergoing orthopedic procedures, studies investigating adults undergoing neurosurgical procedures have not consistently identified an association between VPA use and perioperative hemorrhage.[37,39-41] In a retrospective review of 87 consecutive patients undergoing temporal lobectomy, Ward et al.[40] did not find any difference in the estimated blood loss and need for postoperative blood transfusion between patients who were on VPA, and those who were not. In a subsequent retrospective review of 313 patients undergoing cortical resection, Anderson et al. studied 111 patients on VPA and 202 control subjects who were on antiepileptic drugs other than VPA. Although platelet counts and fibrinogen levels were lower in patients on VPA, there was no significant difference in the estimated perioperative blood loss between the two groups.[41] More recently Kurwale et al. investigated 169 patients with drug-resistant epilepsy undergoing neurosurgical interventions; 91 patients were on VPA and 78 patients were on other antiepileptic drugs. All patients had normal preoperative laboratory test results including platelet counts, bleeding time, PT, and APTT. Average blood loss was not significantly different in the two cohorts.[37]

Conclusions

VPA is a widely used antiepileptic drug with a broad spectrum of efficacy. Multiple hematologic abnormalities have been reported with this medication. The incidence of these abnormalities and their association with perioperative hemorrhage has varied significantly in the published literature. This may in part be explained by differences in study design (retrospective versus prospective), and criteria used to diagnose a bleeding diathesis. For instance, using a VWF:RCo cutoff of 70% to diagnose VWD,[25] or a FXIII cutoff of 70% to diagnose FXIII deficiency,[14] may not have clinical relevance because most patients do not develop bleeding symptoms until these values are much lower. It is also unclear if these effects are dose-related or idiosyncratic with the exception of thrombocytopenia, which appears to be dose dependent. The discrepancy in perioperative hemorrhage may in part be explained by the type of surgery—orthopedic surgeries are typically associated with more bleeding compared with neurosurgical procedures.

More rigorous, prospective trials are needed to assess the clinical burden of VPA-associated coagulopathy. Until such data are available, surgeons, neurologists, hematologists, and anesthesiologists need to be aware of the potential risk of bleeding in patients receiving VPA. A full hemostatic evaluation, including platelet count, PT, APTT, fibrinogen level, VWF:Ag, VWF:RCo, and FXIII levels may be considered in patients on VPA therapy scheduled to undergo major surgical interventions. If any abnormality is detected, hematologists should be involved to make recommendations on perioperative hemostatic strategies. In some instances, and in the setting of significant coagulopathy, it may be reasonable to substitute VPA with another antiepileptic drug or lower the dose (in individuals with thrombocytopenia), postpone surgery by one to two weeks, and repeat the assays. The risks of VPA discontinuation should be weighed against risks of perioperative hemorrhage. When urgent surgical interventions are required in patients receiving VPA, we recommend getting a complete blood count, APTT, PT, and fibrinogen activity. These laboratory assays can be performed urgently in most hospitals. There are no evidence-based guidelines for periprocedure transfusion of platelets and plasma products (i.e., fresh frozen plasma, cryoprecipitate) in this cohort. However, reasonable goals for such patients would be to maintain platelet counts greater than 50×10^9/L (100×10^9/L for neurosurgical procedures).[42] Prospective, adequately powered, multicenter cohort studies would be ideal, but would be difficult to complete. In the interim, gathering well-defined data from retrospective studies or registries will be useful.

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