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Short communication

Valproic acid as an antiepileptic drug: Is there a clinical relevance for the epilepsy surgeon?

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ABSTRACT

Valproic acid (VPA) has been associated with coagulation factors deficiency, platelet dysfunction and hemorrhagic complications. We investigated 169 patients with drug resistant epilepsy (DRE), who underwent surgery, to look for clinical implications of VPA associated bleeding problems. All patients had normal preoperative coagulation profile. VPA was a part of polytherapy in 54% of patients (Group A), however 46% patients were not on VPA (Group B). The groups were comparable with mean age of 17.3 ± 10.3 years. Mean duration of surgery in group A and B were 255 ± 70 and 250 ± 60 min respectively ($p = 0.26$). Average blood loss in group A was 399 ± 254 and 389 ± 228 ml in group B. ($p = 0.62$). The percentage of total blood volume lost was 12.7% (Group A) and 17.7% (Group B) respectively ($p = 0.7$). There were no bleeding complications in either group. Hyperammonemic encephalopathy occurred in 4 patients postoperateively requiring withdrawal or dose reduction of VPA. No mortality was recorded.

We conclude that VPA does not increase clinically relevant perioperative haemorrhagic complications in patients having normal coagulation screen and platelet counts. However, hyperammonemic encephalopathy is observed in 4% of patients in perioperative period, favorably responding to discontinuation of VPA.

1. Introduction

VPA induced coagulopathy is a major concern for epilepsy surgeons despite patients having a normal blood coagulation profile (Gallais et al., 1996; Teich et al., 2004; Unalp et al., 2008). However, quite a few significant VPA coagulopathy associated hemorrhagic complications have been reported (Kumar, 2005; Raghuveer et al., 1989). Few anecdotal reports of difficult hemostasis during surgery and post-operative bleeding episodes requiring evacuation of clots in patients on VPA therapy are available in literature (Cannizzaro et al., 2007; Pohlmann-Eden et al., 2003). Coagulation factor deficiency was claimed to be a cause for the excessive bleeding in these patients. Overall, the incidence of clinically relevant coagulopathy in patients receiving VPA therapy has been reported to be in the range of 4%.

VPA therapy is also known to produce thrombocytopenia in pediatric patients as a result of marrow suppression (Psaras et al., 2008). Despite normal platelet counts, VPA is known to influence the arachidonate cascade leading to inhibition of the cyclooxygenase pathway and the production of thromboxane A2 that causes dysfunction of platelet aggregation (Kis et al., 1999). Kumar et al. reported spontaneous bleeding diathesis in one patient on VPA requiring platelet transfusion (Kumar, 2005).

It is a practice in some centers across the world to discontinue VPA before takings patient for epilepsy surgery. Paucity of literature prompted us to evaluate, if VPA therapy is associated with any increase in clinically significant perioperative hemorrhagic complications in epilepsy surgeries.

Study design: Prospective, observational.

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2. Materials and methods

We studied 169 consecutive patients who underwent surgery for DRE (January 2010 –October 2013) at our centre. Demographic and clinical details, operation details including the volume of blood loss during surgery, duration of surgery, perioperative hemorrhagic complications and the need of blood transfusion were analyzed.

All the patients were admitted in a dedicated epilepsy care unit. Standard DRE-pre surgical evaluation was performed by the neurology team and surgical plan was decided (Tripathi et al., 2008). Pre operative hematological work up included haemoglobin, red blood cells, total leukocytes and platelet count. Coagulation studies CT, BT, prothombin time (PT), and activate partial thromboplastin time (APTT). Serum levels of valproate were obtained in all patients receiving the drug and confirmed to be in therapeutic range of 50–100 μg/ml before surgery.

In the operation theatre, Propofol and fentanyl was used for induction of anesthesia, nitrous oxide and sevoflurane for maintenance and titrated doses of vecuronium for relaxation. Operative time, blood loss, need for transfusion, specific intraoperative events if any, were extensively recorded in operation notes. Patients were shifted to neurosurgical intensive care unit (NSICU) and were managed as per standard protocol. Postoperative CT scans were done in all the patients within usually between 2 and 6 h as per protocol to rule out intracranial hematoma and other operative complications. In patients who were electively ventilated following surgery (especially for hemispherotomies or long duration surgeries), bedside CT scans were performed using a portable CT scanner (Ceretom ® Samsung-NeuroLogica Corporation, Danvers, MA, USA). Blood transfusions given in postoperative period were noted. We further stratified patients in pediatric (≤12 years) and adult (>12 years) populations and analyzed separately. In addition, we also performed subgroup analysis for patients undergoing short duration surgeries (≤4 h) which mainly included lobar resection, callosotomies and long duration surgeries (>4 h) which included multilobar resections, hemispherotomies and disconnections for further clarification of the issue.

3. Statistics

All analyses were performed using the statistical program SPSS version 17. Chi square test was utilized to analysis categorical data. Student *t*-test for equality of means and Levene test for equality of variances were utilized for comparison of means in various subgroups. Mann–Whitney *U* test was used to compare medians (for nonparametric variables). Probability values ≤0.05 in these analyses were considered statistically significant. Log transformation of percentage blood volume loss was done to satisfy statistical assumption of normal distribution followed age adjusted regression analysis to look for any difference with respect to VPA intake.

4. Results

Of the 169 patients studies, 54% (n = 91) patients were on VPA during the preoperative period, while 46% (n = 78) were not on VPA. The mean age in our study group was 17.3 ± 10.3 years. Mean age is significantly lower in VPA group (15 ± 9.5 years) compared to non-VPA group (20 ± 10.5 years) and this difference is also visible in subgroup populations of short and long durations surgeries. In addition, in adult population group, mean age is less in VPA group (21.25 ± 7.5 years) (Table 1).

Mean duration of surgery was 255 ± 70 min in the VPA group and 250 ± 60 min in the non-VPA group (p = 0.26). Average blood loss in the VPA group was 399 ± 254 ml and 389 ± 228 ml in patients who did not receive VPA (p = 0.62). The blood loss when calculated as a percentage of total blood volume in the VPA and non-VPA group was 17.7% and 12.7% respectively (p = 0.01). But, percentage blood volume loss in pediatric patients (25.8 ± 15.8%) was significantly higher than in adult patients (9.6 ± 8.3%) (p = 0.01). Also, patients taking VPA were significantly higher in pediatric age group (40/60) than adult group (51/109), (p = 0.01). Age adjusted regression analysis of percentage blood volume loss after log transformation did not reveal any significant difference in two groups (p = 0.7).

Subgroup analysis revealed a statistically significant difference in blood volume loss in VPA group (13.6 ± 12.4%) compared to non-VPA group (8.2 ± 4.7%) (p = 0.008) in patients undergoing short duration surgeries, which disappeared after age adjusted regression analysis (p = 0.4). This difference can be attributed to significant pediatric population of short surgeries group (p = 0.01).

No significant difference in duration of surgery, blood loss or percentage blood volume loss was observed in any of the subgroups as regards to valproate intake.

Hyperammonemic encephalopathy was recorded in 4 patients in VPA group, which prolonged the recovery and hospital stay. Delayed reversal from anesthesia, unexplained drop in sensorium and unusually delayed recovery in post operative period were main presentations. All patients responded to discontinuation of VPA and administration of sodium benzoate and lactulose. No mortality was recorded in any group.

5. Discussion

Association of VPA with acquired deficiency of coagulation factors is well known for more than three decades; however, only anecdotal reports are available documenting VPA induced coagulopathy(Kumar, 2005; Pohlmann-Eden et al., 2003; Raghuveer et al., 1989). Gerstner et al. (Gerstner et al., 2006) reported around 4% incidence of coagulation factor abnormalities in patient receiving VPA for epilepsy, however, none of these patients presented with bleeding complications.

Coagulations abnormalities and bleeding diathesis is a major concern for surgeons across all the specialties and hence, an initial effort was made by an orthopaedic surgeon to look for clinical relevance of these coagulations disturbances on blood loss during surgery. Winter et al. (Winter et al., 1996) did not find any association with intraoperative or postoperative blood loss with VPA intake during orthopaedic procedures, however, VPA positively correlated with number of blood products used. Similarly, Psaras et al. (Psaras et al., 2008) found no correlation between VPA therapy and blood loss during neurological surgery for brain tumors and authors concluded against discontinuing VPA therapy before any neurosurgical intervention.

Immediate perioperative use of VPA in patients undergoing temporal lobectomies for epilepsy has not been found to cause any hematological side effects and authors favored its use (Ward et al., 1996). However, long term use of valproate is associated with thrombocytopenia and coagulation deficiencies (Kis et al., 1999). Our study included wide spectrum of epilepsy surgeries and also our patients were taking VPA for several years before having surgery. Our study substantiates previous findings by Ward et al., additionally in a more diverse spectrum of epilepsy surgeries and most importantly on long term VPA treatment.

VPA causes deficiency of coagulation factors VIII, IX, XI influencing mainly intrinsic pathways of coagulation, which can be assessed by APTT. Most of the surgical centers screen patients for coagulation disorders routinely with PT and APTT and normal coagulation is a mandatory before surgery. It is very unlikely for patients with normal coagulation parameters to have bleeding complications, which is evident from our study and can be a plausible explanation for paucity of literature on this issue.