Bedside Point of Care Coagulation Testing for Individualized Antivitamin K Reversal: A Prospective Study

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Abstract — A delay in surgery due to laboratory abnormalities may increase mortality in patients with hip fracture. In order to optimize the logistics for urgent surgery in patients with hip fractures and anti-vitamin K treatment, individualized doses of a Prothrombin Concentrate were guided by a bedside whole blood prothrombin time test.

Thirty patients with emergency hip fracture and preoperative anti-vitamin K treatment (warfarin) due to atrial fibrillation were studied during a 3 years period (2010-2012). Intravenous vitamin K was recommended as early as possible after admission to the hospital and after diagnosis of the hip fracture by X-ray, but was not controlled by the authors. Preoperatively the patients were treated with repeated doses of 500 units (U) prothrombin complex factor concentrate (PCC) if laboratory Prothrombin Time International ratio (PT-INR) >1.5 and orthopedic surgeons urged for immediate surgery. Simultaneously whole blood PT-INR and activated prothrombin partial thromboplastin time (aPTT) was checked with a bedside point-of-care HEMOCHRON Jr with blood from the citrated vacutainer test tubes, before these were sent to the laboratory. Both types of PT were checked 10 minutes after the intravenous PCC injection.

The correlation coefficient between routine citrated plasma PT and the whole blood citrated HEMOCHRON® PT was 0.88 (p<0.001). All patients underwent surgery within 24 hours. No plasma was used. Vitamin K was used in 20 of the patients and reduced the need/doses of PCC as compared to patients with no vitamin K treatment. Five mg of iv vitamin K was more effective than 2 mg iv in reducing the need for PCC.

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I. INTRODUCTION

Hip fracture is a common clinical problem that leads to considerable mortality and disability. Comorbidity is more important for mortality in the elderly patients undergoing surgery than age itself.1-3 Whether reducing time-to-surgery for elderly patients suffering from hip fracture results in better outcomes remains subject to controversial debates. Many case series support early surgical repair, although patients who would benefit from delay and further medical work-up have not been well identified.3,4,7,8 Shorter time-to-surgery may be associated with somewhat lower rates of post-operative complications such as decubitus ulcers, urinary tract infections, thrombosis, pneumonia and cardiovascular events, and with somewhat higher rates of others such as post-operative bleeding or implant complications.8 It also shortens the hospital stay.9

In the study by Kirsch et al10 geriatric patients on warfarin before sustaining orthopedic injuries were compared with matched control patients not on warfarin. In comparison with the control group, significant differences were found in time delay from admission to surgery, hospital length of stay, total units of blood transfused, and discharge disposition. No difference was found in number of intensive care unit days, complications or mortality.

Clinicians are frequently called on to correct this coagulopathy in patients receiving oral anticoagulation therapy. Before elective surgery, anticoagulation reversal may be undertaken over several days by discontinuing warfarin or vitamin K treatment, but rapid correction is required in emergency. Compared with human fresh frozen plasma (FFP), prothrombin complex factor concentrate (PCC) provides quicker correction of the international normalized ratio (INR) and improved bleeding control. Although many patients who require rapid reversal of warfarin are currently treated with FFP, PCC should be considered as the proper therapy.11

The standardized test used for evaluating the effect of warfarin is the prothrombin time (PT), which is measured and expressed by INR. Delay in collecting coagulation test results from a central laboratory is one of the critical issues to efficiently control haemostasis during surgery. Portable point-of-care
In the present study, we studied warfarin reversal with bedside individualized titration of the PCC dose being guided by a POC-PT test. This was performed in the operation ward immediately before surgery.

II. METHODS

Thirty hip fracture patients on anti-vitamin K treatment (warfarin) were studied. Approval was obtained from the Regional Ethical Review Board (Lund, Protocol DNR 2010/482) and informed consent was taken from all the patients. The project was graded as a valuable clinical project, but not a research project per se by the Regional Ethical Review Board. During the project period 2010-12 a logistic scheme was introduced at the Lund University Hospital to enable surgery within 24 hours after admission.

Vitamin K was recommended as early as possible after admission at the hospital and after diagnosis of the hip fracture by X-ray, but was not controlled by the authors. All hip fractures underwent surgery within 24 h after admission.

Blood was sampled from large bore indwelling venous catheters; first blood was discarded. Blood samples were collected into citrated plastic vacuum tubes (BD Vacutainer® Coagulation Tube, 2.7 ml, 3.2% citrate, BD Vacutainer systems, Plymouth, UK). Fifteen microliters of the 2.7 ml citrate blood sample were used to analyze POC-PT, followed by another 15 microliters for POC-activated partial thromboplastin time (aPTT) with a bedside POC blood test device, HEMOCHRON Jr (ITC, USA). Then, the blood tube was sent to laboratory for centrifugation and the citrated plasma used for standard laboratory PT.

Laboratory PT-INR was performed using a combined thromboplastin reagent (Stago prothrombin complex assay, SPA+, Stago). The Owren PT assay was calibrated using INR calibrators certified by the Swedish external quality assessment organization (Equalis, Uppsala, Sweden). The reference range for PT (INR) is 0.9–1.2.

The HEMOCHRON Jr, microcoagulation system relies on a mechanical endpoint clotting mechanism in which testing occurs within disposable PT/aPTT cuvettes. The instrument precisely measures 15 microliters of blood and automatically moves it into the test channel of the PT cuvette. Sample/reagent mixing and test initiation are performed automatically, eliminating the need for operator interaction.

After mixing with the reagent, the sample is then moved back and forth within the test channel and monitored by the analyzer for clot formation. Electronic optical detection of a fibrin clot in the blood sample automatically terminates the test. The instrument reports the whole blood number mathematically converted INR and plasma equivalent value in seconds in order to provide a familiar clinical format and thus facilitating accurate clinical test result interpretation. Daily quality controls were performed on the instruments with Electronic System Verification Cartridges.

Immediately pre-operatively the patients were first treated with 500 units (U) of a PCC (Confidex, CSL Behring) if laboratory and HEMOCHRON Jr PT-INR were >1.5. POC-PT and laboratory PT were checked 10 minutes after the intravenous PCC injection (injection rate 250 U/minute). Supplementary doses of PCC (500 U at a time) were given if the initial PCC dose failed to reduce HEMOCHRON Jr-INR <1.5. Laboratory PTs were analyzed with a 30 minutes delay and were only used as a control during this titration procedure. Postoperatively laboratory PT-INR was controlled in the ward as well as development of wound oozing/haematoma and need for more AVK reversal with additional doses of vitamin K or further doses of PCC.

III. RESULTS

All patients underwent surgery within 24 hours. No bleeding complications were seen. No plasma was used. Intravenous K vitamin was used preoperatively in 20 of the patients. K vitamin injection reduced the need for PCC as seen in Table 1. Table 1 identifies actual doses of PCC to normalize PT-INR <1.5. Five mg of iv vitamin K was more effective than 2 mg iv in reducing the need for PCC.

In the 10 patients not receiving preoperative vitamin K, additional doses of 2 mg vitamin K were administrated up to 8 hours postoperatively in 6 patients with laboratory PT-INR >1.5, and 3 of those patients received additional PCC
(500 U) to counteract active oozing from wound (no drainages). No wound haematomas or reoperations were needed. Warfarin was reinstalled on day 2 after surgery and PT-INR became therapeutic (>2.0) on day 6 in all patients. No trend in delay to achieve PT-INR >2.0 was noted in patients that had received the higher dose of vitamin K (5mg) as compared to the lower dose (2mg).

Figure 1 shows the correlations between routine laboratory PT-INR and POC-PT from 30 venous citrated samples analysed preoperatively. The correlation coefficient between routine citrated plasma PT and the whole blood citrated HEMOCHRON® PT was 0.88 (p>0.001). Correlation was lower between POC-PT and POC-aPTT. In some of the patients with PT-INR<1.5; POC-aPTT was higher than our laboratory plasma aPTT reference level (>37s). POC-PT-INRs were all ready after 5 minutes from sampling as compared to the 30 minutes for laboratory PT-INR.

IV. DISCUSSION

The bedside titration of PCC reduced time to surgery and enabled surgery according to logistics within 24 hours of admission. K vitamin injection reduced the need for PCC. No bleeding complications were seen. There was a significant correlation between routine citrated plasma PT and the whole blood citrated HEMOCHRON®-PT. POC-aPTT seemed to be prolonged as compared to POC-PT, but the ITC website defines whole blood normal range to 62.8-88 s as compared to plasma normal range of 23.2-38.7. There are no published studies on effects of warfarin reversal with PCC/vitamin K on whole blood aPTT nor correlating it to laboratory aPTT methods. Also the aPTT reagent use in the HEMOCHRON®-aPTT is not disclosed. There are more than 8 aPTT reagents on the market with different reference values and dose responses to anticoagulants. Therefore it is important to address this issue.

Bleeding complications with anticoagulant drugs appear to occur more frequently in older patients than in younger individuals.13 Advanced age (>75 years), intensity of anticoagulation (INR>4.0), history of cerebral vascular disease (recent or remote), and concomitant use of drugs that interfere with haemostasis [aspirin (acetylsalicylic acid) or nonsteroidal anti-inflammatory drugs] are among the most important variables in determining an individual’s risk for major bleeding with anticoagulants. Older patients often display increased sensitivity to the effects of warfarin, both in the early induction phase and during the long-term maintenance phase of therapy. Conditions such as congestive heart failure, malignancy, malnutrition, diarrhoea and unsuspected vitamin K deficiency, enhance the PT response. The decision to interrupt anticoagulant therapy before elective surgery in elderly patients should evaluate the thrombotic risk of such a manoeuvre versus the risk of bleeding if anticoagulants are continued.

There is little consensus on the optimal perioperative management for most patients on oral anticoagulation with vitamin K antagonists.14 Bridging therapy is not recommended for the majority of patients on oral anticoagulation as most are at low risk for perioperative stroke. Though most clinicians choose an aggressive perioperative strategy for patients with high thromboembolic risk (e.g., mechanical mitral valve replacement) by withholding warfarin perioperatively and using full-dose heparin, prophylactic dose heparin is given for lower risk categories (e.g., bi-leaflet aortic valve replacement and atrial fibrillation). The amount of increase in postoperative major bleeding when full-dose anticoagulation is administered soon after surgery is the main factor in the decision with the least available data. The optimal method for returning the PT-INR to the desired range preoperatively depends upon its degree of initial elevation and whether or not clinically significant bleeding is present.

Baseline PT-INR, but not the size of the maintenance dose, is associated with the rate of normalization of PT after stopping warfarin, but it has limited utility as predictor in clinical practice. Whenever normal haemostasis is considered crucial for the safety, the INR should be checked again before the invasive procedure.15

Rapid reversal of excessive anticoagulation should be undertaken in patients with serious bleeding at any degree of anticoagulation. Since the effect on the PT-INR becomes visible only after 1-3 hours (after intravenous injection, longer duration after oral administration), vitamin K is often overlooked in the acute situation. Early conversant vitamin K treatment, preferably intravenously in severe, life-threatening bleeding, reduces the need for further correction needs to factor concentrates and plasma.
The literature suggests that unresponsiveness to warfarin can continue for 1 week or longer after administration of high-dose (10 mg or greater) vitamin K1. However, there is a lack of supporting data to define the duration and clinical consequences of impaired warfarin response with high doses of vitamin K1 in this setting.

In a case series, 16 four patients receiving indefinite warfarin therapy had received high and, in most cases, repeated doses of vitamin K1 for urgent reversal of therapeutic anticoagulation for an invasive procedure or surgery. The patients displayed impaired warfarin response for 11 days–3.5 weeks after administration of vitamin K1 (10–40 mg). The associated financial burden for the patients was substantial.

Warfarin reversal with vitamin K was successful and facilitated earlier surgery in a study by Tharmarajah et al. 17 The first dose was effective in approximately three quarters of patients. The mean time to surgery in warfarin treated patients not given vitamin K was 111.9 hours; in the intervention group, it was 67.4 hours, giving a mean difference of 44.5 hours (P = 0.01). Vitamin K reduced the PT-INR to less than 2.0 in 74% of patients within 24 hours. There were no complications of vitamin K administration. A dose of vitamin K costs approximately 1/1000 of a hospital bed day cost. A loading dose of warfarin on the second postoperative day took approximately 1 day longer to reach an INR of greater than 2.0 in the intervention patients than in those who had not been given vitamin K.

The advantage in serious bleeding is that the PCC can be administered rapidly (10–15 minutes); for FFP 1–2 hours are needed for blood sampling, blood typing / base test and thawing of FFP. 11–12 A more complete reversal of their anticoagulation is also seen as compared with FFP. Sometimes the recommended plasma dose of 10-15 ml/kg bodyweight is insufficient and doses up to 30 ml/kg bodyweight have been reported. 18–20 Although there are historic concerns regarding potential infectious and thrombotic risks with PCCs, current PCC formulations are much improved. Recombinant activated factor VII is a potential alternative to PCCs, but PCCs are more cost-effective in correcting warfarin-induced coagulopathies.

Empiric treatment with PCC doses according to logarithms adapted to differently prolonged PT-values has been suggested. 15 To compare the efficacy of a "standard" dosage of 20 ml PCC equivalent to about 500 IU factor IX (group A), and an "individualized" dosage based on a target-INR of 2.1 or 1.5, the initial-INR and the patient's body weight (group B) were studied by Schulman. 15 PCC and Vitamin K (10 mg) were administered intravenously. The number of patients reaching the target-INR 15 min after the dosage of PCC was significantly higher in the group treated with an "individualized" dosage, compared to the group treated with a standard dose (89% versus 43%).

A surgical procedure should probably not be performed on patients with a PT-INR level above 1.5. 19 This probably depends on the type of surgery and if regional anaesthesia like spinal or epidural anaesthesia is considered. 20 There are few publications on the optimal PT/aPTT when spinal anaesthesia is safe and national guidelines may differ. Furthermore, there is insufficient evidence available from trials comparing regional versus general anaesthesia to rule out clinically important differences. Regional anaesthesia may reduce acute postoperative confusion but no conclusions can be drawn concerning mortality or other outcomes. 21 A lot of plasma is used to correct high PT-INRs preoperatively to favour spinal anaesthesia – this needs to be further studied.

More patients do get hip protheses initially – half or whole protheses, and this type of surgery bleed more than nailing, plates or compressive screws. 22, 23 With the simpler procedures higher PT-values have been suggested, but are not well studied. Cementing protheses in place seems to reduce pain post-operatively and results in better mobility, but because of the under-reporting of outcomes and the small number of patients involved, no definite conclusions can be made. 24 It is also notable that of all patients with a postoperative hemoglobin level less than 100 g/L, a majority had the most complicated types of fractures and were operated on with a screw and plate fixation, yet only 65% of the patients had blood transfusions. 25 The role of bipolar protheses and total hip replacement is uncertain. Further well-conducted randomized trials are required.

The use of POC testing in critical care patient units has continued to increase since the 1980s. This increase is due to the need for prompt therapeutic interventions that may impact mortality and morbidity, and reduce the overall cost of healthcare for critically ill patients. 26 Many primary care laboratories use POC instruments to monitor patients on anticoagulant treatment. In one study, 27 empirical data from 18 primary care laboratories used the POC instruments Thrombotrack, Coagu-Chek S, or Hemochron Jr. Signature. The total within-lab coefficient of variation was 3.8% and 6.9% for Thrombotrack, Coagu-Chek S, or Hemochron Jr. Signature. The individual agreement with central laboratory test result with coefficient of correlation was found in the range from 0.711 to 0.960. Comparison was less conclusive when PT was expressed in seconds and for aPTT, with significantly shorter clotting times and lower ratios obtained on the POC device. On-site PT (in activity percentage) monitoring would have induced no significant change in FFP transfusion in patients when compared to central laboratory monitoring. Test results were obtained in less than 5 minutes when performed using the POC device versus a median turnaround time of 88 minutes (range: 29-235 minutes) when blood collection tubes were sent to the central laboratory. These results suggest that, in providing a rapid answer, POC-based
V. CONCLUSIONS

The bedside titration of PCC will probably increase the cost benefit of PCC treatment instead of giving a standard dose of PCC. Further studies should focus on, whether a PT-INR goal in hip fracture of >1.8-2 is safe for the surgical procedure (not spinal anesthesia). Also the time necessary to maintain a decreased PT-INR around surgery needs to be studied. Use of POC-PT in the emergency ward and repetitive use in the ward prior to surgery could favor titration of vitamin K doses, also repeated doses. This also holds for optimal PT-control in the immediate postoperative period and in the later warfarin reinstitution phase.

REFERENCES


