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Original Research

Elevated International Normalized Ratio Is Not Associated With Increased Perioperative Morbidity in Podiatric Limb Salvage Surgery: A Retrospective Analysis

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ABSTRACT

The risk of hemorrhage always exists in anticoagulated patients with an elevated international normalized ratio (INR), a risk that must be measured against the necessity for surgical procedures. The objective of the present retrospective medical record study was to assess the safety with which limb salvage procedures can be conducted in patients with an INR >1.4. The medical records of 231 patients who had undergone limb salvage procedures by 1 surgeon at the Yale New Haven Health System from November 2008 through July 2014 were reviewed. All patients were administered foot blocks with monitored intravenous sedation. The patients' demographic data, comorbidities, preoperative anticoagulant use, coagulation profile, intraoperative analgesic administration, estimated blood loss, total operating room time, total postanesthesia care unit time, intraoperative ankle tourniquet use, and postoperative complications within the initial 72 hours were reviewed. We found no differences in intraoperative bleeding, total intraoperative time, or recovery time between the INR <1.4 group (n = 212) and the INR >1.4 group (n = 19). None of the patients experienced any postoperative complications, defined as any cardiac or pulmonary event, the need for invasive monitoring, or admission to the intensive care unit within the initial 72-hour period. Our findings suggest that patients are suitable for undergoing peripheral procedures with foot blocks and monitored intravenous sedation even in the presence of an elevated INR.

The administration of oral anticoagulants is tightly controlled to maintain an appropriate therapeutic margin. Thus, it has been challenging to approximate the ideal level of anticoagulation and the extent to which it should govern or define the indication for treatment. Despite some variation, a recent trend has been veering toward a shift to the lower therapeutic ranges (1). The level of anticoagulation is computed using the prothrombin time and is represented as the international normalized ratio (INR). Various targets of INR for numerous conditions have been suggested (2), indicating more concentrated treatments for patients with an INR within the range of 2.5 to 3.5 in patients with a mechanical heart valve prosthesis (3). Still others have proposed that no substantial reason exists to distinguish among patients and have instead proposed a target INR of 2.0 to 3.0, irrespective of the patient's condition.

From the various previous studies, it was generally agreed that it is necessary to increase vigilance for and avoid high INR values, with a significant association found between the intensity of treatment and the risk of bleeding (1,4–7). Studies, including one conducted in Sweden by Oden and Fahlen (8), demonstrated that a statistically significant increased risk of death from cerebral bleeding exists at INR values of ≥1.5 ($p < .001$). However, at INR values of ≥3.0, no difference was found in the risk of death from all causes compared with the increased risk of death from cerebral bleeding per unit increase of INR value. Furthermore, the target INR was contingent on the nature of the indication for anticoagulation rather than the patient's state of health. Mortality among the patients in that study was lowest at an INR value of 2.2 to 2.3 and increased significantly with correspondingly increasing INR values (8).

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Several studies have also explored the incidence of bleeding in patients with abnormal coagulation test results in various procedures. In the early 1990s, 3 studies assessed the safety profile with which central venous access procedures can be performed in patients with known platelet or coagulation disorders (9–11). In the study by Fisher and Multimer (10), the outcomes of patients with an INR ≥1.5 were assessed for any complications. Only 1 patient reported major bleeding postoperatively due to an unintended arterial puncture, for an event rate of 0.2% (95% confidence interval 0% to 1%). All these cited studies reported that patients with abnormal coagulation profiles could safely undergo central vein cannulation, given the rarity of bleeding complications found in their studies. Similarly, Demeyere et al (12) did not report any abnormal bleeding in 9 of 16 patients who had undergone cardiac surgery without reaching the target INR of ≤1.5. In a review of studies supporting this finding, Segal and Dzik (13) proposed that bleeding predictability using the INR and other abnormal coagulation test results in patients undergoing surgical procedures is limited. The definition of abnormal coagulation test results varied across the studies reviewed, including an elevated prothrombin time, activated partial thromboplastin time, and elevated INR at different cutoff values. A more recent study by Birnie et al (14) in 2013 of the outcomes of patients undergoing pacemaker or defibrillator surgery with bridging therapy with heparin versus uninterrupted warfarin treatment found that the latter group, with a median INR of 2.3, was not associated with any significant adverse perioperative bleeding events. Major thromboembolic and perioperative complications were rare and did not differ significantly between the 2 study groups (14).

In addition to serving as an indicator of an increased risk of bleeding, elevated levels of INR have also been presented as an indicator of a final stage disease. Also, various considerations have been known to affect INR values, including the drug interaction of warfarin with other drugs (8), severe comorbidities (15,16), diarrhea (17), malignancy (15), and malnutrition (18). It is possible that a disruption occurs in coagulation regulation before an elevated INR becomes evident. Jansson et al found an association between elevated levels of thrombomodulin during long-term anticoagulation treatment and an increased occurrence of bleeding (19) and mortality (20). In addition, spontaneous spikes in INR values have often been observed in moribund patients (8).

Therefore, the present study was conducted to assess whether an association exists among postoperative complications, mortality, and bleeding in patients with an elevated INR undergoing podiatric limb salvage surgery. Limb salvage procedures are urgent operations often performed in patients with other medical comorbidities. The risk of thromboembolism must be weighed against the risk of hemorrhage. Most clinicians' preferred normal target is an INR of ≤1.3 before surgery. General anesthesia with controlled airways has been commonly used historically with postoperative follow-up care in critical care units for patients with comorbidities and an American Society of Anesthesiologists (ASA) classification of 3 or 4. Local anesthesia and sedation were found to be safe in a retrospective study by Vadivelu et al (21) of podiatric limb surgery in patients with an ASA classification of 3 or 4. We conducted the present retrospective study to determine whether podiatric limb preservation procedures in patients with an INR >1.4 could be performed safely using local anesthesia and monitored intravenous sedation.

Patients and Methods

After institutional review board approval, the medical records of 275 patients who had undergone limb salvage procedures by 1 surgeon (P.B.) from November 2008 to July 2014 at the Yale-New Haven Hospital were reviewed. Of these 275 patients, 19 had a high (>1.4) INR.

Of the 275 patients, we were unable to retrieve the INR values from the medical records for 44 patients, who were removed from the analysis. Of the remaining patients, 19 had a high (>1.4) INR (group 1) and 212 had an INR <1.4 (group 2). The lower limb salvage procedures included debridement, flap closures, and foot and toe amputations. Patient demographic data, anticoagulant use, preoperative INR level, preoperative coagulation profile, intraoperative analgesic administration, estimated blood loss, total operating room time, total postanesthesia care unit (PACU) time, intraoperative ankle tourniquet use, and complications within a 72-hour postoperative period were compared between the 2 groups. The point of interest for our study was any postoperative complication within the initial 72-hour period, including any pulmonary or cardiac complications such as pulmonary edema, myocardial infarction, stroke, or transfusions secondary to a bleeding event, and admission to the intensive care unit or invasive monitoring. A 2-sample *t* test or Wilcoxon rank sum test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables. All the statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC), and a 2-sided *p* value of < .05 was considered to indicate statistical significance.

Results

A total of 231 patients were included in the analyses of the present study (Table). The demographic characteristics between the 2 study groups were not different, except for age. In the patient group with an INR <1.4 (group 1), the mean age was 58.25 ± 12.63 years versus 73.74 ± 10.35 years in the patient group with an INR >1.4 (group 2; $p < .001$). Of the 212 patients in group 1, 1 (0.51%) had ASA class 1, 12 (6.06%) had ASA class 2, 158 (79.80%) had ASA class 3, and 27 (13.64%) had ASA class 4. In group 2, no patient had ASA class 1 or 2, 15 (78.95%) had ASA class 3, and 4 (21.05%) ASA class 4 ($p = .55$). The median INR in group 1 was 1.0 (interquartile range [IQR] 0.9 to 1.1) and in group 2, was 2.0 (IQR 1.7 to 2.7; $p < .001$). The difference in the median prothrombin time between group 1 (10.9, IQR 10.4 to 11.5) and group 2 (20.3, IQR 18.6 to 23.4) was statistically significant ($p < .001$), as was the median partial thromboplastin time: group 1, 25.7 (IQR 24.2 to 27.7) versus group 2, 31.2 (IQR 29.0 to 39.2; $p < .001$). The preoperative use of warfarin was significantly greater in group 2 with an elevated INR (group 1, median 0.0; IQR 0.0 to 0.0) compared with a median of 4.0 in group 2 (IQR 0.0 to 5.0; $p < .001$). We found no statistically significant differences in the median preoperative aspirin use between groups 1 (median 0.0, IQR 0.0 to 1.0) and 2 (median 0.0, IQR 0.0 to 1.0; $p = .27$) or median clopidogrel (Plavix) use in group 1 (median 0.0, IQR 0.0 to 0.0) versus group 2 (median 0.0, IQR 0.0 to 0.0; $p = .32$).

Despite the elevated INRs, the patients failed to demonstrate increased surgical blood loss or complications. The reported estimated blood loss differed slightly based on the anesthetic record versus the operative report, although both reported minimal blood loss. We recognize that the estimated blood loss is a very subjective and poor determinant of blood loss. However, we included these reported values in our study to demonstrate that the blood loss in these patients was insignificant, with the maximum estimated blood loss reported at 45 mL. Furthermore, no patients required blood transfusions, fresh-frozen plasma, vitamin K, or platelets perioperatively. Most patients in the present study were taking warfarin and/or aspirin for atrial fibrillation and/or numerous comorbidities (i.e., history of stroke, cardiovascular disease). One patient received a pneumatic ankle tourniquet inflated to 250 mm Hg for 24 minutes.

The estimated blood loss according to operative reports in groups 1 and 2 was a median of 8.5 (IQR 0.0 to 15.0) mL and 0.0 (IQR 0.0 to 11.0) mL, respectively ($p = .08$). The median estimated blood loss according to the anesthesia records was slightly greater: 10.0 (IQR 0.0 to 25.0) mL in group 1 and 10.0 (IQR 0.0 to 20.0) mL in group 2 ($p = .73$). No statistically significant difference was found in pneumatic ankle tourniquet use between the 2 groups. Furthermore, no prolonged or significantly different procedure time was found between the 2 groups. The medial total time in the operating room for groups 1 and 2 was 65.0 (IQR 54.0 to 84.0) minutes and 64.0 (IQR 50.0 to 83.0) minutes, respectively ($p = .40$). Similarly, the total recovery time in the PACU did not differ between the 2 groups. The median total PACU time in