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Does international normalized ratio level predict pulmonary embolism?

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Hansen, Patricia; Zmistowski, Benjamin; Restrepo, Camilo; Parvizi, Javad; and Rothman, Richard H, "Does international normalized ratio level predict pulmonary embolism?" (2012). *Rothman Institute Faculty Papers.* Paper 2.
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As submitted to:

Clinical Orthopaedics and Related Research

And later published as:

Does international normalized ratio Level Predict Pulmonary Embolism?

Volume 470, Issue 2, February 2012, Pages 547-554

DOI: 10.1007/s11999-011-2007-7

Running title: **INR Level and PE?**

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Javad Parvizi is a consultant for Stryker Orthopaedics (Mahwah, NJ) and has intellectual properties on SmarTech (Philadelphia, PA); Richard H. Rothman receives royalties and is a consultant for Stryker Orthopaedics (Mahwah, NJ).

Each author certifies that his/her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research

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Abstract (Word count: 249 words)

Background Preventing PE is a priority after major musculoskeletal surgery. There is discrepancy in published data regarding the influence that anticoagulation has on the incidence of PE following joint arthroplasty. The American College of Chest Physicians guidelines recommend administration of oral anticoagulants (warfarin), aiming for an INR level between two and three. However, recent studies show aggressive anticoagulation (INR greater than two) can lead to hematoma formation and increased risk of subsequent infection.

Questions/purposes We asked whether an INR greater than two is protective against PE.

Patients and Methods We identified 9,112 patients with 10,122 admissions for joint arthroplasty between 2004 and 2008. All patients received warfarin for prophylaxis, aiming for an INR level of two or below. Of the 10, 122 admissions, we assessed 609 (6%; 609/10122) for PE using CT, VQ scan, or pulmonary angiography. Of these, 163 patients (1.6%; 163/10122) had a proven PE.

Results Of these 163 patients, 9% (15/163) had an INR greater than two prior to or on the day of work-up compared to 8% (35/446) of patients who were negative. We observed no difference between the INR values in patients with or without PE.

Conclusions We found no clinically relevant difference in the INR values of patients who did or did not develop PE. The risk of bleeding should be weighed against the risk of PE when determining an appropriate target INR for each patient, as an INR less than two may reduce the risk of bleeding while still protecting against PE.

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Level of Evidence: Level III Therapeutic study. See Instructions to Authors for a complete description of levels of evidence.

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Introduction

Pulmonary embolism (PE) is a serious and potentially fatal complication that can develop following total joint arthroplasty (TJA), with an incidence of 1.1 to 1.82% after total knee arthroplasty (TKA) and 0.51 to 0.9% after total hip arthroplasty (THA) [12,18,19]. Patients undergoing TJA are considered to be at higher risk for PE. Prevention of PE following orthopaedic procedures continues to be a priority. For this reason, various scientific groups have devised guidelines for implementation of anticoagulation prophylaxis to minimize this complication [10,11].

In 2008 the American College of Chest Physicians (ACCP) issued updated guidelines regarding postoperative PE prophylaxis in elective hip or knee arthroplasty [10]. These guidelines endorse the use of low molecular weight heparin (LMWH), fondaparinux, or Vitamin-K antagonists to achieve an international normalized ratio (INR) between two and three. These guidelines, however, make the assumption that deep venous thrombosis (DVT) and PE should be treated as the same entity and that the former is likely to lead to the latter. A recently published study discredited this relationship [16]. Further, the ACCP guidelines do not account for the risk or severity of bleeding complications associated with anticoagulation. At an INR of two to three, the incidence of major bleeding complications ranges from 5.0% to 5.6% after TKA and 0.6% to 1.6% after THA [8,9,17]. In those same studies, the rate of minor bleeding complications following TKA and THA reportedly ranges from 21% to 28% and 4.6% to 13.5%, respectively. With the increased risk of bleeding complications, it is important to understand the effectiveness of therapeutic anticoagulation in minimizing PE. We previously demonstrated the low risk of complications with the use of low-dose warfarin (i.e. aiming

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for an INR less than two) for preventing PE [1]. That study was the basis for implementing the use of low-dose warfarin (aiming for an INR less than two) in patients undergoing TJA in 1990.

We therefore asked whether an INR level greater than two, as dictated by the ACCP guidelines, following TJA is protective against PE.

Patients and Materials

From our institutional database we retrospectively identified 9,112 patients who underwent TJA between January 2004 and June 2008 and had at least a single postoperative INR value available. Those patients who underwent work-up for PE yet did not have an INR value on the day of or prior to scan were excluded. During that same time, we treated 9,973 patients with TJA. Therefore, 861 patients were excluded due to lack of complete data, the demographics of these two groups were investigated (Table 1). The 9,112 patients had an average age of 64 years (range, 11-103 years) and had 10,122 admissions for 11,300 procedures (4,727 primary hips, 5,079 primary knees, 803 revision hips, 615 revision knees, and 76 hemiarthroplasties). Patients were followed until discharge from the hospital, on average 6.3 days (range: 2-56 days). Any patients with symptoms indicative of PE were investigated. Since this study observational window ended at discharge, no patients were lost to followup. No patients were recalled specifically for this study; all data was obtained from medical records.

The protocol for anticoagulation at our institution throughout the study period consisted of administration of 1000 IU of intravenous heparin at the time of dislocation of the hip during hip arthroplasty and prior to inflation of the tourniquet during knee arthroplasty.

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In addition, we placed patients on oral anticoagulation (warfarin), aiming for an INR level of two or below. Patients continued on the anticoagulation for a period of six weeks. The institutional guidelines are modeled after the recommendations from the AAOS [11] for prevention of PE after TJA. These guidelines were developed without regard for the prevention of DVT. This conflicts with the recommendations made by the ACCP [10], whose means of PE prevention include prophylaxis against DVT. There were variations based on the risk profile of patients for PE and bleeding. We gave patients at higher risk of PE low molecular weight heparin in addition to oral anticoagulation until their INR level reached therapeutic levels. We considered patients at high risk for PE as those with previous PE, polycythemia vera, and those in a hypercoagulable state. On the other hand, we gave patients at high risk of bleeding aspirin for anticoagulation. We considered patients at high risk for bleeding as those with recent cranio-spinal surgery, active gastric ulcer, and hemophilia. Prophylaxis with warfarin involved administration of the drug on the operative day. We monitored the INR daily while the patient was in the hospital, and dosed warfarin according to their INR level. The mean preoperative INR for the entire cohort of 10,122 admissions was 1.09. The median daily postoperative values for INR were 1.13 (range, 0.67-3.04) on postoperative day (POD) zero, 1.24 (range, 0.6-5.8) on POD one, 1.39 (range, 0.4-7.0) on POD two, 1.32 (range, 0.7-5.3) on POD three, 1.33 (range, 0.9-5.2) on POD four, and 1.41 (range, 0.8-4.3) on POD five (Fig. 1). The proportion of patients with an INR greater than two was 0.7 %, 0.2%, 6.4%, 3.1%, 4.5%, and 8.6% for the POD zero through five, respectively (Fig. 2). We plotted the percentage of patients who had an INR greater than two in the PE positive and PE negative groups against the day of scan, including the five days before and after the scan. The work-up

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92 for PE at our institution followed a standard protocol as well. This protocol underwent
93 some modification over time. In general, we first administered oxygen to patients with
94 hypoxia and monitored them very closely (Appendix). If within five to ten minutes of
95 oxygen therapy hypoxia was not resolved, we imaged these patients for PE, which
96 included multi-detector computed tomography (MDCT), VQ scan and, in rare cases,
97 pulmonary angiography. We evaluated patients with other signs suggestive of PE, such
98 as tachycardia, tachypnea, dyspnea, and so on, thoroughly and, based on the judgment of
99 the evaluating internist, subjected them for PE work-up.

100 From among the 10,122 admissions, 600 patients (609 admissions; 6.0 %) were scanned
101 for PE. This subset had an average age of 69 years (range, 24-96 years) and consisted of
102 424 (73.5%) women. These patients had 710 arthroplasty procedures (194 primary hips,
103 428 primary knees, 38 revision hip, 42 revision knee, and eight hemiarthroplasties) in 621
104 admissions. Following work-up for PE, 163 admissions (163/10,122; 1.6%) were
105 positive for PE and included in the positive PE subgroup. Among the 609 admissions
106 that received work-up for PE, the majority (41.2%; 251/609) were scanned on POD 2
107 (Fig. 1). We assessed their daily INR values to identify any variations in their INR
108 relative to the remaining patients who were negative for PE and the entire arthroplasty
109 cohort. We utilized the Charlson comorbidity index [3], as modified by Deyo et al. [5],
110 to assess comorbidities. This index is adjusted for age. Variables describing differences
111 between PE positive and PE negative patients are reported (Table 2). Furthermore, the
112 same variables are reported for patients with a post-operative INR greater than two versus
113 INR less than two (Table 3).

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To analyze the anticoagulation (INR) levels and confounding variables of the three cohorts we utilized a series of statistical tests. First, the data was tested for normality using the Kolmogorov-Smirnov test. Normal continuous data was assessed using the Student's t-test, and confidence intervals provided clinical significance of variations. Non-normal continuous data was assessed with the Mann-Whitney test, and twenty-fifth and seventy-fifth percentiles were used to represent the variation of data. Chi-squared analysis was used for categorical data. All data analysis was done using SPSS 16.0 (Chicago, IL).

Results

Female gender ($p = 0.04$), body mass index ($p < 0.001$), knee replacement ($p < 0.001$), increasing age ($p < 0.001$), and an increase in age-adjusted Charlson Index ($p < 0.0001$) were risk factors for developing PE (Table 2). Type of arthroplasty (revision versus primary) did not predict development of PE. There were no differences between the confirmed PE positive and confirmed PE negative groups with regards to proportion of patients with an INR greater than two on the day of or prior to the work-up (9.2% in PE positive versus 7.9% in PE negative; $p = 0.55$). On the first day after the scan, the PE negative group tended to have a higher percentage of patients ($p = 0.11$) with an INR greater than two. On post-scan days three, four, and five, there was a higher percentage ($p = 0.009$, 0.0001, and 0.0002, respectively) of PE positive patients with an INR greater than two (Fig.3). Patients with confirmed PE had higher INR on POD five ($p = 0.02$) compared to confirmed PE negative. When aggregating confirmed PE negative patients with patients that were not worked-up, PE positive patients had a higher INR on POD two, three, four, and five ($p = 0.012$, $p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

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Discussion

Pulmonary embolism is a dreaded and life-threatening complication that can develop after TJA, with an incidence of 1.1 to 1.82% following TKA and 0.51 to 0.9% after THA [12,18,19]. The 2008 updated ACCP guidelines regarding postoperative PE prophylaxis in musculoskeletal patients [10], endorsed the use of LMWH, fondaparinux, or Vitamin-K antagonists to achieve an INR between two and three. These guidelines, however, assume that DVT is a proxy for PE. Even more, the ACCP guidelines do not consider the risk of severe bleeding associated with anticoagulation, which ranges from 5.0% to 5.6% following TKA and 0.6% to 1.6% after THA [8,9,17], as well as the risk for minor bleeding complications following TKA and THA (21% to 28% and 4.6% to 13.5%, respectively). Safety and low risk of complications with the use of low-dose warfarin (i.e. aiming for an INR less than two) for preventing PE has been demonstrated [1]. We therefore asked whether an INR level greater than two, as dictated by the ACCP guidelines, following TJA is protective against PE.

This study is limited by a number of issues. First, while the relatively large size of patients undergoing evaluation for PE adds to its strength, some patients in this study may have received work-up for PE following discharge from the hospital that were not disclosed to their treating surgeon. Second, due to the fact that our observational window was focused on in-hospital data only; incidence of PE may be skewed, and PE occurring up to three or more months post-operatively were not captured. Third, due to the retrospective nature of the study, it is not possible to provide an accurate number (although small) of those patients that deviated from the main anticoagulation protocol (i.e. patients with previous PE, polycythemia vera, and those in a hypercoagulable state)

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160 who received an alternate anticoagulation protocol. Fourth, there are no set standards in
161 defining PE and it is plausible that some of the emboli seen on lung scans (MDCT) were
162 fat emboli that could not be distinguished from venous emboli. Fifth, not all patients in
163 this study had pulmonary angiography, which is considered the gold standard for
164 diagnosis of PE. Due to the invasive nature of the test and the costs involved, pulmonary
165 angiography is reserved for only a limited number of patients. Furthermore, not all
166 patients included in this analysis underwent work-up for PE. This led us to separate the
167 cohort into three groups (PE positive, PE negative and not scanned). While we make the
168 assumption that asymptomatic patients were PE negative, this cannot be truly confirmed
169 without invasive work-up. Sixth, this study is only evaluating the efficacy of an INR
170 target (less than two) set at our institution. These results do not exclude the possibility
171 that a lower INR target would be as efficacious at preventing PE.

172 This study highlights some important findings. First, the incidence of PE is low (1.6%)
173 and comparable to literature [14,19] using low-dose warfarin, with no fatal PE during the
174 period of this study. Second, there is no correlation between the level of INR and the
175 development of PE. It appears that PE could develop in any patient, including those with
176 an INR greater than two. These findings raise the possibility that either INR fails to
177 measure the efficacy of warfarin as an anticoagulant or that prophylactic anticoagulation
178 has no effect on the incidence of PE. A study, (130,000 patients), demonstrated that the
179 incidence of PE among patients without anticoagulation prophylaxis (0.12%) is the same
180 as those receiving it (0.095%) [13]. Although, there is a division among the orthopaedic
181 surgeons regarding the most effective modality, they agree that some form of VTE
182 prophylaxis is warranted. Some believe that improvements in surgical and anesthesia

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183 care for patients undergoing TJA have made administration of chemical anticoagulation
184 unnecessary [2].

185 Orthopaedic surgeons consistently take an active role in preventing PE; however, there
186 are key differences between the manner that they and medical physicians approach this
187 complication. First, they observe that 8.9% to 25.6% of TJA patients develop DVT,
188 while only 0.5% to 2.0% developed PE [14,19]. For this reason, the American
189 Association of Orthopaedic Surgeons (AAOS) recommends treating DVT and PE as
190 separate entities. Second, they are committed to minimizing bleeding complications in
191 their surgical patients; these can be as devastating to patients as PE [15]. A study
192 comparing low-dose warfarin with a target INR of 1.5 to two with a historical control
193 group with a target INR of two to three, found no difference in the incidence of DVT, PE,
194 or death [4,7]. Expectedly though, a higher incidence of bleeding complications occurs
195 in the higher target INR group. Major bleeding complications can be a foundation for
196 infection, wound healing problems, functional disability, and prosthetic loosening [7].
197 All of these consequences can lead to reoperation and increase in morbidity and
198 mortality. Third, pneumatic compression boots and aspirin, along with regional
199 anesthesia, are suggested as being non-inferior to chemoprophylactic anticoagulants at
200 preventing PE without the increased bleeding complications [6]. Interestingly, potent
201 anticoagulants like warfarin and LMWH are associated with increased all-cause mortality
202 rates, including PE, when compared to pneumatic compression boots and aspirin [20]. It
203 is from this point of view that the AAOS created the guidelines stating that patients at a
204 standard risk of both PE and bleeding can be given aspirin, LMWH, synthetic
205 pentasaccharides, or warfarin to reach an INR goal of less than or equal to two [11]. A

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previous prospective study from this institution that involved performing preoperative and postoperative VQ scans in a consecutive series of patients undergoing TJA found that low dose warfarin (with an INR goal of less than two) is effective at minimizing development of PE, with a low (2.4%) bleeding complication [1]. Based on these findings, we have used low-dose warfarin as a prophylaxis for prevention of PE in our patients over the last two decades.

The most pertinent finding of this study is that an INR greater than two does not appear to protect against PE. Thus, implementing the recommendations of ACCP [10] in aiming for an INR greater than two may not protect these patients against PE, while exposing them to the undue risk of bleeding and all untoward consequences that may ensue [8,9]. Despite the limitations, we believe our data and that in the literature casts doubt on the belief that administration of aggressive anticoagulation can and does protect patients against development of PE.

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Legends

Fig. 1 Graph shows median INR versus day of surgery (columns, left axis) and histogram displaying PE work-up day of scan relative to POD (area curve; right axis). POD two was the maximum day of scans for both positive and negative PE patients.

Fig. 2 Graph shows percentage of patients with INR greater than two from preoperative to POD five.

Fig. 3 Graph shows percentage of patients with INR greater than two by day of scan (lines; right axis), as well as median INR related to the day of scan (columns; left axis). Day of scan is 0, the five days before the scan is in reverse chronological order as -1 through -5, and the five days after the scan is days 1 through 5. Displays median values between positive PE and negative PE patients. On the day of scan, there was no difference ($p = 0.63$) between INR values. PE positive patients had higher INR values on post-scan days three, four, and five ($p = 0.009$, $p < 0.001$, and $p < 0.001$, respectively).

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