Uncomplicated Removal of Epidural Catheters in 4365 Patients With International Normalized Ratio Greater Than 1.4 During Initiation of Warfarin Therapy

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Background and Objectives: Current guidelines from the American Society of Regional Anesthesia state that an international normalized ratio (INR) of 1.4 is the upper limit of warfarin anticoagulation for safe removal of an epidural catheter. However, these guidelines are based primarily on expert consensus, and there is controversy regarding this recommendation as being "too conservative."

Methods: Prospective (3211) and retrospective (1154) patients undergoing total joint replacement followed by daily warfarin thromboprophylaxis were enrolled in this observational study. All nonsteroidal anti-inflammatory drugs and anticoagulants were held before surgery, and all patients had normal coagulation test results before surgery. Patients were followed twice a day by the acute pain service, no other anticoagulants except nonsteroidal anti-inflammatory drugs were administered, and epidural analgesia was discontinued per institutional protocol. Only patients with INR greater than 1.4 at the time of removal of epidural catheter were included. Neurologic checks were performed for 24 hrs after removal.

Results: A total of 4365 patients were included, and 79% underwent knee replacement and 18% hip replacement. Mean age was 68 yrs, and mean weight was 81 kg. Mean (SD) duration of epidural analgesia was 2.1 (0.6) days. Mean (SD) INR at the time of epidural removal was 1.9 (0.4), ranging from 1.5 to 7.1. No spinal hematomas were observed (0% incidence with 95% confidence interval, 0%–0.069%).

Conclusions: Our series of 4365 patients had uncomplicated removal of epidural catheters despite INRs ranging from 1.5 to 5.9. Removal was only during initiation of warfarin therapy (up to approximately 50 hrs after warfarin intake) when several vitamin K factors are likely to still be adequate for hemostasis.

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Postoperative epidural analgesia has been demonstrated to provide superior analgesia to systemic opioids and may improve postoperative outcomes in selected patients and surgical procedures.[1,2] However, duration of postoperative epidural analgesia may be limited in some patients owing to planned anticoagulation for thromboembolism prophylaxis. Adjusted dose warfarin is the most common agent used for thromboembolism prophylaxis after total knee and hip replacement surgery,[3] and these are common procedures with approximately 680,000 and 437,000, respectively, performed annually in the United States alone (http://hcupnet.ahrq.gov/HCUPnet.jsp?Id=5739CB0D61A04FBB&Form=MAINSEL&JS=Y&Action=%3E%3ENext%3E%3E&_MAINSEL=NationalStatistics; accessed December 6, 2010). It is currently controversial when it is safe or necessary to remove an indwelling epidural catheter after initiation of thromboembolism prophylaxis with warfarin. This is an important consideration as early termination of the epidural catheter may deprive the patient of superior analgesia and postoperative recovery,[4] particularly within the first 48 hrs after surgery.[5] Conversely, unnecessary efforts to reverse anticoagulation to normalize coagulation before removal of the epidural catheter disrupts thromboembolism prophylaxis and may expose the patient to unnecessary blood products such as fresh frozen plasma. Current guidelines from the American Society of Regional Anesthesia (ASRA) state that an international normalized ratio (INR) of 1.4 is the upper limit of warfarin anticoagulation for safe removal of an epidural catheter,[3] which may discourage use of epidural analgesia for postoperative analgesia after total joint replacement. However, these guidelines are based on expert consensus without substantial data, and the guidelines specifically state that there is controversy regarding this recommendation as being "too conservative." Indeed, a recent clinical study demonstrated poor correlation between INR and factor VII levels during initiation of warfarin thromboembolism prophylaxis with continued maintenance of adequate levels for hemostasis despite INR greater than 1.4.[6] An accompanying editorial to this study suggested that the ASRA guidelines be reevaluated[7] followed by a letter to the editor suggesting that further evidence was still required.[8] Specifically, the primary study did not document actual removal of epidural catheters in a large number of patients with INR greater than 1.4. It is a long-standing standard clinical practice at our institutions to remove epidural catheters with INR greater than 1.4 during the early days of warfarin thromboembolism prophylaxis. Thus, we performed this observational, multi-institutional, surveillance study for clinically evident spinal hematoma in patients who had removal of epidural catheters with INR greater than 1.4 to document the suggested data regarding risk-benefit of epidural catheter removal during warfarin therapy.

METHODS

Institutional review board approval was acquired from the Hospital for Special Surgery, Rush University Medical Center, and Thomas Jefferson University. Waivers for individual written consent were granted by the institutional review boards because clinical care and data collection were routine, risk from documentation of our standard care was considered minimal, and it

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TABLE 1. Perioperative Characteristics

	Total (n = 4365)	HSS (n = 1617)	Rush (n = 1594)	TJU (n = 1154)
Age, yrs	68 ± 12	70 ± 10	66 ± 13	67 ± 11
Sex, F/M	2991/1374	1141/476	1110/484	740/414
Weight, kg	81 ± 19	80 ± 18	79 ± 19	86 ± 18
Total knee replacement, n	3486	1617	774	1095
Total hip replacement, n	800	0	770	30
Other surgery	79	0	50	29
Epidural needle				
Tuohy 17 gauge, n	2338	744	1594	
Weiss 17 gauge, n	873	873		
Hustead 18 gauge, n	1154			1154
Epidural catheter 20 gauge, n	4365	1617	1594	1154
No. attempts to place epidural (median/mode)	n/a	1/1	n/a	n/a
Duration of epidural catheter, d	2.1 ± 0.6	2 ± 0.2	2.2 ± 0.7	1.9 ± 0.1

Values are mean ± SD unless otherwise stated.

HSS indicates Hospital for Special Surgery; Rush, Rush University Medical Center; TJU, Thomas Jefferson University Medical Center.

was considered impractical to individually consent the 4365 patients that were included in this survey. A total of 1617 consecutive patients were prospectively enrolled from the Hospital for Special Surgery from August 2007 to May 2010, 1594 consecutive patients from Rush from January 1998 to June 2010. One thousand one hundred and fifty-four had data retrospectively collected from Thomas Jefferson from January 1998 to June 2007. Inclusion criteria were patients undergoing total knee or hip replacement surgery with postoperative epidural analgesia, thromboprophylaxis with warfarin, daily measurement of INR, and subsequent removal of epidural catheter with INR greater than 1.4. Perioperative data were collected including patient demographics, surgical procedure, and INR at the time of removal of the epidural catheter.

At the Hospital for Special Surgery, only patients undergoing total knee replacement were enrolled because warfarin is consistently administered only for this procedure. At Rush and Thomas Jefferson universities, both total hip and knee replacement patients were enrolled. At the Hospital for Special Surgery and Rush, nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin were discontinued for a week before surgery. At Thomas Jefferson, NSAIDs were continued before surgery. Other anticoagulants were discontinued at an appropriate time before surgery to allow normalization of coagulation tests by the day of surgery. Postoperatively, at the Hospital for Special Surgery and Rush, warfarin was administered based on a daily nomogram designed to achieve an INR between 1.8 and 2.5 by postoperative day (POD)4.[9] Warfarin was administered beginning the night of surgery, and the mean daily dose was 4.1 to 4.2 mg. At Jefferson, a different nomogram was used in which 10 mg warfarin was administered beginning the night of surgery, no warfarin was administered on POD1, and then a nomogram-based dose was administered to achieve an INR of 2.[10] No other anticoagulants except NSAIDs were allowed. Blood was drawn

TABLE 2. Anticoagulation Test Results and Number of Epidural Catheters Removed Per Day

	POD1	POD2	POD3
International normalized ratio			
Total	1.7 ± 0.3 (1.5–3.5)	1.9 ± 0.4 (1.5–5.9)	1.8 ± 0.4 (1.5–7.1)
HSS	1.2 ± 0.1 (1.5–3.5)	1.9 ± 0.5 (1.5–5.9)	2.1 ± 0.8 (1.5–7.1)
Rush	1.6 ± 0.1 (1.5–2.0)	1.7 ± 0.2 (1.5–4.6)	1.8 ± 0.3 (1.5–3.9)
TJU	2.1 ± 0.4 (1.7–2.3)	1.8 ± 0.4 (1.5–4.9)	n/a
Prothrombin time, sec			
HSS	11.5 ± 1.2	18 ± 6.1	20.8 ± 9.7
Partial thromboplastin time, sec			
HSS	29.6 ± 15	43 ± 9	37 ± 8.9
Platelet count, n/nL			
HSS	220 ± 65	196 ± 63	206 ± 77
No. epidural catheters removed			
Total	40	4090	140
HSS	5	1595	12
Rush	34	1342	128
TJU	1	1153	0

All values are mean ± SD (range).

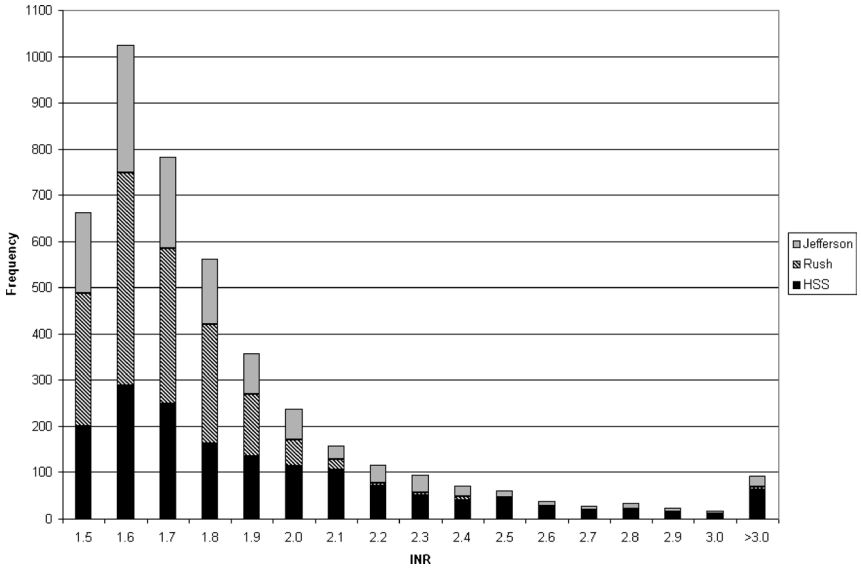

FIGURE 1. Histogram displaying distribution of international normalized ratio (INR) between institutions at the time of epidural catheter removal. HSS indicates Hospital for Special Surgery; Jefferson, Thomas Jefferson University; Rush, Rush University Medical Center.

for routine laboratory processing every morning. Our laboratory reference range for prothrombin time is 9.4 to 11.6, and that for INR is 0.8 to 1.2. Patients are evaluated by the acute pain service at least twice a day and undergo physical therapy twice a day per a clinical pathway. As part of the clinical pathway, the epidural is typically discontinued on POD2 at noon (approximately 36 hrs after warfarin intake) at the Hospital for Special Surgery, POD2 in the morning at Jefferson, and on POD3 at 7:00 AM (approximately 50 hrs after warfarin intake) at Rush. At Hospital for Special Surgery, floor nurses may remove the epidural for INR of 1.4 or less. The acute pain service attending removes epidural catheters for INR greater than 1.4. At Rush and Jefferson, all epidural catheters are removed by the acute pain service nurse. For all institutions, neurologic checks are performed every 2 hrs (including at night) for the next 24 hrs for all patients with INR greater than 1.4. Additional prospective data collection included type of epidural needle and catheter, traumatic placement, and daily coagulation tests.

Statistical Analysis

Descriptive statistics were planned with the incidences and 95% confidence intervals (CIs). The primary outcome was incidence of epidural hematoma after removal of the epidural catheter in the presence of an INR greater than 1.4. Because the observed incidence was 0%, we applied the 3/n formula to estimate an upper 95% CI for an observed incidence of 0%.[11]

RESULTS

A total of 4365 patients were included, and 79% underwent knee replacement and 18% underwent hip replacement (Table 1). Mean age was 68 yrs, and mean weight was 81 kg. Mean (SD) duration of epidural analgesia was 2.1 (0.6) days. Mean (SD) INR at the time of epidural removal was 1.9 (0.4), ranging from 1.5 to 5.9 (Table 2 and Fig. 1). Other coagulation tests were only available from the Hospital for Special Surgery. At the Hospital for Special Surgery, 87% of patients received NSAIDs during warfarin therapy. At Rush, all enrolled patients received a COX-2 inhibitor in addition to warfarin starting from 2004 (56% of patients). At Thomas Jefferson, all patients received either an NSAID or a COX-2 inhibitor in addition to warfarin. No spinal hematomas were observed (0% incidence with 95% CI, 0%–0.069%).

DISCUSSION

In our observational series of 4365 patients, we observed a 0% incidence (95% CI, 0%–0.069%) of clinically evident spinal hematoma after removal of epidural catheters despite INR values from 1.5 to 7.1. Specific aspects of our clinical protocol may have contributed to this null observation. All epidural catheters were removed during initiation of warfarin therapy, concomitant anticoagulants except NSAIDs were withheld, and neurologic checks were performed for the subsequent 24 hrs. Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors have reversible antiplatelet activity, and concurrent use of these agents was allowed in 87% to 100% of our patients as a multimodal analgesic. The ASRA guidelines consider NSAIDs and COX-2 inhibitors to confer a low risk for spinal hematoma when used by themselves but do warn that data on combinations of anticoagulants are lacking.[3] The pharmacology of warfarin has been well described.[3,6] Briefly, warfarin is the most common vitamin K antagonist in clinical use. Warfarin inhibits protein C and factors II, VII, IX, and X. Factor VII has the shortest half-life of 6 to 8 hrs, whereas the other factors' half-lives range from 24 to 80 hrs on average. For effective anticoagulation, plasma levels of vitamin K factors have to be decreased to approximately 20% of normal.[12] For individual factors, levels are typically decreased to 5% for factor VII, 20% for factor IX, and 30% for factor X for effective anticoagulation.[13] During initiation of warfarin therapy, the INR is highly dependent on levels of factor VII owing to its short half-life and is often quite labile. A recent study found weak to modest correlation (R^2 = 0.3–0.6) between factor VII activity and INR during the first 3 days of warfarin therapy after total joint replacement.[6] Furthermore, it is likely that other vitamin K factor levels, especially factors II and X, remain adequate despite increases in INR during the first 48 hrs of initiation of warfarin therapy.[3] Therapeutic

anticoagulation requires reduction of levels of factor II (half-life 48–120 hrs) and factor X (half-life 20–42 hrs), which requires 4 to 6 days.[14] Overall, an elevated INR during initiation of warfarin therapy may not accurately indicate anticoagulation. Such discordance during initiation may provide an inherent safety margin for removal of epidural catheters. Of note, these findings only apply to initiation of warfarin. During discontinuation, the normalization of INR reflects rapid recovery of factor VII, whereas other factors with longer half-lives may not have recovered.[3]

The ASRA guidelines recommend that epidural catheters not be routinely removed if the INR is greater than 1.4 during initiation of warfarin therapy. In such cases, the catheter may be cautiously removed followed by neurologic checks or the warfarin held, particularly if the INR is greater than 3.[3] Notably, the guidelines also state that such recommendations are controversial and that few data exist regarding patients with indwelling epidural catheters that are subsequently anticoagulated with warfarin.[3] There is 1 series of 1000 lumbar anesthetics performed in patients receiving preoperative oral anticoagulants; however, coagulation status at the time of epidural catheter removal was not reported.[15] A combined series of 651 patients receiving warfarin reported no spinal hematomas after epidural catheter removal with a mean INR of 1.4.[16,17] Finally, a set of 1030 patients undergoing total knee replacement had epidural catheters removed without complications despite a mean INR of 1.5.[18] There are currently 2 published case reports describing development of a spinal hematoma after removal of an epidural catheter during warfarin therapy,[19,20] and neither were managed in a similar fashion to our protocol. One patient had her epidural catheter removed when her INR was 6.3. The other patient did not have their epidural catheter removed until after 4 days of warfarin therapy. The stated premise for concern with epidural catheter removal is the potential for the removal process to cause vascular trauma[21] or dislodge a preexisting clot.[22] These considerations are possible; however, epidural catheters may also spontaneously move or become dislodged while awaiting normalization of INR. Furthermore, unnecessary efforts to reverse anticoagulation to normalize coagulation before removal of the epidural catheter disrupt thromboembolism prophylaxis and may expose the patient to unnecessary blood products such as fresh frozen plasma.

Epidural catheters were removed without complications in 89 patients with INR greater than 3. Such an INR value is greater than the typical target for thromboembolism prophylaxis (1.8–2.5) and reflects the lability of warfarin dosing and INR. Warfarin has a narrow therapeutic range and is affected by multiple factors. Patient age, female sex, ethnicity, lower patient weight, liver, cardiac, and renal disease all affect response to warfarin.[3] In addition, there are more than 250 drugs that interact with warfarin including cardiovascular drugs.[23] In patients with enhanced response to warfarin, it may be especially desirable to perform neurologic monitoring after removal of epidural catheters to quickly diagnose and treat an epidural hematoma.

Finally, estimation of incidences of uncommon events after observation of a zero numerator is imprecise. We used a commonly recommended modification of a Poisson distribution (3/n formula) to provide a conservative estimate of maximal risk as noted by upper 95% CI.[11] With this formula, as the n becomes larger, the estimate for 95% CI approaches an exact Poisson solution. Alternative estimates of risk may be calculated by using different frequency distributions (eg, 95% CI of 0.08% with binomial distribution) or more stringent CIs (eg, 99% CI of 0.1% with the 4.6/n formula).[11]

In conclusion, our series of 4365 patients noted uncomplicated removal of epidural catheters during initiation of warfarin therapy despite INRs ranging from 1.5 to 7.1. Our findings do not necessarily contradict the ASRA guidelines because we followed recommendations to cautiously remove catheters and to perform subsequent neurologic checks.

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REFERENCES

1. Liu SS, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. *Anesth Analg*. 2007;105:789–808.
2. Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth Analg*. 2007;104:689–702.
3. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64–101.
4. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology*. 1999;91:8–15.
5. Ilfeld BM, Mariano ER, Girard PJ, et al. A multicenter, randomized, triple-masked, placebo-controlled trial of the effect of ambulatory continuous femoral nerve blocks on discharge-readiness following total knee arthroplasty in patients on general orthopaedic wards. *Pain*. 2010;150:477–484.
6. Benzon HT, Avram MJ, Benzon HA, Kirby-Nolan M, Nader A. Factor VII levels and international normalized ratios in the early phase of warfarin therapy. *Anesthesiology*. 2010;112:298–304.
7. Butterworth JFT, Rathmell JP. Standard care, standards for care, or standard of care? *Anesthesiology*. 2010;112:277–278.
8. Horlocker TT, Heit JA, Wedel DJ, Enneking FK, Rowlingson JC. Safe epidural catheter removal in the patient receiving warfarin: does anybody really know what (prothrombin) time it is? *Anesthesiology*. 2010;113:759–761; author reply 761.
9. Asnis PD, Gardner MJ, Ranawat A, Leitzes AH, Peterson MG, Bass AR. The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. *J Arthroplasty*. 2007;22:213–218.
10. Vives MJ, Hozack WJ, Sharkey PF, Moriarty L, Sokoloff B, Rothman RH. Fixed minidose versus-adjusted low-dose warfarin after total joint arthroplasty: a randomized prospective study. *J Arthroplasty*. 2001;16:1030–1037.
11. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA*. 1983;249:1743–1745.
12. Loeliger EA. The optimal therapeutic range in oral anticoagulation. History and proposal. *Thromb Haemost*. 1979;42:1141–1152.
13. Xi M, Beguin S, Hemker HC. The relative importance of the factors II, VII, IX and X for the prothrombinase activity in plasma of orally anticoagulated patients. *Thromb Haemost*. 1989;62:788–791.
14. Trask AS, Gosselin RC, Diaz JA, Dager WE. Warfarin initiation and monitoring with clotting factors II, VII, and X. *Ann Pharmacother*. 2004;38:251–256.

15. Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. *Anaesthesia*. 1983;38:254–259.
16. Horlocker TT, Wedel DJ, Schlichting JL. Postoperative epidural analgesia and oral anticoagulant therapy. *Anesth Analg*. 1994;79:89–93.
17. Wu CL, Perkins FM. Oral anticoagulant prophylaxis and epidural catheter removal. *Reg Anesth*. 1996;21:517–524.
18. Parvizi J, Viscusi ER, Frank HG, Sharkey PF, Hozack WJ, Rothman RR. Can epidural anesthesia and warfarin be coadministered? *Clin Orthop Relat Res*. 2007;456:133–137.
19. Woolson ST, Robinson RK, Khan NQ, Roqers BS, Maloney WJ. Deep venous thrombosis prophylaxis for knee replacement: warfarin and pneumatic compression. *Am J Orthop (Belle Mead NJ)*. 1998;27:299–304.
20. Badenhorst CH. Epidural hematoma after epidural pain control and concomitant postoperative anticoagulation. *Reg Anesth*. 1996;21:272–273.
21. Janis KM. Epidural hematoma following postoperative epidural analgesia: a case report. *Anesth Analg*. 1972;51:689–692.
22. Helperin SW, Cohen DD. Hematoma following epidural anesthesia: report of a case. *Anesthesiology*. 1971;35:641–644.
23. Harder S, Thurmann P. Clinically important drug interactions with anticoagulants. An update. *Clin Pharmacokinet*. 1996;30:416–444.

