Comparison between Critical Pathway Guidelines and Management of Deep-Vein Thrombosis: Retrospective Cohort Study

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Aim. To compare the key steps of standard deep-vein thrombosis management with the critical pathway practice guidelines, and to assess the outcome of the treatment after 6 months.

Method. This retrospective cohort study (from January 1, 1997 to December 31, 1998) included 172 patients with uncomplicated deep-vein thrombosis of lower extremities, consecutively admitted via emergency room. The data were collected from the entry register in emergency room and from medical charts. The outcome of therapy was assessed 6 months after the acute event.

Results. A bolus dose of heparin was administered to 81 (46%) patients. The recommended initial heparin infusion rate at 1250 U/h was employed in only 26 (15%) patients. Time to activated partial thromboplastin time >60 s was met in 29 (17%) patients. All patients but one received heparin therapy longer than 96 h. The recommended time to a therapeutic international normalized ratio of less than 120 h was achieved in 134 (78%) patients, but the average length of a stay in the hospital exceeded the recommended 5.5 days by 86%. Six months later, compressive ultrasonography revealed 44 (28.9%) cases of complete vein obstruction, 67 (44.1%) cases of partial recanalization and 41 (27%) cases with a normal finding. Recurrent thrombosis developed in 16 patients (10.5%) and acute pulmonary embolism in 4 (2.6%) patients.

Conclusion. Our results considerably differ from the critical pathway guidelines, mainly due to lower initial heparin doses and longer diagnostic assessment of thrombosis etiology. Our approach to deep-vein thrombosis was between the critical pathway guidelines and the conventional regimen. The clinical outcome in our series did not differ significantly from that after the conventional way of treatment.

Key words: anticoagulants; heparin; international normalized ratio; partial thromboplastin time; pulmonary embolism; thromboembolism; thrombolytic therapy; treatment outcome; venous thrombosis; warfarin

The incidence of thrombosis increases sharply with age, from 1 per 100,000 people per year in childhood to nearly 1% per year in elderly (1-4). Major complications of leg deep-vein thrombosis are a disabling post-thrombotic syndrome and acute death from a pulmonary embolism, which occur in 20% and 1-2% of patients, respectively (2).

The practice of managing deep-vein thrombosis evolved from 10-day heparin regimen to short hospitalization (5). These varying practices were favorable for the introduction of clinical algorithms with the purpose to increase efficiency of care and reduce hospital stay (6).

In 1996, Pearson et al (7) published the critical pathway practice guidelines for deep-vein thrombosis as day-to-day recommendations for diagnostic and therapeutic management for this disease.

The aim of our study was to compare the performance of the key steps and processes in the clinical management of deep-vein thrombosis in our institution with the critical pathway guidelines. We wanted to detect possible deviations from this algorithm, as well as their causes. The follow-up examination, at which the outcome of treatment was assessed, was performed 6 months after the acute event. Similar evaluation was conducted in the institution that proposed the critical pathway guidelines and was reported by Schoenberger et al (8).

Patients and Methods

The authors of the critical pathway (7) gave six recommendations to improve the efficiency of deep-vein thrombosis treatment:'1) all acutely hospitalized patients should receive an initial heparin bolus in the emergency
There were 32 cases of recurrent thrombosis. Popliteal level, and 42 had multilevel thromboses). In the calf, whereas 127 patients had proximal vein.

58.7±11.8 years. The average age of 172 patients (79 men and 93 women) who met the eligibility criteria was 58.7±11.8 years.

In 45 patients (26%), the clot was located only in the calf, whereas 127 patients had proximal vein thrombosis (33 at the femoral and 52 at the popliteal level, and 42 had multilevel thromboses). There were 32 cases of recurrent thrombosis.

The average acute bolus dose was 6,297±3,439 U; 81 (46%) patients received 7,500 U of heparin or more, whereas 23 (13%) did not receive a heparin bolus at all (Table 1).

The initial heparin infusion rate therapy was 924±247 U/24 h, 35% bellow the recommended dose (Table 1). The addition of acute bolus rates gave the average value of the whole amount of received heparin at 17,389±4,836 U/12 h. Only 26 patients (15%) received more than 1,250 U in 24 h (Table 1). The coefficient of correlation between the initial heparin dose in 12 h and aPTT after 12 h was 0.752 (p=0.001). Mean aPTT after 12 h of heparin administration was 38±17 s. Only 28 (16%) patients attained aPTT>60 seconds after 12 h (Fig. 1).

There was a significant difference in the initial heparin rates (U/h) in patients at increased risk of bleeding (hypertension) and other patients (873±168 vs. 992±311 U/h; p=0.004).

The mean duration of heparin therapy was 139±54 h, 70% longer than recommended by the critical pathway guidelines (Table 1).

Time to the first INR between 2 and 3 was 111±25 h, the only goal we achieved. This result was achieved in 133 patients before 120 h of therapy. The mean length of hospital stay was 10±3.5 days, almost as twice as aimed by the algorithm (Table 1).

Age showed significant individual correlation with the initial heparin dosage as the criterion variable (r²=0.27; p<0.001), accounting for less than one third of its variability. Hypertension improved the coefficient of correlation to 0.34 (p<0.001).

All patients were discharged from the hospital alive. There was a single case of major bleeding, which stopped after discontinuation of heparin and use of protamine sulphate. Heparin-induced thrombocytopenia was not observed. Acute pulmonary embolism was suspected in 3 patients during the hospital stay, but the diagnosis was rejected by negative lung scans in 2 cases, whereas in the third patient pulmonary angiogram was negative. There were 2 cases of extended thrombosis during the course of heparin therapy, and both were confirmed by contrast venography (Table 2).

| Table 1. Achievement of 6 steps of the critical pathway in 172 patients with deep-vein thrombosis |
| Key steps | Goal¹ | Mean±SD | Goal achieved; No. (%) |
| Heparin bolus rate (U) | >7,500 | 6,297±3,439 | 81 (46) |
| Initial heparin rate (U/h) | 1,250 | 924±247 | 26 (15) |
| APTT² (s) | >60 | 38±17 | 29 (17) |
| Heparin therapy (h) | >96 | 139±54 | 172 (99) |
| Time to therapeutic INR³ (h) | <120 | 111±25 | 134 (78) |
| Length of hospital stay (days) | 5.5 | 10.2±3.4 | 2 (1.2) |

¹According to ref 7. 
²aPTT – activated partial thromboplastin time. 
³INR – international normalized ratio.
The patients were followed for 6 months during the warfarin therapy. INR was monitored at regular monthly intervals or more frequently, if necessary. Thirteen patients (7.6%) died (10 from cancer, 1 patient from intracerebral hemorrhage (INR at admission=2.3), 1 from acute pulmonary embolism, and 1 from myocardial infarction). Three patients were lost to follow-up; they moved and were inaccessible. There were 9 cases of major bleeding, which were treated with vitamin K and fresh frozen plasma. Warfarin therapy was discontinued in 4 patients. That left 152 patients for follow-up examination.

Sixteen patients (10.5%) developed recurrent thrombosis during the anticoagulation therapy, documented by contrast venography. Four (2.6%) patients developed pulmonary embolism (3 were proven by lung scans, 1 by autopsy) (Table 2). The follow-up examination after six months was performed by compressive ultrasonography. There were 44 (28.9%) cases of complete obstruction and 67 (44.1%) cases of partial recanalization, and in 41 (27%) cases the finding was normal. Thirteen (8.6%) patients complained of at least two symptoms suggestive of postthrombotic syndrome: pain, cramps, heaviness, pruritus, and paresis in the affected limb.

Discussion

One of the main goals of the critical pathway guidelines is to shorten the time necessary to attain therapeutic level of aPTT (>60 s in 12 h). As this was achieved in only 29 patients (17%), it was obvious that initial heparin dosage was too low to achieve therapeutic level of anticoagulation. In our institution, acute bolus administration of heparin in emergency room is uncommon. This practice is not given great importance, because the usual time interval from the establishment of deep-vein thrombosis to admittance to the hospital ward ranges from 5 to 10 minutes. The average bolus dose (629±3439 U; range from 0 to 10,000 U) was higher than 5,385±1,775 U, reported by Schoenenberger et al (8). The heparin underdosage was the major shortcoming of our deep-vein thrombosis management. The initial heparin infusion rates (924±247 U/h) were on the average 35% lower than the recommended dosage of 1,250 U/h or dosages obtained by the use of weight-derived nomogram. Schoenenberger et al (8) also reported the initial heparin rates 25% below the recommended ones.

APTT achieved after 12 hours of heparin treatment in our study was far below the targeted >60 seconds. This was obviously due to the lower initial heparin therapy. The attainment of appropriate aPTT is, among other things, an important goal because it signals the proper timing for the initiation of oral anticoagulant therapy (7).

The explanation for the difference can be, at least partially, due to low initial heparin rates in patients with co-morbid states, such as hypertension or advanced age. This subset of patients was treated with significantly smaller rates (873±168 IU/h) of heparin. In our opinion, cautious approach of an attending physician to the patients at high risk of serious bleeding was justified. As delays in achieving appropriate aPTT are reported to increase the probability of recurrent thrombosis or clot extension (15,16), 37 patients (21%) in our study, who achieved targeted aPTT, were well below the recommended practice. Schoenenberger et al (8) also reported that 2/3 of their patients did not attain targeted aPTT.

On the other hand, a single case of major bleeding (gastrointestinal bleeding), a thrombus extension in only 2 patients, and absence of pulmonary embolism, all indicate that, in our setting, careful approach was appropriate, at least regarding acute complications.

<table>
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<tr>
<th>Deep-vein thrombosis</th>
<th>Complications (No, %)</th>
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<tr>
<td></td>
<td>Recurrent deep-vein thrombosis</td>
</tr>
<tr>
<td>Acute</td>
<td>172</td>
</tr>
<tr>
<td>Follow-up (after 6 months)</td>
<td>152</td>
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Heparinization time in our patients was longer by 45% than the recommended value (7).

The conventional approach, developed 30 years ago, recommends 10 days of heparin therapy, with the introduction of warfarin on the 5th day to ensure that therapies overlap for several days (17,18). In our study, heparin therapy lasted 5-7 days, and the initiation of warfarin therapy was delayed for 2-3 days, falling somewhere between the conventional regimen and the critical pathway guidelines (7).

Our patients were advised to start walking on the 3rd day of heparin therapy, as opposed to the critical pathway guidelines for ambulation which recommend the start of walking after 24 hours. Keeping in mind the delay in attainment of adequate aPTT, this advice to patients might have been appropriate.

The concept that the antithrombotic effect of warfarin reflects its ability to lower prothrombin levels, provides a rationale for overlapping heparin with warfarin in the treatment of patients with thrombotic disease, until the factor II level is reduced to the therapeutic range. Given that factor II has a half-life of about 60 hours, an overlap of at least 4 days is necessary (19).

The period for initiating warfarin therapy in our patients was 48-72 hours longer on the average than the recommended value (7), and can be explained by common practice of initiating oral anticoagulants after a few days of heparin therapy. The time interval to therapeutic INR 2-3 was within the recommended limits (7). To reach therapeutic levels quickly without a significant risk to the patients, the critical pathway guidelines recommend an initial dosage regimen of 7.5 mg of warfarin per day for the first 2 days, after which a maintenance dosage may be tailored, based on daily INR results, to meet the needs of each patient in particular (7). The loading dose in our study was 9 mg of warfarin in about 2/3 of patients, and 7.5 mg in the rest of them. This explained the slightly shorter time interval to a full anticoagulation than proposed by the critical pathway guideline (7). The loading dose in 12 patients with hypertension in our study was 6 mg of warfarin, to avoid the risk of bleeding (18,19).

Longer stay in hospital was due to the diagnostic work-up to detect the potential cause of thrombosis (abdominal scan, gynecological examination, urologist consultation, etc.) and, more often, due to the treatment of underlying disease (6).

The 10.5% cumulative incidence of recurrent deep-vein thrombosis after 6 months was higher than the 8.6% rate reported by Prandoni et al (20), possibly due to the higher initial heparin dosages in their study. The incidence of major bleeding was 0.6% (1/172 patients) during the acute phase, compared to 1.6% (6/355 patients) incidence of major bleeding in their study (20). In another study, the similar group of patients had slightly lower rate of vein patency at six months compared to our patients (21).

In conclusion, the critical pathway guidelines regarding the length of hospital stay can hardly be followed in the Croatian health system as long as the system does not provide incentives for shortening of the hospital stay or careful adherence to diagnostic and therapeutic algorithms. The data in this study indicate that the acute management of deep-vein thrombosis was somewhere between the conventional approach and the critical pathway guidelines (7). Its shortcoming reflects in the higher rate of recurrent deep-vein thrombosis, probably due to a low initial heparin dosage, but it also has the advantages of decreased risk of major bleeding and absence of pulmonary embolism. Larger and prospective clinical trials are needed to weigh benefits and shortcomings of these therapeutic approaches.

References


Received: December 17, 2000
Accepted: March 15, 2000

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