Spontaneous spinal hematomas and low-molecular-weight heparin

Report of four cases and review of the literature


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The purpose of this article is to raise awareness of spontaneous spinal hematomas that develop after administration of low-molecular-weight heparin therapy. The authors describe four patients in whom these hematomas developed without precipitating events while receiving a treatment dose of enoxaparin (Clexane) (~1 mg/kg). Spontaneous spinal hematomas (not related to trauma, surgery, or lumbar puncture) are a rare clinical entity. Several causes have been identified, including acquired and congenital clotting abnormalities and underlying vascular lesions. Aspirin, warfarin, tissue plasminogen activator, and heparin have all been implicated in causing spinal hematomas. Concerns regarding the use of low-molecular-weight heparin agents in neuraxis anesthesia have been well documented. Their possible contribution to nontraumatic spinal hematomas has been less well described. The authors believe that low-molecular-weight heparin agents present a small but significant risk of spinal hematoma. This should be considered when prescribing therapy because such a complication may be catastrophic.

KEY WORDS • spinal hematoma • enoxaparin

Low-molecular-weight heparin is increasingly used to provide simple anticoagulation in preventative and therapeutic settings. Spontaneous spinal hematomas (that is, those not related to trauma, surgery, or lumbar puncture) are a rare clinical entity first described by Shiller and colleagues more than 50 years ago. Several causes have been identified, including acquired and congenital clotting abnormalities and underlying vascular lesions. Among the acquired coagulopathies, aspirin, warfarin, tissue plasminogen activator, and heparin have all been implicated in causing spinal hematomas.

There has been substantial documentation in the literature on the association between neuraxis anesthesia, low-molecular-weight heparin, and spinal hematomas. Spinal hematomas arising in the absence of trauma or epidural anesthesia have been rarely reported.

Our goal in this article is to raise awareness of the possibility of spontaneous spinal hematomas arising secondary to low-molecular-weight heparin use. Additionally, we reviewed the literature to determine the presence of other risk factors predisposing to this complication.

Case Reports

All four patients presented to the neurosurgical services of Auckland Public Hospital during a 14-month period. This hospital provides tertiary neurosurgery for a population of 1.8 million people, and all patients were referred from regional hospitals.

We describe four cases of spontaneous spinal hematomas (one subdural and three epidural) in patients treated with low-molecular-weight heparin, detailing presenting signs and symptoms; physical, neurological and imaging findings; management strategies; and outcome after treatment. Table 1 provides a summary of the characteristics and findings.

Case 1

History. This 61-year-old man was admitted to a regional hospital with upper abdominal pain, lower thoracic pain, headache, nausea, and vomiting. His medical history was significant for congestive heart failure and atrial fibrillation. Several causes have been identified, including acquired and congenital clotting abnormalities and underlying vascular lesions. Aspirin, warfarin, tissue plasminogen activator, and heparin have all been implicated in causing spinal hematomas. Concerns regarding the use of low-molecular-weight heparin agents in neuraxis anesthesia have been well documented. Their possible contribution to nontraumatic spinal hematomas has been less well described. The authors believe that low-molecular-weight heparin agents present a small but significant risk of spinal hematoma. This should be considered when prescribing therapy because such a complication may be catastrophic.

Abbreviations used in this paper: APTT = activated partial thromboplastin time; CAD = coronary artery disease; ECG = electrocardiography; MR = magnetic resonance; PR = prothrombin ratio.

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mg of aspirin, glycerine trinitrate, oxygen, morphine, and 70 mg of enoxaparin.

Examination. On examination 4 hours later, the patient exhibited a flaccid paralysis with a T-5 sensory level. His warfarin was reversed with fresh-frozen plasma, and he was transferred to our hospital. Admission blood workup revealed that platelet count, PR, APTT, and fibrinogen assay were within the normal range. Spinal MR imaging revealed an anterior T1–4 spinal hematoma.

Operation. Surgery via a T2–4 laminectomy was performed. An intradural clot was identified; no blood was found extradurally. The clot was noted to be mainly anterior to the cord and was evacuated.

Postoperative Course. The patient’s postoperative course was difficult; he suffered pulmonary edema, pneumonia, and ileus. He was transferred to spinal rehabilitation 6 weeks after admission, and complete T-5 paraplegia persisted at 6-month follow-up study.

Case 2

History. This 64-year-old man presented to a regional hospital with a left lower lobe pneumonia for which he received antibiotic agents. He developed chest pain. Aspirin therapy (150 mg daily) and enoxaparin (80 mg twice daily) were instituted because of suspicion of a pulmonary embolus.

Examination. Seven days after commencing enoxaparin therapy, the patient acutely lost sensation from the nipple line down and was unable to move his legs. He was transferred to our hospital and presented with a flaccid paralysis and a T-7 sensory level. Admission blood workup demonstrated PR, APTT, fibrinogen, and platelet count within the normal range. Spinal MR imaging revealed a C7–T12 epidural hematoma.

Operation. A midthoracic three-level laminectomy was performed. Clotted blood was found in the posterior aspect of the spinal canal and was evacuated.

Postoperative Course. The postoperative course was complicated by pulmonary edema, hypoalbuminemia, and an epidural infection requiring surgical debridement and prolonged antibiotic therapy. The patient was discharged to spinal rehabilitation 2 months following admission, and complete T-7 paraplegia remained at follow-up examination 8 months later.

Case 3

History. This 69-year-old man was admitted to a regional hospital with chest pain between his shoulder blades that radiated down both arms. His medical history was significant for Type II diabetes mellitus, hypertension, hypercholesterolemia, peripheral vascular disease, and dementia. He also suffered neuropathy and retinopathy due to diabetes mellitus and he was on a regimen of insulin therapy. Chest and abdominal computerized tomography scanning was performed to rule out aortic dissection; findings were normal. The pain was considered ischemic (without acute ischemic changes on ECG and in cardiac enzymes); thus acute coronary syndrome was diagnosed and treatment initiated. He was given 150 mg of aspirin and two 90-mg doses of enoxaparin.
Presentation and Examination. Approximately 15 hours later the patient complained of left hand numbness and weakness. The next morning bilateral arm weakness was noted (worse on the left than right) as was left leg weakness. On admission to our institution, he was quadriplegic (except for weak right shoulder abduction and elbow flexion/extension), and had a C-4 sensory level. Admission blood workup demonstrated PR, APTT, fibrinogen, and platelet count within the normal range. Spinal MR imaging revealed a C4–7 posterolateral epidural hematoma.

Operation. Surgery was performed via a C4–7 laminectomy. An acute epidural hematoma was evacuated.

Postoperative Course. Postoperatively there was little improvement—only slight left upper-limb movement, weak flexion of right elbow—and paralysis below. The patient was transferred back to the referring hospital, but he suffered complications. He died 4 months later of sepsis (secondary to a pressure area) and pneumonia, having experienced no significant neurological recovery.

Case 4

History. This 77-year-old man was admitted to a regional hospital with acute myocardial infarction. He received a 90-mg dose of enoxaparin twice a day, as well as a 150-mg dose of aspirin daily, and underwent other standard care measures.

Examination. Two days later the patient developed back pain and proximal leg weakness. Because he had a history of benign prostatic hypertrophy, he required placement of a catheter for urinary retention. Spinal MR imaging performed at the referring hospital revealed a T3–5 spinal hematoma that compressed the cord minimally, and the patient was transferred to our hospital. Admission blood workup demonstrated PR, APTT, fibrinogen, and platelet count within the normal range. The patient exhibited mild weakness of both hip flexors but normal strength in all other muscle groups and no sensory deficit.

Treatment. We elected to treat the hematoma conservatively, and during the next 24 hours the patient’s strength improved.

Posttreatment Course. The patient was discharged to the referring hospital 2 days later and was neurologically intact. After approximately 10 days, he experienced further deterioration that involved a new episode of leg weakness, and a left parietal infarction that was confirmed on CT scanning. Additional care was not discussed with our department and repeated imaging was not performed. At follow-up examination 4 months later, the patient exhibited moderate bilateral leg weakness and required a gutter frame for ambulation.

Discussion

Spontaneous spinal hematomas (unrelated to trauma, surgery, or lumbar puncture) are a rare clinical entity. In a review published in 1997, Lonjon, et al.19 identified 330 cases of epidural hematomas. In 1999 Domenicucci, et al.,8 identified 101 cases of subdural hematomas, although their review included cases in which hematomas arose after lumbar puncture.

Several causes of spinal hematoma have been identified in these patients, including acquired and congenital clotting abnormalities and underlying vascular lesions. Among the acquired coagulopathies, aspirin, warfarin, tissue plasminogen activator, and heparin have all been implicated.4,18,21,22

Concerns regarding the use of low-molecular-weight heparin, in the context of neuraxis anesthesia, have been well described, although an association with nontraumatic spinal hematomas has been less well documented. Between May 1993 and February 1998 the US Food and Drug Administration received 43 reports of spinal or epidural hematomas related to treatment with enoxaparin. During this period enoxaparin was the most widely prescribed low-molecular-weight heparin in the US. In only two of these patients, however, was spinal trauma or lumbar puncture absent.27

We have reported on four patients in whom spinal hematomas developed in the absence of any precipitating event while they were receiving low-molecular-weight heparin therapy. It is notable that in all cases, the enoxaparin (~1 mg/kg twice a day) was prescribed as a treatment dose rather than preventative dose, which has in the past been associated with spinal anesthetic–related hematomas. This dose has been shown in several trials to be at least as effective as unfractionated heparin in the treatment of unstable CAD,3,11,16 deep venous thrombosis,12 and pulmonary embolus.23 As such, its use has increased and will continue to increase in the foreseeable future.

It may be, however, that this higher dose confers a risk of spinal hematoma absent when the lower dose is chosen.
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In a large trial involving the treatment of acute ischemic stroke with low-molecular-weight heparin, investigators found no increased bleeding rate in patients stratified to receive up to an 8000-U dose of certoparin twice daily. At the highest dose of 8000 U twice daily, however, there was a significant tendency for severe bleeding.4 Olson and colleagues23 reported three cases of acute intracranial subdural hematomas in patients receiving treatment-dose enoxaparin, commenting that this bleeding had not occurred in cases involving a lower prophylactic dose.

It is notable that all patients received other anticoagulant preparations such as aspirin (all patients) or warfarin (one patient). The concomitant use of aspirin and heparin was identified as a risk factor in early retrospective studies.28 The increased risk of heparin-associated bleeding when thrombolytic therapy22 or glycoprotein IIb/IIIa antagonists was concomitantly used has also been demonstrated.20 To the best of our knowledge, there is yet to be a confirmed relationship between low-molecular-weight heparin–related bleeding and these preparations.

Other investigators have reported that a higher risk of heparin-induced bleeding was present in older patients.5,15 Although only one of our patients was older than 70 years, age greater than 70 years has been shown to be associated with a clinically important increased risk of major bleeding.2

There is concern in the neurosurgical community about the reversibility of low-molecular-weight heparin. When given in equimolar concentrations, protamine sulfate neutralizes the antithrombin activity of low-molecular-weight heparin but only partially reverses their anti–factor Xa activity, probably because it fails to bind to the very–low molecular-weight heparin chains.14 Although protamine sulfate appears to block bleeding induced by low-molecular-weight heparin in laboratory animals,26 this is not the case in humans. Whether this aspect contributed to the poor neurological outcome demonstrated in our patients remains speculative. Unfortunately factor Xa assays were not performed pre- or postoperatively to assess their anti-coagulation status in this regard.

The effects of low-molecular-weight heparin compared with unfractionated heparin have been discussed in various settings. Each drug group has been used effectively for the treatment of venous thromboembolism,12 unstable CAD,11,13,16 and ischemic cerebral vascular disease.3,20 Analysis of these data shows that low-molecular-weight heparin does not result in an increased risk of major bleeding compared with unfractionated heparin in venous thromboembolism and unstable CAD. The data are inconclusive with respect to the relative risks of major bleeding between the two preparations when used to treat ischemic cerebral vascular disease.

We believe that treatment-dose enoxaparin may not have been strongly indicated in some of our patients. There appears to be a perception that low-molecular-weight heparin is a safe medication, which can be conveniently administered, and has few side effects. As such, treatment may be initiated after a presumptive diagnosis is established but without the necessary investigations to confirm the diagnosis.

Conclusions

We reported on four cases of spontaneous spinal hematomas associated in patients who received therapeutic doses of low-molecular-weight heparin. We hope to raise awareness of this complication and suggest that, because of the incidence of hemorrhagic complications and their potential sequelae, treatment should be reserved for cases in which the pathological entity has been established with certainty.

References


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