Review Article

Prophylaxis against thromboembolism in neurosurgical and head injury patients

Hasan Mohamed, *MD.*

ABSTRACT

Neurosurgical patients are at great risk for venous thromboembolism. Thromboprophylaxis is either with unfractionated heparin or low molecular weight heparin (LMWH). In neurosurgery, this is a matter of debate because of fear from bleeding. Few randomized studies show that chemical prophylaxis is safe after elective neurosurgeries. Prophylaxis with gradual elastic stocking and venous pump may be affective but there are not enough studies and trials examining their efficacy. Larger trials are needed to examine the safety of unfractionated heparin versus LMWH in neurosurgical patients including head injury patients.

Neurosciences 2005; Vol. 10 (3): 200-204

Venous thromboembolic disease (VTE) remains one of the major causes of mortality and morbidity. It is estimated that pulmonary embolism is a direct cause of death in more than 100,000 patients per year in the United States.[1] Various risk factors have been identified for venous thromboembolism. Lengthy surgery, trauma, prolonged immobility, and cancers are among the major risk factors.[2] Neurosurgery, head and spinal cord injury carry significant risks for venous thromboembolism.[1-4] The reported incidence of VTE in neurosurgical patients ranges from 20-50%.[2] Risk factors identified for VTE in neurosurgical patients include cranial surgery, lower extremity weakness, length of surgery and brain tumor.[1-8] A high incidence of VTE after operation for brain tumor even with prophylaxis has been reported.[9-11] Some investigators reported changes in the fibrinolytic profile in favor of thrombosis after brain surgery.[12] Mark et al[13] reported 25% prevalence of pulmonary embolism (PE) in 101 consecutive autopsies of neurosurgical patients, and PE was judged to be a direct cause of death in 50% of these patients. It is worth mentioning that the reported incidence of VTE in neurosurgical patients differs widely, probably due to the different methods used for prophylaxis and for detection of venous thrombosis. In addition, the aim of the investigators in those studies is sometimes for surveillance or for diagnosis of symptomatic patients, and since VTE in many occasions is asymptomatic we suspect a higher incidence of VTE in this group of patients. Prophylaxis against VTE has been found effective after general surgical procedure and trauma, and many reports suggest its superiority to regular surveillance for venous thrombosis in high risk patients.[1,2,14,15]

Cupitt[8] recently reported diversity of practice among neurosurgical units in the United Kingdom regarding VTE prophylaxis in patients with head injury. Regarding the ideal method of prophylaxis, different methods have been used, mainly mechanical methods and recent trials have used heparin and low molecular weight heparin (LWMH).[17-22] There has been different opinion regarding the efficacy and safety of different methods. There have also been several reports on thromboprophylaxis in neurosurgical patients, but most of these are retrospective or prospective case control trials, some of which involved large numbers of patients.[11,23-27]

Chemical thromboprophylaxis with heparin and LMWH. Five randomized studies using

From the Department of Anesthesia and Intensive Care Unit, Salmaniya Medical Complex, Manama, *Kingdom of Bahrain*.

Address correspondence and reprint request to: Dr. Hasan Mohamed, Consultant Intensivist, Department of Anesthesia and ICU, Salmaniya Medical Complex, Manama, *Kingdom of Bahrain*. Tel. +973 9450343. E-mail: hassantdr@yahoo.com

unfractionated heparin or LMWH have been identified. One study used unfractionated heparin and 4 studies used LMWH. The studies that used unfractionated heparin were not blinded, and one study using LMWH was not blinded (**Table 1**). Of notice, these studies used different LMWH with different dosages and different frequencies. The study by Agnelli et al[17] used enoxaparin 40mg once daily in elective neurosurgery and showed significant reduction in the deep venous thrombosis (DVT) rate in the treatment group with no significant major bleeding complications between the control group and the treatment group. However, Nurmohamed, et al[18] used nadroparin and his results were similar to the Agnelli study. Both studies used elastic stockings in the treatment and the control groups. In the study by Melon et al[19] enoxaparin, 20mg once daily was used in the treatment group. Elastic stockings were not used in both groups, and it was found that there was no significant difference in the incidence of DVT in both groups nor significant difference in the hemorrhagic complications and this study was powered to assess safety and not the efficacy. In the study by Dickinson et al[21] enoxaparin 30mg was used at induction and every 12 hours in the 2 groups, and graduated compression stocking in the control group. This study was terminated due to the high incidence of hemorrhagic complication in the treatment group before the attainment of the primary endpoint. All the trials described above used venography for outcome assessment except the study by Dickinson et al,[21] which used Doppler ultrasound for outcome assessment. The only study which used unfractionated heparin, was Cerrato et al,[20] which used heparin 5000U every 8 hours postoperatively after establishing a safe heparin level and showed significant reduction in DVT incidence in the treatment group, without significant difference in the bleeding complication from the control group, however, they used the fibrinogen uptake test for outcome assessment. It is worth mentioning the study by Bostrom et al[22] in which they randomized their patients to unfractionated heparin 5000U twice daily with first dose administered preoperatively, and they used calf muscle stimulation followed by dextran infusion postoperatively in the other group and they used a historical control group. They demonstrated effectiveness of both prophylaxis method without significant hemorrhagic complication, but the study was not blinded and they used a historical control; they also used the fibrinogen uptake test for outcome assessment. One will notice great heterogeneity in these studies with regard to the type, dosage, time of chemical prophylaxis in addition to the test used for outcome assessment. The emergency neurosurgery and head injury patients were not represented in these studies, so you cannot generalize the result of these studies to this group of patients. In a meta-analysis study by Iorio et al,[28] it shows safety and efficacy of LMWH for DVT prophylaxis after elective neurosurgery recommendations for the use of unfractionated heparin could be concluded as there are not enough

Table 1 - Summary of randomized studies for the use of heparin and LMWH for DVT prophylaxis in neurosurgical patients.

Authors	Study Design	Procedure	Method of prophylaxis	Duration of prophylaxis	Outcome assessment	VTE rate in treat-ment group	VTE rate in control group	Significance of VTE rate	Major bleeding in treatment	Major bleeding in control	Significance of bleeding rate
Agnelli et al 1998[17]	Randomized blinded placebo control	Elective neuro-surgery	Enoxoparin 40mg+GCS vs GCS in the control	Within 24hr postop until 8+/-1 days	Venography	22\130 16.9%	43\130 33.1%	S	3\153 2.6%	4\154 2.59%	N/S
Nurmohamed et al 1996[18]	Randomized blinded placebo control	Craniotomy or spinal surgery	Nadroparin 7500u+GCS vs GCS in the control	18-24h postop until 10 days	Venography	31\166 18.7%	47\179 26.3%	S	6\241 2.5%	2\244 0.8%	N/S
Melon et al 1991[19]	Randomized blinded placebo control	Intracranial surgery	Enoxaparin 20mg vs placebo in the control	Postop until 10 days	Venography	10\64 15.6%	14\58 24%	N/S	0\67	0\63	N/S
Dickinson et al 1998[21]	Prospective randomized unblinded	Elective intracranial surgery for tumors	Enoxaparin 30mg+GCS or+SCD or GCS in the control	Until discharge	Doppler U/S	5\45 11.1%	3\22 13.6%	N/S	5\46 10.9%	0\22	S
Cerrato et al 1978[20]	Prospective randomized unblinded	Elective neuro-surgery	Heparin 5000u x3 vs no treatment	Preop for 7 days	Fibrinogen uptake test	3\50 6%	17\50 34%	S	2\50 4%	1\50 2%	N/S

LMWH - low molecular weight heparin, DVT - deep vein thrombosis, VTE - venous thromboembolism, GCS - graduated compression stocking, vs - versus, SCD - sequential compression device, U/S - ultrasound, S - significant, NS - not significant

trials, and the meta-analysis showed the diversity of the type and frequencies of different agents used. Several other non randomized trials have reported safety of unfractionated heparin after neurosurgery.[11,23-27,29] Raabe et al[24] reported low incidence of hemorrhagic complications in 1564 neurosurgical patients with the use of unfractionated heparin. Boeer et al[30] used unfractionated heparin early in patients with spontaneous intracranial hemorrhage and reported better efficacy for DVT prophylaxis and similar bleeding rates to the group started late on heparin. It is probably safe to use LMWH and unfractionated heparin for DVT prophylaxis after elective neurosurgery, however, a larger multicenter randomized study using one protocol for prophylaxis and in different neurosurgical patients including traumatic brain injury and spinal cord injury patients is required to reach firm recommendations for VTE prophylaxis in this group.

Mechanical prophylaxis. Mechanical prophylaxis with pneumatic compression and calf muscle stimulation have been used as a means of prophylaxis in surgical patients in whom heparin is contraindicated or as an adjuvant with heparin to offer more protection. The mechanism of its action is thought to be prevention of blood stasis and possible enhancement of fibrinolysis. Regarding its use as prophylaxis against DVT in neurosurgical patients, 2 randomized studies identified the use of an intermittent compression device in the treatment group against no specific prophylaxis in the control group (**Table 2)**. Both studies used the fibrinogen uptake test for outcome assessment. Both studies showed significant reduction in DVT incidence in the treatment group. The first study by Turpie et al[16] used a pneumatic compression device in the treatment group for 5 days and showed significant reduction in the incidence of DVT in the treatment group, this difference disappeared after discontinuation of the device and the incidence was the same in both groups. In another study by Turpie et al,[31] a pneumatic compression device was used against a graduated compression stocking (GCS) and no specific prophylaxis in the third group and shows that both GCS and pneumatic compression are effective. Bucci et al[32] showed no difference between GCS and pneumatic compression, and both methods were shown to be effective. These studies are not blinded and included a small number of patients. The compliance with these devices is also low and causes discomfort to the patients. Cornwell et al[33] reported a low compliance with the use of sequential compression devices in trauma patients. These devices also cannot be applied to patients with leg injury. Nevertheless, a meta-analysis by Vanek[34] shows the effectiveness of these devices in prevention of proximal DVT in moderate to high risk patients, however, they are not protective against pulmonary embolism. Flinn et al[5] prospectively studied 2643 neurosurgical patients in whom the prophylaxis was by pneumatic compression and elastic stockings and reported a low incidence of thromboembolic events. Several other studies reported efficacy of compression devices in surgical patients.[27,35,36] Different devices are available for DVT prophylaxis, including intermittent compression, sequential intermittent pneumatic compression, and calf stimulation devices. It is difficult to conclude from the literature which device is superior to others, some studies have compared 2 different types of devices in each group and found one type superior to the other. There is also controversy regarding its application, whether thigh high or knee high. If these devices are used properly, they would offer protection against DVT in neurosurgical patients in whom Heparin and LMWH are contraindicated.

Prophylaxis with GCS. Prophylaxis with GCS. The GCS has been used in surgical patients in whom heparin prophylaxis is contraindicated, and found to be effective. The mechanism by which GCS offers protection against DVT is not clearly known, but it is thought to create a pressure gradient which mobilizes the blood from superficial veins to

Table 2 - Summary of randomized studies for the use of heparin and LMWH for DVT prophylaxis in neurosurgical patients.

Authors	Study design	Population	Methods of prophylaxis	Duration of prophylaxis	VTE rate in treatment	VTE rate in control	Outcome assessment	Significance
Turpie et al 1977[16]	Prospective randomized control	Adult potential neurosurgical patients	Intermittent pneumatic device vs no treatment in control	5 days	1\65 1.5%	12\63 19.1%	Fibrinogen uptake test	S
Skillman et al 1978[46]	Prospective randomized control	Adult neurosurgery	Pneumatic compression device vs no treatment in control	Until patient is ambulatory	4\47 8.5%	12\48 25%	Fibrinogen uptake test	S

LMWH - low molecular weight heparin, DVT - deep vein thrombosis, VTE - venous thromboembolism, vs - versus, S - significant

Table 3 - Summary of randomized studies using GCS for DVT prophylaxis in neurosurgical patients.

Authors	Study design	Population	Methods of prophylaxis	Duration of prophylaxis	VTE rate in GCS	VTE rate in control	Outcome assessment	Significance
Turpie et al 1989[31]	Prospective randomized control	Potential neurosurgical patients	GCS vs GCS and pneumatic compression device	14 days	7\81 8.8%	16\81 19.8%	Fibrinogen uptake test	S
Bucci et al 1989[32]	Prospective randomized control	Adult for craniotomy	GCS vs pneumatic compression	Until ambulatory	1\38 2.6%	1\32 3.1%	Impedance plethys-mography	S
Agnelli et al 1998[17]	Randomized placebo control	Adult for elective neurosurgery	GCS + placebo vs GCS + enoxaparin	8 days	43\130 33.1%	22\130 16.9%	Venography	S
Nurmohamed et al 1996[18]	Randomized placebo control	Craniotomy and spinal surgery	GCS + placebo vs GCSZ + nadroparin	10 days	47\179 26.3%	31\166 18.7%	Venography	S

GCS - graduate compression stocking, DVT - deep vein thrombosis, VTE - venous thromboembolism, vs - versus, S - significant

deep veins through the perforators and helps to prevent venous stasis.[37] Two recent meta-analysis evaluating the efficacy of GCS in DVT preventions found them effective against DVT, but they may be more effective if used with other modes of prophylaxis such as heparin.[38,39] There is a total of 4 randomized trials in which GCS was used against heparin or pneumatic compression stocking, with the exception of the study by Turpie et al in which no specific prophylaxis had been used in one of the 3 groups included in the study. The results of these studies are conflicting as GCS shows efficacy in the Turpie and Bucci studies, but in the randomized trials by Agnelli and Nurmohamed in which it is used against LMWH, there was significant DVT in the GCS groups (**Table 3**). This may be explained by the high percentage of brain tumor patients in the Agnelli and Nurmohamed studies in which even heparin prophylaxis may not be adequate.[10] As it is shown to be effective in surgical patients and other groups of patients such as patients with stroke,[30,40-42] and with the lack of significant side effects, they seem to be a reasonable choice in neurosurgical patients when other methods are contraindicated or not available or as adjuvants to other methods in high risk patients.

Prophylaxis by inferior vena cava filter. The use of prophylaxis inferior vena filters (IVC) has not gained popularity as prophylaxis for DVT. It has been used mainly to prevent PE in patients with established DVT in whom anticoagulation is either contraindicated or not effective. No randomized trials have been carried out with IVC filter in neurosurgical patients as the primary method for DVT prophylaxis. Several retrospective studies have evaluated the IVC filter as primary prophylaxis with mixed results.[43-45] Langan et al[43] retrospectively studied 160 trauma patients at high risk for DVT, including traumatic brain injury patients, and reported a low rate of PE with a low rate of complication.[43] Decuosus et al[45] reported a randomized trial using IVC filter as secondary prophylaxis against PE, and shows no difference in the incidence of PE in both groups. Because of the lack of randomized trials, the use of the IVC filter as primary prophylaxis remains undefined.

Acknowledgment. The author wishes to thank Dr. Suhaila E. Al-Jawder for her assistance in the preparation of this manuscript.

References

1. Geets W, Heit J, Clagett P. Prevention of venous thromboembolism. ***Chest*** 2001; 119: 132s-175s.
2. Thromboembolic risk factors (THRIFT) consensus group, risk of and prophylaxis for venous thromboembolism in hospital patients. ***BMJ*** 1992; 305: 567-574.
3. Agnelli G. Prevention of venous thromboembolism after neurosurgery. ***Thromb Haemost*** 1999; 82: 925-930.
4. Burke DT. Venous thrombosis in traumatic brain injury. ***J Head Trauma Rehab*** 1999; 14: 515-519.
5. Flinn W, Sandager G, Silva MB Jr, Benjamin ME, Cerullo LJ, Taylor M. Prospective surveillance for perioperative Venous Thrombosis, Experience in 2643 patients. ***Arch Surg*** 1996; 131: 472-480.
6. Levi A, Wallace C, Bernstein M, Walters B. Venous thromboembolism after brain tumor surgery: A retrospective review. ***Neurosurgery*** 1991; 28: 859-863.
7. Hammond FM, Meighen MJ. Venous thromboembolism in the patient with acute traumatic brain injury: screening, diagnosis, prophylaxis and treatment issues. ***J Head Trauma Rehab*** 1998; 13: 36-50.
8. Cupit JM. Prophylaxis against thromboembolism in patients with traumatic brain injury: survey of UK practice. ***Anesthesia*** 2001; 56: 780-785.
9. Joffe S. Incidence of postoperative deep vein thrombosis in neurosurgical patients. ***J Neurosurg*** 1975; 42: 201-202.
10. Chan AT, Atiemo A, Diran LK, Licholai GP, McLaren Black P, Creager MA. Venous thromboembolism occurs frequently in patients undergoing brain tumor surgery despite prophylaxis. ***J Thromb Thrombolysis*** 1999; 8: 139-142.

11. Inci S, Erbengi A, Berker M. Pulmonary embolism in neurosurgical patients. ***Surg Neurol*** 1995; 43: 123-129.
12. Sawaya R, Ramo O, Glas-Greenwalt P, Wu SZ. Plasma Fibrinolytic Profile in patients with brain tumors. ***Thromb Haemost*** 1991; 65: 15-19.
13. Mark P, Horst M, Diaz F. Neurosurgical patients: at high risk for pulmonary emboli. ***Surg Forum*** 1986; 37: 522-523.
14. Salzman E, Davies G. Prophylaxis of venous thromboembolism. Analysis of cost-effectiveness. ***Ann Surg*** 1980; 191: 207-218.
15. Hull R, Hirsh J, Sackett D, Stoddart G. Cost-effectiveness of primary and secondary prevention of fatal pulmonary embolism in high risk surgical patients. ***Can Med Assoc J*** 1982; 127: 990-995.
16. Turpie A, Gallus A, Beattie W, Hirsh J. Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. ***Neurology*** 1977; 27: 435-438.
17. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo A, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. ***N Engl J Med*** 1998; 339: 80-85.
18. Nurmohamed MT, van Riel AM, Henkens CM, Koopman MM, Que GT, d'Azemar P, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. ***Throm Haemost*** 1996; 75: 233-238.
19. Melon E, Keravel Y, Combes S. Deep vein thrombosis prophylaxis by low molecular weight heparin in neurosurgical patients [Abstract]. ***Anesthesiology*** 1991; 75: A214.
20. Cerrato D, Ariano C, Fiacchino F. Deep vein thrombosis and low dose heparin prophylaxis in neurosurgical patients. ***J Neurosurg*** 1978; 49: 378-381.
21. Dickinson L, Miller L, Patel C, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep vein thrombosis prophylaxis in patients with brain tumors. ***Neurosugery*** 1998; 43: 1074-1081.
22. Bostrom S, Holmgren E, Jonsson O, Lindberg S, Lindstrom B, Winso I et al. Post-operative thromboembolism in neurosurgery. A study on the prophylaxis effect of calf muscle stimulation plus dextran compared to low-dose heparin. ***Acta Neurochir (Wien)*** 1986; 80: 83-89.
23. Barnett H, Clifford J, Llewellyn R. Safety of mini-dose heparin administration for neurosurgical patients. ***J Neurosurg*** 1977; 47: 27-30.
24. Raabe A, Gerlach R, Zimmermann M, Seifert V. The risk of hemorrhage associated with early postoperative heparin administration after intracranial surgery. ***Acta Neurochir*** 2001; 143: 1-7.
25. Wen DY, Hall WA. Complications of subcutaneous low-dose heparin therapy in neurosurgical patients. ***Surg Neurol*** 1998; 50: 521-525.
26. Macdonald R, Amidei C, Lin G, Munshi I, Baron J, Weir BK. Safety of perioperative subcutaneous heparin for prophylaxis of venous thromboembolism in patients undergoing craniotomy. ***Neurosurgery*** 1999; 45: 245-252.
27. Gersin K, Grindlinger G, Lee V, Dennis RC, Wedel SK, Cachecho R. The efficacy of sequential compression devices in multiple trauma patients with severe head injury. ***J Trauma*** 1994; 37: 205-208.
28. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery. A meta-analysis. ***Arch Intern Med*** 2000; 160: 2327-2332.
29. Frim D, Barker F, Poletti C, Hamilton A. Postoperative low-dose heparin decreases thromboembolic complications in neurosurgical patients. ***Neurosurgery*** 1992; 30: 830-833.
30. Boeer A, Voth E, Henze T, Prange H. Early heparin therapy in patient with spontaneous intracerebral hemorrhage. ***J Neurol Neurosurg Psychiatry*** 1991; 54: 466-467.
31. Turpie A, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. ***Arch Intern Med*** 1989; 149: 679-681.
32. Bucci M, Papadopoulos S, Chen JC, Campbell JA, Hoff JT. Mechanical prophylaxis of venous thrombosis in patients undergoing craniotomy: a randomized trial. ***Surg Neurol*** 1989; 32: 285-288.
33. Cornwell E, Chang D, Velmahos G, Jindal A, Baker D, Phillips J. Compliance with sequential compression device prophylaxis in at-risk trauma patients: a prospective analysis. ***Am Surg*** 2002; 68: 470-473.
34. Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. ***Am Surg*** 1998; 64: 1050-1058.
35. Winemiller M, Stolp-Smith K, Silverstein M, Therneau TM. Prevention of venous thromboembolism in patients with spinal cord injury: Effects of sequential pneumatic compression and heparin. ***J Spinal Cord Med*** 1999; 22: 182-191.
36. Nicolaides A, Fernandes J, Polloock A. Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and postoperative deep venous thrombosis. ***Surgery*** 1980; 87: 69-76.
37. Allan A, Williams J, Bolton J, Quensne L. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. ***Br J Surg*** 1983; 70: 1722-1724.
38. Wells P, Lensing A, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism. A meta-analysis. ***Arch Intern Med*** 1994; 154: 67-72.
39. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. ***Cochrane Database Syst Rev*** 2000; CD001484.
40. Scur J, Ibrahim S, Faber R, Quesne L. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis. ***Br J Surg*** 1977; 64: 371-373.
41. Muir K, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of compression stockings for prevention of deep-vein thrombosis after acute stroke. ***QJM*** 2000; 93: 359-364.
42. Holford CP. Graded compression for preventing deep venous thrombosis. ***Br Med J*** 1976; 2: 969-970.
43. Langan EM 3rd, Miller RS, Casey WJ 3rd, Carsten CG 3rd, Graham RM, Taylor SM. Prophylaxis inferior vena cava filters in trauma patients at high risk: follow-up examination and risk/benefit assessment. ***J Vasc Surg*** 1999; 30: 484-490.
44. Wilson J, Rogers F, Wald SL, Shackford SR, Ricci MA. Prophylactic Vena Cava filter insertion in patient with traumatic spinal cord injury: preliminary results. ***Neurosurg*** 1994; 35: 234-239.
45. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. ***N Engl J Med*** 1998; 338: 409-415.
46. Skillman JJ, Collines RE, Coe NP, Goldstein BS, Shapiro RM et al. Prevention of deep vein thrombosis in neurosurgical patients: a controlled randomized trial of external compression boots. ***Surgery*** 1978; 83: 354-358.