8.2. Data extraction

Table 37 Treatment of established VTE in patients with a brain tumor

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity
[SCHMIDT2002] Prospective study Oct 1998 - Jan 2001	11/11 patients	unspecified	Patients with a histologically confirmed malignant brain tumor and proven DVT (Doppler US or venography) No surgery within the 48 hours before anticoagulation 9 glioblastomas, 1 anaplastic oligoastrocytoma et 1 anaplastic astrocytoma	Tinzaparin 175 IU/kg/day for 10 days then 100 IU/kg/day for 3 months Compression stockings for 3 months	No recurrence of VTE	No major bleeding No HIT
[ALTSCHULER1990] Retrospective study 1986 - not specified	23 patients	unspecified	Patients with astrocytoma or glioblastoma (proven by surgical biopsy) and DVT or PE DVT: 15 patients DVT + PE: 8 patients	Continuous IV heparin, then warfarin for 3 months	PE recurrence: 1 patient (bleeding → withdrawal of warfarin→ recurrence → IVCF insertion)	Major bleeding : 4 patientss (gastrointestinal tract) Treatment discontinuation: 8 patients: - 4 patients: gastrointestinal tract bleeding - 3 patients: no DVT on control - 1 patient: best supportive care
[LEVIN1993] Retrospective multicenter study 1977 - 1991	42/49 patients	unspecified	Patients with a brain tumor or brain metastasis and proven DVT or PE	IVCF insertion (n=42) Warfarin (n=5) Inferior vena cava interruption (n=1) No treatment (n=1)	IVCF PE: 11.9 % (5/42) DVT: 21.4 % (9/42)	IVCF insertion-related complications: 3/42 Inferior vena cava or filter thrombosis: 11/42 (26.2%) Anticoagulant treatment: no major bleeding
[SCHIFF1994] Retrospective study Jan 1980 - Jul 1992	52 patients included 42 patients evaluated in the anticoagulant group 10 patients evaluated in the IVCF group	unspecified	Patients with a brain metastasis and proven DVT or PE	IV heparin then warfarin (n=29) IV UFH alone (n=2) Warfarin alone (n=2) IV UFH then SC UFH (n=7) IV UFH, SC UFH then warfarin (n=2) IVCF (n=10) No treatment (n=2)	Anticoagulant group: 12% (5/42), 2 recurrences after anticoagulant discontinuation IVCF (n=10) VTE: 40% (4/10) (2 PE)	Anticoagulant group: Major intracerebral bleeding: 7% (3/42) IVCF group: No bleeding complication 3 patients received anticoagulant therapy for thromboembolic events (2 PE) after IVCF insertion

Table 38 VTE prophylaxis in cancer patients undergoing neurosurgery

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[CERRATO1978] Randomized controlled study Not specified	Arm A: 50/50 patients Arm B: 50/50 patients	7 days	Patients over 40 years of age Elective intracranial neurosurgery No suspicion of DVT on ^{125}I-labeled fibrinogen test Arm A: 50 patients; cancer = 17 Arm B: 50 patients; cancer = 20	Arm A: control Arm B: UFH 5000 IU x3/day for 7 days with an heparin plasma level less than 0.18 units/mL	DVT on ^{125}I-labeled fibrinogen test every day up to Day 7 after surgery Arm A: 17/50 (34%) Arm B: 3/50 (6%); p <0.05	Postoperative hematoma Arm A: 1/50 (2%) Arm B: 1/50 (2%); p=NS Postoperative transfusion Arm A: 25/50 (50%) Arm B: 28/50 56%); p=NS Postoperative hemoglobin levels Arm A: -0.6±1.2 Arm B: -0.7±1.3; p=NS	Not specified
[MELON 1991] Randomized double-blind study Not specified	Arm A: 64/67 patients Arm B: 58/63 patients	10 days	Adult patients Weight between 45 and 90 kg Intracranial surgery (number of patients with cancer not specified) No intracranial bleeding on postoperative CT scan	Arm A: enoxaparin 20 mg/day Arm B: placebo	Phlebography on Day 10 or earlier if symptoms DVT Arm A: 10/64 (15.6%) Arm B: 14/58 (24%); p=NS	No bleeding	Not specified
[CONSTANTINI1994] Randomized controlled study Not specified	103/103 patients	7 days	Patients over 40 years of age Elective intracranial neurosurgery for brain tumor No preexisting changes in coagulation or severe systemic disease, no medication that influenced coagulation Meningioma: 63%; malignant tumor: 37%	Arm A: 1 mL 0.9% NaCl with 5000 IU heparin Arm B: placebo (0.9% NaCl alone) x2/day from H-2 to Day 7 (maximum 14 doses) Beginning of treatment: H-2	DVT Arm A: 2/55 (3.6%) Arm B: 2/48 (4.2%)	Gastrointestinal bleeding Arm A: 2/55 ((3.6%) Arm B: 1/48 (2.1%); p=NS Cerebral hematoma requiring surgery Arm A: 1/55 (1.8%) Arm B: 1/48 (2.1%); p=NS Postoperative transfusion Arm A: 7/55 (12.7%) Arm B: 7/48 (14.6%); p=NS	Day 7 Arm A: 0/55 (0%) Arm B: 1/48 (2.1%) p=NS
[NURMOHAMED1996] Randomized double-blind study Not specified	Cancer patients Arm A: 196/241 patients Arm B: 210/241 patients	56 days	Total population (n=241): patients over 18 years undergoing craniotomy or spinal surgery for a tumor or injury	Graduated compression stockings Arm A: nadroparin 7500 IU/day starting 18-24 h postoperatively Arm B: placebo For 10 days or until discharge Beginning of treatment: H-2	DVT (symptomatic and asymptomatic using Doppler US on Days 6, 8 and 10 post-surgery or venography on Day 10 post-surgery or at discharge Arm A: 31/166 (18.7%) Arm B: 47/179 (26.3%); p=0.047 All events at Day 56: Arm A: 33/241 (20.9%) Arm B: 51/244 (26.3%); p=0.018	Major bleeding Arm A: 6/241 (2.5%) Arm B: 2/244 (0.8%); p=0.087 Minor bleeding Arm A: 4/241 (1.7%) Arm B: 1/244 (0.4%); p=NS All bleeding Arm A: 10/241 (4.1%) Arm B: 3/244 (1.2%); p=0.047	Day 56 Arm A: 22/241 (9.1%) Arm B: 10/244 (4.1%) p=0.026

Table 38 VTE prophylaxis in cancer patients undergoing neurosurgery (continued)

Reference Inclusion period	Number of patients analyzed/included	Follow-up	Population	Intervention	VTE incidence	Toxicity	Death
[AGNELLI1998] Randomized double-blind studiy Not specified	Arm A: 130/153 patients Arm B: 130/154 patients	60 days	Patients >18 years, body weight between 40 and 120 kg undergoing elective cranial or spinal surgery. Meningioma: n=124 Glioma: n=85 Sheath tumors: n=25 Metastasis: n=20 Other tumors: n=45 No tumors: n=8	Thigh-length compression stockings for all patients Arm A: enoxaparin 40 mg/day Arm B: placebo 1/day Beginning of treatment: within 24 h after surgery	Phlebography at day 8±1 and symptomatic confirmed DVT or PE Arm A: 22/130 (17%) Arm B: 43/130 (33%) RR=0.51; 95%CI: [0.33-0.80] p=0.004	Major and minor bleeding Arm A: 18/153 (12%) Arm B: 11/154 (7%) p=0.18	Day 60 Arm A: 6/153 (5%) Arm B: 5/154 (4%) p=NS
[DICKINSON1998] Prospective randomized study Jan 1990 - Dec 1992	66/66 patients	1 month	Patients 18 years of age or older with intracranial neoplasm and craniotomy	Arm A: SCD alone Arm B: enoxaparin 30 mg/day Arm C: SCD+enoxaparin 30 mg/day Duration: up to discharge Beginning of treatment: during anesthesia	Venous duplex ultrasonographic examinations at Day 1-3, Day 5-7, Day 10-14, Month 1 Arm A: 3/22 (13.6%) Arm B: 1/21 (4.7%) Arm C: 2/23 (8.7%) p=NS	Major bleeding Arm A: 0/22 Arm B: 2/21 (9.5%) Arm C: 3/23 (13.1%) Difference between enoxaparin groups and SCD group: p=0.024	Arm A: 1/22 (4.5%) Arm B: 1/21 (4.7%) Arm C: 0/23 (0%) p=NS
[GOLDHABER2002] Randomized double-blind studiy Jun 1996 - Sep 2001	150/150 patients	30 days	Patients undergoing craniotomy with suspected primary or metastatic brain tumor	All patients: intermittent pneumatic compression devices + GCS Arm A: enoxaparin 40 mg morning + placebo evening Arm B: UFH 5000 IU morning and evening Beginning of treatment: within 24 h after surgery	Duplex venous ultrasonography examination the day of discharge Arm A: 9/75 (12%) Arm B: 5/75 (6.7%) p=0.401	Major bleeding Arm A: 2/75 (2.7%) Arm B: 1/75 (1.3%) p=NS	No death during 30 days of follow-up.
[MACDONALD2003] Prospective randomized study Sept 1998 - Dec 1999	97/100 patients	1 month	Patients >18 years Craniotomy Cancer patients Arm A: 28/49 (47%) Arm B: 35/61 (69%)	SCD for all patients Arm A: heparin 5000 IU SC x2/day Arm B: dalteparin 2500 IU x1/day Duration: 7 days Beginning of treatment: during surgery	Duplex ultrasound scanning of lower limbs Day 7 + symptomatic DVT and PE confirmed by ventilation-perfusion scan ,CT scan or angiography at one month DVT Arm A: 0/49 (0%) Arm B: 2/51 (4%) (asymptomatic: n=1) No PE	Intracranial bleeding Arm A: 1/49 (2%) Arm B: 2/51 (4%) p=NS Transfusion Arm A: 4/49 (8%) Arm B: 5/51 (8%) p=NS	Arm A: 1/49 (2%) Arm B: 0/51 (0%) p=NS

Table 39 Meta-analyses: VTE prophylaxis in neurosurgical cancer patients

References	[IORIO2000]	[COLLEN2008]
Bibliographic search	Medline® search up to 1999 Scan of meeting abstracts: period not specified. Scrutiny of the reference list of original articles and review articles, and informal search with colleagues.	Published literature (from 1960 through August 2007) Medline®; PubMed; Cochrane RCT; Embase®; Biosis; PASCAL; Sci Search; IPA; and computer retrieval of information on scientific projects
Included studies	Patients included in trials involving craniotomy 3 placebo-controlled, double-blind clinical trials evaluating LMWH and using venography to assess the endpoint: [AGNELLI1998], [NURMOHAMED1996], [MELON1987] 1 randomized trial with UFH using ^{125}I-fibrinogen scanning: [CERATTO 1978]	Patients included in randomized trials or prospective cohort studies evaluating pharmacologic VTE prophylaxis (with UFH or LMWH) or in randomized trials or prospective cohort studies evaluating mechanical VTE prophylaxis (with ICD or CS): [AGNELLI1998], [BARNETT1977], [BOSTROM1986], [BUCCI1989, [BYNKE1987], [CERRATO1978], [CONSTANTINI2001], [DICKINSON1998], [EPSTEIN2005], [EPSTEIN2006], [FRIM1992], [GERLACH2003], [GOLDHABER2002], [GRUBER1984], [KURTOGLU2004], [MACDONALD1999], [MACDONALD2003], [NORWOOD2002, [NURMOHAMED1996, [PAOLETTI1989, [PRESTAR1992], [ROKITO1996, [SKILLMAN1978, [SMITH1994], [TURPIE1989], [VOTH1992], [WAUTRECHT1996], [WEN1998], [WOOD1997],
Primary endpoint	Thromboembolic events	Objective assessment of deep venous thrombosis
Secondary endpoint	Bleeding (intent-to-treat analysis)	Major and minor bleeding, death
Statistical tests	Calculation of measure outcome with its variance for each study then sum of measure outcomes and variances. Homogeneity of studies tested with an approximate Chi-Square statistic.	RRs were pooled using the Der Simonian and Laird random-effects method. Calculation of the overall rate of event. Calculation of the variance for each outcome with the binomial method. Heterogeneity was assessed visually with Galbraith plots, Q statistics (X^2test) and the I^2 statistic.
Results	VTE Heparins: 66/410 (16.1%) Control: 121/417 (29.0%) RR=0.55; OR=0.48; 95%CI: [0.35-0.66] Number Needed extra Event =7.7; p <0.001 Proximal DVT 19/304 (6.2%) 39/312 (12.5%) RR=0.50; OR=0.48; 95%CI: [0.28-0.83] Number Needed extra Event =16; p=0.008 Major bleeding Heparins: 12/511 (2.3%) Control: 7/511 (1.4%) RR=1.71; OR=1.72; 95%CI: [0.69-4.27] Number Needed extra Event =102; p=0.24 All bleeding events 30/511 (5.9%) 15/511 (2.9%) RR=2.00; OR=2.06; 95%CI: [1.12-3.77] Number Needed extra Event =34; p=0.02 Deaths Heparins: 27/511 (5.3%) Control: 16/511 (3.1%) RR=1.69; OR=1.74; 95%CI: [0.94-3.22]; Number Needed extra Event =39; p=0.08	CD *vs*. CS: 3 studies DVT: RR=0.81; 95%CI: [0.32–1.78] PE: RR=0.49; 95%CI: [0.08–2.80] ICD *vs*. placebo: 2 studies DVT: RR=0.41; 95%CI: [0.21–0.78] PE: RR=0.37; 95%CI: [0.03–4.06] LMWH *vs*. CS: 2 studies DVT: RR=0.60; 95%CI: [0.44–0.81] PE: RR=0.29; 95%CI: [0.05–1.85] LMWH *vs*. ICD: 2 studies DVT: RR=0.79; 95%CI: [0.30–2.12] PE: RR=1.62; 95%CI: [0.35–7.46] LMWH *vs*. UFH: 4 studies DVT: RR=1.46; 95%CI: [0.61–3.51] PE: RR=0.43; 95%CI: [0.08–2.41] UFH *vs*. placebo: 3 studies DVT: RR=0.50; 95%CI: [0.11–2.38] PE: RR=0.96; 95%CI: [0.10–9.06] LMWH *vs*. non-pharmacologic management: 4 studies Minor bleeding RR=2.06 [1.07–3.96] Major bleeding RR=0.95 [0.18–5.09] ICH RR=1.97 [0.64–6.09] Death RR=0.96 [0.47–1.96] UFH *vs*. non-pharmacologic management: 3 studies Minor bleeding RR=1.00 [0.48–2.11] Major bleeding RR=0.85 [0.12–5.99] ICH RR=2.11 [0.39–11.31] Death RR=0.97 [0.13–7.37] LMWH *vs*. UFH: 4 studies Minor bleeding RR=1.28 [0.64–2.59] Major bleeding RR=1.00 [0.18–5.74] ICH RR=1.78 [0.37–8.50] Death RR=0.72 [0.11–4.42]
Authors' conclusions	LMWH and UFH were shown to be effective for VTE prophylaxis in patients undergoing elective neurosurgery without excessive bleeding risk.	In a mixed neurosurgical population, LMWH and ICD are both effective in the prevention of VTE. Sensitivity analyses suggested that certain high-risk groups, such as patients undergoing craniotomy for a neoplasm, may benefit from a combination of prophylactic methods, suggesting the need for a more individualized approach to these patients.