



**Centre for Clinical Effectiveness**

Enhancing patient outcomes through clinical application of the best available evidence

**EVIDENCE CENTRE**  
**CRITICAL APPRAISAL**  
Series 2002: Therapy

## **Anticoagulation therapy as prophylaxis for prevention of DVT or pulmonary embolism in neurosurgery**

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## **SUMMARY STATEMENT:**

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**Publication of materials** – please use the following format when citing this article:

Abdulwadud, O. (2002). Anticoagulation therapy as prophylaxis for prevention of Deep Vein Thrombosis or pulmonary embolism in neurosurgery. [Online]. Available from <http://www.med.monash.edu.au/healthservices/cce/> [Access date..]

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## **REQUEST:**

Anticoagulation therapy as prophylaxis for prevention of Deep Vein Thrombosis or pulmonary embolism in neurosurgery.

## **REQUESTED BY:**

**Cate Wilson**, Project Officer, specialty program, Monash Medical Centre, Clayton.

## **METHODOLOGY**

### **Search Strategy**

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

## Details of Evidence Request

Patient/condition: Patients undergoing neurosurgery (adults age 18 years or older)  
Intervention: Anticoagulation therapy  
Comparison: No anticoagulation therapy, placebo  
Outcomes: Incidence of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), bleeding.

## **Search terms** (see Appendix 2 for exact search strategy)

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient/condition-related	Exp Neurosurgery/ or neurosurgery.mp, exp Neurosurgical procedures/ or neurosurgical procedure\$.mp, exp craniotomy/ or cranial surgery
Intervention-related	Exp anticoagulants/, exp enoxaparin/, exp heparin, exp nadroparin, exp tedelparin
outcome-related	Exp venous thrombosis/ or deep vein thrombosis, DVT, exp pulmonary embolism/ or pulmonary embolism.mp, exp cerebral hemorrhage/ or cerebral hemorrhage.mp

## **Resources Searched**

We searched the following databases and Internet websites:

The Cochrane Library (CD-ROM) 2001 Issue 4  
Medline (OVID)- 1966 to January week 3 2002  
CINAHL (OVID)- 1982 to December week 2 2001  
Current Contents (OVID)- 1993 Week 26 to 2002 Week 06  
Premedline (OVID)- January 31, 2002  
Australasian Medical Index- December 2001

## **Refinements, Searching & Reporting Constraints:**

We included items of evidence that were available to us on 4 February 2002. Having identified the 2000 meta-analysis by Iorio and Agnelli, a restriction period of 2001 was applied while searching the above databases. The search was also restricted to adults (18 years or over) and articles published in English.

## RESULTS:

From our sources we identified 4 articles related to the request and was categorised as follows:

Table 2. Study designs of articles retrieved by search

<b>Study Design</b>	<b>Number</b>
<b>Systematic reviews or meta-analyses</b>	<b>2</b>
Evidence-based clinical practice guidelines	0
<b>Randomised controlled trials</b>	<b>1</b>
Pseudo-randomised controlled trials	0
<b>Controlled trials, cohort or case-control analytic studies</b>	<b>1</b>
Narrative reviews	0

Articles were excluded from further appraisal as follows:

Table 3: Reason for exclusion of article retrieved by search

<b>Reason for exclusion</b>	<b>Number</b>
Review (contains the same one study included in the meta-analysis by Iorio & Agnelli, 2000)	1
Retrospective study (level IV)	1

This left one meta-analysis and one randomised control trial for appraisal. We are reasonably confident these articles represent the most relevant finding published to date based on our refinements, searching and reporting constraints.

## EVIDENCE SUMMARIES

### Format

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

## REFERENCES

### ARTICLE CRITICALLY APPRAISED

- Constantini, S., A. Kanner, et al. (2001). "Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: a prospective, randomized, double-blind study." Journal of Neurosurgery **94**(6): 918-921.
- Iorio, A. and G. Agnelli (2000). "Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery - A meta-analysis." Archives of Internal Medicine **160**(15): 2327-2332.

### ARTICLES NOT CRITICALLY APPRAISED

1) Systematic review (included the same one study reviewed by Iorio & Agnelli, 2000)

- Attia, J., J. G. Ray, et al. (2001). "Deep vein thrombosis and its prevention in critically ill adults." Archives of Internal Medicine **161**(10): 1268-1279.

2) Retrospective study (Level IV)

- Raabe, A., R. Gerlach, et al. (2001). "The risk of haemorrhage associated with early postoperative heparin administration after intracranial surgery." Acta Neurochirurgica **143**(1): 1-7.

# APPENDIX 1

## Copyright

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## Levels of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

- |             |  |
|-------------|--|
| Level I     | Evidence obtained from a systematic review of all relevant randomised controlled trials.   |
| Level II    | Evidence obtained from at least one properly designed randomised controlled trial.   |
| Level III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).  |
| Level III-2 | Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case control studies, or interrupted time series with a control group. |
| Level III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.  |
| Level IV    | Evidence obtained from case series, either post-test or pre-test/post-test.  |

## APPENDIX 2

**Search strategy** (Search terms for Cochrane Library, Medline, CINAHL, PreMedline, Current contents, Premedline, Australasian Medical Index)

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1. Exp Neurosurgery/ or neurosurgery.mp,
  2. Exp Neurosurgical procedures/ or neurosurgical procedur\$.mp
  3. Exp craniotomy/ or cranial surgery.mp
  4. (Skull and surgery).tw
  5. Or/1-4
  6. Exp anticoagulants/
  7. Anticoagula\$.tw
  8. Exp enoxaparin/ or clexane.mp
  9. Enoxaparin.tw
  10. Exp heparin/ or heparin\$.mp
  11. Exp nadroparin/ or nadroparin.tw
  12. Exp tedelparin/ or tedelparin.mp
  13. Or/6-12
  14. Exp cerebral hemorrhage/ or cerebral hemorrhage.mp
  15. Exp pulmonary embolism/ or pulmonary embolism.mp
  16. PE.tw
  17. Exp venous thrombosis/ or deep vein thrombosis.mp
  18. DVT.tw
  19. Exp thrombophlebitis/ or thrombophlebitis.mp
  20. Exp thromboembolism/ or thromboembolism.mp
  21. Or/14-20
  22. 5 and 13 and 21
  23. Limit 22 to (18 years and over and English language)
- 

\$ Wildcard indicating truncation

<p style="text-align: center;"><b>Evidence Summary Systematic Review</b></p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: 80%;"> <p style="text-align: center;">Anticoagulation therapy as prophylaxis for prevention of DVT/Pulmonary embolism in neurosurgery</p> </div>	<p style="text-align: center;"><b>Study 1</b></p> <p style="text-align: center;">Iorio, A. and G. Agnelli (2000). "Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery - A meta-analysis." Archives of Internal Medicine 160(15): 2327-2332</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVEL OF EVIDENCE</b></p>	<p style="text-align: center;">A meta-analysis (Level I)</p>
<p><b>DESCRIPTION:</b> Patient (subjects), Intervention, Comparisons, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Trials:</b> Four randomized controlled studies were identified (three evaluated LMWH and used venography to assess outcome; one evaluated UFH and used I-fibrinogen scanning for outcome assessment).  <b>Patients:</b> Neurosurgical patients (adults age 18 years or older)  <b>Intervention:</b> Heparin [low molecular weight heparin (LMW) or unfractionated heparin (UFH)] for prophylaxis of venous thromboembolism (VTE) in neurosurgery.  <b>Comparisons:</b> Placebo  <b>Outcomes:</b> Thromboembolic events, bleeding, death  <b>Inclusion criteria:</b> Randomised controlled trials</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection, analysis</p>	<p><b>Focused question:</b> Yes  <b>Search strategy:</b> Medline (up to 1999), meeting abstracts, reference list (of original and review articles), and informal search with colleagues. Search terms not stated.  <b>Assessed validity:</b> Yes  <b>Consistent results:</b> The homogeneity of the studies was tested.  <b>Appropriate analysis of results:</b> Yes</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p><b>Thromboembolic events:</b> One hundred eighty seven thromboembolic events were recorded in 827 patients (incidence 22.6%). The incidence of thromboembolic events in the treated and control groups was 16.1% and 29%, respectively. Heparin prophylaxis resulted in a 45% relative risk reduction of VTE (odds ratio [OR], 0.48; 95% CI, 0.35-0.66; P&lt;0.001). The number needed to treat (NNT) was 7.7 (95% CI, 5.4-13.7), i.e., 1 extra VTE would occur in about every 8 patients who are denied treatment. A total of 58 events of proximal DVT were recorded in 616 patients (incidence 9.4%). The NNT for proximal DVT was 16 (95% CI, 9.2-59.5). Treatment with LMWH resulted in a 38% relative risk reduction of VTE (OR, 0.54; 95% CI, 0.38-0.77; P&lt;0.001). The NNT for LMWH was 9.2 (95% CI, 5.9-20.9). Treatment with LMWH resulted in a 50% relative risk reduction for proximal DVT (OR, 0.48; 95% CI, 0.28-0.83; P&lt;0.001). Overall, 195 patients (19.1%) were excluded from the efficacy analysis because venography was not performed or available [101 treated patients (19.8%) and 94 controls (18.4%)]. All patients excluded from the efficacy analysis were followed up for the occurrence of clinically overt thromboembolic events for at least 2 months. At follow-up, 3 patients in the treated group and 7 in the placebo group had a clinically overt thromboembolic event, confirmed by objective testing. After cumulating venography assessment and clinically overt events at follow-up, the results of the meta-analysis for proximal DVT were as follows: number needed for 1 extra event (NNE), 16.7; P = 0 .003; OR, 0.47; 95% CI 0.28-0.77.</p>

<p><b>RESULTS:</b> (cont.) Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p><b>Bleeding:</b> Four deaths were related to bleeding but not to the study treatment. Forty-five bleeding events were observed in 1022 patients (incidence 4.4%). Heparin (both UFH and LMWH) treatment resulted in a 100% relative risk increase of bleeding events (OR, 2.06; low 95% CI, 1.12-3.77; P=. 02). The number needed to harm (NNH) was 34.1 (95% CI, 18.4-234.7). The figures for LMWH were similar: NNH was 32.9 (95% CI, 17.5-284.0). When only major bleeding events were considered, 19 nonfatal events were recorded [incidence 1.8%, 12 (2.33%) occurred in the heparin group and 7 (1.4%) in the control group]. Heparin (both UFH and LMWH) treatment resulted in a 71% relative risk increase of major bleeding events (OR, 1.71; 95% CI, 0.694.27; P=0.24). The NNH for UFH and LMWH or LMWH alone was 102.2 (low 95% confidence limit, 18.4) and 115.3 (low 95% confidence limit, 39.2), respectively. None of the 19 major bleeding events was considered to be related to the study treatments. Of the 12 major bleeding events that occurred in treated patients, 11 were intracranial bleeding and 1 was gastrointestinal bleeding. Of the 7 major bleeding events that occurred in control patients, 6 were intracranial bleeding and 1 was gastrointestinal bleeding.</p> <p><b>Mortality:</b> Forty-three patients (4.2%) died and 61 (6.0%) experienced an adverse outcome event (death, clinically overt pulmonary embolism, and major bleeding). The number needed for 1 extra event (NNE) for death alone was 46.5 and 39.3 for the combined adverse outcome event. None of the deaths was considered to be related with the study treatments. The most common causes of death were intracranial nonhemorrhagic post surgery complications (12 patients, 9 in the treated group and 3 controls), bleeding (4 patients, 2 treated and 2 controls), and pulmonary embolism (3 patients, 1 treated and 2 controls). Of the 4 deaths related to bleeding, in the treatment group one patient started to bleed during surgery and died on the first postoperative day, inadvertently receiving the first LMWH administration 24 hours after surgery, and one other patient died on day 12 from bleeding associated with full-dose anticoagulant treatment instituted for documented VTE. In the control group, one patient died from hemorrhage during a course of oral anticoagulant treatment for venous thrombosis, and another patient had spontaneous intracranial bleeding on day 22. One other patient in the treated group died of cardio respiratory failure, and one in the control group died of tumor progression; in 2 cases the cause of death remained unknown, and in the remaining 20 cases death was generically referred to as events not related to bleeding or pulmonary embolism.</p>
<p><b>AUTHORS COMMENTS:</b> Limitations, implications for practice and research</p>	<p>"Low-molecular-weight and unfractionated heparin have been shown to be effective for prophylaxis of venous thromboembolism in elective neurosurgery without excessive bleeding risk."</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weakness and strength</p>	<p><b>Potential for bias:</b> Yes (search was confined to one database)</p> <p><b>Weakness/es:</b></p> <ul style="list-style-type: none"> <li>• Although their search strategy included cross-references, review of abstracts and Medline, relevant trials may have been missed by not searching other databases such as EMBASE.</li> <li>• Did not report search terms.</li> <li>• Not clear if search was done by both authors</li> <li>• Not clear if data from the primary studies was independently extracted by one or both authors</li> <li>• Not clear if restriction was applied to English language publications in their search strategy</li> </ul> <p><b>Strength/s:</b></p> <ul style="list-style-type: none"> <li>• A meta-analysis of randomised controlled trial</li> <li>• The article is very well written and reads well.</li> <li>• A very clear presentation of data.</li> <li>• Conducted appropriate analysis and pooled data</li> <li>• Assessed the qualities of the included studies</li> </ul>

<p style="text-align: center;"><b>Evidence Summary</b></p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: 80%;"> <p style="text-align: center;">Anticoagulation therapy as prophylaxis for prevention of DVT/Pulmonary embolism in neurosurgery</p> </div>	<p><b>Study 2</b></p> <p>Constantini, S., A. Kanner, et al. (2001). "Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: a prospective, randomized, double-blind study." <i>Journal of Neurosurgery</i> 94(6): 918-921.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVEL OF EVIDENCE</b></p>	<p>A prospective, randomized, double-blind study (level II)</p>
<p><b>DESCRIPTION:</b> Patient (subjects), Intervention, Comparisons, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Setting:</b> Tel Aviv Sourasky Medical Centre, Israel  <b>Patients:</b> Patients undergoing surgery for the removal of a supratentorial brain tumor (n=103, age 40 years or older).  <b>Intervention:</b> Heparin treated group. Heparin (5000 U) injection subcutaneously, together with premedication, 2 hours before surgery and thereafter every 12 hours until full ambulation or for 7 days (maximum 14 doses). The solution was made up of 50 milligrams of heparin chloride diluted in 1 ml 0.9% NaCl (n=55, 27 men and 28 women).  <b>Comparison:</b> Placebo treated group (0.9% NaCl alone) (n=48, 21 men and 27 women).  <b>Outcomes:</b> recurrent bleeding, surgery, blood transfusion, hospital stay, and mortality.  <b>Inclusion/exclusion criteria:</b> Consecutive patients who underwent craniotomy for the removal of a supratentorial brain tumor within a 14-month period were included. Patients who had pre-existing changes in coagulation or severe systemic disease, or who were receiving medication that influenced coagulation were excluded.</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection, analysis</p>	<p><b>Randomisation:</b> Yes, a block randomisation design. It was performed in the pharmacy.  <b>All patients accounted for:</b> Yes  <b>Patients treated equally:</b> Yes  <b>Similar groups:</b> Yes, for age, sex, weight and distribution of tumor histological profiles.</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Protocol was discontinued in 15 patients (7 in heparin-treated and 8 in placebo-treated groups) for the following reasons: required anticoagulation (n=7); signs of GI bleeding (n=3); hematomas on postoperative CT scan (n=3); deceased (n=1 in placebo-treated group); protocol discontinued by mistake (n=1).</p> <p>Signs of GI bleeding were noted in three patients, two in the heparin-treated group (3.6%) and one in the placebo-treated group (2.1%; p=0.18). All bleeding episodes were controlled by conservative means and did not require surgery. Heparin treatment did not increase bleeding tendency by any of the parameters examined. This was true both for the patients taken as a whole and after stratification by sex, age, tumor location, and tumor pathological characteristics. No statistically significant correlation was founded between the duration of anesthesia and the amount of blood lost during surgery. Postoperatively, the calculated RBC mass loss was 619±45 ml in the heparin-treated group and 692±66 ml in the control group (p=0.36). The amount of fluid measured in the subgaleal drain was 200±21 ml and 247±23 ml, respectively (p=0.12). Two or more units of blood were infused postoperatively in 7 patients in each group. Although patients in the placebo-treated group showed a slightly greater need for blood replacement intraoperatively, the difference was not statistically significant.</p> <p>Of the 103 patients in the two groups, 101 postoperative (24-72 hours) CT scans were evaluated. (1 patient died before scanning and in one patient the scan was not available for evaluation.) The amount of blood at the postoperative site was noted and classified into one of four grades. The distribution of grading was similar in the two groups. One patient in the heparin-treated group and 2 patients in the placebo-treated group required surgery for extensive intracranial hematomas.</p>

<p><b>AUTHORS COMMENTS:</b> Limitations, implications for practice and research</p>	<p>“Perioperative minidose heparin is safe for use in patients undergoing craniotomy for supratentorial tumors. This relatively simple and inexpensive measure is recommended as a routine regimen for the prevention of Thromboembolic phenomena (TEPs) in patients undergoing neurosurgery”</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weakness and strength</p>	<p><b>Potential for bias:</b> Low potential for bias. Baseline characteristic of the two groups was similar. Used block randomisation design to allocate study subjects. Statistician was blinded to group allocation (drug assignment) during data analysis. The surgeon was also blinded to group allocation.</p> <p><b>Weakness/es:</b></p> <ul style="list-style-type: none"> <li>• Not clear if proper sample size calculation was performed prior to the study to establish the number of subjects needed in each group. This may be important if incidence/prevalence of bleeding events is low.</li> </ul> <p><b>Strength/s:</b></p> <ul style="list-style-type: none"> <li>• Clear study objective</li> <li>• A prospective, randomized, double-blind study</li> <li>• Study was approved by ethics committee</li> <li>• Patients signed an informed consent form</li> <li>• Baseline patient characteristics was provided</li> <li>• The amount of blood at the postoperative site was classified into four grades for assessment</li> </ul>

## EXPLANATION OF TERMINOLOGY USED IN SPREADSHEET

**Level of evidence:** A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.

**Focussed question:** The review should address a clearly focused issue, in terms of the population studies, the intervention given and the outcomes considered.

**Search strategy:** A description of methods used to identify relevant studies from various computer databases and other sources.

**Systematic review:** The process of systematically locating, appraising and synthesising evidence from scientific studies in order to obtain a reliable overview.

**Validity:** The degree to which reviewers assessed the quality of the studies they included

Of measurement: an expression of the degree to which a measurement measures what it purports to measure; it includes construct and content validity.

Of study: the degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

**Consistent results:** The similarity of results from the included studies. Often called heterogeneity which refers to the differences in treatment effect between studies contributing to a meta analysis (systematic review). If there is significant heterogeneity, this suggests that the trials are not estimating a single common treatment effect.

**Appropriate analysis of results:** When study results are pooled in a meta-analysis it is important that the results are combined in appropriate manner. The studies should be sufficiently similar in study design, the results of included studies should be clearly displayed and reasons for any variation in results should be discussed.

**Potential for bias:** Bias is a systematic deviation of a measurement from the 'true' value leading to either an over or underestimation of the treatment effect. Bias can originate from many different sources, such as allocation of patients, measurement, interpretation, publication and review of data.