

# Review: Heparin reduces venous thromboembolism in neurosurgery but increases the risk for bleeding

Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery. A meta-analysis. Arch Intern Med. 2000 Aug 14/28;160:2327-32.

## QUESTION

In patients having neurosurgery, what is the efficacy and safety of heparin in the prophylaxis of venous thromboembolism (VTE)?

## DATA SOURCES

Studies were identified by searching MEDLINE (up to 1999) and by scanning meeting abstracts and the reference lists of original and review articles.

## STUDY SELECTION

Studies were selected if they were randomized controlled trials (RCTs) evaluating the efficacy and safety of heparin for the prevention of VTE in patients having neurosurgery.

## DATA EXTRACTION

Data were extracted on the study population; treatment type, dose, and duration; follow-up; and outcome assessment. Efficacy was analyzed per protocol ( $n = 827$ ), and safety was assessed by intention to treat ( $n = 1022$ ). The outcome measure and its variance were calculated for each trial and then pooled.

## MAIN RESULTS

4 RCTs met the selection criteria; 3 evaluated low-molecular-weight heparin (LMWH),

and 1 evaluated unfractionated heparin (UH). 3 included a placebo-controlled group, and 1 included an untreated control group. 187 thromboembolic events were recorded in 827 patients (23%) using LMWH or UH. Heparin prophylaxis led to fewer occurrences of VTE ( $P < 0.001$ ) and proximal deep venous thrombosis ( $P = 0.008$ ) (Table). 19 major bleeds were recorded in 1022 patients (2%); none were fatal, and the difference between the heparin and control groups was not significant. Heparin increased the risk for all bleeding

events ( $P = 0.02$ ) (Table). Deaths did not differ between the groups.

## CONCLUSION

In patients having neurosurgery, heparin reduces venous thromboembolism but increases the risk for bleeding.

Source of funding: No external funding.

For correspondence: Dr. A. Iorio, Institute of Internal and Cardiovascular Medicine, University of Perugia, via Enrico Galvani, Perugia, Italy. FAX 39-075-572-2011. ■

### Heparin vs control therapy in venous thromboembolism (VTE) in neurosurgery\*

Outcomes	Heparin	Control	RRR (95% CI)†	NNT (CI)
VTE (LMWH or UH)	16%	29%	45% (27 to 57)	8 (6 to 14)
VTE (LMWH)	18%	28%	38% (18 to 54)	9 (6 to 21)
Proximal deep venous thrombosis (LMWH)	6%	13%	50% (15 to 69)	16 (10 to 60)
			RRI (CI)	NNH (CI)
All bleeding events (LMWH or UH)	6%	3%	100% (12 to 249)	34 (18 to 235)

\*LMWH = low-molecular-weight heparin; UH = unfractionated heparin. Other abbreviations defined in Glossary.

†Calculated from data in article. Follow-up data are not provided for all trials in the meta-analysis.

## COMMENTARY

This meta-analysis by Iorio and Agnelli establishes parenteral anti-coagulation therapy at prophylactic doses as a reasonable option for patients who are having elective neurosurgery and are prejudged to have a lower risk for bleeding.

Uncertainty that it is the best option lingers because of the differing clinical status of benefit as opposed to risk. Benefit is the reduction of potential "bad things," while risk is the increase of actual "bad things." For example, test-detected, mostly clinically occult VTEs are reduced from 29% to 16%, whereas clinically overt hemorrhages (about a third of them major) are increased from 3% to 6%. Of interest is the fate of 195 randomly assigned patients who did not have VTE testing; among them, clinically overt thromboembolism developed in 3 out of 101 treated patients and 7 out of 94 control patients. Hence, considering only clinically overt "bad things," net rates between treated and control groups were similar. Finally, the rates of aggregated serious adverse outcomes (major hemorrhage, death, pulmonary embolism) did not

differ, although > 1000 patients were randomly assigned in the 4 trials that contributed data.

Clinicians who use these results as a basis for treatment will point out that clinically occult VTEs may cause subclinical pulmonary embolism, low-grade fevers, nonspecific leg pain, and other negative phenomena that may prolong hospitalization and adversely affect health. On the other hand, clinically occult bleeding in sensitive neural tissues may also negatively affect recovery and the eventual outcome.

Future trials should be sensitive to outcomes that might reflect the effects of occult thromboembolism and bleeding (e.g., length of stay, destination at discharge, costs, and global ratings of neurologic outcome). In my opinion, further studies using placebo groups are still ethical.

David C. Anderson, MD  
Hennepin County Medical Center  
Minneapolis, Minnesota, USA