and may allow confident institution of appropriate early treatment to restore sinus rhythm, is therefore highly desirable.

Preliminary data has demonstrated that peripheral D-dimer estimation correlates with atrial coagulation activity (Li-Saw-Hee *et al*, 1999). Two studies (Kimura *et al*, 1995; Nakagawa *et al*, 2001) have demonstrated higher D-dimer levels in the presence of low atrial flow, a risk factor for developing atrial thrombus, although another study (Black *et al*, 1993) did report conflicting results. Several studies (Hayashi *et al*, 1991; Yasaka *et al*, 1991; Sakai *et al*, 1994; Heppell *et al*, 1997; Somloi *et al*, 2003) have demonstrated significantly raised D-dimer levels in the presence of atrial thrombus.

Studies that have investigated the clinical utility of D-dimer for exclusion of atrial thrombus in AF have yielded promising results. Using data from the study by Yasaka *et al* (1991), D-dimer excluded atrial thrombus with a negative predictive value (NPV) of 86% in a population with a high prevalence of atrial thrombi (40%). It is possible that the test would perform better in the Emergency Department population. Further, D-dimer had a sensitivity of 100% for the detection of mobile thrombi, which represent a higher embolic risk.

The high NPV of 98% reported by Somloi *et al* (2003) means that, in a population with a 12.3% pre-test probability of atrial thrombus, the post-test probability following a negative test is 2%. If 100 patients were treated according to D-dimer results, one false negative diagnosis would be expected, but early cardioversion would be possible for a further 68 patients without atrial thrombus.

This compares favourably with TOE for detection of atrial thrombus, which has been reported to have a sensitivity of 93.3% and a NPV of 98.9%. As such, for every 100 patients treated according to TOE results, 1 false negative would be expected (Hwang *et al*, 1993). Further, although warfarin has been shown to effectively reduce atrial thrombus, 14% of patients may have residual thrombus following 4 weeks of treatment (Collins *et al*, 1995).

The evidence therefore suggests that D-dimer has great potential for clinical use in the emergency department to exclude atrial thrombus prior to attempted electrical or pharmacological cardioversion. Further evidence from large studies would be desirable before implementation.

It is important to stress, however, that the coagulation system is activated following electric, but not pharmacologic cardioversion (Giansante *et al*, 2000). The risk of atrial thrombus formation and systemic embolism therefore persists even after reversion to sinus rhythm following electric cardioversion. As such, successful electric cardioversion following a negative D-dimer result would not avoid the need for anticoagulation with warfarin. European Society of Cardiology guidelines state that patients should be anticoagulated for 3–4 weeks post-procedure (Fuster *et al*, 2001).

► CLINICAL BOTTOM LINE

D-dimer is promising as an early marker of mural thrombus in atrial fibrillation and may be no less effective than either transoesophageal echocardiography or anticoagulation for 4 weeks. The evidence suggests that a negative result enables safe early cardioversion, although further evidence from large studies would be desirable.

Level of evidence

Level 2 – Studies considered were neither 1 or 3.

BET editor's comment

The authors identified a number of studies that were relevant to the three-part question but were in Japanese language. Although no translator was available, it was felt that excluding

these studies by limiting the search strategy to English language would ignore some important evidence. The abstracts have therefore been tabulated, although it should be recognised that there are significant limitations to appraising only the abstract of a study.

Li-Saw-Hee FL, Blann AD, Goldsmith I, *et al*. Indexes of hypercoagulability measured in peripheral blood reflect levels in intracardiac blood in patients with atrial fibrillation secondary to mitral stenosis *Am J Cardiol* 1999;**83**:1206–9.

Hwang JJ, Chen JJ, Lin SC, *et al*. Diagnostic accuracy of transoesophageal echocardiography for detecting left atrial thrombi in patients with rheumatic heart disease having undergone mitral valve operations *Am J Cardiol* 1993;**72**(9):677–781.

Hayashi I, Miyauchi T, Sakamoto K, *et al*. [Laboratory diagnosis of left atrial thrombi in patients with mitral stenosis] [Japanese] [Abstr] *J Cardiol* 1993;**23**(2):177–183.

Fuster V, Ryden LE, Asinger RW, *et al*. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: Executive summary. *Circulation* 2001;**104**:2118–50.

Giansante C, Fiotti N, Altamura N, *et al*. Coagulation indicators in patients with paroxysmal atrial fibrillation: Effects of electric and pharmacologic cardioversion *Am Heart J* 2000;**140**(3):423–9.

Stoddard MF, Dawkins PR, Prince CR, *et al*. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transoesophageal echocardiographic study. *J Am Coll Cardiol* 1995;**25**:452–9.

Manning WJ, Silverman DI, Waksmonski CA, *et al*. Prevalence of residual left atrial thrombi among patients with acute thromboembolism and newly recognized atrial fibrillation *Arch Intern Med* 1995;**155**:2193–8.

Collins LJ, Silverman DI, Douglas PS, *et al*. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution *Circulation* 1995;**92**:160–3.

Sakurai K, Hirai T, Nakagawa K, *et al*. Left atrial appendage function and abnormal hypercoagulability in patients with atrial flutter *Chest* 2003;**124**:1670–5.

Yasaka M, Miyatake K, Mitani M, *et al*. Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis *Br Heart J* 1991;**66**(1):22–5.

Hayashi I. [Laboratory diagnosis of left atrial thrombi in patients with mitral stenosis] [Japanese] [Abstr] *Fukuoka Igaku Zasshi - Fukuoka Acta Medica* 1991;**82**(11):550–61.

Black IW, Chesterman CN, Hopkins AP, *et al*. Haematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation *J Am Coll Cardiol* 1993;**21**(2):451–7.

Sakai M, Hamamatsu A, Kuboki K, *et al*. [Examinations to detect left atrial thrombus and blood coagulation test analyses in aged patients with atrial fibrillation] [Japanese] [Abstr] *Nippon Ronen Igakkai Zasshi - Japanese Journal of Geriatrics* 1994;**31**(6):447–55.

Kimura T, Yoshida S, Sato K, *et al*. [Relationship between left atrial spontaneous contrast echo and coagulofibrinolytic findings] [Japanese] [Abstr] *Rinsho Byori - Japanese Journal of Clinical Pathology* 1995;**43**(3):275–280.

Heppell RM, Berkin KE, McLenachan JM, *et al*. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation *Heart* 1997;**77**:407–11.

Nakajima K. [The relationship between left atrial thrombus and haematological markers in patients with chronic non-rheumatic atrial fibrillation] [Japanese] [Abstr] *Nippon Ronen Igakkai Zasshi - Japanese Journal of Geriatrics* 2000;**37**(11):903–7.

Nakagawa K, Hirai T, Shinokawa N, *et al*. Aortic spontaneous echocardiographic contrast and hemostatic markers in patients with nonrheumatic atrial fibrillation *Chest* 2002;**121**:500–5.

Somloi M, Tomcsanyi J, Nagy E, *et al*. D-dimer determination as a screening tool to exclude atrial thrombi in atrial fibrillation *Am J Cardiol* 2003;**92**:85–7.

Does clopidogrel increase morbidity and mortality after minor head injury

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A short cut review was carried out to establish whether patients who are on clopidogrel and suffer a minor head injury have an increase in morbidity and/or mortality. Four papers had some data relevant to the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are tabulated. The clinical bottom line is that there is

Table 3

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Rozzelle <i>et al</i> , 1995, USA	Patients aged 65 years or over admitted with a subdural haematoma.	Retrospective cohort	Risk factor for death (logistic regression)	Anti-thrombotic medication use was not associated with hospital mortality.	30% had no documented trauma. Only 31 patients were on anti-platelet treatment.
Mina <i>et al</i> , 2002, USA	37 patients admitted with intracerebral injury and on anticoagulants (including clopidogrel) and 37 matched controls.	Retrospective analysis	Death	14/37 (38%) vs 3/37 (8%) in controls, $p=0.006$	Retrospective study. Only 2 patients were on clopidogrel.
Ohm <i>et al</i> , 2005, USA	90 patients, 50 years or older, taking anti-platelet agents with a traumatic intra-cranial haemorrhage matched to 89 control patients with similar ISS, GCS, age and sex not taking anti-platelet agents.	Retrospective chart review	Mortality	21/90 (23%) study gp vs 8/89 (8.9%) controls, $p=0.016$.	Retrospective review. Different anti-platelet agents used.
			Need for surgery	21/90 (23%) vs 17/89 (19%), NS	Co-morbidity rates were different in the 2 groups. 71% of study gp had 3 or more co-morbidities vs. 35% in the control gp ($p<0.001$). Small numbers.
			Blood transfusion	20/90 (22%) vs 13/89 (15%), $p=0.262$	
			Platelet transfusion	24/90 (27%) vs 5/89 (6%), $p=0.001$	
			FFP transfusion	13/90 (14%) vs 3/89 (3%), $p=0.009$	
Jones <i>et al</i> , 2006, USA	43 injured patients, over the age of 50, documented to be taking clopidogrel (P), matched to controls (C) with similar mechanisms of injury, age, sex and ISS. 25 head injuries in group P (9 SDH/EDH) and 21 head injuries in group C (10 SDH/EDH)	Retrospective chart review	Death	3/9 (33%) in p vs 4/10 (40%) in C, NS	Small numbers
			Need for surgery	6/9 (66%) in P vs 2/10 (20%), $p=0.055$	Retrospective review
			Blood/platelet transfusion	11 in p vs 3 in C, $p<0.015$	Not isolated minor head injury: patients reported were classed as having major head injuries
			Rebleed	5/9 (55%) vs. 1/10 (10%), $p=0.005$	
			ICU stay	5.8 days for p vs 5.3 days for C, NS	
			Hospital stay	11 days for p vs 10.5 days for C, NS	

ED, extradural haemorrhage; NS, not significant; SDH, subdural haemorrhage

insufficient evidence to state that clopidogrel worsens outcomes in patients with a minor head injury.

Three part question

In a patient with a [head injury], does concurrent [treatment with clopidogrel] [increase morbidity and mortality]?

Clinical scenario

A 78-year-old male presents to the emergency department in a coma 2 days after a minor head injury. You note he is taking clopidogrel for treatment of his ischaemic heart disease. CT scan shows a large sub-dural haematoma. You wonder whether the clopidogrel has contributed to the development of this haematoma?

Search strategy

Medline: 1950–2007 April week 1 [(brain injury.mp. or exp Brain Injuries/) OR (craniocerebral trauma.mp. or exp Craniocerebral Trauma/) OR (head injur\$.mp.)] AND [(antithromb\$.mp.exp Platelet Aggregation Inhibitors/or clopidogrel.mp.) OR (platelet aggregation inhibitor\$.mp.)] limit to (humans and english language). EMBASE: [cranio-cerebral trauma OR head injury] AND [clopidogrel OR antithrombocytic agent] LIMIT to humans

Search outcome

Medline yielded 113 papers, EMBASE 58. Four were relevant (table 3).

Comments

The clinical impression is that concomitant with the increase in the number of patients taking clopidogrel, there is a rise in the number of patients on clopidogrel presenting with significant intra-cranial haemorrhage after minor head injury. Whether clopidogrel contributes to the development of the intra-cranial haemorrhage is unclear and there is currently very little evidence addressing this subject. This is perhaps not surprising considering that clopidogrel is a relatively new drug and even with older established anticoagulant and anti-thrombotic drugs such as warfarin and aspirin, there is continued debate about the quality and quantity of evidence delineating their exact role in the development of intra-cranial haemorrhage following head injury.

► CLINICAL BOTTOM LINE

There is insufficient evidence to firmly state that clopidogrel worsens outcomes in patients with minor head injury.

Rozzelle CJ. Wofford JL. Branch CL. Predictors of hospital mortality in older patients with subdural hematoma. *Journal of the American Geriatrics Society* 1995;43(3):240–4.

Mina AA. Knipfer JF. Park DY. *et al.* Intracranial complications of preinjury anticoagulation in trauma patients with head injury. *J Trauma* 2002;53(4):668–72.

Ohm C. Mina A, Howells G, *et al.* Effects of Antiplatelet Agents On Outcomes for Elderly Patients With Traumatic Intracranial Hemorrhage. *J Trauma* 2005;58:518–22

Jones K. Sharp C, Mangram A, *et al.* The Effects of Preinjury Clopidogrel Use On Older Trauma Patients with Head Injuries. *Am J Surg* 2006;192:743–5.