ORIGINAL ARTICLE

Homocysteine and its relationship to deep venous thrombosis in patients undergoing total knee or hip arthroplasty

Mouravas H[2], Verettas D[1], Kazakos K[1], Xarhas K[1], Panagiotou N[2], Ellinas P[2]

[1] Orthopaedic Department, Dimocritio University of Thrace, Alexandroupolis

[2] "Korgialenio Benakio" Red Cross Hospital Athens[2]

Abstract

Backround: The role of hyperhomocysteinemia as an independent risk factor for venous thrombosis after lower limb arthroplasty remains questionable. The objective of this study is to determine the relationship between hyperhomocysteinemia and postoperative thromboembolic events in patients undergoing total hip or knee arthroplasty.

Method: Between September 2004 and June 2006, we studied 172 patients (41 male and 131 female) with mean age 70.2 years (48-85). Total plasma homocysteine as well as other thrombophilic agents (proteinC, protein S, Antithrombin III, Lupus anticoagulants, APC-Resistance) were measured preoperatively. Duplex sonography was performed twice postoperatively, on the 7th day (+/-2) and on the 42th day (+/- 2). Spiral CT was performed when pulmonary embolism was suspected.

Results: Four patients developed deep venous thrombosis from which two developed pulmonary embolism. Only one of these four patients had high levels of total plasma homocysteine.

Conclusions: Total plasma homocysteine does not seem to affect the development of deep venous thrombosis in patients undergoing total knee or hip arthroplasty and receive low molecular weight heparine. Hippokratia 2010; 14 (3): 185-188

Key words: hyperhomocysteinemia, deep venous thrombosis, knee arthroplasty, hip arthroplasty

Corresponding author: Hercules Mouravas, e_mail: mourherc@gmail.com, tel: 24280 93962, 24210 24363, Mobile: 6942 99 00 99

Deep venous thrombosis (DVT) is a major complication of total hip arthroplasty (THA) or total knee arthroplasty (TKA), with potentialy life-threatening consequences. Venographic studies in the absence of thrombophylaxis show that the DVT rates range from 42% to 57% for THA and from 41% to 85% for TKA. The incidence of fatal pulmonary embolism (PE) without any prophylaxis ranges from 0.1% to 2% for THA and for 0.1% to 1.7% for TKA[1]. Modern prophylaxis against DVT has reduced these rates to 4.4%[2] and the incidence of fatal PE to 0.13%- 0.15% after THA and 0.2%-0.7% after TKA[3].

Although the majority of patients undergoing TKA or THA are subjected perioperatively to similar predisposing risk factors, only a subset of patients develop thromboembolism. Recently, there has been a substantial improvement in the understanding of the impact which acquired and heritable thrombophilia have on venous thromboembolism (VTE) occurrence, in a variety of settings. However, whether thrombophilia contributes to VTE in the course of major orthopaedic surgery, has been the subject of only a very few studies. Furthermore, whether preoperative screening for thrombophilias would identify those at particular risk and would be beneficial, or even cost effective, is not yet known.

The role of increased homocysteine -hyperhomocysteinemia- as an independent risk factor for arterial and venous thrombosis has become increasingly appreciated. There are common underlying pathogenetic mechanisms associated with vascular injury leading to these clinical changes. The proposed pathogenetic mechanisms are oxidative damage of the endothelium through suppression of the vasodilator nitric oxide, increasing the levels of asymmetric dimethylarginine, and impaired methylation, vascular smooth muscle proliferation, promotion of platelet activation and aggregation and disruption of the normal procoagulant-anticoagulant balance favoring thrombosis. Homocysteine is formed from methionine by transmethylation reaction. Key enzymes in the rather complex homocysteine metabolic pathway are the cystathionine β synthase (CbS), the methionine synthase (MTR) and the methelenetetrahydrofolate reductase (MTFHR)[4].

The objective of this study was to determine the relationship between hyperhomocysteinemia and postoperative thromboembolic events in patients undergoing THA or TKA.

Materials and methods

Between September 2004 and June 2006, 204 patients underwent primary THA or TKA in two orthopaedic departments. 31 patients were excluded from the study, the criteria for exclusion being a history of DVT or PE (4 patients), ongoing anticoagulation therapy (11 patients), previous operation in the same leg (14 patients), kidney disease (creatinine>2) (2 patients). One patient also excluded from the study because of a periprothetic fracture 23 days after THA. We studied 172 patients (41

Table 1: The occurrence of pathological values of homocysteine and other thrombophilic factors.

Thrombophilic factors	Occurance
Homocysteine >15μmol/L	45 (26.12%)
AT III defisiency < 80%	3 (1.74%)
APC-Resistance < 120 sec	8 (4.51%)
Protein S <63%	2 (1.16%)
Protein C deficiency <70%	2 (1.16%)
Lupus Anticoagulant positive	0 (0%)

male and 131 female) with mean age 70.2 years (48-85). We performed 99 TKA and 73 THA operations. The type of anesthesia was combined spinal and epidural. In all of these patients we administered prophylactic anticoagulant therapy, in the form of Calcium Nordopaine, for six weeks postoperatively.

All blood samples were collected in the morning after overnight fasting. For the measurement of homocysteine serum level we used ¨Abbot Homocysteine (HCY) assay¨, which is based on the fluorescence polarized immunoassay (FPIA) technology, on the IMx analyzer[5] (Abbot Laboratories, Abbot Park, IL). The blood samples were collected in tubes without additive and transferred to the haematology laboratory on ice. Serum samples were stored frozen at -20˚C and measurements of homocysteine level were performed in less than 1 week.

The platelets' count was performed in EDTA anticoagulant whole blood samples using a Coulter LH-750 haematology analyzer (Beckam Coulter Inc.)

The blood samples for the measurement of prothrombin time (PT), INR, partial thromboplastin time (PTT), fibrinogen, D-dimers, fibrin/fibrinogene degradation products in plasma (FDP), antithrombine III (AT III), protein C (PC) and protein S (PS) activity in plasma, activated protein C resistance in plasma (APC-R) and lupus anticoagulants (LA) qualitative determination, were obtained in tubes containing 3.2% (weight/volume) trisodium citrate (9 parts of blood:1 part anticoagulant). The measurements of PT, INR, PTT, fibrinogen and FDP were carried out in less than 2 hours after blood collection while for the rest of the assays plasma was stored frozen in -80˚C and assays were performed in less than 1week. All the measurements and quality control for the above parameters with exception of FDP, were carried out with a STA coagulation automated instrument (Diagnostica Stago, France) in accordance with manufacturer´s instructions. PT and APTT were determined with STA Neoplastin kit and STA-PTT A kit respectively. Fibrinogen quantitive determination by the clotting method of Clauss was performed with the use of STA-fibrinogene kit. D-dimers plasma levels were measured by the immuno-turbidimetric method with the use of STA-Liatest D-di kit. The Diagnostica Stago protein S functional clotting assay was used for the determination of protein S activity. Functional protein C activity was determined in a colorimetric assay (STA- stachrom Protein C, Stago). We also used the STA-stachrom AT III colorimetric assay kit for the quantitative measurement of antithrombin activity in plasma. The APC-R in plasma was assessed with the use of STA- Staclot APC-R kit, for STA analyzer. We used PTT LA, a lupus anticoagulants sensitive reagent kit, for the qualitative detection of LA in plasma.

The diagnosis of DVT was established on clinical grounds and on colour Doppler exam of the lower extremities. The diagnosis of PE was based on Spiral CT findings. All patients were submitted in Duplex sonography which was performed twice postoperatively, the first on the 7th day (+/-2) and the other on the 42th day (+/- 2). Patient follow-up was of 6 weeks.

Statistical analysis

Statistical analysis was performed using statistica start soft (www.startsoft.com). Chi-square test was performed in order to determine differences between observed proportions.

Results

The occurrence of pathological values of homocysteine and other thrombophilic factors is shown on Table 1.

Out of 172 patients, 4 developed DVT from which 2 developed non fatal pulmonary embolism. Only one of these four patients had high levels of total plasma homocysteine, the other 3 having normal values. Using chi-square analysis no significant difference was found between patients with normal and high level of homocysteine as to the frequency of thrombotic events (P value:0.95).

Comparative data between patients with high and normal levels of total plasma homocysteine are presented in Table 2.

All the patients that suffered thrombotic events were women. Specifically, the patient with hyperhomocysteinemia underwent TKA and had DVT on the 40th post op day. Out of the 3 patients with normal homocysteine levels, one suffered DVT on the 7th post op day, following TKA.

The two patients with PE showed no clinical evidence from the limbs and the first ultrasound exam was normal. One of them underwent TKA and suffered PE on the 8th post op day, while the other underwent THA and suffered PE on the 27th post op day. Both PE incidents were manifested with intense dyspnoea but there were no fatalities.

Table 2: Comparative data between patients with high and normal levels of total plasma homocysteine.

General characteristics	Patients with normal levels of homocysteine (127)	Patients with increased levels of homocysteine (45)
Age	69,8	70,5
Sex	103♀-24♂	27♀ - 18♂
BMI	29	28
Operation	75 TKA-52THA	29TKA -16THA
DVT - PE	3	1

Discussion

We performed this study in order to determine the relationship between hyperhomocysteinemia and postoperative thromboembolic events in patients undergoing THA or TKA. Some patients might have a genetic or serologic predisposition that may interact with environmental factors that lead to thromboembolic disease. If these patients could be identified preoperatively, they could be targeted for pharmacologic intervention, sparing many low risk patients from pharmaceutic prophylaxis.

In this study we deal only with symptomatic VTE. We stress the difference between symptomatic VTE and asymptomatic VTE because most studies that have evaluated risk factors for VTE have analysed the relation between demographic or clinical variables and asymptomatic VTE only[6,7]. Unfortunately, risk factors for the development of asymptomatic VTE and symptomatic VTE, the more clinically relevant end point, may be quite different. Using asymptomatic VTE as the surrogate outcome may obscure or distort the relation between a specific risk factor and symptomatic VTE[8]. For example, obesity may be weakly associated with asymptomatic VTE, but strongly associated with the development of symptomatic VTE, a very important finding. Furthermore, reliance on one-time ¨snapshot¨ or the incidence of VTE using venography does not reflect the dynamic process of clot formation and dissolution, which varies over time. For example, in one study of patients who had a negative venograme 7-10 days after THA, 20% had a demonstrable clot 21 days later[3]. Because of such observations, the most clinically useful studies are ones that report hard endpoints such as the incidence of symptomatic VTE.

Our first conclusion is that hyperhomocysteinemia is a fairly common finding among people over 60 years old, an age group particularly prone to conditions that necessitate THA or TKA. A high level of homocysteine (>15μmol/L) was measured in 26.12% of our study´s patient population. The prevalence of hyperhomocysteinemia in the general population is not known. It is observed in approximately 5% but is also age and gender related. Plasma homocysteine levels are higher in men than in women and increase from 10.8 μmol/L at age 40-42 up to 12,4 μmole/L between 65-67 years[9].

Total plasma homocysteine does not seem to affect the development of deep venous thrombosis in patients undergoing total knee or hip arthroplasty and receive low molecular weight heparine (LMWH). Our results are in accordance with most of the published data.

Hypehomocysteinemia is supposed to cause endothelial damage and is associated with an increased risk for arterial and venous thromboembolic events. However, intervention with vitamin supplementation has been shown to successfully restore normal homocysteine concentrations, but without concomitant reductions in disease risk. Thus the mechanistic relation between homocysteine balance and disease states, as well as the value of homocysteine management, remains an area of intense investigation[10,11].

M. Den Heijer et all in a meta-analysis of published epidemiological studies, demonstrate a modest association of homocysteine with venous thromsbosis. The elevated risk associated with the MTHFR 677TT genotype provides some support for causality[12].

Ringwald et al found that patients with at least one homozygous or two heterozygous mutations of MTHFR C677T and A1298C polymorphism, had increased risk for symptomatic DVT after elective THA. Homocysteine levels have not been measured in this study. It also is unclear whether the presence of a heterozygous and especially a homozygous state of MTHFR C677T and/or A1298C polymorphism might result in an increased risk for DVT independently from homocysteine levels[13].

Joseph et al in a prospective study of 569 patients that underwent either THA or TKA and preoperatively studied for thrombotic risk factors, come to the conclusion that Factor V Leiden, prothrombin G20210A, MTHFR C677T mutations were not significant risk factors for VTE[14].

Westrich et all compared 14 patients that underwent THA and suffered PE with 14 patients that didn't suffer PE and concluded that genetic thrombophilia and hypofybrinolysis were more frequent in patients who had pulmonary embolism after THA than in those who had not. The presence of multiple genetic thrombophilic polymorphisms, particularly prothrombin G20210A and AT III, rather than any single genetic prothrombotic abnormality, appears to signal an increased thromboembolic risk in patients undergoing THA. Specifically for homocysteine, there was a nonsignificant ($p>0.05$) trend towards a higher mean homocysteine level in patients with pulmonary embolism than in controls[15].

Mont et all in a similar study of 29 patients, concludes that in order to identify patients at high risk of pulmonary embolism preoperatively, plasminogene activator inhibitor, dillute Russell´s viper venom time, PT, and cholesterol levels were the most predictive. Using at least one of these four measures as a screening test to detect risk of PE, the test is sensitive (100%), and the predictive value of a negative test is high (100%). As for homocysteine, median homocysteine was higher in patients (11.4μmol/L) than in controls (9,9μmol/L). But even in these cases the values were within normal limits, considerably lower than 15μmol/L[16].

Total plasma homocysteine does not seem to affect the development of deep venous thrombosis in patients undergoing total knee or hip arthroplasty and receive LMWH. Hence, preoperative screening of patients for thrombophillic genotypes and haemostatic risk factor, in an attempt to identify a particularly high risk group, is not recommended.

References

1. Colwell CW. The ACCP guidelines for thrombophylaxis in total hip and knee arthroplasty. Orthopedics. 2009; 32: 67-71.
2. Keeney JA, Clohisy JC, Curry MC, Maloney WJ. Efficacy of combined modality prophylaxis including short-duration warfa-

rin to prevent venous thromboembolism after total hip arthroplasty. J Arthroplasty. 2006; 21: 469-475.
3. White HR, Henderson MC. Risc factors for venous thromboembolism after total hip and knee replacement surgery. Curr Opin Pulm Med. 2002; 8: 365-371.
4. Eldibany MM, Caprin AJ. Hyperhomocysteinemia and thrombosis: An overview. Arch Pathol Lab Med. 2007; 131: 872-884.
5. Shiphandler M.T, Moore EG. Rapid, fully automated measurement of plasma homocysteine with the Abbott Imx analyzer. Clin Chem. 1995; 41: 991-994.
6. Salvati EA, Pellegrini VD Jr, Sharrock NE, Lotke PA, Murray DW, Potter H, et al. Recent advances in venous thromboembolic prophylaxis during and after total hip replacement. J Bone Joint Surg Am. 2000; 82: 252-270.
7. Wang CJ, Wang JW, Chen LM, Chen HS, Yang BY, Cheng SM. Deep vein thrombosis after total knee arthroplasty. J Formos Med Assoc. 2000; 99: 848-853.
8. Bucher CH, Guyatt HG, Cook JD, Holbrook A, McAlister AF. Users´ guides to the medical literature: XIX.Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. JAMA. 1999; 282: 771-778.
9. Brustolini S, Giugliani R and Felix TM. Genetics of homocysteine metabolism and associated disorders. Braz J Med Biol Res. 2010; 43: 1-7.
10. Williams KT, Schalinske KL. Homocysteine metabolism and its relation to health disease. Biofactors. 2010; 36: 19-24.
11. Ray JG. Hyperhomocysteinemia: no longer a consideration in the management of venous thromboembolism. Curr Opin Pulm Med. 2008; 14: 369-373.
12. Den Heijer M, Lewington S, Clark R. Homocysteine, MTFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. J Thromb Haemost. 2005; 3: 292-299.
13. Ringwald J, Berger A, Alder W, Kraus C, Pitto PR. Genetic polymorphism in venous thrombosis and pulmonary embolism after total hip arthroplasty. Clin Orthop Relat Res 2009; 467: 1507-1515.
14. Joseph EJ, Low J, Courtenay B, Neil JM, McGrath M, Ma D. A single-centre prospective study of clinical and haemostatic risk factors for venous thromboembolism following lower limb arthroplasty. Br J Haematol. 2005; 129: 87-92.
15. Westrich HG, Weksler BB, Glueck JC, Blumenthal FB, Salvati AE. Correlation of thrombophilia and hypobrinolysis with pulmonary embolism following total hip arthroplasty. J Bone Joint Surg Am. 2002; 84: 2161-2167.
16. Mont AM, Jones CL, Rajadhyaksha DA, Shuler SM, Hungerford SD, Sieve-Smith L, et al. Risk factors for pulmonary emboli after total hip or knee arthroplasty. Clin Orthop Relat Res. 2004; 422: 154-163.