

## Deep Vein Thrombosis Following Hip Fracture and Prevalence of Hyperhomocysteinaemia in the Elderly

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### Abstract

**Introduction:** The prevalence of deep vein thrombosis (DVT) in the West is reported to be as high as 50% after hip surgery. A study performed 14 years ago showed the incidence in Singapore to be <10%. Lately, some case-control and cross-sectional studies have suggested hyperhomocysteinaemia as an independent risk factor for DVT. This study investigates the local incidence of DVT and plasma hyperhomocysteinaemia in elderly patients presenting with proximal hip fracture. **Materials and Methods:** We recruited 104 consecutive patients from April 2001 to November 2001 who satisfy certain criteria. Firstly, patients of both genders who were >55 years old with radiological diagnosis of neck of femur fracture, intertrochanteric or subtrochanteric fracture. Secondly, these patients must not have any haemorrhagic or thrombogenic disease. Thirdly, patients were not given folate and B complex pre- or postoperation. Duplex ultrasound was then done for these patients on the 5<sup>th</sup> to 7<sup>th</sup> postoperative day. **Results:** The incidence of DVT above the trifurcation was 7.7 %, no incidence of pulmonary embolism (PE) was detected. The incidence of hyperhomocysteinaemia was 52.3%. **Conclusions:** The incidence of DVT in the local population after proximal hip fracture is much lower than in the West. The use of DVT prophylaxis in Asians should be selective to avoid incurring extra cost and its associated morbidity. Case-control studies and cross-sectional studies clearly indicate that hyperhomocysteinaemia is an independent risk factor for venous thrombosis. Given the high incidence of hyperhomocysteinaemia in our elderly with hip fracture, the prophylactic correction of hyperhomocysteinaemia with folate and vitamin B supplements is justified.

Ann Acad Med Singapore 2004;33:235-8

**Key words:** DVT prophylaxis, Duplex scan

### Introduction

Western literature reports a high incidence of deep vein thrombosis (DVT) after hip surgery in the absence of prophylaxis. It is reported to be as high as 50% of which 20% to 30% are in the proximal vein.<sup>1,2</sup> The experience in Singapore suggests a lower incidence of <10%.<sup>3</sup> However, a recent publication on Asian patients suggested an incidence of 62.5%.<sup>4</sup> This prompted us to review the literature on the incidence of DVT in Asians and to relook our local incidence following hip fracture.

Hyperhomocysteinaemia is an established risk factor for

arteriosclerosis and vascular disease.<sup>5,6</sup> Lately, there have been some case-control and cross-sectional studies suggesting that it is also an independent risk factor for DVT.<sup>7,8</sup> This study investigates the incidence of hyperhomocysteinemia in our cohort of patients.

### Materials and Methods

We recruited 104 consecutive patients from April 2001 to November 2001 who satisfy certain criteria. Firstly, patients of both genders who were >55 years old with radiological diagnosis of neck of femur fracture,

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intertrochanteric or subtrochanteric fracture. Secondly, these patients must not have any haemorrhagic or thrombotic disease. Thirdly, patients are not given folate and B complex pre- or postoperation.

Data on age, social status, bone mass index, premorbid mobility, exercise level, smoking, alcohol, caffeine intake, type of fracture, comorbid medical conditions, medications, nutrition status and length of time from admission to operation were collected. The investigations included fasting morning level of homocysteine, haemoglobin, total lymphocyte count, calcium level, phosphate level, alkaline phosphatase, albumin, total protein and bone mineral density.

No pharmacological or mechanical prophylaxis measures was employed. Most operations were carried out under regional anaesthesia (80%). The type of operation, implant, surgeon and duration were recorded. Postoperative rehabilitation, ambulation status and length of stay were also noted.

After operation, each patient was monitored closely for signs and symptoms of DVT or pulmonary embolism (PE). Bilateral duplex ultrasound of the lower limb was performed from the 5<sup>th</sup> to 7<sup>th</sup> postoperative day. Duplex scan was carried out earlier or repeated if there was any clinical suspicion of DVT, such as calf pain, lower limb swelling, prominence of superficial veins, skin colouration and fever. If PE was suspected, a duplex and ventilation/perfusion scan were ordered immediately.

The mean age of the patients was 78 years (range, 55 to 98 years). The ratio of female to male subjects was 3:1. The mean bone mass index of our patients was 20.3. In our cohort, 88.5% were non-smokers, 6.7% were smokers and 4.8% erstwhile smokers; 96% were teetotallers and 4% were drinkers. The median number of days to operation was 3. The mean duration of the operation was 62 minutes. Twelve patients were not operated on, but treated with traction.

Two patients who died from acute myocardial infarction were not included in the study. In this cohort, 48% had neck of femur fractures, 51% had intertrochanteric fractures and

1% had subtrochanteric fracture. Finally, 51% of the patients had dynamic hip screw insertion, 25% had hemiarthroplasty done, 11.5% had cancellous screw fixation, 11.5% were treated conservatively and 1% had a condylar blade plating.

## Results

Eight patients (7.7%) had proximal DVT of the index leg detected by duplex scan (Table 1). The median plasma homocysteine level was 15.5 mmol/L (range, 5.7 mmol/L to 30.8 mmol/L). In this cohort, 52.3% were found to have hyperhomocysteinaemia >15 mmol/L. The mean homocysteine levels in the 8 patients with DVT was 20.3 mmol/L whilst the remainder was 16.5 mmol/L. The difference in the means was, however, not statistically significant ( $P = 0.08$ ).

Of the 8 patients with DVT, only 6 had at least 1 clinical sign of DVT. All these patients were subsequently started on low molecular weight heparin and were discharged without any complications or progression of the thrombosis.

There was no statistical association between the incidence of DVT and gender, type of operation, duration of operation or pattern of fracture.

## Discussion

Hip fracture is one of the most common orthopaedic conditions encountered. As a result of immobility and the operation associated with this condition, patients are regarded as having a high risk of developing DVT. There are only a handful of studies carried out in Asia that examined the incidence of DVT associated with hip fracture. The practice of prophylactic prevention of DVT is mainly based on Western literature. Clearly, the genetic make-up of Asians and Caucasians is different. Tinckler first highlighted this in 1964.<sup>9</sup>

In Singapore, Mitra et al<sup>3</sup> prospectively followed up on 72 patients with proximal hip fracture and reported an incidence of 9.7%. In Hong Kong, Mok et al<sup>10</sup> reported an incidence of 8% in 45 patients with proximal hip fracture. In Thailand, Atichartakarn et al<sup>11</sup> examined 50 patients who had undergone hip surgery, including 19 total hip replacements, and found the incidence to be 4%. In Korea,

Table 1. Type of Fracture and Deep Vein Thrombosis

Fracture	Implant	Deep vein thrombosis		Total
		Negative	Positive	
Neck of femur	Hemiarthroplasty	24	2	26
	Cancellous screw	11	1	12
	Conservative	11	1	12
Intertrochanteric	Dynamic hip screw	49	4	53
Subtrochanteric	Condylar blade plate	1	0	1
Total		96	8	104

Kim and Suh<sup>12</sup> reported an incidence of 10% amongst 146 patients undergoing total hip replacement. In Malaysia, Dhillon et al<sup>4</sup> reviewed 88 consecutive patients who had undergone operation for proximal hip fracture, total knee and total hip replacement and reported an incidence of 12.5% for proximal DVT. Venograms were performed in all these studies to diagnose DVT.

The findings of our study agree with those of other studies performed in Asia. A closer scrutiny of the 8 patients revealed that they had other coexisting factors, which predisposed them to DVT. Four of them had an operation time >60 minutes. One had an operation that was carried out 1 week after the fracture. Moreover, 7 of the 8 patients had hyperhomocysteinaemia levels of >15 mmol/L and the remaining patient had a high normal level of 14.6 mmol/L.

Hyperhomocysteinaemia has long been an established risk factor for vascular disease and atherosclerosis.<sup>5,6</sup> There are several cross-sectional and case-control studies to suggest that it may also be an independent risk factor for DVT.<sup>7,8,13</sup> In the study done by den Heijer,<sup>7</sup> it was reported that the matched odds ratio for having DVT with hyperhomocysteinaemia was 2.5. This increased to 4 if the level of homocysteine was 22 mmol/L. There are many hypotheses that explain how hyperhomocysteinaemia may lead to venous thrombosis. One of them suggests that it has a toxic effect on the vascular endothelium and this reduces the activation of protein C, thereby contributing to the thrombotic tendency in the patient.<sup>14</sup> Another effect is that it results in abnormal methionine metabolism which affects the methylation of DNA and cell membranes. This, then, results in stimulation of the clotting cascade.<sup>15</sup> Environmental factors, such as poor folate, vitamins B6 and B12 intake, as well as genetic alteration in metabolism of homocysteine like homocystinuria, have been cited as causes. Fortunately, this condition is easily treated with vitamin B complex and folate supplements, regardless of the cause.

The prospect of diagnosing hyperhomocysteinaemia causing DVT is very tempting as it has a high incidence in the West and the treatment is safe, easy and cheap to administer. This contrasts with other thrombogenic conditions like deficiency in protein C, protein S and antithrombin and resistance to activated protein C, which are uncommon and not treatable. Hyperhomocysteinaemia has a reported incidence of 69.8% in the West<sup>16</sup> and in our cohort the incidence was 52.3%. Interestingly, 7 of the 8 patients with DVT had hyper-homocysteinaemia. However, due to a small sample size, there was no statistical significance in the difference between the mean homocysteine values of both groups.

Although venogram is the gold standard for detecting

DVT, several recent studies have shown that duplex ultrasound is fast becoming the investigation of choice. The specificity and sensitivity of duplex ultrasound in detecting proximal DVT has been consistently reported to be above 90% by several studies.<sup>17-22</sup> White and Helpenstell<sup>23</sup> also reported a positive predictive value of 100% and a negative predictive value of 95% using duplex ultrasound for the diagnosis of DVT. Furthermore, duplex ultrasound is painless, cheap, portable and non-invasive. It avoids the side effects of venograms, which include allergic reactions (3%), post venogram phlebitis (8%), incomplete venous filling (10%), contrast extravasations leading to skin necrosis and possible thrombus precipitation, as reported by Bettmann and Paulin.<sup>24</sup>

The main purpose of treating DVT is to prevent PE. Proximal DVT, defined as above the trifurcation point, is associated with an incidence of PE of as high as 50%.<sup>25</sup> Distal DVT, on the other hand, is associated with <1% risk of PE and a 2% chance of recurrent DVT. In fact, most clinicians would not start antithrombotic therapy for distal DVT.<sup>26</sup> Furthermore, duplex ultrasound is not as sensitive and specific in detecting distal DVT. For the above reasons, our study did not examine distal DVT.

## Conclusions

The incidence of DVT in Singapore after proximal hip fracture is much lower than that in the West. The results of this study concur with those derived 14 years ago and with other Asian studies. Therefore, the use of DVT prophylaxis in Asians should be selective in order to avoid incurring extra cost and its associated morbidity. Case-control studies and cross-sectional studies clearly indicate that hyperhomocysteinaemia is an independent risk factor for venous thrombosis. Although there are no class I evidence that effectively proves the benefit of the low levels of homocysteine, nutritional intervention is still justified given its benefits, low cost, safety and the high incidence of hip fracture amongst elderly patients.

## Acknowledgement

We are grateful to Changi General Hospital for funding this study.

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