# CASE REPORT

# Over-the-counter natural products in cardiac surgery: a case of ginseng-related massive perioperative bleeding

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## **SUMMARY**

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We present a case of massive perioperative bleeding due to severe coagulopathy following urgent aortic and mitral valve replacement. Bleeding was persistent despite prolonged and meticulous surgical haemostasis and required high-volume blood products transfusions. No obvious cause was found to justify the severity of the coagulopathy, which was later attributed to high preoperative intake of ginseng.

This case highlights the powerful activity of certain overthe-counter remedies on haemostasis, in this particular case on coagulation status. This also reminds us the paramount importance of a sound and comprehensive drug history for surgical patients.

## BACKGROUND

Several over-the-counter medications have been shown to have significant untoward effects both directly and through interactions with other conventionally prescribed medications. Ginseng ingestion has been shown to have inhibitory effects on clotting and the normal battery of clotting investigations such as international normalised ratio (INR), activated clotting time and thromboelastogram may not adequately identify such coagulopathy preoperatively. Patients undergoing cardiac surgery receive full heparinisation for establishment of cardiopulmonary bypass (CPB). Heparin is subsequently reversed with protamine sulfate after CPB is discontinued. Medications such as aspirin and low molecular weight heparins are sometimes necessarily administered prior to cardiac surgery and are associated with predictable increased postoperative blood loss and increased transfusion requirements. Over-the-counter medications, such as ginseng, may cause unrecognised life-threatening coagulopathy during and after major surgery.

A 72-year-old Nepalese woman was admitted as

which included diet-controlled type 2 diabetes,

hypertension and gout. She was an ex-smoker,

denied any alcohol or recreational drug use. Ator-

vastatin, furosemide, glimepiride and ramipril had

been started by her admitting hospital along with

#### **CASE PRESENTATION**

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infarction. Intake of over-the-counter ginseng until surgery was later highlighted postoperatively. Coronary angiogram subsequently showed unobstructed coronary arteries; therefore, aspirin and clopidogrel were discontinued 8 days prior to surgery. Examination revealed bibasal crepitations, systolic precordial murmur, mild ankle pitting oedema and no clinical signs of coagulopathy. Echocardiogram demonstrated good biventricular function, severe aortic stenosis and calcified mitral valve leaflets with severe regurgitation. Preoperatively her coagulation studies were all within normal limits.

aspirin and clopidogrel due to suspected myocardial

After standard protocol anaesthesia, full sternotomy was performed. Intravenous heparin was administered and CPB was established. The aortic and mitral valves were inspected, excised and replaced with bovine bioprosthetic valves. Heparin was reversed with protamine sulfate and meticulous haemostasis was performed. Despite adequate protamine and prolonged surgical haemostasis, substantial bleeding continued at a rate of around 800 mL/hour. Sparse clotting formation was noted in the operative field, a rough but often very useful guide to coagulation status. Following extensive surgical haemostasis and blood products transfusions, the chest was closed over two mediastinal drains. After a period of monitoring on the operating table, chest was reopened due to continuing high drain. No specific point of bleeding was found and the chest was again closed over two mediastinal drains, and patient transferred to cardiac intensive care in a stable condition. High drains output persisted for the first 4 hours at a rate of approximately 400-600 mL/hour and eventually coagulation parameters normalised and bleeding ceased during the following 24 hours. Over the following 48 hours coagulation studies improved and bleeding stopped.

Routine prophylaxis subcutaneous heparin at a dose of 5000 units was started on the third postoperative day.

## TREATMENT

To counterbalance the severity of the coagulopathy, and in particular platelets dysfunction, she received several pools of platelets, fresh frozen plasma (FFP), cryoprecipitate and multiple units of packed red cells during haeomostasis.



# **OUTCOME AND FOLLOW-UP**

She remained haemodynamically stable with minimum pharmacological support. She received in total 14 units of red blood cells, 10 units of FFP, 4 units of cryoprecipitate and four pooled platelets. Subsequent recovery was uneventful, and she was discharged home 10 days later.

## DISCUSSION

This case highlights an occult cause of perioperative bleeding due to severe coagulopathy induced by high oral intake of ginseng. Laboratory tests of platelet function, such as bleeding time or near bedside multiplate electrode aggregometry, should be considered in patients with normal platelet count but with history suggestive of possible platelets inhibition. The relationship between ginseng and coagulopathy is important in cardiac surgery and in many other specialties including obstetric and trauma patients. In cardiac surgery, usage of blood products has been closely linked to increased mortality.<sup>1</sup> Many forms of ginseng exist including 'Asian ginseng' (Panax ginseng) and 'American ginseng' (Panax quinquefolius). Ginseng supplementation, like many over-the-counter supplements, can have significant and varied pharmacokinetic effects.<sup>2</sup> Due to wide variation in the constituents and concentration of these supplements, it is often very difficult to predict the effect on the individual patient. Moreover, each brand will have its own ingredients list and therefore its own individual pharmacological effects.

Ginseng itself exhibits its main effect via ginsenosides such as Rp1, derived from Rg3. In vitro experiments have shown its inhibitory effect on collagen-induced platelet activation and thrombus formation through modulation of early glycoprotein VI signalling events.<sup>3</sup>

Anticoagulant effects of ginsenosides Rg1 and Rg2 were also demonstrated in vitro by Li *et al.*<sup>4</sup> Ginsenoside Rg1 shows strong antiplatelet aggregation activity even stronger than traditional aspirin, indicating that it may be used as an antiplatelet drug.<sup>5</sup>

Although ginsenosides have an inhibitory effect on platelet function, the anticoagulant effect of warfarin is impaired when concurrent supplementation with ginseng is administered.<sup>6</sup> In the study of Yuan *et al* comprising small human trial of 20 healthy patients, INR was significantly reduced by 0.19 (95% CI 0.36 to 0.07) after 2 weeks of ginseng intake compared with placebo. Like many 'herbal' preparations, their interactions, resulting in increased or decreased effects with prescription medications, are secondary to modulation of the cytochrome P450 (CYP) enzymes. Malati *et al*<sup>7</sup> have shown ginseng to induce cytochrome 3A and after 28 days of supplementation, to significantly increase clearance of other commonly used medications.

However, contradictory evidence from Kim *et al*<sup>8</sup> suggests that ginseng has no relevant potential to cause CYP enzyme-related interactions. Gurley *et al*<sup>9</sup> have shown mild inhibition of CYP2D6 mediated by *Panax ginseng* in the elderly population, but CYP1A2 activity did not appear to be affected.

According to the current evidence, The Natural Medicines Database classifies *Panax ginseng* interaction with anticoagulants/ antiplatelets as moderate (high severity and unlikely occurrence)

#### Learning points

Over-the-counter herbal supplements are not always benign remedies and can have potent effects on coagulation.

- A detailed pharmacological history is fundamental and should include herbal remedies and supplements.
- Ginseng interacts with coagulation dynamics by inhibiting collagen-induced platelet activation.
- Platelet function tests such as bleeding time or multiplate aggregometry should be considered preoperatively in patients with history suggestive for ginseng intake.
- Although its effect is variable and cannot be easily predicted, perioperative intake of ginseng should be discouraged.

with level of evidence B, suggesting caution with this combination.<sup>10</sup>

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