

Case Report

Acute-on-chronic subdural hematoma in a patient taking Red Clover herbal supplement: A case report

Samuel Hall, Eleanor Walshe¹, Claudia Ajayi¹, Kevin Boyle¹, Colin Griffith

Department of Neurosurgery, Wessex Neurological Centre, Southampton General Hospital, ¹Neurosciences Intensive Care Unit, Wessex Neurological Centre, Southampton General Hospital, Southampton, UK

E-mail: *Samuel Hall - Samuel.hall@doctors.org.uk; Eleanor Walshe - eleanorwalshe@doctors.org.uk; Claudia Ajayi - cajayi@doctors.org.uk; Kevin Boyle - Kevin.boyle@uhs.nhs.uk; Colin Griffith - colin.griffith@uhs.nhs.uk
*Corresponding author

Received: 07 May 17 Accepted: 24 October 17 Published: 21 February 18


Abstract

Background: Herbal supplements are commonly used, however, their side-effect profiles are poorly understood and not subject to the same scrutiny as prescribed medications. Some herbal supplements such as St Johns' Wort are accepted to interfere with clotting pathways, however others, including Red Clover have theoretical bleeding risks based on coumarin content with very little underlying evidence.

Case Description: This case reports a 65-year-old woman who suffered a spontaneous acute-on-chronic subdural hemorrhage with a significant postoperative re-hemorrhage. She had no other risk factors for coagulopathy other than a history of taking Red Clover supplements for postmenopausal symptoms. Her normal INR combined with an intraoperative thromboelastogram confirmed a coagulopathy which was more consistent with anti-platelet effects than coumarin toxicity. After tranexamic acid and platelet transfusions she had no further bleeding and made an uneventful recovery.

Conclusion: This case highlights another risk factor for intracranial hemorrhage and the importance of a thorough drug history. The mechanism of Red Clover induced coagulopathy appears to be mediated through anti-platelet actions, which is consistent with *in-vitro* evidence reporting its role in preventing platelet adhesion.

Key Words: Herbal supplements, subdural hematoma, red clover

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/sni.sni_174_17
Quick Response Code:


INTRODUCTION

Anti-thrombotic therapy is a well-recognized contributory factor in subdural hemorrhage (SDH) and is usually seen in the context of warfarin treatment or anti-platelet therapy. In one series of 300 patients with acute SDH, 49% were taking anti-thrombotic medication; however, this was not associated with an increased risk of hematoma recurrence.^[3] Despite the known association between herbal supplements such as St John's Wort, Ginkgo, ginger, and garlic to cause an increasing

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Hall S, Walshe E, Ajayi C, Boyle K, Griffith C. Acute-on-chronic subdural hematoma in a patient taking Red Clover herbal supplement: A case report. *Surg Neurol Int* 2018;9:43.
<http://surgicalneurologyint.com/Acute-on-chronic-subdural-hematoma-in-a-patient-taking-Red-Clover-herbal-supplement--A-case-report/>

propensity for bleeding, they are overlooked by 90% of clinicians when taking medical drug history.^[4]

Red Clover (*trifolium pratense*) is a herbal supplement widely used for the mitigation of menopausal symptoms because it contains estrogenic compounds. The role of clover species in causing intracranial hemorrhage has been known since the 1920s with the discovery of sweet clover hemorrhagic syndrome in cattle which proved to be the first step in the development of warfarin. In addition to coumarin derivatives, Red Clover contains phenolic compounds which inhibit platelet adhesion and reduce platelet factor 4 release.^[2]

The literature contains only one case of intracranial bleeding due to Red Clover where a patient suffered a spontaneous, nonaneurysmal subarachnoid hemorrhage.^[1] This case presents a female patient who suffered an acute-on-chronic SDH requiring craniotomy and repeat craniotomy for re-accumulation likely due to Red Clover consumption. It serves to raise awareness of the importance of inquiring about herbal compounds in drug history as a predictor of a patient's surgical bleeding risk.

CASE REPORT

A 65-year-old previously fit and well lady presented after collapsing with a sudden onset severe headache and nausea. She then developed a dense left hemiparesis and her GCS dropped to 6 (E1 V1 M4). Upon arrival at the emergency department she was intubated, and a computed tomography of the brain (CTB) revealed a 17 mm deep right acute-on-chronic SDH with 12 mm of midline shift. She had no history of trauma, did not take any regular medication (nor any sporadic doses of aspirin or nonsteroidal anti-inflammatory drugs in the months prior to admission), consume excess alcohol, or have any other cause for coagulopathy. She underwent a CT angiogram which did not show a vascular abnormality.

The patient underwent emergency craniotomy and evacuation of the SDH. Excellent hemostasis was noted during this operation. Postoperatively, she was admitted to neurointensive care where she remained intubated. After 4 hours, her GCS motor score dropped from 5 to 1 with equal and reactive pupils so she underwent a further CT scan. This showed a reduction in the size of subdural clot with persisting midline shift which was managed conservatively; 6 hours later her GCS had normalized and she was subsequently successfully extubated. However, in the next 2 to 3 hours, she became very drowsy and was no longer moving her left arm. A further CTB showed re-hemorrhage and she was taken back to theatre for repeat craniotomy and evacuation of SDH. This time her scalp was found to be "very oozy" with both subdural and extradural hematoma. Intraoperatively,

a thromboelastogram (TEG) was performed, and the results (R 2.8, angle 34.4, and MA 19.6) were consistent with impaired platelet functioning. Based on these results, she was given 1 g tranexamic acid, 1 pool of platelets, and 2 units of cryoprecipitate. Her INR, APTR, and fibrinogen remained in the normal range throughout admission.

Eight hours post procedure she was awake and obeying commands. Postoperatively, she received a further 1 g tranexamic acid, 2 units of FFP, and 10 mg vitamin K to cover subgaleal and subdural drain removals.

Further questioning into her history revealed that she had been taking Red Clover for the preceding 8–10 years (364 mg per day of standardized Red Clover extract containing 40 mg isoflavones, as recommended by the manufacturer) as an over-the-counter herbal preparation for relief of menopausal symptoms. Red Clover was deemed to be a causative factor in her SDH and subsequent re-bleeding based on the abnormal TEG report showing impaired platelet functioning and absence of trauma or any other cause for coagulopathy.

A final CTB showed an improved SDH and reduced mass effect. Clinically, she was GCS 15 with a very mild right hemiparesis. She was transferred to her local neurosurgical unit for rehabilitation on postoperative day 3. At 6-month follow-up, she had returned to baseline functioning with no residual neurology.

DISCUSSION

SDH is a common neurosurgical condition which is often preceded by head trauma. The mainstay of treatment is surgical evacuation of the hematoma; recurrence of the clot is a well-recognized complication associated with increased morbidity and length of hospital stay. One series did not show a significant difference in recurrence rates for patients taking anti-thrombotic therapy;^[3] however, this is confounded by the fact that their coagulation defects were reversed preoperatively.

There are many herbal supplements which are known to affect either the coagulation cascade or platelet aggregation such as St Johns' Wort, Ginkgo, ginger, and garlic.^[4] To our knowledge, the only reported case of intracranial bleeding associated with herbal supplements is a nonaneurysmal subarachnoid hemorrhage in a patient taking Red Clover.^[1] The mechanism underlying Red Clover induced coagulopathy is assumed to be due to the coumarin derivatives, hence, the contraindication for its use alongside warfarin; however, *in-vitro* evidence has shown that it also has negative effects on platelet activity through inhibition of platelet adhesion.^[2]

This patient's intraoperative TEG demonstrates an impaired ability to form a platelet plug despite the

normal plasma concentration of platelets, which would explain the re-hemorrhage and significant soft-tissue bleeding during the second craniotomy. There was no indication to perform a TEG during the first craniotomy which would have confirmed that her platelet functioning was impaired on admission to hospital; however, without a cause for her platelet quality to have dramatically changed in the intervening 12 hours, it can be assumed that a TEG would have been abnormal as well. The TEG report and absence of trauma or any other risk factor for coagulopathy in the clinical history suggests that the Red Clover was also contributory to the formation of the initial SDH. Based on the patient's coagulation studies, the anti-platelet effects of Red Clover may be as important as their coumarin content; however, this requires further investigation beyond the scope of this article.

Herbal supplements are not subject to the same stringent controls as medications, and this lack of regulation and awareness puts patients at risk of major hemorrhagic events and postoperative complications. This case study serves to raise awareness of the potential serious events arising from seemingly harmless herbal supplements.

In summary, this case of recurrent acute SDH in a patient taking Red Clover supplements highlights the importance of a thorough drug history in assessing the

surgical patient. Furthermore, it widens the known range of contributing factors in acute and/or chronic SDH.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Friedman JA, Taylor SA, McDermott W, Alikhani P. Multifocal and recurrent subarachnoid hemorrhage due to an herbal supplement containing natural coumarins. *Neurocrit Care* 2007;7:76-80.
2. Kolodziejczyk-Czepas J, Sieradzka M, Wachowicz B, Nowak P, Oleszek W, Stochmal A. The anti-adhesive and anti-aggregatory effects of phenolics from *Trifolium* species *in vitro*. *Mol Cell Biochem* 2016;412:155-64.
3. Panczykowski DM, Okonkwo DO. Premorbid oral antithrombotic therapy and risk for reaccumulation, reoperation, and mortality in acute subdural hematomas. *J Neurosurg* 2011;114:47-52.
4. Wang CZ, Moss J, Yuan CS. Commonly Used Dietary Supplements on Coagulation Function during Surgery. *Medicines (Basel)* 2015;2:157-85.