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CASE REPORT

Post-operative epidural haematoma as complication of overconsumption of dried fruit in lumbar spinal surgery: a case report and review of the literature

Elsje-Márie Geldenhuys[1] · Mohammed Z. Ebrahim[1] · Ruan Grobler[1] · Marietjie A. Stander[2] · Janine Colling[3] · Adriaan J. Vlok[1]

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Abstract

Purpose Mebos, a traditional South Africa confection consisting of dried, pulped, and sugared apricots, is rich in fibre and vitamins, but also contains salicylic acid, flavonoids, and citric acid. We report a case of postoperative surgical site bleeding in a healthy patient who consumed approximately 2 kg of mebos per day prior to his elective spinal surgery.

Methods The clinical course of a previously healthy 54-year-old male patient with cauda equina syndrome secondary to lumbar spinal stenosis who underwent surgical intervention with subsequent bleeding into the surgical site is discussed. The cause was investigated through biochemical analysis, thromboelastometry (ROTEM®) and mass and absorption spectrometry were applied to assess flavonoid, citric acid, and salicylic acid content.

Results ROTEM® revealed an abnormal clotting profile with an increased clot forming time, suggesting intrinsic coagulopathy. Mass and absorption spectrometry revealed a high total flavonoid content as well as citric acid concentration in the mebos. Salicylic acid was at detection limits of the instrument.

Conclusion Results highlighted the effect of flavonoids and citric acid and therefore explain the abnormal clotting profile in this patient. Inhibition of coagulation prior to elective surgery is a known contraindication and may pose great risks in spinal surgery. In the present report, we demonstrated an association between inhibition of coagulation and an excess of the flavonoids content and citric acid concentration in mebos consumed in the days prior to elective spinal surgery.

Keywords Spinal surgery · Haematoma · Complication · Anticoagulation · Mebos

Introduction

First mentioned in 1793, "Mebos", from the Japanese "umeboshi", is a traditional South African confection consisting of brine-soaked sundried, pulped and sugared apricots [1]. Besides being high in fibre, vitamins and flavonoids, apricots are known to have high levels of salicylic acid (SA), even more so when dried and processed [2, 3]. The SA concentration in fresh apricots have been measured at 2.58 mg/100g [3, 4]. SA reversely inhibits arachidonic acid, a precursor in the cyclooxygenase-thromboxane pathway, and subsequently platelet aggregation, but the inhibition will only last if SA remains in circulation [4]. Aspirin, a synthetic acetylated derivative of SA, irreversibly inhibits the cyclooxygenase-thromboxane pathway, leading to permanent inhibition of the platelet during its lifespan [4]. The effects of certain South African plant extracts on coagulation were studied by Cordier and colleagues and concluded that extracts with increased SA concentrations, had a significant impact on the intrinsic pathway of the coagulation cascade, by increasing the prothrombin time (PT) and subsequently the bleeding time [5].

In recent years, increased emphasis has been placed on flavonoids and their role in antiplatelet activity. Although the classification of flavonoid compounds is diverse, both

✉ Adriaan J. Vlok
ianvlok@sun.ac.za

1 Division of Neurosurgery, Department of Surgery, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

2 Mass Spectrometry Unit, Central Analytical Facilities, Stellenbosch University, Stellenbosch, South Africa

3 Vibrational Spectroscopy Unit, Central Analytical Facilities, Stellenbosch University, Stellenbosch, South Africa

in vitro and in vivo studies have illustrated flavonoid-dependent inhibition of platelet aggregation [6–8]. In mice with acute pulmonary thrombosis, pentamethylquercetin (PMQ), a flavonoid derivative, was shown to inhibit thrombus formation and thereby increase the survival rate by 90% when compared to the control group [7]. In addition to PMQ, pycnogenol, catechin and epicatechin, all flavonoid constituents, have been shown to increase the activated partial thromboplastin time (aPTT) and PT, leading to anticoagulation defects [6, 9, 10]. It seems that flavonoids inhibit platelets in a dose-dependent manner, by altering arachidonic acid metabolism [6, 11]. Current research has been unable to quantify the minimum dose or concentration to cause significant clotting abnormalities.

Citric acid is a weak organic acid that acts as substrate in the tricarboxylic acid, or Krebs cycle [12, 13]. After citric acid is absorbed into the circulation, it combines with calcium ions in the blood to produce non-ionic calcium compounds. As calcium ions play a vital role in regulation of the coagulation cascade, the reduced ionic calcium concentration subsequently prevents coagulation [12–14]. In 2013, Zhang and co-workers investigated the anticoagulative effects of citrate in patients receiving continuous renal replacement therapy (CRRT) and was found to be not inferior to low molecular weight heparin (LMWH) or heparin with regards to anticoagulant efficacy [14]. High doses of citric acid have also been associated with side effects such as metabolic acidosis, convulsions and tetany, all potentially fatal conditions [12, 15]. Studies have shown that citrate has virtually no anticoagulant effect when ionic calcium levels remain higher than 0.50 mmol/L, however, at ionic calcium concentration of 0.33 mmol/L or less, almost complete inhibition of coagulation occurs [16, 17].

Epidemiological studies have previously indicated that a diet rich in fruits and vegetables, favours cardiovascular health and promotes a healthier lifestyle [18, 19]. In vivo and in vitro studies have shown antiplatelet and antithrombotic effects in a variety of fruits and vegetables, including pineapple, plums, spinach, grapes, garlic beetroot and onions amongst others [18, 20, 21]. Different mechanisms of platelet inhibition have been described in the literature with each of the fruit and vegetable mentioned, which range from platelet receptor modification, altered enzyme activity and proteolysis of active metabolites in the extracts [18, 20, 21].

When searching PubMed Central, ScienceDirect and Scopus, and to our knowledge, limited, if any, literature is available on the effects of mebos, its constituents and clotting abnormalities, even more so in the neurosurgical setting. We therefore present a case of postoperative bleeding complications following overconsumption of mebos, a product rich in citric acid and flavonoids. Written informed consent was obtained from the patient.

Case description

A 54-year-old male with a previous uncomplicated anterior cervical discectomy and fusion in 2006, presented to our hospital with a one-week history of perineal paraesthesia, bowel and bladder incontinence and severe lower back pain radiating down the left leg. Neurologic examination revealed reduced power (3/5) and altered sensation in the L5 dermatome on the left. Magnetic resonance imaging (MRI) confirmed a large disc bulge with posterior extrusion at the L4/5 level resulting in severe spinal canal and lateral recess stenosis, accounting for the symptoms and signs (Fig. 1).

A laminectomy and discectomy at the level of L4/L5 with left-sided L5 decompression was subsequently performed without incident. The patient was evaluated postoperatively and clinically improved. Approximately 12 h later, the patient complained of new-onset weakness in the right leg affecting the L4 myotome. An urgent MRI was requested and demonstrated a large postoperative epidural haematoma. A wound exploration and evacuation of the haematoma was performed, with the surgeons commenting on difficulty achieving hemostasis. Power remained 2/5 in the right L4 myotome while the left leg fully recovered in the postoperative period. The patient has no history of any anticoagulation therapy prior to or during the initial surgery, nor did the patient have any significant medical history, including that of a clotting disorder. No medication was taken pre-operatively.

Pre-operative laboratory results were normal. At the time of clinical deterioration, the PT was elevated (15.2 s, normal ranges: 9.9–12.3 s). Due to the healthy individual and minimal risk-factors, this was not done pre-operatively. Arterial blood gas showed Ca^{2+} of 1.15 mmol/L.

Rotational thromboelastometry (ROTEM®; ROTEM, Germany) was requested three days after the emergency surgery. Measurements included the extrinsic thromboelastometry (EXTEM) and intrinsic thromboelastometry (INTEM) to assess the extrinsic and intrinsic pathways in the clotting cascade, respectively. A fibrinogen thromboelastometry (FIBTEM) to assess the function of clotting factors after platelet activation was included.

Of the three profiles, the EXTEM measurements were all within normal limits. The INTEM, on the other hand, illustrated abnormal clot forming values as indicated by the prolonged clot formation time (CFT). This indicates an intrinsic pathway abnormality (Fig. 2).

The patient was further investigated to determine possible reasons for his abnormal clotting profile. Upon detailed history, considered irrelevant to mention initially by the patient, it was found that he consumed a large amount of mebos during the week prior to his initial spinal surgery,

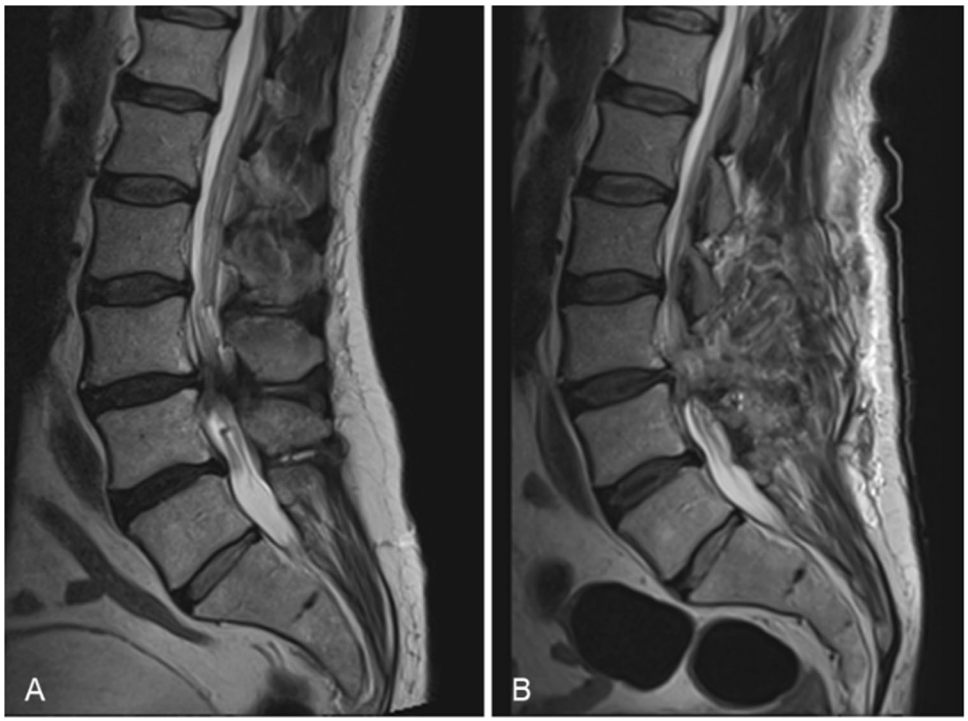
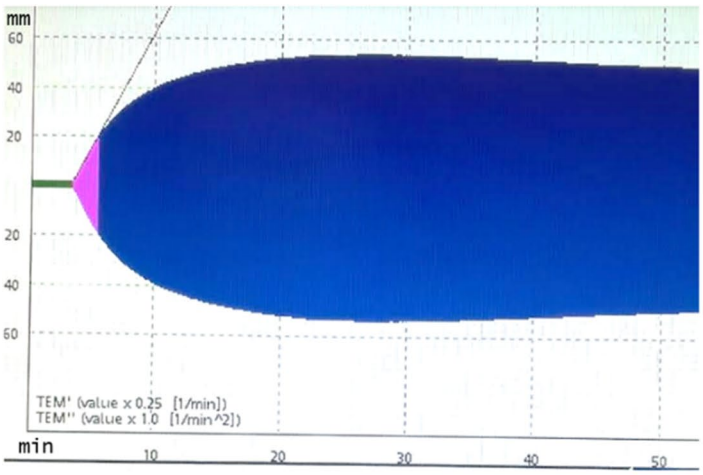


Fig. 1 T2-weighted sagittal MRI demonstrating disc prolapse at the level L4/L5 pre-operatively (**A**), and the post-operative epidural hematoma (**B**)



Parameter	Patient Value	Normal Values
CT	206	100-240
CFT	121*	30-110
α angle	68	70-83
MCF	54	50-72
ML	16*	0-15
A5	35*	38-63

Fig. 2 Illustration of the ROTEM® tracing indicating the INTEM measurements. CT: Clotting time; CFT: Clot formation time; MCF: Maximum clot firmness; ML: Maximum lysis; A5: Amplitude 5 min after CT; abnormal values (*)

approximately 1kg per day. In addition, he admitted to eating a 2 kg container of mebos in the last 24 h with the last intake of up to six hours prior to his surgery.

A sample of the mebos was obtained, processed and extracted with 50% methanol to perform mass spectrometry to measure the total salicylic and citric acid concentrations.

Salicylic acid was measured at 2.1 mg/kg, while citric acid in the same sample and relative to the salicylic acid measured at 2612.4 mg/kg. Although the salicylic acid concentration was at detection limits of the instrument and therefore not high, a significant peak of citric acid was seen (Fig. 3). This translates to 5.2 g of citric acid consumed in the 24 h prior to surgery.

A Thermo Scientific GENESYS™ 180 UV/Vis spectrophotometer and aluminium chloride method was used to quantify the total flavonoid content. From the absorption spectrometry findings, it was noted that the total flavonoids found in the mebos extract, was measured at 2.447 mg RE/g DW (Fig. 4) (Table 1).

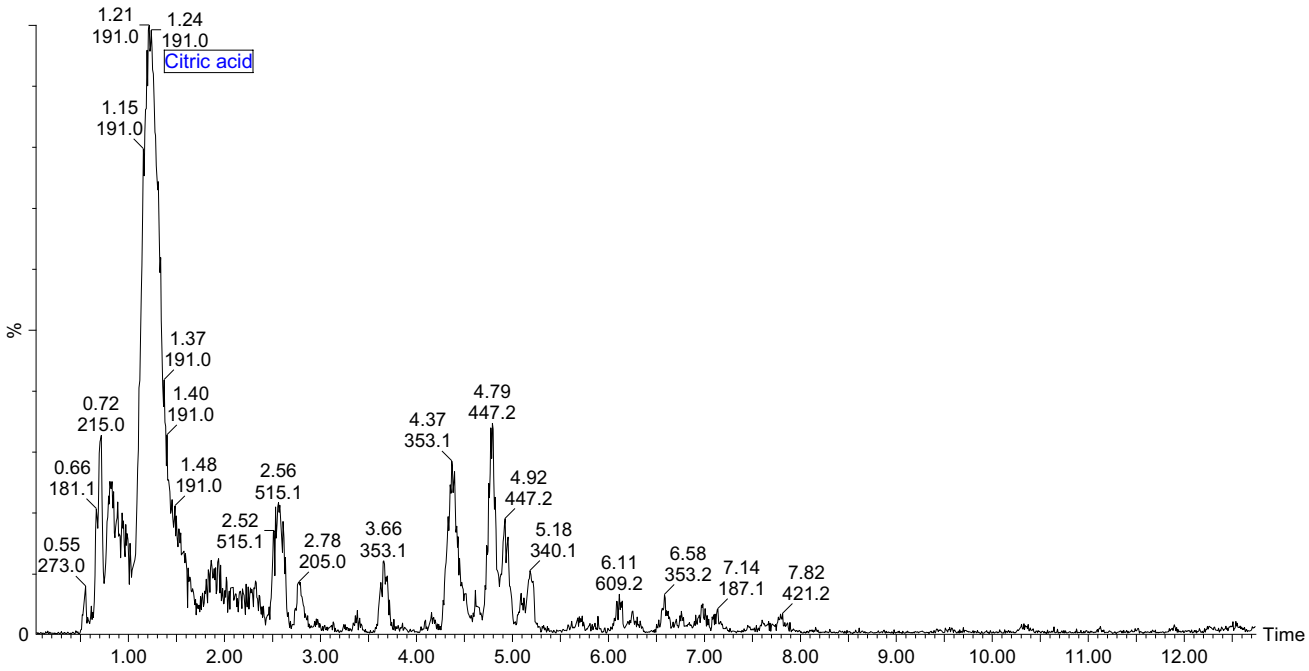
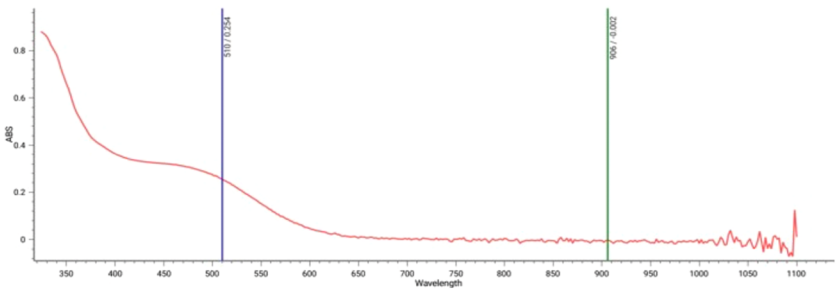


Fig. 3 Total ion chromatogram illustrating the peak of citric acid in the sample of mebos evaluated



Sample	Replicates	mg RE / g DW
Mebos A	1	2.377
Mebos B	2	2.377
Mebos C	3	2.588
Mean	**-**	**2.447**

Fig. 4 Absorption spectrum of total flavonoids from the mebos extract (scanned between 325 and 1100 nm). The measurements were expressed as rutin equivalents (RE: Rutin equivalents; DW: Dry weight)

Table 1 Conversion of values obtained from mass and absorption spectrometry of the mebos

Compound/acid	Values as obtained from mass and absorption spectrometry of mebos			
	mg/kg	mg/g	mg/dL	µmol/L
Citric acid	2612.40	2.61	261.24	–
Total flavonoids	2447.00	2.45	0.25	21.64

Discussion

As surgeons, we are aware of the adverse reactions associated with anticoagulant therapy prior to spinal surgery. Strict protocols exist to prevent anticoagulant-associated complications in the postoperative period, starting with relevant history taking including drugs linked to a hypocoagulable state. After the patient presented with an inexplicable bleed into the surgical site in the absence of anticoagulant therapy or inherent clotting pathology, further investigation into the abnormal clotting profile was necessitated. This case report demonstrated the cumulative effects of both flavonoids and citric acid on inhibition of the coagulation cascade in a patient with a high intake of mebos in the days preceding his elective spinal procedure.

The clotting cascade is a complex and dynamic process in which a variety of coagulation proteins, factors and ions interact to maintain a balance between thrombogenesis and haemolysis [22]. Primary haemostasis, the initial pathway to form a platelet plug, is dependent on adequate platelet adhesion, activation and aggregation [22]. Flavonoids have

been shown to inhibit platelets in a dose-dependent manner [8, 11]. It has been reported that a set of 30 different flavonoids inhibit platelet aggregation at concentrations between 0.12 and 122.0 µmol/L [8]. Similarly, Liang et al. [7] demonstrated an in vivo dose-dependent adenosine diphosphate (ADP) induced platelet inhibition at a concentration of 2.0 µmol/L. Our total flavonoid concentration in this study was measured at 21.64 µmol/L, which is well within the platelet aggregation inhibitory concentration. In addition, collagen has been shown to contribute to platelet aggregation [23]. Laing and co-workers have shown that flavonoids inhibit collagen function at a concentration of 0.50 µg/ml [7]. Our study demonstrated a concentration of 0.87 µg/ml, which may further exacerbate platelet dysfunction.

Ionized calcium plays an important role in regulation of the coagulation cascade and have been shown to prevent coagulation at reduced ionized calcium concentrations [12–14]. Our patient had an ionized calcium concentration of 1.15 mmol/L. The ionized calcium concentration at which clinically significant side effects occur, have not been studied in detail [24]. Although, our value is at the lower end of normal, it must be considered that these values were obtained more than 24 h after the patient had his initial surgery. Although no formal calcium levels, baseline liver functions and albumin levels were obtained prior to his elective procedure, the possibility remains that it may have been reduced. In addition, the patient was given lactated Ringer's, which contains a calcium concentration of approximately 1.4–1.5 mmol/l [25], during the initial procedure. A low ionized calcium concentration at time of admission, which may further contribute to his abnormal coagulation, can therefore not be ruled out and the true value of ionized calcium may have been even lower at the time of the initial surgery.

Although the primary culprit of anticoagulation in this case was initially thought to be salicylic acid, it was found to be at detection limits of the mass spectrometer and therefore not high enough to inhibit platelet function.

Conclusion

This case report serves as proof that dried fruit contains a variety of compounds and naturally occurring acids, which may have an influence on physiological processes, especially when the consumed in excess.

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Declarations

Conflict of interest No conflict of interest was reported by any of the authors.

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