

Hawthorn Herb Increases the Risk of Bleeding after Cardiac Surgery: An Evidence-Based Approach

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ABSTRACT

Objectives: Hawthorn extract consumption is becoming more widespread among the Jordanian population with cardiovascular disorders. We conducted this prospective observational longitudinal study to determine the impact of hawthorn extract on bleeding risk in patients who undergo cardiac surgery.

Methods: A prospective observational study was performed on 116 patients who underwent cardiac surgery in the period between June 2014 and May 2015. Patients were divided into two groups: Group I (patients recently consumed hawthorn extract) and Group II (patients never consumed hawthorn extract). Endpoint measures included the rates of reopening to control bleeding, early mortality, duration of intensive care unit stay, total in-hospital stay period, and duration and amount of chest tube drainage.

Results: Hawthorn patients had a significantly higher rate of postoperative bleeding necessitating take back to the operating room compared to the control group (10% versus 1%; $P = .03$) respectively. The overall mortality rate for group I and II was 4% and 0% respectively; $P = .17$. Chest tubes were kept in for longer times in group I compared to group II (54 ± 14.6 versus 49 ± 14.7 hours respectively; $P = .01$). Group I stayed longer in the intensive care unit compared to group II (24 versus 22 hours respectively; $P = .01$). The total in-hospital stay period was comparable between the two groups.

Conclusion: Hawthorn extract consumption does increase the potential for bleeding and the amount of chest tube output after cardiac surgery.

INTRODUCTION

Hawthorn, *Crataegus* species, is a plant that usually grows in the northern parts of Europe, the Mediterranean region, Asia, and North America [Dahmer 2010]. The extract of

these shrubs consists of either the bright green leaf or the white flower or the bright red berry, or may be a combination of all these parts. The extract can be prepared as powder (sachets) or liquid. Hawthorn preparations have been used for many conditions, such as gastrointestinal disorders, bronchial asthma, and hyperlipidemia [Dahmer 2010; Fong 2002]. The first report that demonstrated the usage of hawthorn extract in various cardiovascular disorders dates back to the first century [Weihmayr 1996]. The primary biological components of the hawthorn extract are believed to be the oligomeric procyanidins and flavonoids [Dahmer 2010]. The physiologic action is shown to be through the enhancement of the vascular endothelial nitric oxide release, which leads to vasodilation [Miller 1998]. A previous meta-analysis published by Pittler and colleagues [Pittler 2003], which included thirteen studies, demonstrated some potential beneficial effects in patients with chronic heart failure.

Being a natural herb, Hawthorn extracts gained wide usage among patients with cardiovascular disease. Apart from its presumed benefits, it has been assumed to be a safe medication since it is natural. However, among the patients who consumed this herb and were sent for cardiac surgery, a tendency toward excessive bleeding was noticed among cardiac surgeons in our cardiac surgery unit at Queen Alia Heart Institute compared to their counterpart patients who were not taking these herbs.

The benefits and drawbacks of hawthorn extract therapy have been a concern for investigators in the field of cardiovascular disease in the current era, however, many conclusion about its role in this field have not been supported by evidence-based trials. Hence, we conducted this prospective observational study to investigate the impact of recent hawthorn extract consumption in patients who underwent adult cardiac surgery on adverse outcomes related to excessive bleeding tendency.

MATERIALS AND METHODS

This study was approved by the institutional review board of the Royal Medical Services, Amman, Jordan, as well as by the Jordan University of Science and Technology, Irbid, Jordan. The patients' charts who had recently consumed hawthorn extract and who underwent cardiac surgical procedures were reviewed prospectively, from June 2014 to June 2015.

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To conduct a uniform study design, and to decrease the confounding factors, we excluded patients who had emergency or salvage cardiac surgery, patients in shock status, patients with previous cardiac surgery, patients with congenital or acquired bleeding tendency, and patients less than 21 years of age.

Over a one-year period, starting in June 2014, 48 adult patients who had recently consumed hawthorn extract underwent primary cardiac surgical procedures by a group of six surgeons in Queen Alia Heart Institute. Patients reported that they had boiled the hawthorn leaves and were drinking the extracted water daily. Patients' demographics, echocardiographic, and surgical data were collected prospectively from the hospital records.

Two treatment cohorts were created including patients who had recent consumed hawthorn extract (Group I, n = 48), and a matched cohort who had not consumed hawthorn extract (Group II, n = 68). The study primary endpoints were

the rates of reopening to control bleeding and early mortality. Secondary endpoints were duration of intensive care unit (ICU) stay, total in-hospital stay period, and duration and amount of chest tube drainage.

Endpoint Definitions

1. Take back to the operating room was defined as any return to the operating room within 48 hours of the surgery due to excessive bleeding or hemodynamic derangement.
2. Early mortality was defined as any death that occurred during the same hospitalization period or within 30 days of the surgery.
3. Chest tube output was defined as the total amount of chest tube drainage in the postoperative period.
4. Chest tube duration was defined as the total duration of time during which the chest tubes were kept in, which was measured in hours.

Table 1. Preoperative Characteristics

	Control, n = 69 (Group II)	Intervention, n = 48 (Group I)	P
Demographic data			
Age, y	58.2 ± 8.9	55.4 ± 9.6	.11
Sex, F/M, n	8/61	4/44	.56
Body mass index, kg/m ²	29.5 ± 4.5	28.4 ± 4.4	.45
Comorbidities			
Arterial hypertension, n (%)	43 (62)	32 (67)	.63
Insulin-dependent diabetes mellitus, n (%)	0 (0)	2 (4)	.17
Non-insulin-dependent diabetes mellitus, n (%)	35 (51)	17 (35)	.13
Stable angina, n (%)	0 (0)	1 (2)	.41
Unstable angina, n (%)	1 (0)	0 (0)	.59
Smoker, n (%)	19 (28)	13 (27)	.95
Preoperative laboratory parameters			
PCV	40.3 ± 4.8	41.2 ± 3.9	.24
Platelets	242.9 ± 70.9	278.3 ± 102	.20
Prothrombin time	13.3 ± 0.7	13.6 ± 0.9	.13
INR	1.02 ± 0.07	1.03 ± 0.08	.18
Serum creatinine, mg/dL	1.07 ± 1.2	0.91 ± 0.2	.66
Preoperative medications			
Aspirin, n (%)	66 (96)	47 (98)	.64
Plavix, n (%)	1 (1)	1 (2)	1.00
Beta-blockers, n (%)	64 (93)	45 (94)	1.00
Statin, n (%)	65 (94)	46 (96)	1.00
Symptoms			
NYHA class I-II, n (%)	64 (93)	41 (85)	.22
NYHA class III-IV, n (%)	0 (0)	4 (8.3)	.03

INR indicates international normalized ratio; NYHA, New York Heart Association; PCV, packed cell volume.

5. Intensive care unit stay was defined as the total duration in hours during which the patient stayed in the ICU.
6. In-hospital stay period was defined as the total duration in days that the patient spent in the hospital before dismissal.

Statistical Analysis

Data were analyzed by the use of SPSS software, version 19 (SPSS, Chicago, IL, USA). We compared groups using the Student t test or the Mann-Whitney U test for independent samples, where appropriate. Dichotomous data were compared using the Fisher exact test, and 95% confidence interval estimates for the mean or median difference were conducted. $P < .05$ was considered to indicate a statistically significant difference.

Operative Protocol

In both cohorts, general endotracheal anesthesia was conducted. Conduits used were the great saphenous vein harvest in an open method and the left internal mammary artery in the classical pedicled method. For patients who had valve replacements, the standard operative preparations were the same as for patients who underwent coronary artery bypass grafting, and the choice of valve replacement, whether mechanical or biological, was left to surgeon selection for each.

Heparin was given in a dose of 1-3 mg/kg before cardiopulmonary bypass, and an activated clotting time (ACT) was maintained above 480/second during the pump time using adjunct doses of heparin whenever needed. The pump run was maintained at 2.4 L/min with mild hypothermia in both cohorts. Mean perfusion pressure during the bypass period ranged between 60-70 mmHg. Heparin reversal was achieved using protamine sulfate in 1:1 ratio after completion of the procedure. Drying of the patients was accomplished as per each surgeon's method and closure after being satisfied.

RESULTS

Table 1 summarizes the baseline demographics for the patients in both cohorts. Patients in both cohorts were matched in terms of sex, age, comorbidities, coagulation profiles, and preoperative drug regimen. Patients in the hawthorn group were more likely to be in advanced symptomology status, in terms of New York Heart Association (NYHA) class than the control group. Additionally, we emphasized the intra and postoperative characteristics and interventions in Table 2 for both groups. There were no significant differences between the hawthorn consumption group and the control group in: the number of diseased coronary arteries, type of surgery performed, blood and blood product transfusion in the first 48 hours post-surgery, duration of pump time

Table 2. Intra- and Postoperative Characteristics/Interventions

	Control, n = 69 (Group II)	Intervention, n = 48 (Group I)	P
Number of diseased coronary arteries			
LMCA, n (%)	2 (3)	0 (0)	.51
1 VD, n (%)	1 (1)	0 (0)	1.00
2 VD, n (%)	5 (7)	2 (4)	.69
3 VD, n (%)	61 (88)	44 (92)	.76
Type of Surgery			
CABG, n (%)	68 (99)	47 (98)	1.00
AVR, n (%)	2 (3)	0 (0)	.51
MVR, n (%)	1 (1)	2 (4)	.56
CABG and AVR, n (%)	2 (3)	0 (0)	.51
CABG and MVR, n (%)	1 (1)	1 (2)	1.00
Blood and blood product transfusion in the first 48 hours post- surgery			
Packed red blood cells, n (%)	45 (65)	32 (67)	1.00
Fresh frozen plasma, n (%)	13 (19)	13 (27)	.36
Platelets, n (%)	9 (13)	10 (21)	.31
Duration of pump time (CPB), min	79.4±20.5	77.6±27.4	0.68
Duration of aortic cross-clamp, min	48.4±13.9	46.4±20.5	0.54
Immediate postoperative ACT	128.8±9.2	130±11.9	0.87

ACT indicates activated clotting time; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; LMCA, left main coronary artery; MVR, mitral valve replacement; VD, vessel disease.

Table 3. Postoperative Primary and Secondary Endpoints

Outcomes	Control, n = 69 (Group II)	Intervention, n = 48 (Group I)	P
Reopening due to bleeding, n (%)	1 (1)	5 (10)	.03
Early mortality, n (%)	0 (0)	2 (4)	.17
Chest tube duration, minutes, mean \pm SD	49 \pm 14.7	54 \pm 14.6	.01
Total drain output, mL, mean \pm SD	729.7 \pm 441	1056.8 \pm 896	.01
Duration of stay in ICU, hours, median (interquartile range)	22 (18.5-32)	24 (20-48)	.01
Duration of stay in hospital, days, median (interquartile range)	6 (5-7)	6 (5-6)	.08

ICU indicates intensive care unit; ACT, activated clotting time; NYHA, New York Heart Association; INR, international normalized ratio; PCV, packed cell volume; AVR, aortic valve replacement; MVR, mitral valve replacement; VD, vessel disease; CABG, coronary artery bypass grafting; LMCA, left main coronary artery.

(cardiopulmonary bypass), duration of aortic cross clamp, or in the immediate postoperative ACT (Table 3).

Reopening for Bleeding

In total 5 (10%) patients in the hawthorn group needed early reexploration to control bleeding, while only 1 (1%) in the control group had reopening for bleeding issues; $P = .03$. All the bleeding reports from the hawthorn group demonstrated generalized tissue and surface ooze with no documented surgical cause.

Early Mortality

Early mortality was higher in the hawthorn extract group than the control group (2% versus 0% respectively); however, it did not reach statistical significance ($P = .17$).

Chest Tube Duration (Hours)

The duration of chest tube duration was longer in the hawthorn extract group compared to the control group (54 \pm 14.6 versus 49 \pm 14.7 hours, respectively; $P = .01$).

Chest Tube Output (mL)

The amount of chest tube drainage was higher in the hawthorn extract group than in the control group (1056.8 \pm 896 versus 729.7 \pm 441 mL respectively; $P = .01$).

Intensive Care Unit (ICU) Stay Period (Hours)

Patients who had consumed hawthorn extract stayed longer in the ICU compared to the control group (24 [20-48] versus 22 [18.5-32] hours, respectively; $P = .01$).

Total In-Hospital Stay Period (Days)

Both cohorts had comparable duration of in-hospital stay period: group I (6 [5-6] days), while group II (6 [5-7] days); $P = .18$.

DISCUSSION

Bleeding after cardiac surgery is a serious complication that may lead to an increase in the need for reexploration, longer ICU stay, more blood transfusions, and higher stroke risk [Christensen 2012; Stone 2012]. Etiology of bleeding

after cardiac surgery is multifactorial, and may be related to patient-related factors, complexity of the surgical procedure, and postoperative issues [Lopes 2015]. Many different drug regimens are administered before or early after cardiac surgery that may increment the potential for bleeding. Nowadays, herbal medicine and crataegus extract in particular are gaining increasing usage across the Jordanian population, especially for patients with ischemic heart disease, on the assumption that it has potential protective properties for the cardiovascular system [Omeish 2011]. The increased bleeding episodes among patients who undergo cardiac surgery who are using hawthorn extract therapy drew attention for the cardiac surgeons at Queen Alia Heart Institute as a cautious reminder of the potential role of this remedy in this phenomenon. Hence, we conducted this prospective observational study to investigate the role of hawthorn extract on the risk of bleeding after cardiac surgery.

Bleeding after cardiac surgery is a serious complication that most cardiac surgeons try to avoid by paying great attention to adequate homeostasis during surgery. There are few reports [Wang 2013; Shatoor 2012] that describe the impact of crataegus extract on coagulation cascades in the animal models, and none of them investigated this effect in the human being. A previous report by Shatoor and colleagues [Shatoor 2012] demonstrated the anti-platelet activity of crataegus extract in albino wistar rats at variable dosage regimens. This activity was explained by the increase in bleeding time, decrease in plasma levels of thromboxane B₂, and a reduction in the platelet aggregation activity [Shatoor 2012].

Platelet dysfunction does occur frequently after cardiac surgery, due to the fact that patients are on different regimens of preoperative anti-platelet therapies and cardiopulmonary bypass induced platelet activation and consumption [Farani 2013]. The concomitant use of hawthorn extracts with conventional anti-platelet drugs could initiate some pharmacological interactions, by certain mechanisms that are not yet clarified. It is possible that the perception of diminished platelet activity could be due to an augmented effect of the hawthorn extract in the media of disturbed homeostatic mal-leoli in the perioperative period. This may explain the significant increase in the number of bleeding episodes in the

hawthorn cohort compared to the control group, since all other variables that may impose a bleeding risk were comparable between the two cohorts.

As previously outlined, excessive bleeding episodes due to coagulopathy induced by the cardiopulmonary bypass circuit may result in higher rates of morbidity and mortality [Thiele 2014]. Two patients died early after surgery in the hawthorn group, one of them had reopening for bleeding control followed by multiple visits to the operating theater for mediastinal wash out. The other patient had severe left ventricular dysfunction with poor quality coronary targets, and was taking hawthorn for this purpose, and couldn't be weaned from the cardiopulmonary bypass machine despite all attempts to support him. None of the control group had early mortality after surgery, however this did not reach statistical significance; $P = .17$.

An increase in the rate of bleeding after cardiac surgery and prolongation of the chest tube output may increase other morbidities, but of more importance for surgeons is the prolongation of the ICU and hospital stay periods. Although these endpoints were not the primary endpoints in our study, we think that avoidance of hawthorn extract may shorten the duration of ICU and hospital stay for patients undergoing cardiac surgery.

The rates of postoperative chest tube drainage and duration were increased in patients who consumed hawthorn extract compared to the control cohort; the significance of the increased chest tube drainage and duration could be of high importance. A report by Lee and colleagues [Lee 1995] demonstrated that in 76% of the 43 pediatric cardiac surgery units surveyed in the United States, they continued their antibiotic prophylaxis while the chest tubes were still in place. It is a policy among surgeons in Queen Alia Heart Institute also to extend the antibiotic duration until the chest drains are out, and this act may lead to the wider spread of resistant microorganisms as well as patients' exposure to the untoward side effects of the antimicrobial therapy.

Conclusion

Hawthorn extract does increase the potential for bleeding and the amount of chest tube output after cardiac surgery. We recommend running a randomized controlled trial involving larger patient cohorts that include further elaboration on platelet function tests.

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