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Research Article

SUPPLEMENT USE AND GASTROINTESTINAL BLEEDING

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ABSTRACT

Objective: The use of supplements, such as vitamins, over the counter (OTC) agents, and herbal remedies have become a popular complementary therapy for a variety of conditions. There have been case reports describing an increased risk of bleeding associated with these supplements. Our objective was to test the hypothesis that there is an increased incidence of gastrointestinal bleeds among patients who take supplements.

Methods: This was a prospective cohort, survey-based study of 100 patients seen at MSMC from February 2013 to August 2013. Data included patient age, sex, ethnicity, country of origin, alcohol use, medical comorbidities, information regarding previous gastrointestinal (GI) bleeds, laboratory values, as well as the use of supplements, multivitamins, and anticoagulants.

Results: Overall, 32% of patients who had gastrointestinal bleeding consumed supplements. More patients in the supplement group took NSAIDS 52.9% vs.27.9%, p =0.07), whereas more patients in the no supplement group took the combination of ASA and clopidogrel (25.6% vs. 5.9%, p = 0.08). Patients in the supplement group were less likely to have an elevated international normalized ratio (INR between 1.3-2.0: 6.3% vs. 22.1%, p = 0.05). Patients not taking supplements were significantly more likely to have no intervention done (14.7% vs. 0%, p = 0.02).

Conclusion: Supplement use within the community is very common. Although non-significant, patients taking supplements appeared to have more severe gastrointestinal bleeds that required more interventions. Larger studies are needed to better define the risks of GI bleeding with particular supplements.

Keywords: alternative medicine; gastrointestinal bleeding; herbal supplements

INTRODUCTION

The use of supplements, such as vitamins, over the counter (OTC) agents, and remedies have become popular complementary therapies for a variety of conditions [1, 2]. Total sales of herbal and dietary supplements in the United States (US) were $4.8 billion for 2008, a 10.6 percent increase since 2004 [3]. Data from the 2007 National Health Interview Survey (NHIS) showed that 17.7 percent of US adults had used supplements in the previous year [4]. The safety of supplements is largely unknown, as only a few systemic studies have ever been completed. Knowledge about adverse effects comes predominantly from case reports and small clinical trials [5-16]. Many supplements are associated with clinically significant side effects, most notably bleeding. Ginkgo biloba, for example, used primarily in the treatment of dementia, has been associated with bleeding at multiple sites [9-15].

Upper gastrointestinal (GI) bleeding is a common medical condition that results in high patient morbidity and mortality and medical care costs. In a study from a large health maintenance organization in the US, the annual incidence of hospitalization for acute upper GI bleeding was approximately 100 per 100,000 adults; with incidence twice as common in males and increasing with advancing age [17]. Meanwhile, lower GI bleeding accounts for approximately 20-33% of episodes of GI hemorrhage, with an annual incidence of about 20-27 cases per 100,000 people in western countries.

Case reports and small clinical studies have described an increased risk of bleeding with specific supplements in the fields of dentistry [18] dermatology [19], ophthalmology [20] plastic surgery [21], and otology and laryngology [22]. To our knowledge, there have been no studies evaluating an association between supplementation (vitamins, OTC agents, herbal remedies) and GI bleeding. In this large prospective, cohort single institution study, we set out to examine our hypothesis that particular supplements increase patient's risk for GI bleeding. We also hope to document the prevalence of the use of supplements among a very diverse population.

MATERIALS AND METHODS

This prospective cohort, survey-based study was conducted following approval by the Mount Sinai Medical Center (MSMC) institutional review board. Informed consent was obtained from all participating patients. One hundred randomly selected patients admitted to MSMC by both the medicine and surgical services, from February 2013 to August 2013 were enrolled in the study. All patients who met inclusion criteria until a total of 100 patients were reached were included in the study. Patients were included in the study if: (1) They were admitted for GI bleeding; (2) GI bleeding was an incidental finding; or (3) GI bleeding developed during the course of their hospital stay. Internal medicine residents at our institution were responsible for surveying patients using the data collection sheet (Table 1). Patients were excluded if they lacked capacity to provide informed consent, did not speak English or Spanish, were younger than 18, or were pregnant. GI bleeding was confirmed through one of the following methods: (1) Visualization of overt hematemesis, melena, or hematochezia; (2) Nasal-gastric lavage or endoscopic/colonoscopy visualization of bleeding; (3) Positive fecal occult blood test.

After enrollment in the study, patient medical data was obtained from the patient and from paper and electronic medical records. Data included patient age, sex, ethnicity, country of origin, alcohol use, medical comorbidities, information regarding previous GI bleeds, laboratory values (INR and platelet count), as well as the use of supplements, multivitamins, and anticoagulants. Patients were followed for the duration of their hospital stay. Diagnosis, treatment (e.g., pRBC transfusions, endoscopic intervention, surgery), time spent in the intensive care unit (ICU), length of hospital stay, and the overall survival rate was recorded for all patients.

Patients who were taking herbal supplements (i.e. garlic, ginseng), vitamin supplements associated with GI bleeding (i.e., vitamins C and E, but not multivitamins), or who were taking an OTC supplement associated with bleeding (i.e. fish oil, flax oil) were all

classified as taking a supplement and were grouped together. Those patients not taking any of the aforementioned vitamins or supplements were groups together as not taking supplements. When the diagnosis of GI bleeding was made, patients at our institution generally had blood work drawn, which included a CBC, coagulation studies (PT/PTT), and a complete metabolic profile with renal and liver function tests. Transfusion practices were generally physician and patient dependent. Hemodynamically unstable patients or patients with significant cardiac disease were generally transfused at higher hemoglobin thresholds. Immediate endoscopic/surgical treatment and admission to the ICU was generally reserved for patients with profuse GI bleeding or those who were hemodynamically unstable. Stable patients generally underwent endoscopic intervention within the first 24 hours. If patients had more than one GI bleed during the course of their hospital stay, each source was listed.

A major bleed was defined as a drop in hemoglobin greater than or equal to 2 g/dL or the need for a transfusion of greater than or equal to 2 units of pRBC's. Endoscopic intervention was defined as injection therapy, thermal coagulation, hemostatic clips, argon plasma coagulation, and combination therapy. Patients were considered positive for supplement consumption if they used supplements daily for at least two weeks prior to hospital admission. They were considered positive for anticoagulant medication usage, if intake within two weeks prior to admission. Data was reported as percentages. Categorical data were cross-tabulated and their association was assessed using the Chi-square test of independence using the statistical package SPSS version 20 11.0 and Microsoft Excel. All tests were two-sided, and the Type I error was 0.05.

RESULTS

Of the 100 patients enrolled in the study, in which there were zero dropouts or exclusions, the median age at current GI bleed diagnosis was 71 years. Most of the patients were Hispanic (48; 48%) males (60; 60%), who were born in the US (45; 45%), were older than age 60 (61; 61%), and who drank less than 10 alcoholic beverage per week (83; 83%; Table 2). Thirty-two percent of patients in the study reported taking supplements in the two weeks before hospital admission, with the most common supplements being fish oil (7; 21.9%) and vitamin C/E (12; 37.5%). Sixty percent of patients took a blood thinner within two weeks prior to admission. Among this group, the most commonly reported blood thinners used were aspirin (ASA; 40; 66.7%), clopidogrel (19; 46.3%), non-steroidal anti-inflammatory agents (NSAIDS; 22; 36.7%), and warfarin (9; 15.0%), with the most common blood thinner combination being ASA and clopidogrel (12; 20.0%). Most patients in the study had a normal platelet count (79; 79%), with normal liver function (79; 79%), normal coagulation (INR: 0.7-1-3; 77; 77%), and the absence of end-stage renal disease (ESRD; 94; 94%). Forty-eight percent of patients had a previous GI bleed, with almost half occurring within the past 6 months (23; 47.9%). The most common cause of GI bleeding was UGI in origin (51; 51%), with PUD (14; 24%) being the most common source. The most common intervention needed was transfusion only (61; 61%), and of those patients receiving transfusion, 53 (53%) required more than 1 unit of pRBCs. Most patients had a length of hospital stay between 1-4 days (40; 40%), with a minority requiring admission to the ICU (32; 32%).

Overall, 32% of patients who had gastrointestinal bleeding consumed supplements. Although not statistically significant, patients who took supplements were older (> age 60: 21 (65.6%vs. 40 (58.8%), p = 0.52), more often female (15 (46.9% vs. 25 (36.8%), p = 0.34), drank less alcohol (<10 drinks/week: 55 (80.9% vs. 28 (87.5%, p = 0.41) and more frequently consumed concomitant multivitamin supplements (13 (40.6% vs. 16 (23.5%, p = 0.08; Table 3). There were no differences between the two groups based on ethnicity or country of birth. Patients taking supplements were non-significantly less likely to have taken anticoagulation within the previous two weeks (17 (53.1% vs. 43 (63.2%, p = 0.34). More patients in the supplement group took NSAIDS (52.9% vs. 12 (27.9%, p =0.07), whereas more patients in the no supplement group took the combination of ASA and clopidogrel (11 (25.6% vs. 1 (5.9%, p = 0.08). Meanwhile, patients in the supplement group were significantly less likely to have an elevated international normalized ratio (INR; INR between 1.3-2.0: 2 (6.3% vs. 15 (22.1%, p = 0.05). Patients in both groups were equally likely to have a history of a GI bleed (16 (50.0%) vs. 32 (47.1%, p =0.78), but those in the supplement group were non-significantly more likely to have had multiple bleeds in the past (>1: 7 (43.7%) vs. 9 (28.1%, p = 0.78) and within the past 6 months (10 (62.5%) vs. 15 (46.9%, p = 0.31). Although there were similar causes for GI bleeds in both groups (UGI: 14 (43.8% vs. 35 (51.5%), p = 0.47), patients in the supplement group were non-significantly more likely to be transfused (23 (71.9%) vs. 38 (55.9%), p = 0.13) with multiple units of packed red blood cells (pRBCs) (18 (56.3%) vs. 35 (51.5%), p =0.66). Patients in the no supplement group were significantly more likely to have no intervention done (10 (14.7%) vs. 0 (0%, p = 0.02). Although ICU admission rates were similar between the two groups (10 (31.3% vs. 22 (32.4%, p =0.91), patients in the supplement group had non-significant longer ICU stays (>/=3 days: 6 (60.0% vs. 8 (36.4%, p = 0.21), longer total hospital stays (>/= 5-8 days: 12 (37.5% vs. 18 (26.5%, p = 0.26), and a higher rate of mortality (1 (3.1% vs. 1 (1.5%), p = 0.58).

DISCUSSION

Patient Population

Our patient population was made up of predominantly older males; consistent with previous large epidemiologic studies of patients who have GI bleeds [23]. The incidence of alcohol abuse amongst our participants was higher than that in general public [24], although this may be accounted for due to rates of higher alcohol abuse in this patient population. Thirty-two percent of the patients in our study reported taking at least one supplement, and this was consistent with the range seen in other studies [18-62%; 25-26]. However, it is important to note that in a study by Kaye et al., 70% of patients failed to disclose their supplement use during preoperative assessment [27]. In our study, composed of predominately older individuals, it is not surprising that within two weeks prior to admission, 60% of the patients had taken some form of blood thinner, most commonly aspirin for primary/secondary prevention of cardiovascular events. Among our patient population, the incidence of upper GI bleeding was much more common than lower GI bleeding, with the most common upper GI source being peptic ulcer disease (PUD; 29.2%) and the most common lower GI source being diverticulosis (10%). This finding is consistent with larger epidemiological studies [28, 29]. Despite having a relatively high rate of ICU admissions (32%), there was a relatively low mortality rate (2%) compared to previous studies [30].

Supplement use vs. No Supplement use

Previous studies have suggested that supplements were most likely to be taken by older, more educated, Hispanic women who lived in the western part of the US [31]. Although not significant, our study supported that older women were more likely to use supplements. There were no differences between the two groups based on ethnicity/race or country of birth. Those patients who took supplements were more likely to consume less alcohol/per week, which is consistent with the idea that those who take supplements attempt to live healthier lifestyles. Not surprisingly, those patients who took supplements were more likely to also take a multivitamin. This finding suggests that those patients who use complementary therapies may be more open to using additional complementary therapies.

Despite taking less combination anticoagulation medications (ASA and clopidogrel, p = 0.08), having lower platelet counts and INRs, consuming less alcohol [known to increase bleeding; 32], and having a lower rate of cirrhosis, patients in our supplement group appeared to have more severe GI bleeds. Whereas patients in the no supplement group were significantly more likely to have no intervention/transfusion for their bleed, supplement patients appeared to require more transfusions, longer ICU and overall hospital stays, and had an overall higher mortality rate. Our results provide further evidence that supplements may increase the risk severity of GI bleeding independent of other bleeding risks, and this can have a detrimental effect on patient health. Although both

groups of patients had similar causes for their bleeding and similar percentages in terms of a history positive for GI bleeds, those patients in the supplement group were significantly more likely have "ischemic colitis" as the cause of their GIB, and were non-significantly more likely to have had multiple bleeds within the past 6 months. These results suggest that supplements place patients at an increased risk for bleeding, particularly for recurrent bleeding in those patients who are predisposed. Interestingly, the INRs were greater in the no supplement group, despite reports from multiple previous studies that particular supplements increase the risk of bleeding by not only interacting with warfarin, but also by directly impacting the INR [33, 34]. Also, there was a trend toward more NSAID use in the supplement group (p = 0.07). Although these results suggest that the increased severity of GI bleeding was secondary to more severe PUD from increased NSAID use, we also cannot rule out that patients taking supplement had worse bleeding secondary to the supplement effect on platelet aggregation.

Supplements

Our study was unique as it was one of the first reports documenting the prevalence of supplement use among a very diverse community (Table 3). Although the use of supplement was once thought to be rare, evidence suggests that it is becoming much more common (1), and with a broad spectrum of agents used. Although it is thought that there are many different types of supplements used by patients within the community [35], the patients in our study used only a limited number of supplements (Table 4). The supplements used by patients in our study included fish oil, vitamin c, vitamin e, mistletoe, dandelion, ginger, garlic, and COQ10. The prevalence of particular supplements was similar to that in larger studies [36]. All of these supplements have been associated with bleeding through a variety of mechanisms impacting both platelet and coagulation function [37-45]. These agents have also been found to increase bleeding by interacting with other anticoagulants and antiplatelet agents via the cytochrome p450 system [46].

The modern age of supplements began in 1994 with the passage of the Dietary Supplement Health and Education Act, which declared that herbal and dietary supplements were "foods" and were exempt from safety and efficacy requirements [47]. In 1999, a new FDA labeling regulation was enacted which required dietary supplements to provide a complete list of ingredients, but did not require a list of interactions, side effects, warnings, or contraindications [31]. The absence of regulation equated to a lack of standardization of supplements and little assurance of predictable potencies, contamination control, and accurate labeling [48]. Lack of physician knowledge regarding supplements [26] and lack of patient disclosure regarding the use of supplements was seen across numerous medical specialties [27]. There were numerous case reports of perioperative bleeding complications related to supplements and physicians in most surgical fields adopted policies requiring patients to discontinue supplements 2-3 weeks before surgery and not restart them until 2-3 weeks after [47].

Strengths/Limitations

In this prospective cohort study, we documented the high prevalence of supplement use among a diverse population of patients with GI bleeding. The small sample and survey-based nature of the study had an inherent limitation of limited power and self-reporting bias, respectively. Despite this limitation, it appeared that patients taking several different types of supplements had more severe GI bleeds that required more interventions.

CONCLUSION

Although not significant, supplement use was also associated with longer hospital stays and an overall higher mortality rate. In order to better inform patients, physicians, and policy makers, larger studies are needed to better define the GI bleeding risks associated with particular supplements.

Table 1: Data collection sheet used to survey n = 100 patients with gastrointestinal bleeds who were taking supplements.

Date	_____						
Age	_____						
Sex	Male	Female					
Ethnicity	White	African American	Hispanic	Asian	Afro-Caribbean	Middle Eastern	Unknown
Country of Origin	_____						
Comorbidities	Von Willebrand disease	Hemophilia	Leukemia	Idiopathic thrombocytopenic purpura	Disseminated intravascular coagulation	Vitamin K deficiency	ESRD
Supplement	Garlic Vitamin C	Gingko-biloba Vitamin E	Ginger Other (please specify)	Ginseng	Fish oil	Flax Oil	Coq 10
Length of time on supplement	_____						
Multivitamin use	Yes	No	If yes, please specify brand.				
Combination supplement	Yes	No	If yes, please specify brand.				
Anticoagulation taken in the last 2 weeks	Aspirin	Clopidogrel	NSAIDS	Coumadin	Rivaroxaban	Dabigatran	Enoxaparin
Last INR level	0.7-1.3	1.3-2	>2				
Last platelet count	>/=150,000	100,000-150,000	50,000-100,000	20,000-50,000	<20,000		
History of GI Bleed	Yes	No	If yes, please specify date and #				
History of Liver Disease	Cirrhosis	Increased Liver Function Tests	None				
Type of current bleed	Major	Minor	(Major bleed= decrease in hemoglobin of >/= 2 g/Dl. or requiring 2 Units of				

			packed red blood cells	
Source	Upper PUD Esophagitis Varices Gastric Cancer Esophageal Cancer Gastric antral vascular ectasia Erosive Gastritis Dieulafoy's lesion Mallory-Weiss Tear	Lower Diverticulosis Hemorrhoids Colon Cancer Ischemic Colitis Inflammatory Bowel Disease Infectious Colitis Meckel's Diverticulum Angiodysplasia Duodenitis		
Intervention	Nothing	Transfusion	Endoscopic	Surgery
Length of Hospitalization	_____			
ICU	Yes	No		
Death due to GI Bleed	Yes	No		
Alcohol Use	>/=30 drinks/week	10-30 drinks/week	<10 drinks/week	None

Table 2: Demographic, laboratory, diagnosis, treatment, and prognostic variables for n=100 patients diagnosed with GI bleeding from February 2013-August 2013 at Mount Sinai Medical Center.

Category		Number (%)
Age	<60	39 (39)
	>60	61 (61)
Sex	Male	60 (60)
	Female	40 (40)
Alcohol use	<10 drink/week	83 (83)
	>/=10 drinks/week	17 (17)
Ethnicity	Caucasian	39 (39)
	Hispanic	48 (48)
	AA	12(12)
	Other	1 (1)
Country of Birth	USA	45 (45)
	Caribbean	35 (35)
	Central America	6 (6)
	South America	4 (4)
	Europe	7 (7)
	Other	3 (3)
Supplement Use	Yes	32 (32)
	No	68 (68)
# of supplements	1	23 (71.9)
	2	7 (21.9)
	3	1 (3.1)
	4	1 (3.1)
Type of supplement	Fish Oil	7 (21.9)
	Vitamin C/E	12 (37.5)
	Garlic	1 (3.1)
	Ginger	1 (3.1)
	Multiple	5 (15.6)
	Other	6 (18.8)
Multivitamin	Yes	29 (29)
	No	71 (71)
Anticoagulation previous 2 weeks	Yes	60 (60)
	No	40 (40)
Aspirin	Yes	40 (66.7)
	No	20 (33.3)
Clopidogrel	Yes	19 (46.3)
	No	41 (53.7)
Warfarin	Yes	9 (15.0)
	No	51 (85.0)
Non-Steroidal Ant-inflammatory	Yes	22 (36.7)
	No	38 (63.3)
Rivaroxaban (Xarelto®, Janssen Pharmaceutica, Belgium)	Yes	1 (1.7)
	No	59 (98.3)

Anticoagulation Combination	ASA+ Clopidogrel	12 (20.0)
	ASA+NSAIDS	4 (6.7)
	ASA+ Clopidogrel+NSAIDS	3 (5.0)
	ASA+warfarin+NSAIDS	1 (1.7)
	ASA+ warfarin	1 (1.7)
	ASA+ Clopidogrel+ warfarin	2 (3.3)
	Clopidogrel+ warfarin	1 (1.7)
	ASA+rivaroxaban	1 (1.7)
Platelet Count	>/=150K	79 (79)
	<150K	21 (21)
Liver Function	Normal	79 (79)
	Increased LFT's	10 (10)
	Cirrhosis	11 (11)
End-Stage Renal Disease	Yes	6 (6)
	No	94 (94)
INR	0.7-1.3	77 (77)
	1.3-2	17 (17)
	>2	6 (6)
History of GI bleed	Yes	48 (48)
	No	52 (52)
Previous bleed w/n 6 months	Yes	23 (47.9)
	No	25 (52.1)
Source of previous GI bleed	PUD	14 (29.2)
	Varices	2 (4.2)
	Diverticulosis	5 (10.4)
	Hemorrhoids	6 (12.5)
	AVM	4 (8.3)
	Other	17 (35.4)
# of previous bleeds	1	29 (60.4)
	>1	19 (39.6)
	UGI	51 (51)
Source of current GI bleed	LGI	25 (25)
	Unknown	24 (24)
	PUD	24 (24)
	Esophagitis/gastritis/duodenitis	13 (13)
	Mallory Weiss Tear	4 (4)
	Varices	7 (7)
	Gastropathy	3 (3)
	Diverticulosis	10 (10)
	Hemorrhoids	3 (3)
	Colon Cancer	3 (3)
	AVM	1 (1)
	Ischemic colitis	2 (2)
	Other	11 (11)
	Unknown	24 (24)
Intervention	Transfusion Only	61 (61)
	Endoscopic Intervention	20 (20)
	Surgery	8 (8)
	No Intervention	11 (11)
# of units given	0-1	47 (47)
	>1	53 (53)
Length of Hospital Stay (days)	1-4	40 (40)
	5-8	30 (30)
	>8	30 (30)
ICU	Yes	32 (32)
	No	68 (68)
Length of ICU stay (days)	<3	18 (56.3)
	>/=3	14 (43.8)
Death due to GI bleed	Yes	2 (2)
	No	98 (98)

AA: African American, ASA: Aspirin, NSAIDS: Non-steroidal anti-inflammatory, PUD: Peptic ulcer disease, UGI; Upper Gastrointestinal, LGI: Lower Gatsrointestinal, AVM: Arteriovenous malformation, LFT: Liver function test, ICU: Intensive care unit

Table 3: Comparison between patients who took supplements and those who did not. *chi-squared test

Category		Supplement use (n=32)	No supplement use(n=68)	p-value*
Age	<60	11 (34.4)	28 (41.2)	0.52
	>60	21 (65.6)	40 (58.8)	
Sex	Male	17 (53.1)	43 (63.2)	0.34
	Female	15 (46.9)	25 (36.8)	
ETOH use	<10 drink/week	28 (87.5)	55 (80.9)	0.41
	>/=10 drinks/week	4 (12.5)	13 (19.1)	
Ethnicity	Caucasian	12 (37.5)	27 (39.7)	0.83

	Hispanic	15 (46.9)	33 (48.5)	0.88
	AA	5 (15.6)	7 (10.3)	0.44
	Other	0 (0)	1 (1.5)	0.49
Country of Birth	USA	14 (43.8)	31 (45.6)	0.86
	Caribbean	11 (34.4)	24 (35.3)	0.93
	Central America	3 (9.4)	3 (4.4)	0.33
	South America	1 (3.1)	3 (4.4)	0.76
	Europe	3 (9.4)	4 (5.9)	0.52
	Other	0 (0)	3 (4.4)	0.23
Multivitamin	Yes	13 (40.6)	16 (23.5)	0.08
	No	19 (59.4)	52 (76.5)	
Anticoagulation previous 2 weeks	Yes	17 (53.1)	43 (63.2)	0.34
	No	15 (46.9)	25 (36.8)	
ASA	Yes	10 (58.8)	30 (69.8)	0.42
	No	7 (41.2)	13 (30.2)	
Clopidogrel	Yes	5 (29.4)	14 (32.6)	0.81
	No	12 (70.6)	29 (67.4)	
Warfarin	Yes	3 (17.6)	6 (14.0)	0.72
	No	14 (82.4)	37 (86.0)	
NSAIDS	Yes	9 (52.9)	12 (27.9)	0.07
	No	8 (47.1)	31 (62.1)	
Rivaroxaban	Yes	0 (0)	1 (2.3)	0.53
	No	17 (100)	42 (97.7)	
Anticoagulation Combination	ASA+ Clopidogrel	1 (5.9)	11 (25.6)	
	ASA+NSAIDS	2 (11.8)	2 (4.7)	0.08
	ASA+ Clopidogrel+NSAIDS	1 (5.9)	2 (4.7)	0.32
	ASA+ warfarin +NSAIDS	1 (5.9)	0 (0)	0.84
	ASA+ warfarin	0 (0)	1 (2.3)	0.11
	ASA+ Clopidogrel+ warfarin	1 (5.9)	1 (2.3)	0.53
	Clopidogrel+ warfarin	1 (5.9)	0 (0)	0.49
	ASA+rivaroxaban	0	1 (2.3)	0.11
				0.49
Platelet Count	>/=150K	26 (81.3)	53 (77.9)	0.70
	<150K	6 (18.8)	15 (22.1)	
Liver Function	Normal	24 (75.0)	55 (80.9)	0.50
	Increased LFTS	5 (15.6)	5 (7.4)	0.20
	Cirrhosis	3 (9.4)	8 (11.8)	0.72
ESRD	Yes	2 (6.3)	4 (5.9)	0.94
	No	30 (93.8)	64 (94.4)	
INR	0.7-1.3	27 (84.4)	50 (73.5)	0.23
	1.3-2	2 (6.3)	15 (22.1)	0.05
	>2	3 (9.4)	3 (4.4)	0.33
History of GI bleed	Yes	16 (50.0)	32 (47.1)	0.78
	No	16 (50.0)	36 (52.9)	
Previous bleed w/n 6 months	Yes	10 (62.5)	15 (46.9)	0.31
	No	6 (37.5)	17 (53.1)	
Source of previous GI bleed	PUD	4 (25.0)	10 (31.3)	0.65
	Varices	0	4 (12.5)	0.14
	Diverticulosis	2 (12.5)	3 (9.4)	0.74
	Hemorrhoids	4 (25.0)	2 (6.3)	0.06
	AVM	2 (12.5)	2 (6.3)	0.46
	Other	4 (25.0)	11 (34.4)	0.51
# of previous bleeds	1	9 (56.3)	23 (71.9)	0.28
	>1	7 (43.7)	9 (28.1)	
Current GI bleed	UGI	14 (43.8)	35 (51.5)	0.47
	LGI	10 (31.3)	22 (32.4)	0.91
	Unknown	8 (25.0)	11 (16.2)	0.29
	PUD	8 (25.0)	16 (23.5)	0.87
	Esophagitis/gastritis/duodenitis	4 (12.5)	9 (13.2)	0.92
	Mallory Weiss Tear	0 (0)	4 (5.9)	0.16
	Varices	2 (6.3)	5 (7.4)	0.84
	Gastropathy	0 (0)	3 (4.4)	0.23
	Diverticulosis	2 (6.3)	8 (11.8)	0.39
	Hemorrhoids	1 (3.1)	2 (2.9)	0.96
	Colon Cancer	0 (0)	3 (4.4)	0.23
	AVM	0 (0)	1 (1.5)	0.49
	Ischemic colitis	2 (6.3)	0 (0)	0.04
	Other	5 (15.6)	6 (8.8)	0.31
	Unknown	8 (25.0)	11 (16.2)	0.29
Intervention	Transfusion Only	23 (71.9)	38 (55.9)	0.13
	Endscopic Intervention	7 (21.9)	13 (19.1)	0.75
	Surgery	2 (6.3)	7 (10.3)	0.51
	No intervention	0	10 (14.7)	0.02

# of units given	0-1	14 (43.8)	33 (48.5)	0.66
	>1	18 (56.3)	35 (51.5)	
Length of Hospital Stay (days)	1-4	11 (34.4)	29 (42.6)	0.43
	5-8	12 (37.5)	18 (26.5)	0.26
	>8	9 (28.1)	21 (30.9)	0.78
ICU	Yes	10 (31.3)	22 (32.4)	0.91
	No	22 (68.8)	46 (67.6)	
Length of ICU stay (days)	<3	4 (40.0)	14 (63.6)	0.21
	>/=3	6 (60.0)	8 (36.4)	
Death due to GI bleed	Yes	1 (3.1)	1 (1.5)	0.58
	No	31 (96.9)	67 (98.5)	

ETOH: Alcohol, AA: African American, ASA: Aspirin, NSAIDS: Non-steroidal anti-inflammatory, PUD: Peptic ulcer disease, UGI; Upper Gastrointestinal, LGI: Lower Gatsrointestinal, AVM: Arteriovenous malformation, LFT: Liver function test, ESRD: End-stage renal disease, ICU: Intensive care unit.

Table 4: The comprehensive list of supplements used by patients in our study compared with Kaufman et al. (2002) 36, the suggested uses of the supplements, their mechanism of action, and their affect on INR.

List of Supplements	Incidence (%)		Uses	Mechanism of Increased Risk of bleeding	Effect on INR55
	Zeichner et al. (2013) (n=100)	Kaufman et al. (2002)36 (n=2590)			
Fish oil aka Eicosapentaenoic acid	11	0	Hypertriglyceridemia, coronary artery disease, inflammation48, 49	Decreased thromboxane A2 production, prolonged bleeding time, Platelet aggregation inhibitor	Increase
Mistletoe	1	0	Circulatory and respiratory disorders, cancer prevention50	Unknown	-
Vitamin C	13	9.1	Antioxidant, gout, common cold51	Unknown	Increase
Vitamin E	5	10	Cancer prevention, antioxidant, anti-athersclerosis52, 53	Intrinsic pathway inhibition, Platelet aggregation inhibitor	Increase
Ginger	1	0	Nausea, bloating dyspepsia, arthritis, stress reduction41, 54	Platelet aggregation inhibitor	Increase
Garlic	2	1.9	Antihypertensive, anti-asthmatic, antipyretic, antihelmenthic45	Platelet aggregation inhibitor (collagen, thromboxane, ADP)	Increase
CoQ10	3	0	Heart disease, migraine headaches, antihypertensive47	Vitamin K inhibition	Increase
Dandelion	1	0	Infection, liver and biliary dysfunction47	Unknown	-
Milk Thistle	1	0	Liver disease, diabetes, high cholesterol, cancer prevention47	Unknown	Increase
Zinc	2	2.2	Skin diseases, liver and kidney dysfunction47	Unknown	-
Multivitamin	29	26	Antioxidant	-	-

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