PAPER

The Rate of Bleeding Complications After Pharmacologic Deep Venous Thrombosis Prophylaxis

A Systematic Review of 33 Randomized Controlled Trials

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Hypothesis: Major bleeding complications from pharmacologic deep venous thrombosis (DVT) prophylaxis are infrequent.

Design: Systematic review of the MEDLINE database from 1965 to August 2005, using the terms *DVT*, *prophylaxis*, *general surgery*, and *heparin*.

Setting and Patients: Randomized controlled trials evaluating pharmacologic DVT prophylaxis in patients undergoing general surgery.

Main Outcome Measures: Eight complication categories: injection site bruising, wound hematoma, drain site bleeding, hematuria, gastrointestinal tract bleeding, retroperitoneal bleeding, discontinuation of prophylaxis, and subsequent operation.

Results: Fifty-two randomized controlled trials studied DVT prophylaxis; 33 randomized controlled trials with 33 813 patients undergoing general surgery evaluated pharmacologic prophylaxis and quantified bleeding complications. Of the minor complications, injection site bruising (6.9%), wound hematoma (5.7%), drain site bleeding (2.0%), and hematuria (1.6%) were most common. Major bleeding complications, such as gastrointestinal tract (0.2%) or retroperitoneal (<0.1%) bleeding, were infrequent. Discontinuation of prophylaxis occurred in 2.0% of patients and subsequent operation in less than 1% of patients. When analyzed by high- vs low-dose unfractionated heparin, the lower dose had a smaller rate of discontinuation of prophylaxis ($P=.02$) and subsequent operation ($P=.06$).

Conclusions: Knowledge of bleeding complication rates is important for surgeons because DVT prophylaxis may soon be implemented by Medicare as a quality measure. This level 1 evidence report shows that bleeding complications requiring a change in care occur less than 3% of the time and seem reduced with lower-dose prophylaxis. Given these findings, most patients undergoing general surgery could receive pharmacologic prophylaxis safely.

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WITH THE TREND TOward improving outcomes in surgery using evidence-based guidelines, prevention of venous thromboembolism through promotion of deep venous thrombosis (DVT) prophylaxis is increasing. Guidelines have been created, perhaps most notably by the American College of Chest Physicians,[1] that recommend pharmacologic DVT prophylaxis with low-dose unfractionated (LDU) heparin or low-molecular-weight (LMW) heparin for all patients undergoing general surgery who are at moderate or high risk for DVT. In addition, the goal of the Surgical Care Improvement Project, a quality improvement collaboration sponsored in part by the Centers for Medicare and Medicaid Services, the Centers for Disease Control and Prevention, the American College of Surgeons, the Department of Veterans Affairs, and others, is to decrease surgical complications by 25%. Deep venous thrombosis prevention is 1 of the 4 target areas, and the Surgical Care Improvement Project[2] may suggest incorporation of the American College of Chest Physicians' guidelines.

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Deep venous thrombosis prophylaxis has long been considered important in surgical patients. In general surgery, up to 40% of patients will develop a DVT without prophylaxis and the presence of malignant disease increases this risk at least 2-fold.[1] Despite these high risks, physicians have

largely been left on their own to determine the proper prophylaxis for their patients and many have avoided pharmacologic prophylaxis because of its associated bleeding complications. It has recently been shown that 25% of high-risk abdominal surgery patients receive no prophylaxis and 50% receive inadequate prophylaxis.[3]

Before requiring surgeons to use LDU heparin or LMW heparin as the first-line modality of DVT prophylaxis, it is important to determine how an increased use of pharmacologic prophylaxis will affect the rate of bleeding complications. Thus, the present study performs a systematic review of all randomized controlled trials (RCTs) to determine the rate of major and minor bleeding complications in patients undergoing general surgery who are receiving pharmacologic DVT prophylaxis. Moreover, analyses are performed to ascertain whether associations exist between pharmacologic dosing and type of bleeding complications.

METHODS

LITERATURE SEARCH

MEDLINE (1966–August 2005) was searched for studies involving DVT prophylaxis in general surgery. Key words included were *DVT*, *prophylaxis*, *general surgery* and *heparin*. Search results were limited to English-language RCTs involving general surgery, urology, gynecology, and thoracic (excluding cardiac) surgery patients. A manual bibliographic survey of all identified articles was performed to identify additional studies. In addition, bibliographic surveys of previous meta-analyses and systematic reviews of DVT prophylaxis were performed.

STUDY SELECTION

For the articles identified in the literature search, inclusion criteria were RCTs of pharmacologic DVT prophylaxis with information reported on bleeding complications. Control groups were included if they received placebo injections. Exclusion criteria were RCTs that did not provide information on complications or did not include a pharmacologic prophylaxis group.

DATA COLLECTION

Data were abstracted from each RCT and then independently reviewed by each of us. Disagreements were resolved by consensus. Data abstracted for all studies included name of first author, journal, year of publication, number of patients randomized, patient age, patient sex, presence of malignancy, type of surgery, intervention type and duration, and number of bleeding complications. The complication rate was calculated using the number of complications as the numerator and the number of potential patients as the denominator. Complications were analyzed if they were recorded by more than 1 RCT and had clinically descriptive titles that all of the authors agreed allowed for comparison between RCTs. For example, "injection site bruising" was deemed comparable between studies, while "minor bleeding" was not. Eight complication categories were identified: injection site bruising, wound hematoma, drain site bleeding, hematuria, gastrointestinal (GI) tract bleeding, retroperitoneal (RP) bleeding, discontinuation of prophylaxis, and subsequent operation. The complications were analyzed on a complication rather than a patient level (ie, 1 patient could have 3 complications that were reported separately).

ANALYSIS

The average age for all patients receiving prophylaxis combined and each of the intervention groups was calculated for each complication category using a weighted average of the mean age from each RCT. When the average age was not provided for a particular subgroup within a study, the mean age of the entire sample was substituted. When the average age was not provided for any of the patients in a study, these patients were excluded from the weighted average age calculation. The percentage of males was calculated for all prophylaxis patients combined and each of the intervention groups using the number of males as the numerator and the total number of patients as the denominator. Again, when an RCT did not provide sex information for a subgroup, the percentage of males from the overall sample was substituted, and if the study did not provide sex information on any patients, then these patients were excluded from the sex calculation. This same procedure was also used to determine the percentage of patients with malignancy. Studies that did not provide malignancy information were excluded from the malignancy calculation.

Patients were pooled from all studies into 5 groups based on intervention received: a high dose of LMW heparin, a low dose of LMW heparin, a high dose of LDU heparin, a low dose of LDU heparin, and placebo. For LMW heparin, high dose was defined as greater than 3400 U/d; and for LDU heparin, high dose was defined as 5000 U 3 times per day. These definitions are consistent with previous reviews and guidelines.[1,4]

The overall rate of each complication for all pharmacologic prophylaxis combined and for each of the 5 intervention groups was calculated by identifying each study that provided information on each of the 8 complication groups. All the potential patients for each complication were pooled as the denominator and those with the complication were used as the numerator. Complication rates were compared by pharmacologic intervention using a standard t test; 2-sided $P<.05$ was considered statistically significant. All analyses were performed using Stata, version 9.1 (Stata Corp, College Station, Tex).

RESULTS

STUDY INFORMATION

Fifty-five RCTs that studied DVT prophylaxis in patients undergoing general surgery were identified through the initial literature search. Of these 55 RCTs, 33 studies[5-37] were included in the present review (**Table 1**). Pharmacologic DVT prophylaxis and quantified bleeding complications were evaluated in 33 813 patients undergoing general surgery. The publication date of these studies ranged from 1975 to 2004. All RCTs initiated prophylaxis preoperatively. Most studies gave the first dose 2 hours preoperatively, while some gave the first dose the night before surgery. The duration of prophylaxis ranged from 4 to 10 days (median, 7 days). Most studies explicitly stated that they encouraged early ambulation and discontinued prophylaxis on full ambulatory status or discharge from the hospital. Complications were monitored by a daily clinical examination in most studies. The interventions, type of operation, and complications recorded by each RCT are listed in Table 1. The 33 813 patients underwent the following types of operations: 20.3%, colorectal; 19.4%, abdominal surgery not otherwise specified; 15.6%, hepatobiliary; 12.1%, gynecologic; 9.6%, esophageal/GI; 9.8%, hernia; 7.1%, other; 4.4%, urologic; and 1.7%, noncardiac thoracic. **Table 2** provides the patient demographic

Table 1. Study Information

Source	Type of Surgery	Blinding	Interventions*	Complication Outcomes Examined: Injection Site Bruising	Wound Hematoma	Drain Site Bleeding	Hematuria	GI Tract Bleeding	RP Bleeding	Discontinue Prophylaxis	Subsequent Operation
Baykal et al,[31] 2001	Major gynecologic cancer surgery	Double	LDU heparin, 5000 U tid Enoxaparin, 2500 U qd	No	Yes	No	No	No	No	No	No
Bergqvist et al,[9] 1990	Major abdominal surgery	Double	LDU heparin, 5000 U bid Dalteparin, 5000 U qd	Yes	Yes	No	No	No	No	No	No
Bergqvist et al,[23] 1995	Elective general abdominal surgery	Double	Dalteparin, 2500 U qd Dalteparin, 5000 U qd	No	Yes	No	No	No	No	Yes	Yes
Boneu,[24] 1993	Major abdominal, gynecologic surgery	Double	LDU heparin, 5000 U bid Reviparin, 1750 U qd	No	Yes	Yes	No	No	No	No	No
Borstad et al,[32] 1992	Major gynecologic surgery	Double	LDU heparin, 5000 U bid Dalteparin, 2500 U qd	No	Yes	No	No	No	No	No	No
Caen,[10] 1988	Major general surgery	Double	LDU heparin, 5000 U bid Dalteparin, 2500 U qd	Yes	Yes	No	No	No	No	No	No
Covey et al,[28] 1975	Major abdominal, pelvic, HN, noncardiac thoracic surgery	Blind	LDU heparin, 5000 U bid Control (placebo injections)	No	Yes	No	No	Yes	No	No	No
Di Carlo et al,[35] 1999	Elective abdominal, pelvic, noncardiac thoracic surgery for malignancy	Double	LDU heparin, 5000 U tid with GCS on 65 patients Dermatan sulfate group excluded	No	No	No	No	No	No	Yes	No
ENOXACAN Study Group,[19] 1997	Elective abdominal, pelvic, cancer surgery	Double	LDU heparin, 5000 U tid Enoxaparin, 40 mg qd	Yes	No	No	No	No	No	Yes	No
European Fraxiparin Study (EFS) Group,[33] 1988	Elective abdominal surgery	None	GCS plus: LDU heparin, 5000 U tid Nadroparin, 7500 U qd	No	Yes	No	Yes	No	No	No	No
Fricker et al,[20] 1988	Elective abdominal, pelvic, cancer surgery	None	LDU heparin, 5000 U tid Dalteparin, 2500 U preoperatively and 5000 U qd postoperatively	Yes	No	No	Yes	No	No	Yes	No
Gallus et al,[29] 1976	Major abdominal, noncardiac thoracic surgery	Not specified	LDU heparin, 5000 U tid Control (placebo injections)	No	Yes	No	No	No	No	No	No
Gazzaniga et al,[7] 1993	General surgery	Not specified	LDU heparin, 5000 U bid Enoxaparin, 20 mg qd	Yes	No	Yes	No	No	No	Yes	Yes
Haas and Flosbach,[25] 1993	Major abdominal, pelvic surgery	Not specified	Enoxaparin, 20 mg qAM Enoxaparin, 20 mg qHS	No	Yes	No	Yes	Yes	Yes	No	Yes
Ho et al,[15] 1999	Major colorectal surgery	Double	Enoxaparin, 20 mg preoperatively, then 40 mg qd Control (placebo injections)	Yes	Yes	Yes	No	No	No	No	Yes
Howard et al,[36] 2004	Elective surgery (orthopedic, HN, and vascular included)	None	Enoxaparin, 20 mg qd plus GCS: T.E.D. anti-embolism stockings (thigh length) (The Kendall Co, Mansfield, Mass), anti-embolism stockings (thigh and knee length) (MediUSA Inc, New York, NY)	No	Yes	No	No	No	No	No	Yes
Joffe,[21] 1976	Major elective abdominal surgery	Not specified	LDU heparin, 5000 U tid Pentosan polysulfate sodium group excluded Control (no prophylaxis)	Yes	Yes	No	No	No	No	No	No
Kakkar and Murray,[26] 1985	Elective general surgery	Double	LDU heparin, 5000 U bid Nadroparin, 7500 U qd	No	Yes	No	No	No	No	Yes	No

(*continued*)

Table 1. Study Information (cont)

Source	Type of Surgery	Blinding	Interventions*	Complication Outcomes Examined: Injection Site Bruising	Wound Hematoma	Drain Site Bleeding	Hematuria	GI Tract Bleeding	RP Bleeding	Discontinue Prophylaxis	Subsequent Operation
Kakkar et al,[18] 1993	Major elective abdominal surgery	Not specified	LDU heparin, 5000 U bid Dalteparin, 2500 U qd	Yes	Yes	No	No	No	No	Yes	Yes
Kiil et al,[37] 1978	Elective thoracic, abdominal, lower extremity surgery	Double	LDU heparin, 5000 U bid Control (placebo injections)	No	No	No	No	No	No	No	Yes
Koppenhagen et al,[14] 1992	Elective abdominal surgery	Double	LDU heparin, 5000 U tid Sandoparin, 3000 U qd	Yes	Yes	No	Yes	No	No	No	No
Lausen et al,[34] 1998	Elective abdominal, noncardiac thoracic	Blinded to evaluator	GCS for 1 wk plus: Tinazaparin, 3500 U qd for 1 wk Tinazaparin, 3500 U qd for 4 wk	No	No	No	Yes	Yes	No	No	No
Liezorovicz et al,[8] 1991	Major abdominal, pelvic, noncardiac thoracic surgery	Double	LDU heparin, 5000 U bid Tinazaparin, 2500 U qd Tinazaparin, 3500 U qd	Yes	Yes	No	No	No	No	No	No
Marassi et al,[30] 1993	Elective GI tract cancer surgery	None	Nadroparin, 7500 U qd Control (placebo injections)	No	Yes	No	No	No	No	No	No
McLeod et al,[16] 2001	Major colorectal surgery	Double	LDU heparin, 5000 U bid Enoxaparin, 40 mg qd	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nurmohamed et al,[6] 1995	Major general surgery	Double	LDU heparin, 5000 U tid Enoxaparin, 20 mg qd	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Author unlisted,[12] 1984	Major abdominal surgery	Double	LDU heparin, 5000 U bid Control (placebo injections) 3 groups involving dihydroergotamine excluded	Yes	Yes	No	No	No	No	Yes	No
Schmitz-Huebner et al,[13] 1984	Major abdominal surgery	Double	All with GCS plus: LDU heparin, 5000 U bid 2 groups involving unknown LMW heparin excluded	Yes	Yes	No	No	No	No	Yes	No
Torngren and Forsberg,[22] 1978	Major elective GI surgery	Not specified	LDU heparin, 5000 U bid Control (placebo injections)	Yes	Yes	No	No	No	No	No	No
Torngren,[27] 1980	Major abdominal surgery	None	LDU heparin, 5000 U bid plus GCS (thigh) on one leg and nothing on the other	No	Yes	No	No	Yes	No	Yes	No
Torngren et al,[11] 1984	Elective major general surgery	Double	LDU heparin, 5000 U bid 2 groups involving an unknown semisynthetic heparin analogue excluded	Yes	Yes	No	No	No	No	Yes	No
Tsimoyiannis et al,[5] 1996	Elective abdominal, pelvic, abdominal wall surgery	Not specified	Enoxaparin, 20 mg, or nadroparin, 0.3 mL, qd Enoxaparin, 40 mg, or nadroparin, 0.6 mL, qd 2 groups involving micronized, purified flavonoid fraction (Daflon) were excluded	Yes	Yes	No	No	No	No	No	No
Valle et al,[17] 1988	Major general surgery	Double	Nadroparin, 7500 U qd Control (placebo injections)	Yes	Yes	No	No	No	No	No	No

Abbreviations: bid, 2 times a day; GCS, graduated compression stockings; GI, gastrointestinal; HN, head and neck; LDU, low-dose unfractionated; LMW, low-molecular-weight; qAM, every morning; qd, every day; qHS, every night; RP, retroperitoneal; tid, 3 times a day.

*Enoxaparin, dalteparin, reviparin, nadroparin, sandoparin, and tinazaparin are all types of LMW heparin.

Table 2. Patient Demographic Characteristics by Type of Complication

Type of Complication	Average Age, y		Males, %		Malignancy, %	
	Pharmacologic Prophylaxis Group	Control Group	Pharmacologic Prophylaxis Group	Control Group	Pharmacologic Prophylaxis Group	Control Group
Injection site bruising	61.4	62.1	41.8	52.0	45.5	71.0
Wound hematoma	60.4	61.2	42.6	52.0	33.1	45.0
Drain site bleeding	58.6	63.0	49.0	54.0	44.0	96.0
Hematuria	59.0	NA	47.3	NA	24.5	NA
GI tract bleeding	58.5	60.0	46.9	48.1	20.9	38.5
RP bleeding	58.4	NA	46.7	NA	20.1	NA
Discontinue prophylaxis	63.0	NA	41.0	NA	53.0	NA
Subsequent operation	60.3	64.6	44.7	54.1	30.4	47.6

Abbreviations: GI, gastrointestinal; NA, data not available; RP, retroperitoneal.

information, including age, sex, and rate of malignancy, by each of the 8 complication groups.

INJECTION SITE BRUISING

Eighteen RCTs[5,8-18,21-33,37] evaluating the complication of injection site bruising in 13 574 patients were identified. Of the 13 215 patients receiving any pharmacologic prophylaxis, 6.9% had injection site bruising. Of 2460 patients receiving a high dose of LMW heparin, 3.4% developed bruises, vs 6.8% of 4720 patients receiving a low dose of LMW heparin. For patients receiving LDU heparin injections, 8.3% of the high- and low-dose groups (of 1703 and 4691 patients, respectively) developed bruises. For the 359 patients receiving placebo injections, 2.8% developed bruises. The LDU heparin groups had higher rates of bruising than the LMW heparin groups ($P=.04$). The group that received a low vs a high dose of LMW heparin had a higher rate of bruising ($P<.001$).

WOUND HEMATOMA

Twenty-six RCTs[5,8-18,21-34] evaluating the complication of wound hematoma in 27 225 patients were identified. Of the 26 371 patients receiving any pharmacologic prophylaxis, 5.7% developed wound hematomas. Of the 4032 patients who received a high dose of LMW heparin, 4.0% developed wound hematomas, vs 6.6% of 15 389 who received a low dose of LMW heparin. Of the 1737 patients who received a high dose of LDU heparin, 5.5% developed wound hematomas, vs 4.2% of 5213 who received a low dose of LDU heparin. Of the 854 patients receiving placebo injections, 0.8% developed wound hematomas. The group receiving a high vs a low dose of LDU heparin had a higher rate of wound hematomas ($P=.02$). The group receiving a low vs a high dose of LMW heparin had a higher rate of wound hematomas ($P<.001$).

DRAIN SITE BLEEDING

Five RCTs[6,7,15,16,24] evaluating the complication of drain site bleeding in 5476 patients were identified. Of the 5307 patients receiving any pharmacologic prophylaxis, 2.0% had drain site bleeding. Of 787 patients receiving a high dose of LMW heparin, 1.8% developed drain site bleeding, vs 2.0% of 1934 patients receiving a low dose of LMW heparin. Of 719 patients receiving a high dose of LDU heparin, 0.4% developed drain site bleeding, vs 2.8% of 1867 patients receiving a low dose of LDU heparin. Of the 169 patients receiving placebo injections, 0.6% developed drain site bleeding. No statistical differences in rates of drain site bleeding were identified, with the exception of the lower rate in the group receiving a high dose of LDU heparin ($P=.01$).

HEMATURIA

Seven RCTs[6,14,16,20,25,33,34] evaluating the complication of hematuria in 16 049 patients were identified. Of the 15 406 patients receiving any pharmacologic prophylaxis, 1.6% had hematuria. Of 1771 patients receiving a high dose of LMW heparin, 5.8% developed hematuria, vs 0.4% of 10 967 patients receiving a low dose of LMW heparin. Of 2025 patients receiving a high dose of LDU heparin, 4.7% developed hematuria, vs 0.2% of 643 patients receiving a low dose of LDU heparin. None of the studies evaluating for hematuria had patients receiving placebo injections (**Table 3**). For LMW and LDU heparin, the high-dose groups had higher rates of hematuria than the low-dose groups ($P<.001$).

GI TRACT OR RP BLEEDING

Six RCTs[6,16,25,28,29,35] evaluating the complication of GI tract bleeding in 12 980 patients were identified. Of the 12 928 patients receiving any pharmacologic prophylaxis, 0.2% had GI tract bleeding. Of the 52 patients receiving placebo injections, 1 (1.9%) had GI tract bleeding. Three RCTs[6,16,25] evaluating the complication of RP bleeding in 12 642 patients were identified. Of the 12 642 patients receiving any pharmacologic prophylaxis, 0.08% had RP bleeding. None of the studies evaluating for RP bleeding had patients receiving placebo injections.

DISCONTINUATION OF PROPHYLAXIS

Twelve RCTs* evaluating the complication of discontinuation of pharmacologic DVT prophylaxis in 10 540

**References 7, 11-13, 16, 18-20, 23, 26, 27, 35.*

Table 3. Complication Rates by Type of Complication

Type of Complication	No. of RCTs	Sample Size of Potential Patients: Pharmacologic Prophylaxis Group	Sample Size of Potential Patients: Control Group	Complications, Mean (Range), %: LMW Heparin Group: High	LMW Heparin Group: Low	LDU Heparin Group: High	LDU Heparin Group: Low	Total Pharmacologic Prophylaxis Group	Control Group
Injection site bruising	18	13 574	359	3.4 (1.1-7.1)	6.8 (0.5-16.3)	8.3 (2.0-20.0)	8.3 (0.6-15.7)	6.9 (0.7-20.2)	2.8 (0-7.6)
Wound hematoma	26	26 371	854	4.0 (0-8.6)	6.6 (0-9.1)	5.5 (0-9.2)	4.2 (0.6-19.0)	5.7 (0-19.0)	0.8 (0-3.2)
Drain site bleeding	5	5307	169	1.8 (2.1-3.0)	2.0 (0.6-5.2)	0.4 (0.4)	2.8 (1.2-6.1)	2.0 (0.6-5.6)	0.6 (0.6)
Hematuria	7	15 406	NA	5.8 (0.2-10.0)	0.4 (0-0.5)	4.7 (0.3-9.6)	0.2 (0.2)	1.6 (0.2-9.8)	NA
GI tract bleeding	6	12 928	52	1.0 (1.0)	<0.1 (0.04-0.3)	0.4 (0.4)	0.5 (0-1.0)	0.2 (0.04-2.5)	1.9 (1.9)
RP bleeding	3	12 642	NA	0.3 (0.4)	<0.1 (0.03-0.1)	0.4 (0.4)	0.2 (0.2)	<0.1 (0.03-0.3)	NA
Discontinue prophylaxis	12	10 540	NA	2.0 (1.5-5.0)	1.7 (0.9-2.3)	3.3 (2.1-5.0)	1.9 (0-7.1)	2.0 (0-7.1)	NA
Subsequent operation	9	20 618	822	1.0 (0.4-1.5)	0.5 (0.2-1.0)	1.8 (1.8)	1.0 (0.2-1.7)	0.7 (0.3-1.3)	0.7 (0.6-0.8)

Abbreviations: GI, gastrointestinal; LDU, low-dose unfractionated; LMW, low-molecular-weight; NA, data not available; RCT, randomized controlled trial; RP, retroperitoneal.

patients were identified. Of the 10 540 patients receiving any pharmacologic prophylaxis, 2.0% had prophylaxis discontinued. Of 2446 patients receiving a high dose of LMW heparin, 2.0% did not complete the prescribed prophylactic regimen, vs 1.7% of 3431 patients receiving a low dose of LMW heparin. Of 1024 patients receiving a high dose of LDU heparin, 3.3% did not complete the prophylactic regimen, vs 1.9% of 3639 patients receiving a low dose of LDU heparin. There were no statistical differences between the subgroups, except for the group receiving a high dose of LDU heparin, which had a higher rate of discontinuation of prophylaxis ($P=.02$).

SUBSEQUENT OPERATION FOR BLEEDING PROBLEMS

Nine RCTs† evaluating the complication of subsequent operation in 21 440 patients were identified. Of the 20 618 patients receiving any pharmacologic prophylaxis, 0.7% underwent subsequent operation for bleeding problems. Of 1768 patients receiving a high dose of LMW heparin, 1.0% underwent subsequent operation, vs 0.5% of 14 369 patients receiving a low dose of LMW heparin. Of 719 patients receiving a high dose of LDU heparin, 1.8% underwent subsequent operation, vs 1.0% of 3762 patients receiving a low dose of LDU heparin ($P=.06$). Of the 822 patients receiving placebo injections, 0.7% required subsequent operation, which is identical to the subsequent operation rate for patients receiving pharmacologic prophylaxis. The group receiving a high vs a low dose of LMW heparin had a higher rate of subsequent operation ($P=.008$). The group receiving a high vs a low dose of LDU heparin had a higher rate of subsequent operation, which approaches statistical significance ($P=.06$).

COMMENT

This study evaluated 33 RCTs including 33 813 patients undergoing general surgery to determine the rate of bleeding complications associated with pharmacologic DVT prophylaxis. Pharmacologic prophylaxis was divided into 4 categories based on type and dose of medication, and 8 categories of complications were examined. In general, the rate of bleeding complications was low. Minor complications, including injection site bruising, wound hematomas, drain site bleeding, and hematuria, were significantly more common than major complications, such as GI tract or RP bleeding. Changes in care in the form of discontinuation of pharmacologic prophylaxis and subsequent operation occurred in 2.0% and 0.7% of patients, respectively.

Rates of injection site bleeding and wound hematomas (the 2 most common complications) were significantly higher for the groups receiving pharmacologic DVT prophylaxis vs the placebo group. Injection site bruising was more prevalent in the LDU heparin groups. This may not be surprising given that the groups receiving a high and a low dose of LDU heparin received 3 and 2 injections, respectively, per day vs the LMW heparin groups, which received predominantly 1 injection per day (or 2 with some forms of LMW heparin). Injection site bruising had paradoxical findings in that it was more prevalent for the group receiving a low vs a high dose of LMW heparin. This is likely because of 2 large studies[6,7] that involved pharmacologic prophylaxis with a low dose of LMW heparin and set the high end of the range for the 18 RCTs evaluating injection site bruising. For wound hematomas, there was a higher rate for the group receiving a high vs a low dose of LDU heparin, as expected. However, as with injection site bruising, there was paradoxically a higher prevalence of wound hematoma for the group receiving a low vs a high dose of LMW heparin. Again, this may be because of 1 large study[25] that used pharmacologic prophylaxis with a low dose of LMW heparin and that lies at the upper limit of the range for the 26 RCTs evaluating wound hematoma.

Drain site bleeding and hematuria were relatively infrequent minor complications. Drain site bleeding with pharmacologic prophylaxis showed no statistically significant difference from the placebo group, although this

†*References 6, 7, 15, 16, 18, 23, 25, 36, 37.*

may be limited by a small sample size of patients receiving placebo. All pharmacologic intervention groups seemed statistically similar, except for the group receiving a high dose of LDU heparin, which had a lower rate of drain site bleeding. A combination of the high and low dose of LDU heparin groups demonstrated a drain site bleeding rate of 2.2%, which was more consistent with the rate of the LMW heparin groups. For the complication of hematuria, we saw the expected trend, with the high-dose groups (of LMW and LDU heparin) having higher rates of hematuria than the low-dose groups (of LMW and LDU heparin). However, the 2 studies[20,33] on the high end of the hematuria rate range included only the high-dose groups.

In general, the rate of major complications, such as GI tract (0.2%) or RP (<0.1%) bleeding, was extremely low. In addition, complications requiring a change in care, such as subsequent operation (0.7%) or discontinuation of prophylaxis (2.0%), were also infrequent. The subsequent operation rate for bleeding problems for pharmacologic prophylaxis vs placebo was identical, at 0.7%. Further analysis of studies reporting discontinuation of prophylaxis demonstrated a higher rate in the high dose of LDU heparin prophylaxis group. There did not seem to be any influential outlier studies; however, the higher rate of discontinuing prophylaxis may be because of the higher rate of minor complications, such as injection site bruising and wound hematoma, in the high dose of LDU heparin group. In addition, patients may be more likely to refuse their injections given that this group requires 3 injections per day vs 1 or 2 injections for the other groups.

An additional concern with the use of pharmacologic DVT prophylaxis is its safety in conjunction with neuraxial anesthesia. While anesthesiologists often cite an increased risk of spinal hematoma, this risk may be acceptable. Guidelines from the American Society of Regional Anesthesia allow neuraxial anesthesia use with pharmacologic prophylaxis as long as there is appropriate caution, with patient selection as follows: avoiding patients with known clotting disorders, avoiding patients receiving thienopyridine platelet inhibitors (clopidogrel and ticlodipine) within 2 weeks of operation, waiting until trough blood levels of heparin for those already receiving prophylaxis, delaying prophylaxis if a hemorrhagic aspirate is performed, removing the epidural catheter 2 hours before the next scheduled heparin injection, waiting 2 hours after removal to resume injections, and always monitoring for symptoms of spinal hematoma when using epidural anesthesia and pharmacologic prophylaxis concurrently.[38]

Our study has some limitations, including biases inherent to systematic reviews, weaknesses of the individual RCTs, and complication-level abstraction of our results. This study, like all systematic reviews, is subject to publication bias. In addition, we limited our search to English-language articles, but this has not been shown to significantly alter the results of systematic reviews.[39] Although we included only RCTs to strengthen the validity of our results, there were weaknesses in the individual studies. In addition, for some of the studies, the severity of the complication was not clear. For example, some studies provided an explanation of major complications (eg, patient had GI tract bleeding that required discontinuation of prophylaxis), while others merely provided the number of patients with GI tract bleeding. Finally, we were not able to examine complications on the patient level, so it is likely that 1 patient may have had a wound hematoma requiring subsequent operation, but this would be counted as 2 separate complications rather than 1. Therefore, the reported complication rates likely overestimate the incidence of complications at the patient level.

The present systematic review demonstrates that there is a small, but measurable, rate of minor bleeding complications, such as injection site bruising and wound hematoma, associated with pharmacologic DVT prophylaxis. Major complications, such as GI tract or RP bleeding, are rare, and subsequent operation occurs no more often with pharmacologic prophylaxis than with placebo injections. Although previous studies[4,40] have looked at the rate of wound hematoma or subsequent operation, to our knowledge, this is the first detailed evaluation of the bleeding complications associated with pharmacologic DVT prophylaxis. Thus, given the potential consequences of DVTs in our patients, it seems safe to proceed with pharmacologic prophylaxis for patients undergoing general surgery at moderate or high risk for developing a DVT.

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DISCUSSION

Peggy Knudson, MD, San Francisco, Calif: Thromboembolic events are preventable causes of morbidity and mortality in surgical cases. Indeed, as mentioned by the authors, DVT prevention is 1 of the 4 targeted areas of the National Surgical Care Improvement Project (SCIP) in attempting to decrease surgical complications. Dr Leonardi and his coauthors have undertaken the formidable task of reviewing 33 randomized control studies including 33 813 general surgery patients in order to determine the rate of bleeding complications associated with the use of anticoagulants used for DVT prophylaxis. It is reassuring to learn that major complications, such as GI bleeding and the need for surgical reexploration related to the use of low-dose heparin compounds perioperatively, occur in less than 1% of the general surgical population. I do have a few questions.

There is no mention of the "need for transfusions" as a complication of pharmacologic prophylaxis. Is this complication not included in any of the studies quoted?

There are several paradoxical findings in the study. For example, patients who received lower doses of LMWH [low-molecular-weight heparin] had significantly higher rates of wound hematomas than those receiving higher doses of LMWH. Can this finding be explained by the differences in absorption of subcutaneously administered heparin across patient populations? An alternative explanation might be that by "pooling" the results for different preparations of LMWHs, the authors have inadvertently disguised true differences in the effectiveness of different heparin molecules. Would the authors care to comment on this?

Failure to order DVT prophylaxis on the part of the physician can be due to a number of factors, including a simple error

of omission, a failure to recognize the high-risk patient, a lack of knowledge regarding the most effective prophylactic method for a particular patient, a lack of faith in the studies demonstrating their effectiveness in preventing DVT/PE [pulmonary embolism], and a concern for bleeding complications.

The authors have provided us with reassurance that bleeding complications should not prevent us from ordering pharmacologic prophylaxis. Can the authors address the other 4 factors that must be overcome before DVT prophylaxis becomes standardized among our general surgical patients?

James W. Holcroft, MD, Sacramento, Calif: You didn't mention anything about intracranial bleeding. It doesn't seem to be mentioned very often in the literature on prophylaxis for DVT. I assume that is because it is infrequent. At the same time, it can be devastating. Could you comment on that particular complication?

Orlo H. Clark, MD, San Francisco: (1) Do you know the frequency of PE and whether anticoagulation made any difference? (2) Was there a difference in the incidence of PE in different regions of the country? (3) Anticoagulation has been reported to increase the incidence of wound infection after hip surgery, presumably due to bleeding. Do you have any data regarding infections?

Lawrence D. Wagman, MD, Duarte, Calif: My question is a little bit about the denominator that goes into the randomized trials. I think we all know in the United States very few patients actually end up in RCTs, even though they may have the precise disease that we want to study. Did you have any sense of the 33 000 patients who were studied, how many patients were available? In other words, did the criteria for allowing the patients into the trial select the population that would give you a lower bleeding risk to start with? Did the exclusion criteria restrict entry to a group of patients that have bleeding risks that are different from the "average" patient we must decide to prophylax? I think this is a very important issue in studying this problem and generalizing the conclusion.

In about a month, the National Comprehensive Cancer Network will be publishing a set of guidelines that will once again enhance and increase the support of this prophylactic approach.

Michael G. Florence, MD, Seattle, Wash: Did you look at the issue of timing of pharmacologic prophylaxis with epidural anesthesia and to what extent epidurals decrease DVT? Did you also look at the issue of length of prophylaxis since some recommend continuing as an outpatient and, in that setting, the issue of monitoring for heparin-induced thrombocytopenia (HIT)?

Thomas R. Russell, MD, Chicago, Ill: I would like to ask the authors to expand a little more on the SCIP, which is obviously funded by CMS [Centers for Medicare & Medicaid Services]. They have the money, and they are determining a lot of these processes of care that we are going to have to live with. This is a fairly simple process of care to be utilized today. Where do you think this is going, this program, SCIP, with respect to developing this metric, namely, prophylaxis for DVTs. Where do you think this additionally could develop in this area or in other areas? In other words, what is the future of the SCIP, which is a process measure, and how might it relate to the National Surgical Quality Improvement Program, which is really an outcome base of looking at surgical outcomes?

Dr Ko: In terms of answering the questions, Dr Knudson first asked about the need for transfusion. For this study, transfusion was recorded in more than 1 RCT; however, because this variable is often difficult to interpret (ie, we cannot distinguish a transfusion given for blood loss from pharmacologic prophylaxis vs blood loss from surgery itself vs a low blood count prior to operation), we decided not to use this variable. In other studies we had performed, we have found that in order to interpret blood transfusion data, other variables are needed at the patient level, and such variables were not available to us in this systematic review.

Dr Knudson's second question was about the paradoxical results. In response to this inquiry, it depends on the specific studies included in the analysis. If a study had a large sample size, only looked at low-dose heparin, but for example had a high rate of hematoma, that affects the overall aggregated outcome results. I think this is what occurred (ie, that pooling of the studies resulted in the paradoxical findings).

Finally, Dr Knudson talked about a kind of more broad-scale question of the factors of why people might not receive adequate prophylaxis. As you can see from the Stratton et al[3] study, appropriate use of DVT prophylaxis is probably an issue. That study reported that 25% of people undergoing high-risk abdominal surgeries didn't receive DVT prophylaxis and 50% received it inadequately. Why? First, could it be an error of omission? A simple answer is "probably yes," but it should not be happening. This may be a great area to have a systems-based reminder in place to minimize, or prevent altogether, such errors of omission. It could easily be part of a checklist in the preoperative period.

Dr Knudson's second reason was the failure of providers to recognize high-risk patients. This could also have contributed to poor adherence since the *Chest* guidelines can be somewhat complex. Still, for most general surgical abdominal operations, the lead author of the *Chest* guidelines (Geerts) has made the categorization pretty straightforward, with primarily 3 risk groups. I suspect it is easier in terms of assessing, assigning, and, thus, identifying the high-risk patients.

A third potential explanation for the lack of adherence to DVT prophylaxis guidelines is the lack of knowledge of such guidelines. This is probably a strong contributor because at many hospitals, providers do not know the specific guidelines. Fourth, could there be a lack of faith in evidence? I think this is an important point because in this day and age we are trying to tout evidence-based medicine. We seem to want everything to be RCT evidence. The problem is that we are probably not going to have enough level 1 evidence for the care that we provide—even in something as frequently studied as DVT prophylaxis in general surgery patients. Even with the 33 RCTs we reviewed, we could think up numerous additional RCTs that would be needed to be performed in order to more adequately and definitely determine how DVT prophylaxis should and should not be given. I think in light of the lack of enough RCTs, the next step is to systematically take our best level of evidence and marry it to formal expert panel rating, such as the RAND Appropriateness Methodology. So a lack of faith in evidence is probably a contributing factor to suboptimal adherence, but maybe we should readjust what we are asking for, and while we are awaiting more RCTs to be performed, we should try to figure out what we can do with the level and amount of data we have.

To Dr Holcroft, intracranial bleeding was actually in only 1 of the 33 RCTs and, thus, we did not report it. As you may have expected, it was very rare.

Dr Clark asked about the incidence of other complications. In this particular study, we did not look at the outcome measures of wound infection, DVT, or PE; we just looked at the bleeding complications. As such, we did not look for geographical variation in incidence of complications. If it is similar to other diseases and processes of care, I suspect that geographical variation does exist.

Dr Wagman asked about the denominators for the included RCTs. I think this is in line with issues regarding the exclusion criteria. As you might expect, the RCTs we reviewed had different levels of exclusion criteria, but for the most part they were reasonable in terms of inclusion/exclusion criteria. The most common exclusion was for patients who were at risk of bleeding (ie, patients with known bleeding disorders).

Dr Florence asked about the prophylaxis in epidurals. This is a big issue for a lot of hospitals because it really takes away a potential mechanism or tool for pain control, and also anesthesiologists do not seem to like pharmacological prophylaxis for patients getting an epidural. In this regard, there is a consensus group guideline that was published a couple of years ago that addresses this issue by reviewing the literature and making recommendations. Basically, their bottom line suggestion is that probably with low-dose heparins, LMW or unfractionated heparin, it is probably acceptable to perform epidurals or spinals as long as certain specific guidelines are followed. For example, there has to be a period of 2 hours between the injection and the placement of the epidural. If, when performing the epidural, there is blood in the drawback, then they should not go forth with the epidural. And, obviously, epidurals should not be performed in high-risk bleeding patients.

Dr Florence also asked about length of prophylaxis. As you can imagine, with 33 studies over a 20-year period, the duration of prophylaxis varied. According to the most recent interpretation and recommendation by Geerts et al of the *Chest* guidelines (for the SCIP), the recommendation is to continue pharmacologic prophylaxis until discharge for general surgery patients.

Another question pertained to HIT. It was not addressed in our presentation, but the rates of HIT from our reviews are about 2% to 3% for unfractionated heparin. It is less than 1% for LMWH.

And, finally, Dr Russell asked about the SCIP. This is a program that you have probably heard of, and, if not, you most likely will soon. The aim of SCIP is to reduce surgical complications by 25% by 2010. There are 4 topic areas. One is reducing venous thromboembolism complications, another is decreasing cardiac complications (ie, with β-blocker use), another is the surgical infection prevention (ie, with the prophylactic antibiotic use), and the last one is decreasing ventilator-associated pneumonias in the ICU [intensive care unit].

In terms of the question of where we are now, I think the SCIP program and its aims are an appropriate starting point, being the core issues in surgery that we should all be performing. And, more important, if we do not provide DVT prophylaxis in 25% and it is inadequate in 50%, we have some work to do. However, once we get to a better level of adherence, I think we should go further to more advanced items in terms of improving the quality of care, such as using measures for specific diseases like cancer or measures for specific procedures. We are just starting now, but I suspect we will soon be addressing more advanced levels of care. In this regard, I think that the NSQIP [National Surgical Quality Improvement Program], which offers us risk-adjusted outcomes, is a great tool because we would not only know our outcomes, but we could also study and identify the process to outcomes links and, thus, further improve the quality of surgical care we are providing. Improving the quality of surgery is going to be an iterative process and will probably require an armamentarium of data—and smart people to plan and develop the measures. I think that while it's just the beginning, we're moving in the right direction.