Postcholecystectomy Abdominal Bile Collections

Crystine M. Lee, MD; Lygia Stewart, MD; Lawrence W. Way, MD

Hypothesis: The clinical syndromes caused by bile collections in the abdomen span a wide spectrum and their natural history and risks are not fully appreciated.

Design: Analysis of 179 patients with bile fistulas after cholecystectomy, of which 154 patients had undrained bile collections.

Objective: To characterize the manifestations and natural history of abdominal bile collections.

Setting: A tertiary care teaching hospital.

Patients and Methods: The clinical findings in 179 patients with bile fistulas resulting from iatrogenic laparoscopic bile duct injuries and other miscellaneous operations between 1990 and 1999 were analyzed. The group of main interest consisted of 154 patients with undrained bile collections. Of these 154 patients, 21% had serious complications, including sepsis and multiorgan failure. The data were analyzed to identify the variables associated with this undesirable outcome.

Main Outcome Measures: Symptoms, physical findings, course of illness, and laboratory and imaging findings.

Results: The clinical manifestations of intra-abdominal bile collections were initially discounted in 77% of patients, so the problem went unsuspected for a variable and often lengthy period. Abdominal pain and tenderness (bile peritonitis) gradually developed in 18% of patients with bile ascites. There were no differences in the initial clinical findings in this group compared with those who did not develop peritonitis. Nineteen percent of patients with undrained bile collections experienced serious morbidity. The initial clinical findings did not differ in these patients compared with those with a less complicated illness. Serious illness, however, was associated with the following: (1) a longer period of undrained bile (15.4 vs 9.2 days, \( P = .04 \)) and (2) a higher incidence of infected bile (45% vs 7%, \( P = .001 \)).

Conclusions: (1) Prominent abdominal pain and tenderness developed in only 21% of patients with abdominal bile collections; (2) the symptoms caused by bile collections were often subtle and their significance was overlooked, which resulted in a delay in diagnosis; (3) the early clinical findings could not distinguish patients who did become critically ill from those who did not; and (4) seriously ill patients more often had delayed drainage and infected bile. Still, failure to drain a bile collection within just 5 days resulted in serious illness in a few patients. Surgeons must watch for the clinical manifestations of bile ascites after laparoscopic cholecystectomy. This diagnosis should be suspected whenever persistent bloating and anorexia last for more than a few days; failure to recover as smoothly as expected is the most common early symptom of bile ascites. If bile collections were promptly diagnosed and drained, the rate of serious illness resulting from this complication would decline.

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Bile collections within the peritoneal cavity have various causes, but they most often occur as a manifestation of bile duct injury or some other technical complication of laparoscopic cholecystectomy. Unless drains have been used, a bile leak leads to accumulation of bile in the abdomen. Previous reports have suggested that bile peritonitis, with guarding and rebound tenderness, is the principal manifestation of an abdominal bile collection, but this is actually an uncommon presentation early in the patient’s course.\(^1\)\(^6\) While a few patients do have such clinical findings, most have much milder symptoms, best referred to as bile ascites.\(^7\)

With the advent of laparoscopic cholecystectomy, the incidence of bile duct injuries, and hence, bile collections in the abdomen, has increased.\(^6\)\(^9\) This study defines the syndromes associated with abdominal bile collections and shows how best to manage patients with this problem.
PATIENTS AND METHODS

One hundred seventy-nine patients with bile fistulas were referred for evaluation to the University of California San Francisco Medical Center between 1990 and 1999. Of these 179 patients, 25 (14%) had a drain placed at the time of the first operation. The other 154 (86%) did not initially have drains placed and developed abdominal bile collections. Of this latter group, 74 had drains placed and 79 did not before a definitive operation was performed to treat the fistula. Twenty-one percent of the patients were men and 79% were women; the average age was 46 years (range, 18-86 years).

PREOPERATIVE DIAGNOSES AND INDEX OPERATION

The preoperative diagnoses were chronic cholecystitis (65%), acute cholecystitis (32%), and miscellaneous (3%). The first, or index, operation was laparoscopic cholecystectomy in 94% of patients, open cholecystectomy in 3%, a nonbiliary operation in 2%, and a complex biliary operation in 1%. In 21% of patients who had a laparoscopic cholecystectomy, the procedure had been converted to an open cholecystectomy to improve exposure (4%), treat a bile duct injury (13%), or perform a common bile duct exploration (4%).

TYPE AND LOCATION OF BILIARY INJURIES

The biliary injuries in the patients who underwent a laparoscopic cholecystectomy were classified as follows: class 1, 8% (partial transection of the common bile duct); class 2, 21% (injury to the common hepatic duct due to clips or cautery); class 3, 54% (excision of a portion of the common duct and/or hepatic ducts); and class 4, 15% (damage to the right hepatic duct). The remaining 2% had cystic duct stump leaks (2 patients) or bile leaks from a duct in the liver bed (1 patient).

DEFINITION OF TERMS

The following definitions will be adhered to in this article. Abdominal bile collection, sometimes abbreviated as “bile collection,” refers to the presence of undrained bile in the abdomen and includes 2 subcategories, bile ascites and bile peritonitis. The term bile ascites is used for bile collections without prominent abdominal pain and tenderness. Bile peritonitis is the term used when a patient with an abdominal bile collection manifests prominent abdominal pain and tenderness. Bile peritonitis, as used herein, does not imply that the bile was infected.

STATISTICS

Using the Statview 5.0 statistical program, the data were analyzed by analysis of variance, the Fisher exact test, or the χ² test.

RESULTS

CLINICAL PRESENTATION

Of the 179 patients, 25 (14%) had a drain placed at the index operation that functioned properly, while undrained bile (ie, a bile collection) developed in 154 patients (86%). These 154 patients constitute the group of principal interest in this report, although the 25 patients with drains will also be described. Table 1 gives the symptoms in those with drained and undrained bile fistulas at initial presentation. Cholangitis was initially present in 26% of patients without drains and in 21% of patients with drains (P, not significant); 11% of patients with undrained bile had sepsis, compared with 7% of those whose fistulas were drained (P, not significant).

Bile drainage was often managed expectantly for long periods (average period, 13.9 days; range, 1-45 days) before a diagnostic workup was performed. Even when imaging studies had identified a bile fistula, these patients were followed up for an average of 30.2 days (range, 2-189 days) before a definitive repair was performed. Seventy-one percent of these patients developed symptoms during this period, most likely due to malfunction of the drains; 20% developed serious complications. One patient in this group eventually died of sepsis.

DIAGNOSIS

In 23 (13%) cases, the injury was recognized at the index operation. In this situation, the primary surgeon repaired the bile duct immediately (39%), placed drains and instituted nonoperative treatment (36%), or placed drains and transferred the patient to a tertiary care center for biliary reconstruction (25%).
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in—only 5 patients (3%) had bile peritonitis as the initial pre-
own diagnosis was 16.8 (25.0) days for all patients with intra—
abdominal bile collections.

Overall, a symptomatic bile collection was initially missed
more than a half of patients; their symptoms were considered non-
specific or insignificant. The mean (± SD) time to diag-
nosis remained elusive even after the first outpatient checkup.
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abdominal bile collections.

The injury went unrecognized in 156 patients (87%) at
the index operation. Of these, 139 (89%) were dis-
charged home without a diagnosis; 25 (18%) of these pa-
tients left the hospital with bothersome malaise, an-
orexia, and nausea that in retrospect warranted more
attention. In 35 (25%) of these patients, the diagnosis re-
mained elusive even after the first outpatient checkup.
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in 77% of patients; their symptoms were considered non-
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abdominal bile collections.

### BILE PERITONITIS VS
### BILE ASCITES

Only 5 patients (3%) had bile peritonitis as the initial pre-
senting syndrome caused by the bile collection. The in-
cidence of cholangitis (100% vs 25%, P = .04), sepsis (100% vs
6%, P = .004), and leukocytosis (16.2 × 10⁹ vs
12.6 × 10⁹, P = .03) was greater in those who initially pre-
sented with peritonitis compared with those who did not.

Patients with bile ascites who ultimately developed bile peritonitis had a higher incidence of malaise and abdom-
nal discomfort (Table 2). Fever, abdominal tenderness, and jaundice were initially found in 45% of pa-
tients who developed bile peritonitis and in only 3% of patients who did not (P < .001). Cholangitis was ini-
tially present in 36% of patients who later developed bile peritonitis and 21% of patients who did not (P, not
significant). Laboratory findings were not different and the
time to diagnosis was not different between the 2

### BILE IN THE ABDOMEN

The mean (± SD) amount of bile recovered when drains
were inserted into the bile collections was 713 (901) mL.
The amount was substantially larger in patients who de-
veloped bile peritonitis than in those with only bile ascites
(Table 2). Bile collections greater than 500 mL were present
in 79% of patients with bile peritonitis and in 13% of
patients with bile ascites (P = .002). Drainage had not been
instituted in 42% of patients within 7 days of the index opera-
tion and in 19% within 14 days of the index operation.

### PATIENTS WITH
### SERIOUS COMPLICATIONS

Twenty-one patients with bile collections had 1 or more of
the following serious complications: sepsis (10%), ab-
scess formation (11%), pancreatitis (3%), respiratory fail-
ure (3%), gastrointestinal bleeding (1%), transdiaphrag-
matic bile fistula formation (1%), necrotizing fasciitis
(1%), pulmonary embolism (1%), and stroke (1%). Chol-
angitis developed in 25% of patients with these other seri-
sous complications. Two patients died of sepsis and mul-
tigang system failure.

The initial clinical presentation was not different be-
tween those who developed serious complications and those who did not. Patients with serious complications
had undrained bile present for 15.4 ± 9.1 days, while those
without serious complications had undrained bile for
9.2 ± 10.7 days (P = .045). Serious complications devel-
oped in 45% of patients with infected bile compared with
7% of those with uninfected bile (P < .001). Severe com-
lications were not confined to patients whose bile was
allowed to go undrained for long periods: 4 patients with
undrained bile developed severe complications within 5
days of the index operation.

### EARLY VS LATE DRAINAGE

The clinical course of patients whose bile collection
was drained early (< 10 days after cholecystectomy) was com-
pared with those whose collection was drained late (≥ 10
days after cholecystectomy) (Table 3). Fifty-four per-
cent of patients whose bile was drained 10 days after their
cholecystectomy had fever, compared with 29% of those
whose bile was drained less than 10 days after their cho-

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**Table 2. Findings in Patients Who Ultimately Developed Bile Peritonitis Compared With Those Who Did Not (Bile Ascites)**

<table>
<thead>
<tr>
<th>Bile Peritonitis (n = 32)</th>
<th>Bile Ascites (n = 147)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms at initial presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>94</td>
<td>63</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>94</td>
<td>70</td>
</tr>
<tr>
<td>Nausea</td>
<td>56</td>
<td>42</td>
</tr>
<tr>
<td>Anorexia</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Signs at initial presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>74</td>
<td>36</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>79</td>
<td>24</td>
</tr>
<tr>
<td>Jaundice</td>
<td>61</td>
<td>48</td>
</tr>
<tr>
<td>Distention</td>
<td>61</td>
<td>32</td>
</tr>
<tr>
<td>Laboratory tests at initial presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count, × 10^9/L†</td>
<td>13.8 (5.2)</td>
<td>12.9 (4.8)</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L†</td>
<td>56 (41)</td>
<td>67 (55)</td>
</tr>
<tr>
<td>Bile collection parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile volume, mL†</td>
<td>1633 (907)</td>
<td>406 (697)</td>
</tr>
<tr>
<td>Days with undrained bile‡</td>
<td>9.9 (5.6)</td>
<td>10.8 (14.0)</td>
</tr>
<tr>
<td>Days with draining bile‡</td>
<td>9.6 (15.1)</td>
<td>16.1 (35.2)</td>
</tr>
<tr>
<td>Days with bile in the abdomen†</td>
<td>19.5 (16.3)</td>
<td>26.4 (37.6)</td>
</tr>
<tr>
<td>Intra-abdominal bile never drained prior to definitive therapy</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>Infected fluid collection</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

*All data are given as percentages unless otherwise indicated. NS indicates not significant.
†Data are presented as mean (SD).
‡Intra-abdominal bile was drained by percutaneous or operative placement of drains, or by drains placed during the index operations.
§Serious complications are defined in the text.
The diagnosis of a bile fistula was made by observation of bile drainage from drains placed at the index operation (13%) or the wound (1%), or discovery of a fluid collection on ultrasound, computed tomographic (CT) scan, or HIDA scan (86%). Ultrasound scanning (69%) was the imaging test most commonly ordered, followed by CT (55%) and HIDA scans (39%). Computed tomography (CT) was the most sensitive (55%) and HIDA scans (39%) followed. Ultrasound scans, the next most sensitive study, was only 87%. An exploratory laparotomy was performed (rather than percutaneous drainage) just to drain the bile collection in 14% of patients. The presence of a drain did not guarantee that a bile collection would be avoided; drains can malfunction. Therefore, CT scans should be obtained early in the management of a patient with an unplanned external bile fistula, more or less routinely, to check on the adequacy of drainage.

Some patients in this review were known from imaging studies to have intra-abdominal bile collections, but they were followed up expectantly with the expressed hope that the bile would be reabsorbed from the abdominal space. Nevertheless, reabsorption of bile collections larger than 4 cm was rare and unpredictable. Furthermore, there is no support for such a treatment strategy in the literature. As this and other studies show, the morbidity and mortality rates can be high in patients with undrained bile collections. Because morbidity is greater the longer treatment is delayed, physicians caring for these patients must have a high index of suspicion for a biliary injury, learn to recognize the clinical features of bile ascites, and investigate and treat patients who have these symptoms.

The evidence suggests that if bile collections were never drained, most patients would eventually become gravely ill from superinfection. The following factors correlated with a worse outcome: length of time bile was left in the abdomen and the development of superinfection. Animal research has shown that bile salts are the toxic agents subjected these patients to 2 laparotomies instead of 1, as a second procedure was required later to repair the bile duct injury.
The important point of this study is that once a bile collection has been drained, the major potential for immediate serious illness has usually been eliminated. This allows the injury to be fully delineated and treatment to be planned and carried out in an unhurried manner.

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REFERENCES


DISCUSSION

Donald L. Kaminski, MD, St Louis, Mo: Drs Lee, Stewart, and Way have retrospectively evaluated the clinical significance of bile in the peritoneal cavity associated with biliary tract injuries. They have demonstrated that the clinical abdominal findings may be subtle and that these subtle abdominal findings frequently result in a delay in diagnosis. They indicate that suspicion should be raised when a patient is not doing well after a cholecystectomy, demonstrating anorexia, abdominal distention suggesting an ileus, and fever. These findings should raise the surgeon’s suspicion and institute appropriate diagnostic studies. I have 3 theoretic disagreements with the authors’ evaluation of these patients. I guess I am too old and too simple to have my misconceptions changed. The attempt to separate the presence of bile in the peritoneal cavity into patients who have ascites vs those who have peritonitis seems to me superficial and not worthwhile. Bile produces a chemical peritonitis associated with cytokine release and alterations in fluid transport across peritoneal membranes, suggesting that an inflammatory process is present. The attempt to designate bile in the peritoneal cavity as representing ascites suggests that it’s innocuous, and I don’t believe that bile in the peritoneal cavity is innocuous.

Similarly, the attempts by the authors to distinguish bile in the peritoneal cavity as representing ascites from those patients who have peritonitis based on a retrospective analysis of clinical physical findings may not be highly reliable. Second, the terminology of bile ascites and bile peritonitis as emphasized in this article excludes the frequent presentation associ-
ated with this problem; namely, a localized collection of bile in the right upper quadrant. Many patients have a biloma, not bile ascites or bile peritonitis.

Lastly, to not correlate the type of injury and treatment from the analysis of the consequences of the presence of bile in the abdominal cavity excludes the 2 factors that in my experience are associated with determining the sequelae of the presence of bile in the peritoneal cavity; namely, is the leak controlled and is the fistula adequately drained?

I have 2 questions for the authors. Could you give us an idea how many patients required drains placed outside of the right upper quadrant? This would suggest to me that if there is a local indication to place a drain anywhere besides the right upper quadrant, ultrasound would allow these patients to be treated by percutaneous drainage, obviating the need for a CT scan.

Second, do you feel that serum bilirubin measurements correlate with the quantity of bile in the peritoneal cavity? Dr Lee’s presentation was excellent, the article was full of wonderful information to assist surgeons in managing these patients, and I highly recommend it to you.

Mitchel P. Byrne, MD, Evanston, Ill: I have 2 questions. I wonder if this is a skewed population and if we in practice will not see this rate of bile duct injury as the cause for this problem. In normal practice, the usual cause seems to be liver bed leakage more so than bile duct injury. In those patients, repeat laparoscopy is such a simple modality that evacuates all of the bile, both in the right upper quadrant and the rest of the abdomen. It avoids the need for interventionists, both in radiology and gastroenterology. I wonder if you have used this in selected patients. For instance, if you had operated on a patient and were confident that there was no bile duct injury, would you consider repeat laparoscopy?

William W. Turner, Jr, MD, Jackson, Mo: The authors looked at initial drainage at the index operation, but didn’t present any conclusions about its efficacy or lack thereof. I would be interested to know whether they were able to draw any conclusions about the role of index procedure drainage.

Thomas A. Stellato, MD, Cleveland, Ohio: I also have a problem with the premise that suggests that a bile collection is equal to a bile duct injury. We described our own series of patients, and our paradigm is quite different from that of the authors. We feel that a CT scan should not be performed because once a collection is seen, it mandates you to percutaneous drainage. Our first image of choice is a HIDA scan. We found it to be 100% sensitive, and if a leak is identified, it doesn’t necessarily mean that a bile duct injury is present. Our next step would be an ERCP to define whether an injury is present or whether it is a simple leak from a cystic duct or the gallbladder bed. In that paradigm, we have stented these patients endoscopically and do not have to resort to either reoperation or drainage at all, and all patients have recovered.

Edward H. Phillips, MD, Los Angeles, Calif: I would be interested to know how many of these patients with daily diagnosis were treated as outpatients and/or kept overnight and discharged. The earlier a patient is discharged, obviously the more difficult it is to diagnose a bile leak. We tend to keep our patients overnight and find that the patient’s heart rate is a key clinical determinant of problem. No one gets discharged with a tachycardia. The tachycardia may not be due to a bile leak, a biloma, or anything serious, but we have found that a normal heart rate usually precludes a significant complication. So I was wondering whether the vital signs of these patients were looked at both prior to discharge and on follow-up at the clinic.

Ronald G. Latimer, MD, Santa Barbara, Calif: What percentage of the patients with their defined bile ascites or bile peritonitis had normal intraoperative cholangiograms?

Ernest E. Moore, MD, Denver, Colo: You provide cogent data that indicate that early recognition of the bile collection is critical to minimize the sequelae. This seems to be a compelling argument for the routine use of surveillance ultrasound by the operating general surgeon in the clinics as well as the office. You alluded to a 70% accuracy. Could you expand on the shortcomings of ultrasound, because this is certainly not consistent with surgeons’ experience with ultrasound in the emergency department.

William C. Chapman, MD, Nashville, Tenn: I would like to support the authors’ comments regarding imaging and assessment of the patient who is having problems after cholecystectomy. I think there is a common tendency to attribute symptoms and fluid collections to a trivial leak from the gallbladder fossa and this approach commonly leads to late referral. So I think whether the imaging study uses CT scans, HIDA scans, or ultrasound can certainly be argued. I think the point that the authors are making is that thorough early investigation is critical to eliminate major bile leakage as a possible factor.

I have a couple of questions. First, could you tell us about the specific complications that occurred in those patients who did have infected bile, and second, what recommendations could you make for management in patients who had drains placed? Do you follow up for a prolonged interval those patients who do have bile duct injury after drain placement, or do you operate on them early after discovery of the bile duct injury?

James J. Peck, MD, Portland, Ore: My concern is the 7% of patients who were asymptomatic. What prompted you to study these patients? Were they all patients who had drains in place? What percentage had cystic duct leaks or leaks from the accessory duct in the gallbladder fossa and were really just small bilomas?

Dr Way: A main point is that surgeons expect bile in the abdomen to always produce clinical peritonitis, meaning pain and tenderness. Although bile uniformly produces histologic peritonitis, the clinical findings can range from almost no pain to severe pain. The reason for the differences from patient to patient is unknown. Thus, abdominal pain and tenderness are insensitive criteria for making the diagnosis of bile in the abdomen; for an unpredictable period, pain and tenderness are absent in most patients. In this report we have referred to abdominal bile collections without severe symptoms as bile ascites, regardless of whether the collection was localized or diffuse. Because there is risk of miscommunication unless words are used in the same way, we defined them precisely in this article.

Because the data were collected retrospectively, does this affect the validity of the conclusions? On the contrary. Retrospective data collection is a positive feature of the study. First, it would probably be impossible to conduct a study like this prospectively, but that is not the point. The advantage of the retrospective aspect is that the analysis is based on statements in the hospital records that preserve the thoughts of those caring for the patients at the moment. The characteristic of these statements would be quite different if collected as part of a prospective study. In that case, the data would not accurately reflect existing surgical practice.

About 20% of patients had drains in places other than the right upper quadrant. The volume of bile obtained on the initial catherization varied from about 100 mL to several liters, and the greater the volume, the more likely additional drains would be needed. The right upper quadrant drained most of the bile. If a second drain was required, it was usually in the pelvis.

The serum bilirubin level only loosely correlated with the volume of bile in the abdomen. Bilirubin levels rise because of reabsorption of bilirubin from the abdomen. They rarely exceeded 2 to 5 mg because the liver eliminates extra bilirubin according to first-order kinetics (the higher the serum bilirubin concentration, the greater the bilirubin load excreted).
cause bilirubin levels remained so low, they were often dismissed as clinically insignificant.

We were dealing with a skewed population in the sense that there were few patients with leaks from the cystic duct stump or gallbladder bed. Nevertheless, the conclusions are unaffected. The principal misconceptions identified in this study are that a collection of bile (1) always produces severe pain and (2) can be left untreated as long as the patient looks and feels well. These assumptions are false regardless of the source of the leak.

In treating leaks of the cystic duct stump or the liver bed, one should not rely entirely on a bile duct stent placed at ERCP if there is also an abdominal accumulation of bile, as there usually is. Counterdrainage is indicated or serious infection may develop. Just because a bile duct stent alone has worked a few times does not mean that it will the next time. One patient who was brought to our attention, who was not part of this study, died solely because the importance of removing the abdominal bile had not been recognized. Drains placed at the index operation usually worked well.

The presence of an abdominal bile collection does not always mean a bile duct injury has occurred, but if the collection is greater than 4 cm, one should assume that there is a significant leak until an ERCP proves otherwise. From our retrospective vantage point, the surgeon remained convinced for too long that the operation was uncomplicated in many cases of leaks.

In this series, HIDA scans were misleading for the diagnosis of a bile leak and, too often, a false-negative study incorrectly suppressed tentative concerns about a possible leak. Although accurate in some cases, HIDA scans overlooked many significant leaks. Furthermore, when a HIDA scan was positive, another imaging test (ie, CT or ultrasound scan) had to be done to insert drains into the collection. Therefore, a negative HIDA scan was unreliable, and a positive scan required the alternative study anyway.

ARCHIVES OF INTERNAL MEDICINE

A Meta-analysis Comparing Low-Molecular-Weight Heparins With Unfractionated Heparin in the Treatment of Venous Thromboembolism: Examining Some Unanswered Questions Regarding Location of Treatment, Product Type, and Dosing Frequency

Lisa R. Dolovich, PharmD; Jeffrey S. Ginsberg, MD; James D. Douketis, MD; Anne M. Holbrook, MD, PharmD, MSc, FRCPC; Gillian Cheah, BScPharm

Objectives: To compare the efficacy and safety of unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) and to examine current controversies in the treatment of venous thromboembolism (VTE) (ie, setting, product type, and frequency of administration).

Methods: Data were abstracted from MEDLINE, HEALTH, previous reviews, personal files, clinical experts, and conference abstracts. Randomized controlled trials of patients diagnosed with acute VTE that compared LMWHs with UFH were included. Independent duplicate assessment was done for methodological quality and data extraction. Data are reported as pooled relative risks (RRs) and 95% confidence intervals (CIs) comparing LMWHs with UFH as determined by the random effects model.

Results: Thirteen studies were included. There was no statistically significant difference in risk between UFH and LMWHs for recurrent VTE (RR, 0.85 [95% CI, 0.65-1.12]), pulmonary embolism (RR, 1.02 [95% CI, 0.64-1.62]), major bleeding (RR, 0.63 [95% CI, 0.37-1.05]), minor bleeding (RR, 1.18 [95% CI, 0.87-1.61]), and thrombocytopenia (RR, 0.85 [95% CI, 0.45-1.62]). There was a statistically significant difference for risk of total mortality (RR, 0.76 [95% CI, 0.59-0.98]) in favor of LMWHs. Inpatient treatment may reduce the risk of major bleeding vs outpatient therapy. Once-daily therapy is as safe and effective as twice-daily therapy when compared indirectly. Different products could not be statistically compared, but qualitative analysis shows that there are no apparent differences in efficacy and safety.

Conclusions: Low-molecular-weight heparins are at least as effective as UFH in preventing recurrent VTE. It is unlikely that LMWHs are superior in the treatment of VTE, but they do show a statistically significant decrease in total mortality. No differences were seen in the development of recurrent VTE dependent on treatment setting. There were no apparent differences between once-daily and twice-daily therapy or among products. Inpatient therapy may be associated with less major bleeding; therefore, if LMWHs are given in the outpatient setting, patients should be rigorously monitored. (2000;160:181-188)

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