



Evaluation of the Effect of the Blood Stopper; Ankaferd in Management of Post Laparoscopic Cholecystectomy Liver Bed Bleeding

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Abstract: *Introduction:* The incidence of bleeding complications during laparoscopic cholecystectomy remains a frequent reason for conversion. Ankaferd Blood Stopper is a unique medicinal plant extract that has historically been used as a hemostatic agent and has been approved for the management of external hemorrhage and dental surgery bleeding. The aim of this study was to evaluate the effect of Ankaferd as a bleeding stopper; in the management of liver bed bleeding in post laparoscopic cholecystectomy. *Patients and Methods:* A total of 120 patients; 60 for each group; group A (laparoscopic cholecystectomy with cauterization of gallbladder bed of the liver) and group B (laparoscopic cholecystectomy with application of Ankaferd drops by laparoscopic injector into gallbladder bed). *End points:* The primary end point of the study was measurement of the intraoperative bleeding as a result of application of both techniques; ankaferd instillation and cauterization of gallbladder bed of the liver. The secondary end points were estimation of the amount and characteristics of postoperative discharge till removal of drains, length of hospital stay and postoperative wound infection. *Results:* The operative time in group A was 85±34.5 minutes while in group B, it was 56±20.5 minutes. The mean amount of intraoperative bleeding was 58.1±29.97 ml and 37±14.47 ml in group A&B respectively. The mean amount of postoperative fluid drainage was 41.75±12.9 ml in group A while in group B was 30±6.75 ml and the hospital stay, It was 51.6±15.35 hours for patients of group A versus 31.8 ±8.5 hours for patients of group B respectively with significant distribution { $P \leq 0.001$ }. *Conclusion:* Ankaferd rapidly achieves hemostasis allowing surgeon to control bleeding properly and therefore the amount of operative bleeding, the operative time and the amount of postoperative fluid discharge on using ankaferd is statistically reduced.

Keywords: Laparoscopic Cholecystectomy, Bleeding, Liver Bed, Ankaferd

1. Introduction

Laparoscopic cholecystectomy (LC) has established itself firmly as the 'gold standard' for the treatment of gallstone disease [1] but it may be associated with some complications such as significant hemorrhage if not recognized and treated in a timely manner it is considered the most frequent cause of procedure-related mortality in laparoscopic cholecystectomy after anaesthesia-related death [1, 2]. The incidence of bleeding complications during laparoscopic cholecystectomy requiring transfusion or reoperation has been reported to be

relatively rare, occurring in 0.1 % in those patients undergoing LC [3] and this bleeding remains a frequent reason for conversion [4, 5]. Ankaferd Blood Stopper (ABS, Ankaferd Health Products Ltd, Turkey) is a unique medicinal plant extract that has historically been used as a hemostatic agent in Turkish traditional medicine [6]. As a medicinal product, ABS has been approved for the management of external hemorrhage and dental surgery bleeding in Turkey, based on safety and efficacy reports supporting its sterility

and nontoxicity [7]. The aim of this study was to evaluate the effect of Ankaferd as a bleeding stopper; in the management of liver bed bleeding in post laparoscopic cholecystectomy.

2. Patients and Methods

2.1. Patients

This study represented a parallel prospective randomized clinical trial where patients were divided randomly into two main groups; A and B. Group A patients were subjected to laparoscopic cholecystectomy with cauterization of gallbladder bed of the liver for mild and moderate bleeding and those of Group B patients were subjected to laparoscopic cholecystectomy with application of Ankaferd drops by laparoscopic injector into gallbladder bed for mild and moderate bleeding bed and in all patients, subhepatic drain was inserted. A total of 120 patients; 60 for each group were enrolled for the present study, their ages ranged between 32–65 years. The study started from January 2014 to December 2016 in Crimean Medical Academy named after S. I. Georgievsky Crimean Federal University named after V. I. Vernadsk Russia in department of general and gastrointestinal surgery and patients with marked obesity (BMI > 35) and ASA grade II and beyond were excluded.

Written consents were obtained from all patients before the study and the steps of both operative interferences were explained to all patients. The local ethics committee had approved all operative procedures. Ethical approval for this study department of general and gastrointestinal surgery Crimean Medical Academy named after S. I. Georgievsky Crimean Federal University named after V. I. Vernadsk, Russia.

2.2. Surgical Teams & Study Sites

Operations were performed in the department of general and gastrointestinal surgery Crimean Medical Academy

named after S. I. Georgievsky Crimean Federal University named after V. I. Vernadsk Russia by the same surgical team.

2.3. Operative Techniques

The skin is initially prepared using chlorhexidine starting from the nipple line to the groins and laterally to the anterior superior iliac spine bilaterally. The operative field is then draped with sterile drapes. Placement of ports and instruments is then taken out for exposure of the operative field and starting of dissection. The importance of good exposure and delicate dissection is put in mind. The cystic duct and artery must be carefully dissected and identified in the triangle of Calots to obtain the critical view. This critical view is achieved when the two structures; the cystic duct and artery are obtained before any structures are clipped or transected and after that, mobilization and removal of gallbladder is to be completed.

It is important to be alert for any aberrant vessels and ducts that may arise from the liver bed and enter directly into the gallbladder. Before the last strands connecting the gallbladder to the liver are divided, a final inspection of the gallbladder fossa and the clipped cystic structures should be carried out. Any bleeding points in the gallbladder fossa were dealt with according the study protocol at this time, before the gallbladder is completely separated from the liver. In case of group A patients, cauterization of gallbladder bed of the liver is to be achieved to secure proper haemostasis of the bed using the electrocauterization technique. However, in group B patients, irrigating of the bed is performing using the blood stopper ankaferd ampoule {figure 1} to achieve and secure proper haemostasis of the bed. Instillation of the blood stopper ankaferdin performed using the endoscopic injector as shown in figure 2. Proper hemostasis of gall bladder bed was evident within very few seconds {figure 3}. After that subhepatic intraperitoneal drain is done in both groups.



Figure 1. Shows the blood stopper; ankaferd ampoule.



Figure 2. Shows the endoscopic injector.

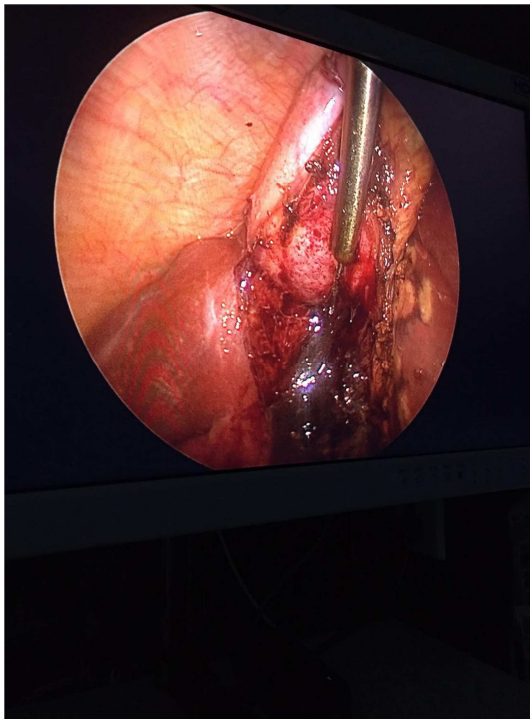


Figure 3. Shows proper hemostasis of gall bladder bed within very few seconds while the injector was in place.

2.4. End Points

The primary end point of the study was measurement of the intraoperative bleeding as a result of application of both techniques; ankaferd instillation and cauterization of gallbladder bed of the liver. The secondary end points were estimation of the amount and characteristics of postoperative discharge till removal of drains, length of hospital stay and

postoperative wound infection.

3. Results

There was no statistical significant difference between the two groups as regard age, sex and body mass index (Table 1). The operative time in group A ranged between 40 to 140 minutes with mean value as 85 ± 34.5 minutes while in group B, it ranged between 30 to 120 minutes with mean value as 56 ± 20.5 minutes and this difference in both groups was statistically significant ($P \leq 0.001$). The mean amount of intraoperative bleeding was 58.1 ± 29.97 ml in group A while in group B was 37 ± 14.47 ml with significant distribution ($P \leq 0.001$). The mean amount of postoperative fluid drainage was 41.75 ± 12.9 ml in group A while in group B was 30 ± 6.75 ml with significant distribution ($P \leq 0.001$). As regard the hospital stay, It was 51.6 ± 15.35 hours for patients of group A versus 31.8 ± 8.5 hours for patients of group B respectively with significant distribution ($P \leq 0.001$) as shown in table 2 and graph 1.

Table 1. Showing characteristics of both groups regarding age, sex and body mass index.

		Group A	Group B	P value
Age	Age < 50	39	37	NS
	Age > 50	21	23	
Sex	Male	22	23	
	Female	38	37	
BMI	MBI < 25 [22---24.9]	16	18	
	MBI < 30 [25---29.9]	24	23	
	MBI > 30 [30---34.9]	20	19	

Therefore, the mean total hospital stays in days for patients in group B were 5.7 ± 2.32 days compared with 2.4 ± 1.1 days in group A with significant distribution ($P \leq 0.0001$).

Table 2. Showing the operative and postoperative outcomes.

Group	Operative time	Operative bleeding	Postoperative drainage	Hospital stay
A	85 ± 34.5	58.1 ± 29.97	41.75 ± 12.9	51.6 ± 15.35
B	56 ± 20.5	37 ± 14.47	30 ± 6.75	31.8 ± 8.5

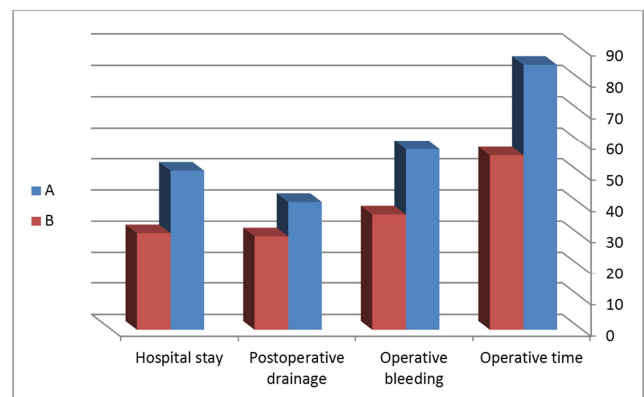


Figure 4. Shows the operative outcome in both groups.

4. Discussion

Various clinical, laboratory and ultrasonic parameters are known helping to predict the preoperative difficulty level of cholecystitis patients subjected to laparoscopic maneuver [1, 8, 9]. According to the preoperative factors to predict the operative difficulty and hence the operative outcome, our series have male gender, age, BMI and upper abdominal previous surgery to be risk factors for difficult scoring. Our data came in concordance with those of papers of same interest [1, 8, 9, 10]. These factors affect the operative time, intraoperative bleeding, hospital stay and over all morbidity [11, 12].

The average operative time in patients subjected to laparoscopic cholecystectomy scheduled for non-complicated cholecystitis was 30.8 minutes as reported in our previous data [13] and in case of acute cholecystitis with difficult dissection on Calot's triangle, the operative time will become much more than in case of non-complicated cholecystitis [1, 9]. An interesting study on analysis of patients with difficult laparoscopic cholecystectomy reported that longer operation time is related in part to the difficulty in exploring calot's triangle [11]. Previous studies have identified male gender, obesity, previous upper abdominal surgery, acute cholecystitis, intra-abdominal adhesions and a low degree of surgical expertise as risk factors predicting a prolonged operative time in conventional laparoscopic cholecystectomy [14, 15].

Visual estimation is the most common method to estimate intraoperative blood loss, but it is not the most accurate. Estimating blood loss might be difficult, especially if most of the blood is absorbed by surgical gauze and not collected in the suction bottle. Although many methods for estimation are available, e.g., the gravimetric method (weighing of the pre- and post-procedure gauze), most are not in routine use either due to their unavailability or time-consuming nature during surgical procedures [16, 17]. Estimation of intra-operative blood loss is governed by visual method and the clinical assessment with collaboration with the anesthetist. Regarding visual estimation of blood loss; a standard absorptive gauze measuring 30 cm X 30 cm was used. When it was soaked by 50 % the means that it contains about 25 ml of blood and if totally soaked; 100% this means that it contains 75 ml of blood [1].

Some authors have documented bleeding requiring either transfusion or reoperation or less serious intraoperative and postoperative bleeding. Intraoperative and postoperative bleeding may have been further divided into internal (peritoneal cavity of retroperitoneal space) and external (abdominal wall) bleeding based on the localization [18] and bleeding complications requiring reoperation occurred in 0.5 % of the cases [19]. Intra-operative bleeding usually occurs during the performance of the procedure, either at the time of creation of pneumoperitoneum or as a consequence of improper dissection and operating technique and the vessel injuries are the most devastating, occurring almost exclusively during creation of pneumoperitoneum or during dissection within the Calot's triangle [20]. Several

pharmacologic agents have been used topically or by local injection to stop bleeding during laparoscopic surgery. Some surgeons used a gauze sponge soaked with epinephrine solution to control minor bleeding in the gallbladder fossa. In the light of that study, we added adrenaline into the hydrodissection solution to decrease bleeding. However, injection of adrenaline between the gallbladder and liver did not affect bleeding from the dissection area [21]. Topical hemostatic agents are used to ensure adequate hemostasis during laparoscopic cholecystectomy. Floseal in acute cholecystitis is said to be safe, effective in controlling bleeding, and results in a lower conversion rate compared with cholecystectomy without hemostatic agents. Floseal® (Baxter International, Inc., Deerfield, IL) hemostatic matrix as an adjunct to surgical techniques to achieve hemostasis of the resected areas in patients undergoing laparoscopic cholecystectomy for acute cholecystitis [22]. Bleeding from the gallbladder bed initially either was attempted to control by application of electrocautery or by applying direct pressure with gauze inserted into the abdomen through the 10 mm trocar. tisseel® was injected to the gallbladder bed if bleeding could not be controlled by these methods. The gallbladder bed was observed at least for 5 minutes following complete hemostasis for the possibility of bleeding [23]. As the first intervention in this type of bleeding many surgeons use electro-cautery. In cases where this often effective method fails; LigaSure, laparoscopic suture placement and direct pressure with a gauze sponge are being used. In particular, the use of electrocautery is known to create a risk for postoperative bile leakage. While applying these procedures the amount of bleeding should be followed [23, 24].

In similar study of same interest, the mean amount of blood loss was 80-88 ml [25] and in other one was 105 ml when using standard electrocoagulation [26]. The well-known methods to achieve hemostasis of gallbladder bed bleeding are to use electro-cautery, LigaSure, laparoscopic suture placement and direct pressure with a gauze sponge. In particular, the use of electrocautery is known to create a risk for postoperative bile leakage. However fibrin glue is used as local hemostatic agent but the mean time spent on bleeding control to achieve hemostasis was 23.9 minutes [23] while on using Floseal locally, bleeding ceased within 10 minutes after laparoscopic application of this hemostatic agent to the gallbladder bed [22]. In the present study, using ankaferd by injection into the gallbladder bed rapidly achieve hemostasis allowing surgeon to control bleeding properly and therefore the amount of operative bleeding in ankaferd group was statistically reduced. The efficacy of ABS depends on direct contact with the bleeding surface and the amount of ABS used is dependent on the extent of bleeding. ABS is applied at increasing doses until hemostasis is achieved, up to a maximum dose of 84 mL with no detected adverse systemic effect [7]. ABS application to a patient with major gastrointestinal bleeding is successfully controlled within seconds with no post-procedural complications [27, 28].

The mean amount of fluid drainage in patients undergoing cholecystectomy for acute calculous cholecystitis was 50 mL

[29] and in other study was 127 ml [23]. In the present study, the mean amount of postoperative fluid drainage in ankaferd treated patients was about 30 ml and this may be due to ABS causes neither a foreign object reaction nor thrombocyte activation [30] and allows the regeneration process to be completed with minimal signs of inflammation [31]. ABS is unlike other local hemostatic agents because its mechanism of action is based on forming a polymerized protein network which becomes a focal point for sedimentation of erythrocyte aggregates. The unique mechanism of action of ABS offers a major advantage; not only does it provide hemostasis in patients with normal hemostatic parameters, it can also ensure hemostasis during bleeding episodes in patients with primary and secondary hemostasis impairment, unlike other agents [6, 7, 30].

5. Conclusion

Ankaferd blood stopper action is based on forming a polymerized protein network for sedimentation of erythrocyte aggregates that lacks neither foreign body reaction nor thrombocyte activation. Ankaferd rapidly achieves hemostasis allowing surgeon to control bleeding properly and therefore the amount of operative bleeding, the operative time and the amount of postoperative fluid discharge on using ankaferd is statistically reduced.

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