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Does the LigaSure Vessel Sealing System Provide Benefit in Mortality in Regards to Hepatic Resections?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine – Georgia Campus
Suwanee, Georgia

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not using the LigaSure device provides any benefit in mortality in patients undergoing hepatic resection surgery.

STUDY DESIGN: Review of three English language randomized control trials published in 2007, 2009 and 2012.

DATA SOURCES: Data sources obtained for this review primary studies published in peer-reviewed journals, found using PubMed.

OUTCOMES MEASURED: Patient mortality, defined as death within 30 days of the surgical procedure.

RESULTS: The study done by Dokleptic and et al had 3 patient mortalities occur. The deaths occurred on post op days three, four and nine and were due to pulmonary embolism, acute myocardial infarction and heart failure, respectively.⁸ Zero mortalities occurred in the remaining two studies.^{9,10}

CONCLUSIONS: The results of the studies showed that LigaSure did not provide a benefit in mortality compared to the clamp crushing method, the cavitron ultrasonic surgical aspirator (CUSA) method and to ultrasonic shears.

KEY WORDS: Hepatic; LigaSure; Liver; Resection

INTRODUCTION

Liver cancer is the sixth most common cancer worldwide.¹ For the year 2018, it was estimated that 42,220 adults in the United States would be diagnosed with primary liver cancer. It was also predicted that 30,200 deaths would occur in 2018 due to liver cancer, with about 68% of these deaths being men and 32% being women.² Since 1980, the incidence of liver cancer has tripled.² From 2010-2011, the number of hospitalizations for liver cancer was 44,071.³ Based on these statistics, it is inevitable that a physician assistant or other health care provider will encounter a patient with liver disease, no matter the subspecialty. The median cost of hospitalization for liver resection surgery has more than doubled in the 10 years from 1997 to 2007—from \$23,856 to \$50,758.⁴ These numbers do not take into account the additional follow up visits, costs of the diagnostic imaging studies performed prior to the surgery or the cost of other adjunctive treatments if used. The most common etiology of primary liver cancer is hepatocellular carcinoma (HCC).⁵ HCC, cholangiocarcinoma and metastatic disease are among the most common causes of malignant hepatic tumor.⁵ In reference to benign liver tumors, hemangiomas are the most common type, occurring in about 1-5% of adults.⁶ Additional common types include adenomas and focal nodular hyperplasia.⁵

Risk factors for solid liver tumors include smoking, using oral contraceptive pills, parasitic infections, anabolic steroid use, and non-alcoholic fatty liver disease.⁵ When talking about HCC specifically, risk factors include alcohol abuse, obesity, cirrhosis, type II diabetes, and chronic viral hepatitis.⁵ Regardless of the specific disease diagnosed, solid liver tumor disease presents with similar symptoms across all patients. Patient symptoms may include localized abdominal pain, weight loss, early satiety, jaundice, palpable abdominal masses, or ascites.⁵ It is a possibility that patients will be asymptomatic.⁵ During a workup of solid liver tumor diseases,

laboratory blood work needs to be checked. Elevations in laboratory results such as serum alpha-fetoprotein levels, liver function tests including ALT, AST and ALP levels, and bilirubin levels support. But do not confirm, a diagnosis of a solid liver tumor.⁵ Prolonged PT time may be seen as well.⁵ One of the first diagnostic imaging studies performed when a liver tumor is on the differential diagnosis is an abdominal ultrasound. However, the diagnostic test of choice for solid liver tumors is an abdominal CT with contrast.⁵ Alternatively an MRI can be done.⁵ Fine needle biopsies can be used in order to confirm a diagnosis that was unclear from the laboratory tests imaging studies.⁵ The treatment for liver tumors depend on the disease type and its extent. For example, liver disease that has not spread past the liver or invaded the blood stream, have surgery as a potential treatment option.⁷ Whereas, metastatic liver disease may not qualify for surgical treatment.⁷ Procedural treatment options that do not remove portions of the liver include trans-arterial embolization, radiofrequency ablation, and radioembolization.⁷ These three treatments directly destroy the tumor by either disrupting its blood supply or by using high frequency electricity to kill the cells.⁷ Surgical removal treatment options for liver tumors include hepatic resection of the affected portion or liver transplantation in severely damaged livers.

Liver resection has been shown to be a curative treatment for patients with some benign and malignant liver tumors.⁵ One of the traditional techniques used is known as the clamp crushing method, where the liver parenchyma is crushed by a small Kelly clamp.⁸ The clamp crushing method is considered the gold standard for surgical resection.⁸ Another popular technique is the Cavitron Ultrasonic Surgical Aspirator (CUSA). This technique uses ultrasonic vibration to break down the parenchyma while simultaneously irrigating and aspirating the

field.⁸ The ultrasonic shears also use vibration, as well as pressure, to denature proteins in the parenchyma and collapse the vessels.⁹ The LigaSure vessel sealing system uses energy and pressure to fuse the vessels in the liver parenchyma.⁹ The LigaSure vessel sealing system is being proposed to evaluate if there is a more effective and less fatal technique for hepatic resections in patients with hepatic tumors. This review evaluates three randomized control trials comparing LigaSure to other current resection techniques.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not using the LigaSure device provides any benefit in mortality patients undergoing hepatic resection surgery. The hypothesis about the objective is that LigaSure provides more benefit in mortality than the comparative surgical methods in adults undergoing hepatic resection.

METHODS

Three randomized control trials were selected to create this evidence based medicine (EBM) review⁸⁻¹⁰. The population studied in these trials included adult patients who undergoing hepatic resection surgery. The intervention in each study was the LigaSure vessel sealing system. The study conducted by *Campagnacci and et al* compared LigaSure to ultrasonic shears.⁹ In the study done by *Doklestitic and et al*, compared LigaSure to the clamp crushing method as well as to the cavitron ultrasonic surgical aspirator.⁸ The final study conducted by *Ikeda and et al* compared LigaSure to the clamp crushing method.¹⁰ This EBM review focuses on one specific outcome, patient mortality. The studies observed if any mortalities occurred and if LigaSure provided a benefit in mortality compared to the comparison methods listed

previously, depending on the study. Mortality was defined as death within 30 days of the surgical procedure.

The three randomized control trials were selected via PubMed databases by using four keywords; “LigaSure”, “hepatic”, “liver”, and “resection”. Each study was published in peer-reviewed journals and in English. These specific articles were selected based on their relevance to the clinical question being addressed and if the outcomes measured were patient-oriented evidence that matters (POEMs). Inclusion criteria consisted of the articles being randomized control trials, published after the year 2007 and that the patients were adults over the age of 18. The only exclusion criteria for this review was that the patient population could not consist of children, under the age of 18. **Table 1** displays the demographics and characteristics of each randomized control trial selected for this EBM review. P-values were used as a statistic in each study as well as an additional statistic for continuous data. The statistic used in the study conducted by *Campagnacci and et al* was the unpaired student t-test.⁹ In the study done by *Doklestic and et al*, two statistics were used; ANOVA and Kruskal-Wallis.⁸ The Wilcoxon rank sum test was the statistic used in the study done by *Ikeda and et al*.¹⁰

Table 1: Demographics & characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Campagnacci (2007) ²	RCT	24	39-81	All eligible hepatic resection patients enrolled during a 21 month period	Cirrhosis, Child-Pough B-C classification, pre-operative concrete suspicion of extrahepatic disease or multiple	0	EBVS LigaSure vs. ultrasonic shears for hepatic resections

					hepatic disease that is not amendable to complete resection, ASA greater than stage III		
Dokles-tic (2012) ⁸	RCT	60	Avg age: 57.88 ± SD (15.83)	Hepatectomy for benign and malignant liver tumors in patients with adequate functional reserve of the heart, lungs and kidneys.	Cirrhosis	0	LigaSure vs. clamp crush technique vs. CUSA for liver resection
Ikeda (2009) ¹⁰	RCT	120	20-85	Patients 20-85 y.o. scheduled to undergo hepatic resection of some benign or malignant hepatobiliary disease and acceptable coagulation profile (platelet count $\geq 5 \times 10^4/ul$, prothrombin time activity $\geq 50\%$, bleeding time ≤ 5 minutes	Other malignant diseases, bilio-enteric reconstruction cases, impossibility of inflow occlusion, and living donors of grafts for liver transplantation	0	Vessel sealing system LigaSure vs. clamp crushing method for liver transection

OUTCOMES MEASURED

For this EBM review, the primary outcome measured was mortality of the patient.

Mortality was defined as death of the patient within 30 days of the hepatic resection surgical procedure.

RESULTS

For this EBM review, three randomized control trials that compared the LigaSure vessel sealing system to various different dissection techniques for adult patients undergoing hepatic resection surgeries were analyzed. **Table 2** displays the mortality results organized by each study and the dissection technique used.

Table 2: Patient mortalities compared by study and by resection technique

	LigaSure	Clamp Crushing	CUSA	Ultrasonic shear
Campagnacci ⁹	0	-	-	0
Doklestic ⁸	1	2	0	-
Ideka ¹⁰	0	0	-	-

In the study done by *Doklestic and et al*, the patients were selected from an emergency surgery clinic in Serbia.⁸ Sixty patients with hepatic tumors that were undergoing liver resection surgery from November 2008 to August 2010 were selected for the study.⁸ Patients were excluded if they had been diagnosed with cirrhosis and included “liver tumors in patients with adequate functional reserve of the heart, lungs and kidney.”⁸ Thirty-nine patients in this study had malignant liver tumors due to metastatic colorectal carcinoma, HCC, gallbladder carcinoma, and cholangiocarcinoma.⁸ The remaining 21 patients had benign liver disease such as hemangiomas, adenomas, focal nodular hyperplasia, simplex cysts and echinococcal cysts.⁸ Three different resection techniques were compared, LigaSure, CUSA and the clamp crushing method. Each technique group consisted of 20 randomized patients.⁸ The surgeries for each group were performed by a single operating team and were kept blinded to the patients group assignments until they were in the operating room.⁸ The total mortality was 5%.⁸ There were no mortalities in the group of patient that received the CUSA technique.⁸ Two of the three deaths in this study occurred in the group of patient that received the clamp crushing method. Both

deaths were due to surgical complications. One patient died from a pulmonary embolism and the other died from an acute myocardial infarction.⁸ The third and final death in the study occurred in the LigaSure group. The patient in this group who died “had a malignant cardiac arrhythmia disorder and heart failure with previous history of cardiac disease”.⁸ The p-value for mortality in this study was >0.05 .⁸ A p-value of <0.05 was needed to be considered statistically significant.⁸

The study conducted by *Campagnacci and et al* was comprised of 24 patients undergoing hepatic resection for malignant or benign lesions, during a 21 month period.⁹ Patients were excluded if they had cirrhosis, Child-Pough B-C classification, pre-operative concrete suspicion of extrahepatic disease or multiple hepatic disease that was not amenable to complete curative resection, and American Society of Anesthesiologists (ASA) physical status classification greater than stage III.⁹ Twenty-one of the eligible patients had malignant liver tumors from either HCC or metastatic colorectal carcinoma.⁹ The remaining three patients had benign liver tumors from hemangiomas or intrahepatic lithiasis.⁹ All patients completed the study and were randomized into the LigaSure group or into the ultrasonic shears harmonic scalpel.⁹ Each of the resection surgeries were performed by a surgical team who had previously conducted at least 50 hepatectomies, as well as supervised by two expert surgeons.⁹ The two expert surgeons were blinded to the group assignments up until the day of the surgery.⁹ There was no mortality recorded for either group, see **Table 2**. No further statistics were given for mortality.⁹

In the study performed by *Ikeda and et al*, there were 165 patients who were undergoing hepatic resection surgery, at the Tokyo University Hospital, for benign or malignant

hepatobiliary disease.¹⁰ Of those 165, 120 qualified and all completed the study.¹⁰ A majority of the 45 patients were excluded for one of the following reasons; high risk of hemorrhage, required an additional surgical procedure, unable to undergo inflow occlusion or refusal to participate. All 120 patients had malignancy in the form of either primary or metastatic liver carcinoma.¹⁰ Half of the patients were randomized into the LigaSure vessel sealing group while the other half were randomized into the clamp crushing group.¹⁰ The results of these group placements were not blinded to the surgical team.¹⁰ Each surgery was performed by three consultants and three trainees.¹⁰ No mortalities in either group occurred which is shown in **Table 2.**¹⁰ The p-value was considered statistically significant at <0.05 with a 95% confidence interval.¹⁰ There was no p-value for mortality calculated due to the fact that it did not occur.

DISCUSSION

The three randomized control trials reviewed, showed that the LigaSure vessel sealing system, in comparison to other resection techniques, did not provide a benefit in mortality. In fact, each technique provided similar mortality outcomes across all studies. In the United States, about 44 million people have no health insurance, and another 38 million have inadequate health insurance.¹¹ Surgical procedures and hospital stays are costly even for those with insurance coverage. Patients with hepatic tumors may not be able to afford hepatic resection surgeries or be able to obtain follow up care. With the LigaSure instrument, there is an additional fifty dollar fee charged for each disposable hand piece used during the operation.¹⁰ When compared to the Kelly clamp, the cost is increased and provides no added benefit. The study performed by *Doklestitic and et al*, mentions that a cost analysis of the devices

was not included.⁸ Future studies can address this limitation and perform this analysis to strengthen their results.

The most common indication for hepatic resection surgery is a malignant tumor, often being HCC.¹² However, patients with intermediate HCC, advanced HCC or HCC with portal hypertension, are not recommend to receive hepatic resection as a first line therapy due to a higher risk of mortality.¹³ The studies were limited in regards to blinding. Two of the three articles expressed how the surgeon and surgical team were blinded up until the day of the surgery.^{8,9} The additional article stated that no blinding had occurred.¹⁰ In the study done by *Campagnacci and et al*, based on their calculations, a sample size of 34 patients was needed to be statistically large enough.⁹ This study contained only 24 patients.⁹ The study performed by *Ikeda and et al*, containing 120 patients, stated that a sample size of 108 patients was needed to be statistically significant.¹⁰ In the study conducted by *Doklestic and et al* there was no statement made in regards to an appropriate sample size.⁸ Another limitation in this study was that there was no long term follow up or focus on the long term outcomes.⁸

CONCLUSION

As surgical technology advances, surgical procedures must progress just as quickly. The studies provided in this EBM review failed to prove that there was benefit in mortality with the LigaSure vessel sealing system, when compared to other resection techniques. It is understood that each surgery cannot be identical. Factors such as patient's comorbid conditions, surgeon experience and skill level, and access to certain surgical devices can impact the results of the surgery.

Future study is warranted to determine whether the LigaSure technique provides benefit in patient mortality. Aside from providing a cost analysis, these studies could try to reduce the discrepancies by setting stricter inclusion criteria. Even though this might reduce the sample size, having patients with similar medical histories and co-morbid conditions could strengthen the results. Since the incidence rates of liver tumor continue to increase, this treatment technique should continue to be studied.

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