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THUNDERBEAT™ INTEGRATED BIPOLAR AND ULTRASONIC FORCEPS IN THE WHIPPLE PROCEDURE: A PROSPECTIVE REGISTRY TRIAL

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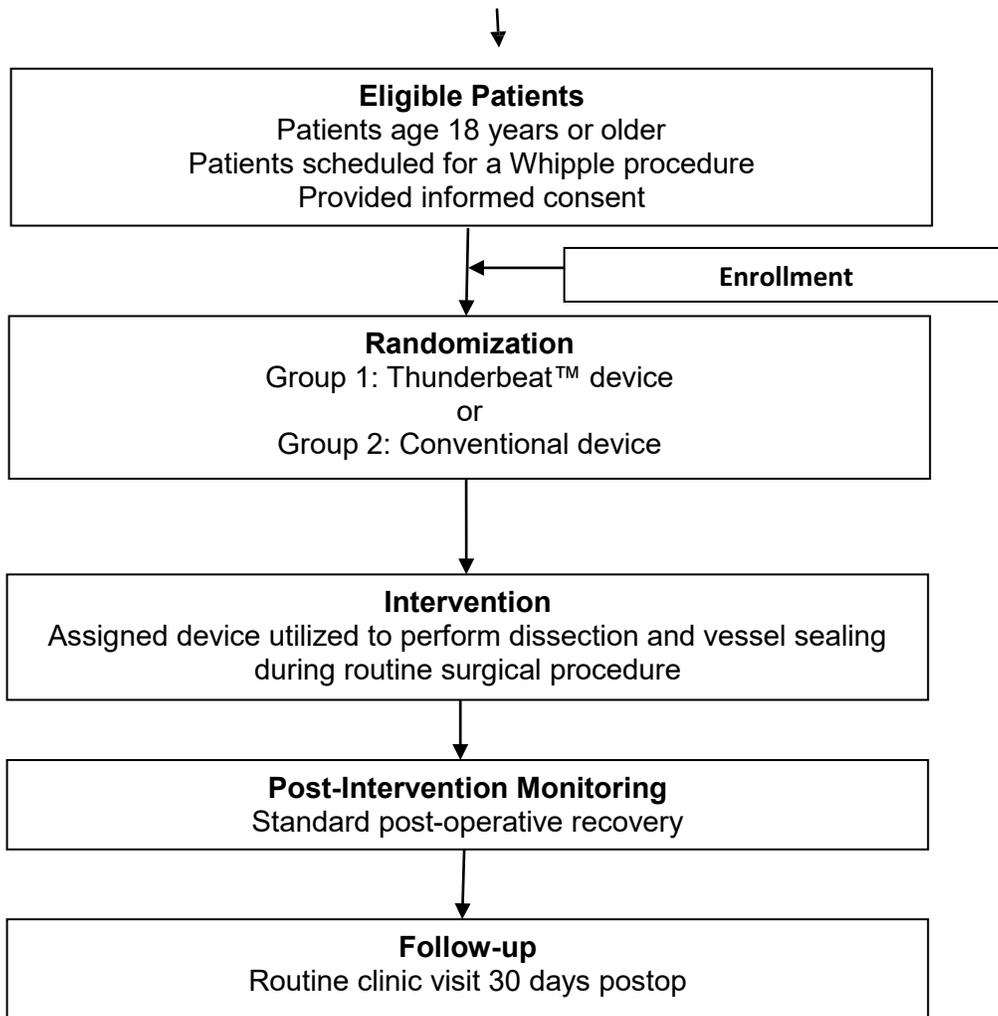
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TREATMENT SCHEMA



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1.0 BACKGROUND AND RATIONALE

1.1 Whipple Procedure

The procedure was originally described by Alessandro Codivilla in 1898. A.O. Whipple improved it in 1935. The Whipple procedure is the standard method for therapy of cancerous tumors, inflammation and stenosis near the head of the pancreas.

Approximately 100 patients undergo an elective Whipple procedure at Washington University Medical Center each year.

1.2 Thunderbeat™

As the pancreas is fed by many vessels, it is necessary to use lots of ligatures, clips and sutures for hemostasis after dissection. This dissection technique is very time consuming and requires numerous changes of instruments. The devices we currently have available for use in the operating suite are EnSeal and LigaSure. A new type of surgical scissors that delivers ultrasonically generated frictional heat energy and electrically generated bipolar energy simultaneously, known as the Thunderbeat™ (Olympus, Japan), is now an available alternative for dissection and hemostasis. [1-2]

Thunderbeat™ was provided FDA clearance in March 2012 for use in open, laparoscopic, and endoscopic surgery, or in any procedure in which cutting, vessel ligation (sealing and cutting), coagulation, grasping and dissection is performed.

The Thunderbeat™ device provides the first integration of both bipolar and ultrasonic energies delivered simultaneously from a single multi-functional instrument. This integration provides the surgeon the ability to rapidly cut tissue with ultrasonic energy and to create reliable vessel seals with bipolar energy without having to change devices. The current is provided by a special generator and contains a very high capacity with a low voltage. The body's proteins, such as collagen and elastin, are converted so a permanently sealed zone results. As the tissue between the branches is sealed, lateral thermic tissue damages can be limited to a minimum. Several authors have described a tendency of reduced intraoperative blood loss with bipolar energy devices. Other trials show reduced operating time when a bipolar device is utilized in several surgical procedures, such as thyroid, hepatic, urologic, hemorrhoidectomy and gynecology surgery. [3-7]

Correct dissection in the operating field is very important to avert secondary bleeding or other complications, which might cause re-operation or elevate the patients' morbidity and mortality.

The main difference between the predicate devices and the Thunderbeat™ seal and cut mode is that Thunderbeat™ uses ultrasonic and high frequency bipolar energy simultaneously to seal and cut tissue.

2.0 OBJECTIVES

2.1 Primary Objective

This is a prospective observational feasibility/QI registry trial to evaluate operative blood loss and post-operative morbidity following use of the Thunderbeat™ device during the Whipple procedure. This will be compared to patients whose Whipple procedure will be performed using conventional dissection and hemostasis techniques.

2.2 Secondary Objectives

1. To determine the operative time of the Whipple procedure when performed using the Thunderbeat™ device. This will be compared to patients whose Whipple procedure will be performed using conventional dissection and hemostasis techniques. Will this device reduce the amount of time spent in the operating room for both the patient and the surgeon?
2. To determine the cost of using the Thunderbeat™ device during the Whipple procedure. This will be compared to patients whose Whipple procedure will be performed using conventional dissection and hemostasis techniques. Will the use of this device be fiscally feasible?

3.0 PATIENTSELECTION

3.1 Inclusion Criteria

1. Scheduled to undergo an elective open or laparoscopic Whipple procedure
2. At least 18 years of age.
3. Karnofsky performance status \geq 80% (see Appendix A).
4. Able to understand and willing to sign a written informed consent document.

3.2 Exclusion Criteria

1. Pregnant or breastfeeding.
2. Surgeon's opinion at the time of dissection that the subject's well being (e.g. bleeding or other independent acute health problems) would be compromised.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

The following information is required to confirm patient eligibility prior to registering patient:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials

4. Copy of signed consent form
5. Planned date of enrollment
6. Completed eligibility checklist, signed and dated by a member of the study team
7. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

All patients must be registered through the Siteman Cancer Center database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Preoperative Evaluation

Eligible patients will have standard evaluations, procedures, and laboratory testing as determined necessary by their surgeon preoperatively.

5.2 Randomization

Sixty patients will be recruited according to the sample size calculation. Randomization will be performed by a Research Patient Coordinator and the patient assigned to the Thunderbeat™ group or the conventional group in a 1:1 ratio. Randomization will only occur after the patient has signed the informed consent and will be documented in the case report file as well as communicated to the treating surgeon.

Thunderbeat™ group (n=30)

In the Thunderbeat™ group, dissection and hemostasis of vessels will be performed using the Thunderbeat™ device (Olympus, Japan).

Control group (n=30)

In the conventional group, scissors, ligatures, clips and sutures will be used for dissection and hemostasis as necessary.

Minimizing treatment bias

A standardized operation technique will be used in both groups. The same Thunderbeat™ device will be used throughout the length of the study. The participating surgeons will have had experience performing at least 100 Whipple procedures to guarantee comparable treatment of patients.

Minimizing measurement bias

The patients will be blinded to the assigned operating technique. Surgeon's blinding will not be possible due to the different techniques used during the operation.

5.3 Operative Procedure

The surgical procedure will be conducted as planned. The surgeon will follow the subject's assigned group assignment (Thunderbeat™ or conventional) unless determined to be potentially

detrimental to the optimal care of the patient. At that point, all techniques for dissection and hemostasis may be utilized as the surgeon deems necessary.

At least 5 of the procedures will be videotaped for future use to produce educational and training materials. No identifying information will be contained in the video.

The measurement of estimated blood loss (EBL) will come from the intraoperative anesthesia notes where (EBL) is recorded during each surgical procedure in Allscripts and Clindesk. The estimate of operative blood loss is measured by volume in the suction canisters and pads and is historically documented by the operative nursing staff during the operation.

5.4 Postoperative Care

The post operative management is standard of care for all patients who undergo the Whipple procedure and will not be altered by their participation in this study.

5.5 Duration of Follow-Up

Patients will be followed for 90 days following their surgical procedure. Postoperative complications and adverse events will be closely monitored. Patients will be followed until resolution or stabilization of the adverse event. Please see Appendix B for Study Visit Schedule.

5.6 Criteria for Removal from Study

If at any time the constraints of this protocol are considered to be detrimental to the patient's health (e.g. bleeding or other acute health problem) and/or the patient no longer wishes to proceed with the protocol intervention, the patient should be removed from the study and the reason(s) for discontinuation documented in the case report forms.

Otherwise, the patient will receive the intervention and be followed as described.

6.0 ADVERSE EVENT REPORTING

6.1 Adverse Events

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:<http://www.hhs.gov/ohrp/policy/advevtguid.html>

The surgeon will discuss the expected risks of the surgery with the participant and participant and a separate surgical consent for the surgery acknowledging the risks. Expected risks of the surgery are listed below.

- **Perioperative complications:**
iatrogenic injury, convert from laparoscopic approach to open procedure, use of other

hemostatic devices or therapies, blood transfusion

- **Postoperative complications:**

Secondary bleeding/hematoma, delirium, failure to thrive, urinary retention, surgical site infection, urinary tract infection, C-diff, colitis, ileus, delayed gastric emptying, fistula, anemia, pneumonia, intraabdominal abscess, atrial dysrhythmia, myocardial infarction, cellulitis, deep vein thrombosis/pulmonary embolism, anastomotic leakage, re-intervention (operational), blood transfusion, sepsis, death.

The above are complications of the surgical procedure and may be experienced by all patients on whom a Whipple procedure is performed. Surgical complications are routinely identified and documented during the data abstraction process for the American College of Surgeons National Surgical Quality Improvement Program® (NSQIP). NSQIP has very detailed and specific definitions used to assess these postoperative morbidities. For the purposes of this study, the NSQIP definitions for the surgical complications will be utilized.

Surgical complications will not be considered adverse events associated with the study, unless unanticipated and possibly related to the use of the Thunderbeat device. If an adverse event is reported, details related to the event will be obtained from medical record review and direct communication with the PI for severity and relatedness assessment. The adverse event will then be recorded as part of the research and reported as necessary. If it is determined by the PI that the event is anticipated from surgery and not related to the device, it will not be reported as an adverse event as part of this study.

6.2 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Potential perioperative complications that could occur due to the use of the Thunderbeat device include but are not limited to:

- **Thunderbeat Device**:**

Cracking, breaking, or deformation of the components of the Thunderbeat™ probe tip or jaw, or the detaching of the fragment from the Thunderbeat probe tip or jaw during or after the surgical procedure, and burning of unintended tissue. Probe damage detected during surgery will trigger audible and visual generator alarms.

***Please note that these risks may not occur during surgery and that they are the same risks as using any other similar device for the same indication that is currently on the market.*

6.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subject's research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.4 Serious Noncompliance

Definition: noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.5 Protocol Exceptions

Definition: A planned deviation from the approved protocol that is under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

6.6 Reporting to the Human Research Protection Office (HRPO) at Washington University:

The PI is required to promptly notify the IRB and Olympus, the study sponsor, of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of HRPO.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to HRPO within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.7 Time frame for Reporting Required Events

Reportable adverse events that are determined to be unanticipated and related to the Thunderbeat device will be recorded and reported for 90 days following the Whipple procedure. Events considered to be possibly, probably, or definitely related to standard of care therapy will not be reported.

Deaths	
Any reportable death while on study or within 90 days of study	Immediately, within 24 hours, to PI and the IRB
Adverse Events/Unanticipated Problems	

Any reportable adverse events that are related and unanticipated problems as described above in Section 6.2 (other than death)	Immediately, within 24 hours, to PI and within 10 working days to the IRB
All adverse events that are related and unanticipated problems regardless of grade and attribution should be submitted cumulatively	Include in DSM report
Noncompliance and Serious Noncompliance	
All noncompliance and serious noncompliance as described in Sections 6.3 and 6.4	Immediately, within 24 hours, to PI and within 10 working days to the IRB

7.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Eligibility Checklist Demographics Clinical Characteristics Medical/Surgical History Form	Prior to starting treatment. Data collection will be captured in RedCap.
Intra-operative Findings Operative and Post-procedural Form	Following receipt of operative report Following receipt of discharge summary Data collection will be captured in RedCap.
Adverse Event Assessment	At the time of any unanticipated and related event
Follow-Up Form: First and Second postop visit	Approximately 30 and 90 days following surgery following routine clinic visit for post-surgical evaluation Data collection will be captured in RedCap.

8.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) and to Olympus, the study sponsor, semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least monthly and provide an annual report to the Quality Assurance and Safety Monitoring (QASM) Committee. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician

- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious adverse events on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of a research related adverse event, the AE will be reported to the HRPO according to institutional guidelines and to Olympus, the study sponsor.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Objectives and Endpoints

The primary objective of the study is to determine if the use of the Thunderbeat™ device provides a reduction in operative blood loss. The measurement of operative blood loss will come from the intraoperative anesthesia notes where estimated blood loss is recorded during each surgical procedure.

The secondary objectives are intraoperative and postoperative morbidity, hospital length of stay and operative time.

Primary endpoint

The primary endpoint will be the estimated operative blood loss. The estimated blood loss will be measured per the standard of care and will be documented in the operation log.

Secondary endpoints

- Operation time measured from the beginning of the surgical procedure (incision of the skin) to the end of the surgical procedure (closure of the skin).
- Anesthesia time measured from the initiation of anesthesia induction to the time of extubation
- Perioperative complications:
 - Iatrogenic injury
 - Need for conversion from laparoscopic approach to open procedure
 - Need for the use of other hemostatic devices or therapies
 - Intraoperative requirement of blood product transfusion
- Postoperative complications through 90 days from day of surgery:
 - Secondary bleeding/hematoma
 - Wound infection
 - Gastroparesis
 - Postoperative pancreatic fistula
 - Intraabdominal abscess

- Anastomotic leakage
- Re-intervention (operational)
- Postop requirement for blood product transfusion
- Hospital mortality
- Overall cost of the operation, calculated by the indirect and direct costs during the hospital stay and the costs accumulated 90 days postoperatively

9.2 Study Design

To achieve comparable groups for known and unknown risk factors randomization will be performed as unistratified block randomization with random block sizes in a 1:1 allocation ratio. Allocation to treatment will be carried out by means of a computer-generated random study numbers with group assignment.

9.3 Sample Size

Appropriate sample size is calculated based on assumption of difference of 20 percent in blood loss in favor of the Thunderbeat™ device as compared with conventional techniques. This difference is considered clinically relevant based on previous similar studies [9-11]. A sample size of 60 is considered sufficient to prove this difference, if present (alpha error set at 0.05, power>80 percent).

Approximately 100 patients per year undergo a Whipple procedure at Washington University Medical Center. The estimated time frame to enroll 60 patients is approximately 18 to 24 months.

The total expected enrollment is 60 patients: 30 Thunderbeat and 30 conventional.

9.4 Data Analysis

Data analysis for this study will be descriptive in nature. Demographic and clinical characteristics of the sample, as well as intraoperative findings and post-surgery complications will be summarized using descriptive statistics. The incidences of surgical complications and procedure-related adverse events will be calculated, and the confidence intervals will also be provided.

Patients assigned to the Thunderbeat™ group will be compared with those who had conventional techniques using χ^2 tests for categorical variables and Student's t-tests for continuous variables. For the t-tests equal variances were not be assumed, unless significant by Levene's test. Mann-Whitney *U* tests will be utilized for non-normally distributed variables. Two-tailed *P* values 0.05 will be considered statistically significant.

Multivariate analyses for intraoperative blood loss (mL), operative time (minutes), postoperative morbidity (any grades 1–5 and major grades 3–5), and hospital length of stay (days) will be performed using binary logistic regression and linear regression models to examine the relationship between intervention groups and examined outcomes and to identify potential confounders. The results of multivariate analyses will be expressed as odds ratios with corresponding 95% confidence intervals. All analyses will be performed using SPSS 20.0 statistical software (SPSS Inc.Chicago, IL).

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APPENDIX A: Karnofsky Performance Scale

Description	Percent(%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0

APPENDIX B: STUDY VISIT SCHEDULE

	Baseline	Intervention	Follow-Up		
	Screening ²	Day of Surgery	Hospital Discharge	30 Day Post-Op Visit ³	90 Day Status ⁵
Past medical history ¹	X				
Informed consent	X				
Physical exam ⁴	X				
Operating time from skin incision to closure (mins)		X			
Anesthesia time (mins)		X			
Intraoperative estimated blood loss (cc)		X			
Administration of blood products		X	X		
Peri and postoperative complications		X	X	X	X
Hospital length of stay			X		
Mortality			X	X	X

¹Study-relevant past medical and surgical history

²Screening procedures to be completed within 60 days of surgery.

³To be performed 30 days from day of surgery \pm 14 days.

⁴Baseline height, weight, gender, karnofsky performance status, medications from pre-surgical physical examination

⁵Medical records (inpatient and outpatient) will be reviewed by a study team member for additional postoperative complications. No direct contact or clinic visit required.