Reading Hospital – Tower Health
Research Protocol

Negative splenic angiogram– is embolization needed?

Adrian Ong, MD
Reading Hospital Division of Trauma, Dept of Surgery
420 South Fifth Avenue, West Reading, PA 19611
Ph 484-628-5906 / F 484-628-4880
Adrian.Ong@towerhealth.org

Collaborators and their Institutional Affiliations:
Name: Rachel Yoo, MD, PGY-2
Institutional Affiliation: General surgery resident
Study Responsibilities: Chart abstraction, record review, manuscript compilation, main investigator.

Name: Christopher Butts, DO, PhD
Institutional Affiliation: Reading Hospital Tower Health, Department of Surgery
Study Responsibilities: Chart abstraction, record review, manuscript compilation

Name: Alison Muller, MSPH, MLS^{ASCP} Clinical Research Coordinator
Institutional Affiliation: Reading Hospital Tower Health, Department of Surgery
Study Responsibilities: Chart abstraction, record review, manuscript compilation, statistical analyses

Funding Source(s): none

A. SPECIFIC AIMS

Primary Aim:

1. To evaluate the outcomes of embolization versus expectant management of blunt splenic injuries when splenic angiography is negative.

Secondary Aims:

1. To evaluate practice variations in U.S. trauma centers regarding splenic angioembolization.

2. To evaluate the factors affecting failure of splenic salvage in patients undergoing splenic angiography.

B. RESEARCH QUESTION(S) AND HYPOTHESIS(ES)

For patients with a negative splenic angiography after blunt trauma, does angioembolization (AE) improve 30-day splenic salvage?

H_O: AE for negative splenic angiogram does not improve 30-day splenic salvage.
H_A: AE for negative splenic angiogram improves 30-day splenic salvage.

C. BACKGROUND AND SIGNIFICANCE

Angioembolization (AE) in the management of splenic trauma is an established strategy to maximize the likelihood of splenic preservation. In a multicenter study of four level 1 centers, the two centers with a higher splenic AE usage (19% and 11%) compared to the two lower usage (1%, 4%) centers had a higher odds of splenic salvage (odds ratio=3.2, 95% CI 1.7-6.3) [1] .

Criteria for angiography currently include contrast blush (CB) or extravasation from the spleen on computed tomography (CT) and any high grade (IV-V) splenic injury even in the absence of CB. Bhullar et al. in a retrospective study concluded that that even in high grade injuries in the absence of CB, AE was indicated, as the absence of CB in high-grade injuries did not exclude active bleeding[2]. In their series, for high grade injuries without CB, the rate of failure of nonoperative management (NOM) was 0% with AE for all regardless of angiographic findings, compared to 26% when no angiography was performed. Therefore, they advocated liberal AE regardless of angiographic findings.

A randomized trial of prophylactic AE versus surveillance and embolization if necessary was carried out by Arvieux et al[5]. Inclusion criteria were grade III splenic injuries with large hemoperitoneum, grade IV or V injuries seen on CT. Patients with CB were excluded. After day five, 29% of those in the surveillance group required AE as opposed to 1.5 % in the prophylactic group ($p<0.001$). Regarding splenectomy, 6.3% of the surveillance group required splenectomy versus 0% of the prophylactic group ($p=0.12$). The authors found that high grade injuries were a risk factor for failure compared with grade III injuries, but also concluded that a strategy of surveillance was equivalent to prophylactic AE in terms of splenic salvage. However, the almost 30% rate of repeat angiography suggested that prophylactic embolization was of value.

Some studies have suggested that AE does not increase the success rate of NOM. Harbrecht et al found that angiography did not affect the success of NOM[6]. In particular, the success rate of NOM was similar whether patients did or did not undergo embolization at the time of angiography (embolization, 80%, 16 of 20 patients versus no embolization, 77.8%, 5 of 7 patients). Duchesne et al. also found that proximal AE did not improve outcomes compared to splenectomy[7].

A prior study by Haan et al. found that in 86 negative splenic angiograms, there was an 8% failure rate if managed expectantly without AE[3]. In a follow up study, Haan et al. found that of 368 patients managed nonoperatively, 166 had a negative angiogram[4]. Of these 166,

overall splenic injury grade was 2.9 and overall nonoperative salvage rate was 94%. Only five of these patients underwent repeat angiography of which three had AE. Based on these two studies, it appeared that the failure rate of NOM with expectantly managing a patient with a negative angiogram was low.

Besides local complications such as groin hematoma and rebleed, the rate of splenic related complications is generally low (0-11%) but not negligible after AE. In a study of 88 patients with splenic AE, 10 (11%) had splenic related complications requiring intervention (splenic infarct, abscess)[8]. In another study of splenic AE, 3 of 232 (1.3%) had splenic infarcts[9].

Most studies have focused on CT findings and not on the actual lesions found on angiography, as the indication for embolization. This study proposes to evaluate the outcomes of embolization vs no embolization based on angiographic findings. While the decision to perform embolization is less controversial when angiography demonstrates focal bleeding or a vascular abnormality (contrast extravasation, pseudoaneurysm, arteriovenous fistula, abrupt vessel truncation), it is more debatable when the angiogram is "negative." In the only randomized trial of embolization versus expectant management for splenic injuries, Arvieux et al randomized patients based on CT findings, and not angiographic findings, and thus angiographic lesions in the trial were not evaluated[5]. It is also unclear exactly what is meant by a "negative" angiogram in the literature.

D. RESEARCH DESIGN AND METHODS (including data analysis)

D1. Inclusion and Exclusion Criteria:

Inclusion: (Must meet all of the following)

- Aged 16 to 89
- Sustaining a blunt trauma mechanism of injury
- Splenic injury seen on admission CT
- Received splenic angiography.

Exclusion criteria:

- Transfer from another hospital
- Transferred out to another hospital
- Laparotomy prior to splenic angiography
- Time of injury to admission > 24 hours.
- Splenic hematoma or laceration without antecedent traumatic episode (i.e., "spontaneous")
- Prior splenectomy

Study period: 5 years (approx. years 2018 to 2022)

A "positive" splenic angiogram is defined as one where there is bleeding or a vascular abnormality, as manifested by the following: contrast extravasation or blush, pseudoaneurysm, arteriovenous fistula or abrupt vessel truncation.

A "negative" splenic angiogram is defined as one where there is no bleeding or vascular abnormality and includes the following findings: area of focal hypoperfusion, displacement of splenic arterial vasculature (due to subcapsular hematoma)[10].

Although the main focus is on outcomes of negative splenic angiography, in order to perform a comprehensive assessment of embolization practices, we propose the inclusion of all subjects who received splenic angiography (whether positive or negative) during the study period.

D2. Subject Recruitment:

This a retrospective multi-center study that is approved and endorsed by the American Association for the Surgery of Trauma Multi-institutional Trials Committee (AAST-MIT Committee) (Multi-Institutional Studies - The American Association for the Surgery of Trauma (aast.org). The AAST MIT is a national repository of investigator-initiated studies in trauma and critical care that have been vetted and approved by the MIT Committee. The study will be hosted by Reading Hospital.

Pending approval by the Reading Hospital IRB, details of the study and data to be collected will be posted on the AAST MITC website, together with the formal IRB approval letter. Interested centers throughout the United States will access the website and elect to participate. Each center will seek IRB approval at their respective institution prior to participation.

D3. Subject Screening Process:

Subjects will be identified retrospectively from the trauma registry of each participating trauma center according to the inclusion and exclusion criteria.

D4. Informed Consent Process

This is a retrospective chart review and involves no prospective contact with subjects. We seek a waiver of informed consent.

D4.3 Waiver/Alteration of Informed Consent

- The research involves no more than minimal risk to subjects.
- The research cannot be carried out practicably without the waiver or alteration.

- The waiver or alteration will not adversely affect the rights and welfare of the subjects as the data is pre-existing in the medical record and no interventions or patient interactions are planned.
- No PHI will be recorded.

D4.4 Waiver of the Requirement for Documentation of Informed Consent

This research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

D5. Study Procedures:

Participating centers will identify patients from their respective hospital trauma registries retrospectively. Individual data user agreements will be executed between Reading Hospital and the participating centers as needed. Each center will input their abstracted patient data into REDCap hosted by Reading Hospital. Participating centers will be restricted to accessing only their data, in REDCap. Participating centers that wish to conduct further analysis of the collaborative data can request a full data set from Reading Hospital.

Duration of the study is anticipated to be 1 year.
Anticipated minimum number of participating trauma centers=10
Anticipated enrollment per center: 100-150
Anticipated enrollment for Reading Hospital: 150

D5.1 Data Collection:

A data collection sheet is included in the submission.

D5.2 Statistical Analysis:

D5.2.1 Sample Size Estimation and Rationale:

Arvieux et al. found that almost 30% of patients required a second angiography if no prophylactic embolization was done[5]. The prevalence of repeat embolization in trauma centers across the U.S. is unclear. It is reasonable to assume that a substantial proportion would undergo splenectomy if repeat embolization were not performed. Haan suggests that the failure rate was 8% if embolization was not performed after a negative angiogram[3]. Thus, we assume that the failure rate (need for splenectomy) would be 10% if no embolization was performed. Assume: Splenectomy rate = 3% (embolization group) vs 10% (no embolization group); and ratio embolized: not embolized= 3:1, with alpha = 0.05, power = 80%, N=342 embolized vs 114 not embolized patients will be required.

Further assume that sample consists of 50% OIS grade ≤ III and 50% OIS grade IV and V. In order to separately analyze these two grade subsets, we will require approximately 600 embolized vs 300 non embolized patients.

D5.2.2 Data Analysis:

Primary outcome:

1. Splenectomy within 30 days

Secondary outcomes:

1. Repeat splenic angiography
2. 30-day mortality
3. Complication rate for angiography and embolization
4. Packed red blood cell units used at 4 hours and 24 hours.

Subjects will be divided into two groups:

1. Those who underwent embolization
2. Those who did not at the first (or only) splenic angiography.

Bivariate tests of association will be used to compare groups and outcomes. To control for independent variables and account for center-level "clustering," multilevel mixed - effects regression modeling will be performed accounting for patient-level characteristics and center-level characteristics as fixed effects and the cluster-specific random effect.

D6. FDA Regulated Studies (Drugs and Devices):

This study is limited to retrospective chart review. No patient interaction is planned. No drugs, devices or interventions are planned.

E. PROTECTION OF HUMAN SUBJECTS

E1. Risks to the Subjects

There is no more than minimal risk to the subjects. There is no prospective contact with subjects nor interventions planned. Abstracted data will be stored in REDCap with access limited to study staff. PHI will not be stored.

E2. Potential Benefits of the Proposed Research to the Subjects and Others

This is a retrospective analysis, where no patient contact is planned. Although there is no direct benefit expected for the study participants, we anticipate that this study will add to the collective knowledge of splenic angiography and benefit future patients.

E3. Importance of the Knowledge to be Gained

Understand variations in practice between trauma centers regarding the management of angiographic findings seen during splenic angiography, and to evaluate outcomes of management differences.

E4. Data And Safety Monitoring Plan

This study is limited to retrospective chart review. No patient interaction is planned. No drugs, devices or interventions are planned.

E5. Reportable Events:

This study is limited to retrospective chart review. No patient interaction is planned. No drugs, devices or interventions are planned.

F. REFERENCES/LITERATURE CITATIONS

1. Bannerjee A, et al. Trauma center variation in splenic artery embolization and spleen salvage: A multicenter analysis. J Trauma Acute Care Surg. 2013;75: 69-75.
2. Bhullar IS, et al. At first blush: Absence of computed tomography contrast extravasation in Grade IV or V adult blunt splenic trauma should not preclude angioembolization. J Trauma Acute Care Surg. 2013;74: 105-112.
3. Haan J, et al. Admission Angiography for Blunt Splenic Injury: Advantages and Pitfalls. J Trauma. 2001;51: 1161–1165.
4. Haan J, et al. Nonoperative Management of Blunt Splenic Injury: A 5-Year Experience. J Trauma. 2005;58: 492–498.
5. Arvieux C, et al. Effect of Prophylactic Embolization on Patients with Blunt Trauma at High Risk of Splenectomy. A Randomized Clinical Trial. JAMA Surg. 2020; 155: 1102–1111.
6. Harbrecht BG, Ko SH, Watson GA et al. Angiography for blunt splenic trauma does not improve the success rate of nonoperative management. J Trauma. 2007 Jul;63(1):44-9.
7. Duchesne JC, et al. Proximal splenic angioembolization does not improve outcomes in treating blunt splenic injuries compared with splenectomy: a cohort analysis. J Trauma. 2008; 65: 1346-51.
8. Ekeh AP, et al. Complications arising from splenic embolization after blunt splenic trauma. Am J Surg. 2005; 189 :335-9.

9. Clements W, et al. SPLEnic salvage and complications after splenic artery EmbolizatioN for blunt abdomINal trauma: the SPLEEN-IN study. CVIR Endovasc. 2020; 3: 92.
10. Hagiwara A, et al. Nonsurgical management of patients with blunt splenic injury: efficacy of transcatheter arterial embolization. AJR Am J Roentgenol. 1996;167:159-66.

GLOSSARY

(All definitions are from the current Reading Hospital IRB SOP, version date April 2020)

Clinical investigation means any experiment that involves a test article and one or more human subjects and the results of which are intended to be submitted to or held for inspection by the Food and Drug Administration as part of an application for a research or marketing permit.

Clinical trial means research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

Human subject (OHRP) means a living individual about whom an investigator (whether professional or student) conducting research:

i. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Human Subject (FDA) means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue,

legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Local Context refers to local circumstances, preferences, and variability. It includes issues such as variation in language, economic issues, state or local laws, and institutional policies.

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:

a. Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, which focus directly on the specific individuals about whom the information is collected.
b. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
c. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
d. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered a sponsor, and the employees are considered investigators.

Sponsor-Investigator means an individual who both initiates and conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving a subject. The term does not include any person other than an individual, e.g., corporation or agency.