Protocol Title: Surgicel Snow in Gynecological Surgery

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Background:

Surgicel Snow is a topical hemostatic agent for use during surgical procedures. Topical hemostatic agents are classified into four categories based upon functional characteristics: mechanical agents, biological agents, flowable sealants, and fibrin sealants. The mechanical agents are further subcategorized by origin of component monomers including porcine gelatin, bovine collagen, oxidized regenerated cellulose, and polysaccharide spheres. The effectiveness, risk profile, and mechanism of action differ by hemostatic classification. Like the other mechanical agents, Surgicel Snow forms a physical barrier that blocks blood flow while providing a large surface area for the rapid formation of a fibrin clot. As a mechanical agent derived from oxidized regenerated cellulose, Surgicel Snow shares with other mechanical hemostatic agents, the benefits of a favorable risk profile. It is relatively inexpensive, rapidly absorbed (14 days), rarely induces a local inflammatory response or fibrosis, and no reported potential for inducing immunological response or anaphylaxis. A possible added benefit of oxidized regenerated cellulose topical hemostats is the antimicrobial effect of the lowered pH with the barrier layer (1). As is the case for all mechanical agents, the effectiveness of Surgicel Snow is limited by the need of an intact coagulation mechanism, as it will not enhance the rate of thrombus formation without adequate levels of coagulation factors. Surgicel Snow is generally used for minimal to mild bleeding from focal or widespread sources (2).

The use of oxidized regenerated cellulose has been shown to reduce length of stay and resource utilization in cardiovascular and neurosurgical procedures (3). With the exception of a small number of studies on myomectomy and conservative ovarian surgery (4-9), there is a paucity of evidence to support a benefit associated with the use of topical hemostats during gynecological surgery. Although it is known that all of the agents presently

approved by the FDA are capable of shortening the bleeding time associated with surgical incisions, there are no studies to show comparative efficacy or clinical impact with respect to estimated blood loss, transfusion rates or overall cost of care (10). Because of this lack of quality studies, there are few guidelines available for usage by clinical situation or by type of hemostatic agent. Notwithstanding the generally high level of confusion among gynecologic surgeons concerning indications for using topical hemostatic agents, it appears that these agents are being used with increasing frequency (11). The need for additional studies on the clinical impact of topical hemostatic agents during gynecologic surgery is clear.

The gynecologic procedures that provide the most interesting opportunities for clinical research on topical hemostatic agents at present are hysterectomy, resection of deeply infiltrating endometriosis, surgical management of active pelvic inflammatory disease, and sacrocolpopexy. These procedures share the requirement for dissection of the pelvic retroperitoneal spaces and are thereby associated with the risk of venous oozing adjacent to vital structures that limit the options for standard hemostatic methods. The retroperitoneal space of the pelvis (12) include the pararectal space, paravesical space, retropubic space, vesicovaginal space, rectovaginal space, and the presacral space (Triangle of Cote). The retroperitoneal spaces are potential spaces that are created by dissection to facilitate the identification, mobilization, and excision of pelvic retroperitoneal structures such as the ureters, iliac vessels, lymphatics, deeply invasive endometriosis, and residual ovaries. As the boundaries between structures of different embryological origins, the retroperitoneal spaces are generally avascular. These avascular planes are bordered by richly vascularized structures that can be easily disrupted by the dissection required to develop these space or by manipulation of the structures bordering these spaces. Bleeding

from the development of the pelvic retroperitoneal space is generally minimal and frequently, but not always, requires no specific hemostatic measures. Bleeding from mobilization or excision of retroperitoneal structures, such as during lymphadenectomy and dissection of cervical or intra-ligamental leiomyoma, has a greater propensity for blood loss and will frequently require standard hemostatic measures such as vascular clips, suture ligation, or electrosurgical methods for control. Although retroperitoneal bleeding occurs in a minority of the proposed procedures, the nature of bleeding within the retroperitoneal space is similar among the three procedures proposed.

The results of extensive bleeding in the retroperitoneal spaces include significant blood loss with dissection along the extraperitoneal fascial planes, as well as intraperitoneal collection, hematoma, and abscess. Patients with postoperative pelvic collections may present with symptoms of fever, rectal pain, or lower abdominal pain (13). Treatment often requires IR (interventional radiology) drainage and readmission for inpatient parenteral antibiotic therapy. The initial approach to hemostasis in the pelvis depends on the nature of bleeding encountered. When bleeding is encountered during pelvic dissection, evaluation of the extent and sources of bleeding, as well as its anatomic location and proximity to vital structures are the first requirements. The process of evaluating bleeding requires inspection of the bleeding sites augmented by irrigation, suctioning, and blotting with gauze. Through this process, the rate (minimal, mild, moderate, and severe)[1], distribution

[1] Estimated as blood loss in 10 second observation time as follows

1. minimal less than 2 cc
2. mild 2-3 cc
3. moderate 3-5 cc
4. severe >=5

(local vs. diffuse), anatomic site (i.e., if in close proximity to vital structures), and source of blood loss (small arterial, venous or capillary) is ascertained.

Objectives:

This study would examine the efficacy of Surgicel Snow vs. direct compression in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective in patients undergoing laparoscopic or robotic assisted laparoscopic hysterectomy. The intraoperative inclusion bleeding characteristics are minimal and mild retroperitoneal bleeding and moderate retroperitoneal bleeding that has been adequately reduced by standard surgical methods.

Design:

The proposed research method will use a randomized, concurrent control, no blinding. We are limiting our study to retroperitoneal dissection hysterectomy only to control for the expected variation in bleeding among the potential procedures. We propose to randomize 60 patients - 30 to the treatment group and 30 to the control group. The patients participating in this study would be patients scheduled for hysterectomy at Norwalk Hospital and Danbury Hospital under the direction of Dr. Thomas Rutherford, Dr. John Garofalo, and Dr. Robert Samuelson.

The patient population is drawn from throughout the State of Connecticut. Indications for hysterectomy will include benign, complex benign uterine and adnexal pathology, as well as gynecologic oncology cases. Vaginal hysterectomy procedures and open abdominal procedures will be excluded. Complex benign pathologies are those that are likely to require retroperitoneal dissection and or ureterolysis, (e.g., cervical leiomyoma, endometriosis, etc.

Peritoneal access for hysterectomy will include open laparotomy, standard multiport laparoscopy, and robotic assisted laparoscopy. All patients scheduled for indicated procedures will be screened for inclusion. Once consented, patients will be randomized to the control group or the treatment group. The control group will receive standard of care, and the treatment group will receive Surgicel Snow. A random number generator will be used to determine test vs. control in blocks of 10.

For patients with qualifying bleeding (rated on initial evaluation as at least "mild") who have been randomized to receive Surgicel Snow, a single thin layer of dry Surgicel Snow will be applied over the area of bleeding and positioned firmly in direct contact to the areas of bleeding with blunt surgical instruments. Surgicel Snow will be left in the cavity to be absorbed. Dry gauze will not be placed over the material. No adjuncts will be added to the enhance hemostasis, but patients with small arteriolar bleeding will have pressure maintained on the bleeding site for 60 seconds. Control patients will be managed with direct compression with gauze pads or laparotomy pads for four minutes. If hemostasis is not achieved by compression after four minutes, the source and rate of bleeding will be reevaluated and management will be determined by the surgeon. If the surgeon uses SurgicelSnow to achieve hemostasis at some point after 4 minutes, the patient will be included in the control group, but his/her data will be and flagged for the analysis. Hemostasis will be defined as the absence of free-flow bleeding, specified as no new appearance of blood from the bleeding site. Pinpoint or petechial bleeding that appears but does not grow, or saturation of blood into the hemostat that may have occurred prior to or during the application of hemostatic agent that did not spread during the observation period, will not be considered free-flow bleeding. Control and treatment patients who do

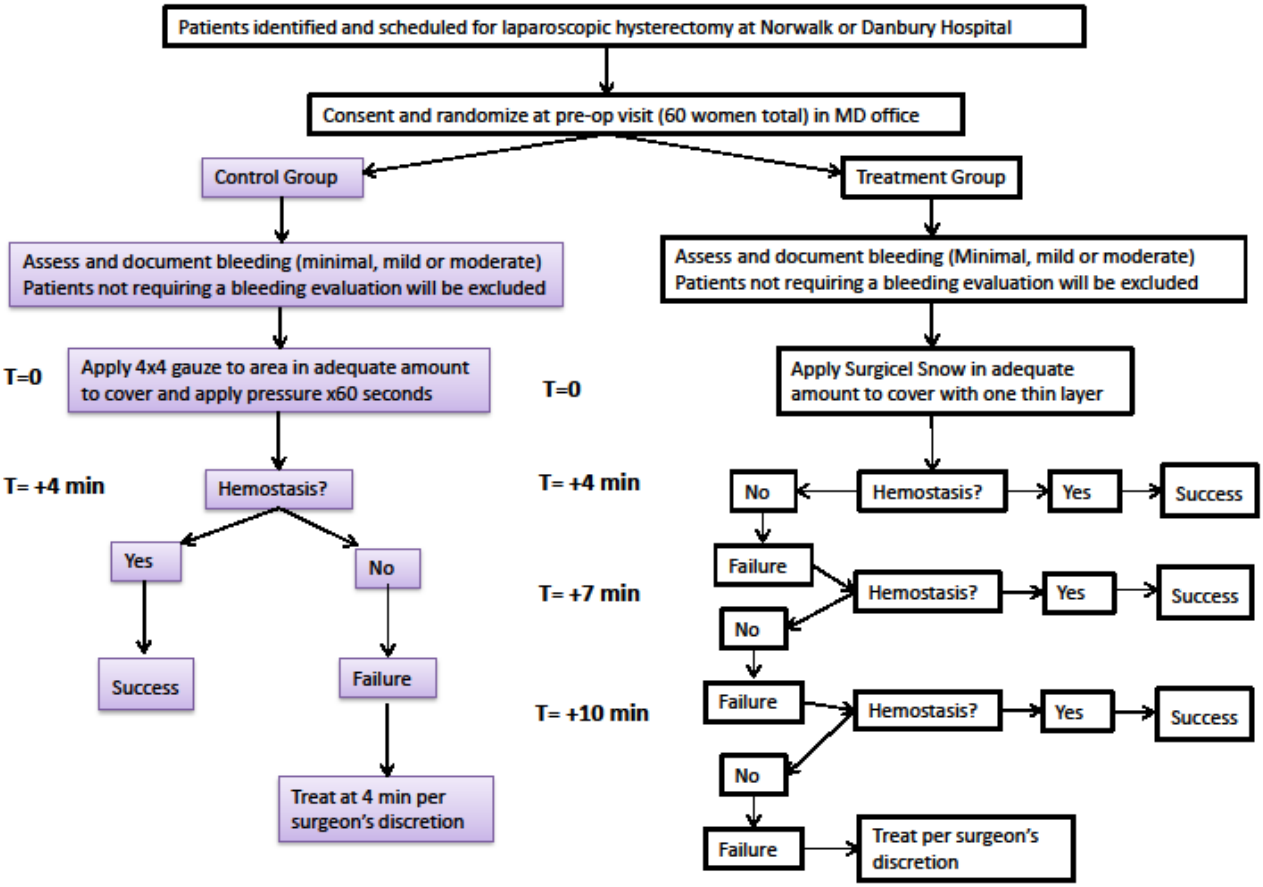
not require a topical agent to achieve hemostasis, thus not requiring a bleeding evaluation will be excluded from the study.

For control patients, hemostasis failures at 4 minutes will be managed as per judgment of the primary surgeon, most likely be the use of a topical sealant. For treatment patients, hemostatic failure at 4 minutes will be reassessed for rate of blood loss and if the rate of loss is estimated at less than 25 cc per minute, additional observations will be made at 7 and 10 minutes. If failure of hemostasis at 4 minutes with an estimated loss of ≥25 cc/min, patient will be managed as per judgment of surgeon. Persistent bleeding at the 10 minute observation point will be treated as per the surgeon's judgment. The nature of the bleeding will be recorded throughout the study.

Follow-up visits at 2 weeks (+/- 1 week) and 6 weeks (+/- 1 week) will be scheduled to determine if the patient has had a symptomatic collection or pelvic abscess. All subsequent procedures will be recorded, particularly those to manage bleeding.

The physician will take the time to describe the potential risks and benefits of the study as outlined in the consent form, to the patient. This will be reiterated by the assigned research coordinator. Only patients who have signed appropriate consent forms will be included in the study. Trained coordinators will be used and all standard safety protocols of the Clinical Research Department will be followed. The trained research coordinators will collect data at time of surgery. Should there be an adverse event, this will be documented and reported to the Principal Investigator (PI) and the IRB.

Intraoperative Flow Diagram



Selection and withdrawal of subjects:

Inclusion criteria:

1. Women ≥18 years of age

2. Women scheduled for standard multiport laparoscopic, single site laparoscopic, and robotic assisted laparoscopic hysterectomy.

2. Sites of surgery include Norwalk Hospital and Danbury Hospital.

3. Indication for surgery includes benign, complex benign, and malignant conditions.

4. Signed informed consent

Exclusion criteria:

1. Vaginal hysterectomy or open abdominal hysterectomy;

2. Congenital or acquired coagulation disorder including recent (within 7 days of surgery) therapeutic anticoagulation or use agents affecting platelet function, other than low dose aspirin. (Preoperative prophylactic heparin is not an exclusion criterion.)

3. Hysterectomy at the time of sacrocolpopexy.

4. Ovarian cancer

Participants may be withdrawn from the study at their request. Should a participant choose to withdraw from the study, no further clinical data will be collected on that patient and there will be no subsequent follow-up. In the event that a participant chooses to withdraw from the study, an additional study participant may be recruited to replace her.

Treatment of subjects:

Participants may continue all regular medications before and during the study.
The consent process will be incorporated into the consult visit prior to surgery.

Assessment of Efficacy:

The proposed clinical endpoints are time to hemostasis and failure to achieve hemostasis. Because multiple factors other than retroperitoneal bleeding contribute to the total intraoperative blood loss, we believe that the intraoperative estimated blood loss is not a pure indicator of the efficacy of a topical hemostatic agent for control of retroperitoneal bleeding. The determination of the primary endpoint of time to hemostasis is based upon a modification of the methods used by Hutchinson, et al in Cellulose (15). Secondary endpoints will include total operative time, intraoperative blood loss, blood transfusion, postoperative hemoglobin decrease, rate of postoperative symptomatic fluid collection,

postoperative pelvic abscess, and total cost for care from day of operation until six week (+/- 1 week) postoperative visit.

Assessment of Safety:

Whereas Surgicel Snow is generally used for minimal to mild bleeding from focal or widespread sources, should there be an adverse event related to the study conduction, this will be documented and reported to the study's PI. The PI will evaluate whether the adverse event involves risk to participants or others. If so, the PI may choose to change the protocol, change the consent form, require that all participants already enrolled be notified and/or re-consented, or suspend or terminate the study.

Statistical Analysis:

All data will be collected in paper format and transferred to an electronic database where all PHI will be removed and replaced with a study number. After conducting descriptive analyses, we will compare the treatment and control group on the primary and secondary outcomes. Multivariate analyses will be used to control for any observed variation between the study groups. Statistical significance will be assessed at $p < 0.05$.

It is anticipated that 60 participants will be enrolled in this study. The study will be terminated once all patients have completed their 6 week (+/- 1 week) follow-up post-surgery.

D**irect Access to Source Data Documents:**

The study's data collection sheet outlines when each data point will be collected. The study's PI, primary study coordinator, and co-authors will have access to all study data. These data will be used for study purposes only, and will be stored on a password-

encrypted drive at the Danbury Hospital Department of Research office. Data may be released to regulatory agencies as necessary, including the US Food and Drug Administration, Department of Health and Human Services agencies, BRANY, the Danbury Hospital IRB, accrediting agencies, and data safety monitoring boards.

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