Protocol

Title: Skin Adhesive Glue versus Skin Stapling Comparing CLOSure Effectiveness in Colorectal Cancer Surgery (CLOSE Trial)

Investigational product: 2-octyl cyanoacrylate (Leukoplast® Skin Adhesive, Chemence medical, Inc., USA)

Protocol number: NCT 06549803

Study design: A multicenter, non-inferiority, randomized controlled trial with two parallel comparison arms.

Number of participating centers: 3 centers of tertiary hospitals in South Korea (the Catholic Colorectal group)

STUDY PROTOCOL

From March 2022

Version 1.0

1. Background

Surgical site infection (SSI) represents one of the most common and costly postoperative complications following colorectal surgery, with reported incidence rates ranging from 4% to 15% depending on patient and procedural factors. SSI prolongs hospitalization, increase healthcare costs, and is associated with reduced patient qulity of life. Optimizing skin closure technique is a potentially modifiable determinant of SSI risk.

Skin stapling devices have long been the standard method for fascial and skin closure in abdominal surgery due to their speed, ease of application, and secure wound apposition. However, stapled wounds have been associated with greater postoperative pain, visible scarring, the need for subsequent staple removal, and in some series, higher SSI rates compared with suture-based alternatives.

Skin adhesives, including 2-octyl cyanoacrylate formulations (e.g., Leukosan Adhesive), form a flexible, watertight microbial barrier within seconds of application, eliminating the need for suture or staple removal and potentially reducing pain and improving cosmesis. Retrospective data have suggested that skin adhesive may be associated with lower SSI rates and reduced wound care costs compared with skin staples in colorectal procedures. However, prospective randomized controlled evidence comparing the two approaches specifically with respect to SSI incidence and cost-effectiveness in the laparoscopic colorectal cancer setting is currently absent from the literature.

This trial is designed to address this evidence gap by directly comparing skin adhesive with conventional skin stapling in patients undergoing elective laparoscopic or robotic colorectal cancer surgery at three high-volume tertiary referral centers.

2. Objectives

2.1 Primary objective

To demonstrate the non-inferiority of 2-octyl cyanoacrylate skin adhesive compared with conventional skin stapling with respect to the incidence of SSI within 30 days of surgery, assessed at the time of hospital discharge. SSI is defined according to Centers for Disease Control and Prevention criteria and includes both superficial incisional SSI and deep incisional SSI.

2.2 Secondary objective

To compare postoperative pain intensity (VAS score, 0-10) at postoperative days 1 and 3.

To compare length of hospital stay.

To compare the incidence of major postoperative complications within 30 days

To compare total operative times (minutes).

To compare total wound-related cost-effectiveness between the two groups, including device cost and wound dressing service cost.

To assess wound healing quality and patient satisfaction via a validated questionnaire administered at the outpatient clinic visit one week after discharge.

3. Methods

3.1 study design

This is a prospective, randomized, open-label, multicenter, non-inferiority trial. The trial is reported in

accordance with the standard protocol items

3.2. Eligibility Criteria

3.2.1 Inclusion criteria

1) Adults patients aged 19-80 years

2) ASA physical status classification I –III

3) Histologically confirmed or clinically suspected colorectal adenocarcinoma scheduled for elective curative resection by laparoscopic or robotic surgery

4) Written informed consent provided prior to enrollment

3.2.2 Exclusion criteria

1) Age over 80 years

2) Simultaneous resection of ≥2 abdominal organs

3) Known hypersensitivity to cyanoacrylate compounds

4) Uncontrolled diabetes mellitus

5) Emergency surgery

6) Inability or unwillingness to provide informed consent

3.3 Interventions

3.3.1. Experimental group – Skin adhesive

Following fascial closure, the skin edges are approximately with subcutaneous absorbable sutures and the epidermal layer is sealed with 2-octyl cyanoacrylate skin adhesive (Leukosan Adhesive). The adhesive is applied in three thin layers with 30 second drying intervals per manufacturer instructions. No additional wound ressing is applied.

3.3.2. Control group- conventional skin stapling

Following fascial closure, the subcutaneous layer is sutured by Vicryl and skin is approximately using a disposable skin stapler (Visistat Regular). Staples are placed at approximately 5mm intervals. Standard wound dressings are applied. Staples are removed at the discretion of the attending surgeon, typically a postoperative day 7-10.

3.4 Randomization

Randomization was performed using a computer-generated sequence created by the Department of Biostatistics at Seoul St. Mary's Hospital. Allocation was stratified by surgical approach (laparoscopic vs robotic-assisted) and tumor location (colon vs rectum). Within each stratum, block randomization with variable block sizes (4,6, and 8) ensured balance while minimizing predictability.

Allocation concealment was achieved through a centralized, web-based system managed by an independent biostatistician not involved in patient recruitment, enrollment, or outcomes assessment. Patients were randomized

the day before surgery in a 1:1 ratio to either the skin adhesive (Bond) or skin stapling (Stapler) group. Treatment allocation was concealed from all clinical staff until assignment.

3.5 Blinding

This was an open-label trial; patients and clinicians were not blinded. However, outcome assessors were blinded to treatment assignment. Physicians performed postoperative wound assessment on the day of discharge, and statistical analyses were conducted without knowledge of group assignment until completion.

The open-label design was necessary duet to the visibly distinct nature of the interventions. To minimize potential independent clinical nurse specialists, not involved in surgery or allocation, conducted wound evaluations and patient satisfaction surveys.

3.6. Outcomes

3.6.1 primary Endpoint

Incidence of SSI (superficial or deep incisional) within 30 days of surgery.

3.6.2 Secondary Endpoints

Outcomes	Measurement Tool	Time point
Pain score	Visual Analogue Scale (VAS, 0-10)	POD1, 2, and 3
Length of hospital stay	Day from surgery to discharge	At discharge
Operative time	Minutes (skin incision to wound closure)	Intraoperative
Major complications	Clavien-Dindo classification	Within 30 days
Cost effectiveness	Dressing supply cost, dressing service cost, Dressing frequency	Until discharge
Patient satisfaction and wound quality	Validated wound questionnaire, investigator wound assessment	1 week postop discharge OPD visit

3.7. Data Collection

Baseline variables will be collected preoperatively and include: age, sex, body mass index (BMI), ASA class, diabetes mellitus status, smoking history, prior abdominal surgery, preoperative serum white blood cell count (WBC), and C-reactive protein (CRP). Intraoperative data will include operative technique, type of resection, specimen extraction incision length, operative time, and estimated blood loss. Postoperative data will include histopathological results (tumor type, TNM stage), SSI occurrence, VAS pain scores, length of stay, complications, wound care resource utilization, and patient-reported satisfaction.

All data will be recorded on standardized case report forms (CRFs) and entered into a password-protected electronic database. Source data verification will be performed quarterly by the principle investigator.

3.8 Sample size calculation

Sample size was calculated in consultation with the department of Biostatics, Seoul St. Mary's Hospital. The reference SSI rate following skin stapling in laparoscopic colorectal surgery was estimated at 5.8%, based on published literature (Lee CS et al, 2020). The non-inferiority margin was set at 0.99 percentage points (i.e., the absolute difference in SSI rate between the skin adhesive and stapling groups must not exceed 0.99% in favor of stapling for the tissue adhesive to be declared non-inferior).

Using a one-sided Z test (unpooled), one-sided alpha of 0.025, and power of 80%, the required sample size is 152 participants per group, for a total of 304 participants. No adjustment for anticipated dropout has been made because both interventions are applied at the time of surgery; however, a 10% safety margin may be considered at the interim review.

Analysis of Non-Inferiority Tests of Two Independent Proportions

Numeric Results for Non-Inferiority Tests Based on the Difference: P1 - P2
H0: P1 - P2 ≥ D0. H1: P1 - P2 = D1 < D0. Test Statistic: Z test (unpooled)

Target Power	Actual Power	Target N1	N2	N	Ref. P2	P1|H0 P1.0	P1|H1 P1.1	NI D0	D1	Diff Alpha
0.80	0.80233	152	152	304	0.0580	0.0679	0.0100	0.0099	-	0.0480
										0.0250

Note: Direct Binomial distribution calculations for alpha and power were only used when both N1 and N2 were less
than 100. In all other cases, Normal approximation was used.

Report Definitions
Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.
Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 and N2 are the number of items sampled from each population.
N is the total sample size, N1 + N2.
P2 is the proportion for Group 2. This is the standard, reference, or control group.
P1 is the treatment or experimental group proportion. P1.0 is the largest treatment-group response rate that still yields a non-inferiority conclusion. P1.1 is the proportion for Group 1 at which power and sample size calculations are made.
D0 is the non-inferiority margin. It is the difference P1 - P2 assuming H0. D1 is the difference P1 - P2 assumed for power and sample size calcualtions.
Target Alpha is the input probability of rejecting a true null hypothesis. Actual Alpha is the value of alpha that is actually achieved.

Summary Statements
Sample sizes of 152 in group one and 152 in group two achieve 80% power to detect a non-inferiority margin difference between the group proportions of 0.0099. The reference group proportion is 0.0580. The treatment group proportion is assumed to be 0.0679 under the null hypothesis of inferiority. The power was computed for the case when the actual treatment group proportion is 0.0100. The test statistic used is the one-sided Z test (unpooled). The significance level of the test was targeted at 0.0250.

3.9 Statistical Analysis

All analyses will be performed using SPSS version 27.0 (IBM Corp) or R version 4.3 or later. The primary non-inferiority analysis will be conducted on both the per-protocol (PP) population and the intention-to-treat (ITT) population; non-inferiority will be claimed only if both analyses are concordant.

The primary endpoint (SSI rate) will be analyzed using a one-sided Z test for the difference in proportions, with the 95% confidence interval for the difference (skin adhesive minus stapling) reported. Non-inferiority will be concluded if the upper bound of the 95% confidence interval is below the pre-specified non-inferiority margin of 0.99 percentage points.

Continuous secondary endpoints (VAS, length of stay, operative time, cost) will be compared using the Student's t-test or Mann-Whitney U test as appropriate. Categorical variables (complication rates, patient satisfaction categories, pathological stage) will be analyzed using the chi-square test or Fisher's exact test. A two-tailed p-value of <0.05 will be considered statistically significant for all secondary comparisons.

4. Study Schedule

			Study Period					
		Enrollment	**Allocation**	**Post-allocation**				**Close-out**
	Time point	**-2 to 0 day**	**Operation day**	**Postoperative day 1**	**Postoperative day 2**	**Postoperative day 3**	**Discharge**	**First OPD f/u**
Enrollment	Eligibility screen	O						
	Informed consent	O						
	Randomization		O					
	Allocation		O					
Intervention	Experimental intervention		O					
	Control intervention		O					
Assessment	Demographical data	O						
	Medical history	O						
	Laboratory	O	O		O		O	
	Parameters of surgical procedure		O					
	VAS score		O	O	O	O		
	Documentation of SSI		O	O	O	O		O
	Documentation of other complication		O	O	O	O		O
	Length of hospital stay							O
	readmission							O
	Patient questionnaire							O
	Pathologic results							O
	Cost outcomes							O

5. Safety considerations

5.1 Anticipated Adverse Events

Both study interventions represent standard of care wound closure modalities routinely used in clinical practice. No additional risk is introduced beyond routine postoperative wound complications. Anticipated adverse events include:

- Wound dehiscence

- SSI (Superficial or deep incisional)
- Allergic or contact dermatitis (potential for tissue adhesive group)
- Staple-site pain or hypersensitivity (skin stapling group)

5.2 Stopping Rules and Withdrawal Criteria

An individual participant will be withdrawn from the study if:

- The participant withdraws consent at any time
- The participant receives wound-healing-modifying medications (immune-suppressants or systemic corticosteroids) not present at baseline
- The participant undergoes an unplanned additional abdominal surgery within the observation period

There are no predefined stopping rules for the overall trial, as both interventions carry minimal incremental risk beyond standard care.

5.3. Adverse Event Reporting

All adverse events will be recorded from the time of randomization through the 30-day follow-up visit. Serious adverse events (SAEs) will be reported to the IRB within 24 hours of the investigator's awareness and managed according to institutional and national regulatory guidelines.

Reference

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3. Merkow RP, Ju MH, Chung JW, et al. Underlying reasons associated with hospital readmission following surgery in the United States. *JAMA - J Am Med Assoc*. 2015;313(5):483-495. doi:10.1001/jama.2014.18614

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