Original Study

ANNALS OF SURGERY OPEN

OPEN

N-Butyl-2-Cyanoacrylate Adhesive Versus Absorbable Tacks in Laparoscopic Groin Hernia Repair: A Multicenter Randomized Clinical Trial

Clayton C. Petro, MD,* Benjamin K. Poulose, MD,† Michael J. Rosen, MD,* Alfredo M. Carbonell II, DO,‡ Adel G. El-Ghazzawy, MD,§ Jeremy A. Warren, MD,‡ Emanuele Lo Menzo, MD,§ Ajita S. Prabhu, MD,* David M. Krpata, MD,* Samuel Szomstein, MD,§ Vimal Narula, MD,† Crystal F. Totten, MD,‖ Kelly R. Haisley, MD,† Andrew C. Bernard, MD,‖ Henrik O. Berdel, MD,‖ Jessica K. Reynolds, MD,‖ Zachary D. Warriner, MD,‖ John S. Roth, MD‖

Objective: We aimed to determine whether n-butyl-2-cyanoacrylate (NB2C) adhesive is a safe and effective mechanism for nonpenetrating mesh and peritoneal fixation during laparoscopic groin hernia repair.

Background: Chronic pain after laparoscopic groin hernia repair has been associated with penetrating fixation, but there had been no US Food and Drug Administration–approved devices for nonpenetrating fixation in this context.

Methods: Patients undergoing laparoscopic transabdominal preperitoneal (TAP) or totally extraperitoneal (TEP) groin hernia repair with mesh at 1 of 5 academic medical centers were randomized to mesh (TAP/TEP) and peritoneal (TAP) fixation with NB2C adhesive or absorbable tacks. The primary outcome was improvement in pain (visual analog scale [VAS]) at 6 months. The noninferiority margin was 0.9 ($\alpha = 0.025$; $\beta = 80\%$). Recurrence, successful use of the device, quality of life, and rates of adverse events (AEs) were secondary outcomes.

Results: From 2019 to 2021, 284 patients were randomized to either NB2C adhesive or absorbable tacks (n = 142/142). Patient and hernia characteristics were comparable, and 65% were repaired using a TAP approach. The difference in VAS improvement at 6 months with NB2C adhesive was not inferior to absorbable tacks in intention-to-treat and per-protocol analyses, respectively (0.25 [95% CI, −0.33 to 0.82]; $P = 0.013$; 0.22 [95% CI, −0.36 to 0.80], noninferiority $P = 0.011$). There were no differences in secondary outcomes including recurrence, successful use of each device to fixate the mesh and peritoneum, quality of life, and additional VAS pain scores. Rates of adverse and serious AEs were also comparable.

Conclusions: NB2C adhesive is safe and effective for mesh fixation and peritoneal closure during laparoscopic groin hernia repair.

Key Words: inguinal hernia, groin hernia, TEP, TAP, adhesive, cyanoacrylate, tacks, fixation

INTRODUCTION

Compared to a traditional open tension-free Lichtenstein repair, minimally invasive approaches to groin hernia repair are well known to have less postoperative pain/paresthesias, earlier return to work/activity, less chronic postoperative inguinal pain (CPIP), and improved patient satisfaction for both the transabdominal preperitoneal (TAP) and totally extraperitoneal (TEP) laparoscopic approaches alike.[1–4] Still, there is evidence that penetrating fixation with staples or tacks during laparoscopic repairs can be associated with acute and chronic pain. In particular, CPIP—new pain lasting more than 3 months after repair—can be moderate or severe in approximately 5%–10% of patients.[5,6] Meanwhile, nonfixation of the mesh carries a risk of mesh migration, leaving patients prone to recurrence, mesh contraction, or erosion.[7–11] Even if penetrating mesh fixation is avoided, TAP repairs still require additional penetrating fixation for peritoneal closure after mesh placement.

An alternative to penetrating fixation during laparoscopic groin hernia repair is surgical adhesive, but none currently has a

*From the *Department of Surgery, Center for Abdominal Core Health, Cleveland Clinic Foundation, Cleveland, OH; †Department of Surgery, Center for Abdominal Core Health, The Ohio State University Wexner Medical Center, Columbus, OH; ‡Department of Surgery, Prisma Health Upstate, University of South Carolina School of Medicine, Greenville, SC; §Overlake Medical Center, Department of Surgery, Bellevue, WA; and ‖Department of Surgery, University of Kentucky College of Medicine, Lexington, KY.*

This study was funded by Advanced Medical Solutions Group PLC.

Trial Registration Number: NCT04009213

Disclosure: No authors were reimbursed for the preparation of this manuscript. Dr Petro discloses consulting fees from BD, Surgimatix, and Advanced Medical Solutions. Dr Poulose discloses salary support from the ACHQC and research support from BD. Dr Rosen discloses salary support from the ACHQC and is a board member of Ariste Medical with stock options. A.M. Carbonell II discloses honoraria from WL Gore and Associates, Intuitive Surgical, Ethicon, Inc, Medtronic, and Deep Blue Medical Advances. Dr Warren discloses honoraria from Intuitive Surgical, Ethicon, and Johnson & Johnson. Dr Lo Menzo discloses honoraria for being an Advisory Board Member of Diagnostic Green. Dr Prabhu is a consultant for Verb Surgical and CMR Surgical, as well as a speaker and research support for Intuitive Surgical. Dr Roth discloses relationships with Becton Dickinson (grant and consultant), WL Gore (grant), Advanced Medical Solutions (grant), Abbvie (grant and consultant), and Medtronic (consultant). The remaining authors have no disclosures.

SDC *Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).*

Reprints: Clayton C. Petro, MD, Center for Abdominal Core Health, Digestive Disease and Surgery Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, A-100, Cleveland, OH 44195. E-mail: petroc@Ccf.Org

Annals of Surgery Open (2024) 3:e462

Received: 10 January 2024; Accepted 17 June 2024

Published online 15 July 2024

DOI: 10.1097/AS9.0000000000000462

US Food and Drug Administration (FDA)–approved indication for this purpose in the United States. Cyanoacrylate polymers are one such adhesive with which surgeons have grown familiar, given their use in topical skin closures since the late 1990s.[12] Now, a novel device has been designed for the laparoscopic deployment of n-butyl-2-cyanoacrylate (NB2C, LIQUIFIX FIX8) to fixate mesh and—when applicable—close the peritoneum during laparoscopic inguinal hernia repair. Following CE-marking in the European Union, independent evaluations of the product have found it to be safe and effective in this context.[13,14] In this multicenter randomized clinical trial, we aim to evaluate whether NB2C adhesive is not worse than penetrating fixation with absorbable tacks, specifically in regards to postoperative pain improvement after laparoscopic groin hernia repair. Safety, efficacy, and quality of life are important secondary outcomes and will be monitored in order to apply for an FDA-approved indication for use.

METHODS

Study Design and Oversight

This study was a single-blinded multicenter randomized parallel-group trial designed to evaluate the clinical performance and safety of the NB2C adhesive device (LIQUIFIX FIX8) in patients undergoing laparoscopic groin hernia repair. The study was registered with the FDA as an investigational device exemption trial (#G190018), ClinicalTrials.gov (NCT04009213), and was conducted and reported in accordance with the Consolidated Standards of Reporting Trials guideline.[15] Ethical approval for the study was granted by the institutional review board at each of 5 participating US sites where a prespecified study-specific monitoring plan was maintained. A clinical events committee met regularly to assure timely and accurate reporting of adverse events (AEs). A comprehensive protocol is provided (Supplement 1 http://links.lww.com/AOSO/A381). There were 2 notable amendments to the protocol. First, the descriptions for recording the precise location of adhesive and tack deposition were changed after May 2020. Finally, remote/virtual follow-ups were permitted for visits after 14 days due to the COVID-19 pandemic.

Enrollment

Eligible patients were consenting adults at least 22 years old (per FDA) and had either a primary or recurrent unilateral or bilateral inguinal or femoral hernia amenable to a laparoscopic TAP or totally extraperitoneal (TEP) groin hernia repair with a porous mesh (≥4×6 in: 3D Max, 3D Max Light, Bard, Inc; Parietex 2D TEC, Parietex TET 3D, Medtronic) by 1 of 21 surgeons. Patient demographics, comorbidities, medications (including opioids), operative history, and operative details were recorded. Once the groin dissection was complete, patients were randomized intraoperatively at a 1:1 ratio based on randomly permutated blocks per site to the investigational adhesive device or an absorbable tacker (AbsorbaTack, Medtronic) and were followed for 1 year.

Surgical Intervention

Presurgical assessment and operative interventions for laparoscopic TEP and TAP groin hernia repair were conducted according to the investigational sites' standard of care up until the point of mesh fixation (TEP/TAP) and peritoneal closure (TAP) when patients were randomized. For patients undergoing bilateral repairs, the initial randomization was also applied to the contralateral repair.

Patients randomized to the experimental arm underwent mesh fixation and peritoneal closure—when necessary—utilizing the NB2C adhesive device. Surgeons were trained to use the adhesive device before enrollment and clinical cases were proctored until they were comfortable (Supplement 1 http://links.lww.com/AOSO/A381). Briefly, the experimental device deploys permanent adhesive, an NB2C monomer in liquid form. This is supplied in a thin-walled, sealed glass vial by a laparoscopic 5-mm-diameter cannula, with a handle at the proximal end incorporating a loading chamber, filter, piston chamber, and trigger. The distal tip of the device is open to allow the adhesive to be dispensed from it (Fig. 1). After drying the surgical field, drops of adhesive anchors were serially deployed on the mesh/tissue interface, which was held in place for 10 seconds following deposition. Mesh fixation points were at the discretion of the surgeon and could occur anywhere on the prosthetic, including below the inguinal ligament in the triangles of "doom" and "pain." For peritoneal flap closure during TAP procedures, intra-abdominal pressure was dropped to 8 mm Hg. The adhesive was then deployed on the superior flap before approximating the inferior flap to secure the tissue/tissue interface. The quantity and location of adhesive deposition were documented for each patient. Any unintended deposition of adhesive was documented and removed.

Patients randomized to the control arm underwent mesh fixation ± peritoneal closure with an absorbable tacking device (Absorbatack) according to the standard of care provided by

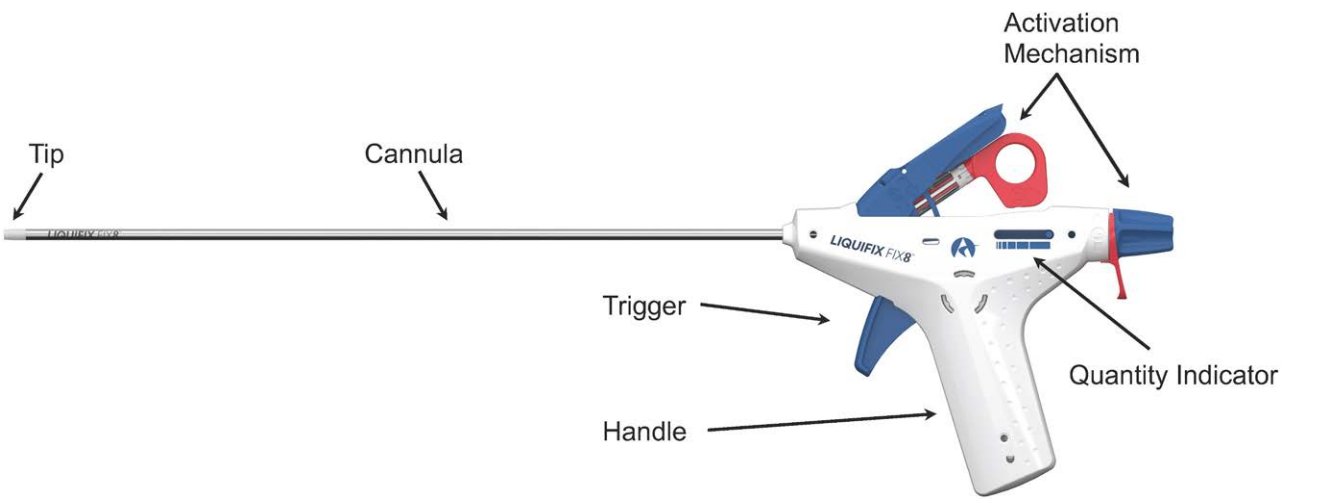

FIGURE 1. LiquiFix Fix8 device.

TABLE 1.

Patient Demographics, Comorbidities, and Hernia Characteristics

Randomization	NB2C (n = 142)	Absorbable Tacks (n = 142)
Demographics		
Age, y	61 (53.00–69.00)	59 (50.00–69.00)
Gender (male)	132 (93%)	138 (97%)
Race		
White	128 (90%)	121 (86%)
Black or African American	13 (9.2%)	16 (11%)
Asian	1 (0.7%)	3 (2.1%)
Multiracial	0	1 (0.7%)
Ethnicity		
Hispanic or Latino	4 (2.8%)	4 (2.8%)
Comorbidities		
Body mass index, kg/m^2	25.8 (24.1–28.1)	25.3(23.1–28.2)
Cardiovascular disease	70 (49%)	57 (40%)
Respiratory disease	34 (24%)	26 (18%)
Endocrine disease	28 (20%)	23 (16%)
History of substance abuse	17 (12%)	7 (5%)
Immunosuppression	5 (3.5%)	4 (2.8%)
Hernia characteristics		
Previous groin hernia repair	39 (28%)	29 (20%)
1	31 (22%)	27 (19%)
2	5 (3.5%)	1 (0.7%)
≥3	1 (0.7%)	1 (0.7%)
Bilateral	53 (37%)	62 (44%)
Left	91/195 (47%)	98/204 (48%)
Right	104/195 (53%)	106/204 (52%)
Multifocal	24/195 (12%)	33/204 (16%)
Direct	70/194 (36%)	90/204 (44%)
Indirect	124/194 (64%)	114/204 (56%)
Femoral	4/195 (2%)	2/204 (1%)
Primary or largest <3cm	94/195 (48%)	108/204 (53%)
Primary or largest ≥3cm	101/195 (52%)	96/204 (47%)

Continuous variables are presented as median and interquartile range, and categorical variables are presented as percentages.

participating surgeons. Likewise, the quantity and location of tack deployment were documented for each patient.

A deidentified digital photograph was taken to document each mesh fixation and peritoneal closure. Any deviation or supplementation from the randomized arm for mesh or peritoneal fixation was documented in order to perform intention-to-treat and per-protocol analyses. Additional details regarding the procedures and use of the experimental device can be found in Supplement 1 http://links.lww.com/AOSO/A381.

Study Outcomes and Data Collection

Notably, while patients were masked to the intervention, patient-reported outcomes were collected and patient assessments were performed by surgeons and coordinators who were not blinded to the intervention. The primary outcome of the study was the improvement in pain as measured by the visual analog scale (VAS, 0 = no pain to 10 = most pain imaginable) from the worst pain experienced within 1 month of the screening visit to 6 months after hernia repair. Secondary efficacy outcomes included hernia recurrence, successful use of each device to fixate the mesh and peritoneum as reported by the surgeon, quality of life, and additional VAS pain scores. Postoperative opioid consumption was also documented. A secondary safety endpoint included the capture of AEs. Hernia recurrence was assessed at 14 days, 3 and 6 months, and then as needed up to 1 year by physical exam and confirmed by ultrasound if necessary. For patients seen virtually, any concern for a bulge or recurrence prompts an in-person visit and clinical assessment or imaging when necessary. Quality of life was assessed using the Carolinas comfort scale (CCS).[16] Patient questionnaires and AEs were accrued preoperatively, postoperative days 0/1, 7, and 14, 1, 3, 6, and 9 months, and 1 year (see Supplement 1 http://links.lww.com/AOSO/A381, Table 2).

Power Calculation

For the primary effectiveness endpoint on change from baseline pain (worst pain experienced within 1 month of screening visit) to 6 months on VAS, a 2-sample *t* test was used to calculate the sample size using PASS 15 power analysis and sample size software (NCSS LLC, UT, USA). The mean change was assumed to be the same, and the standard deviation was assumed to be the same at 2.4 for both the NB2C adhesive and absorbable tacks for TAP and TEP laparoscopic groin hernia repair. The noninferiority margin was set to 0.9, alpha at 0.025, and the target statistical power at 80%.[17,18] Under these assumptions, a total sample size of 226 subjects was required for the study. With an attrition rate of about 20%, a total of 284 subjects (142 per arm) were enrolled.

Statistical Analysis

Block sizes of 4 and 6 were used for randomization. There were no planned interim analyses performed other than progress reports submitted to the FDA and local institutional review boards. To test the change from baseline to 6-month VAS between NB2C adhesive and absorbable tacks, a general linear model (ANCOVA) was run using SAS Proc GLM, with the treatment arm and laparoscopic repair technique (TAP or TEP) as covariates (SAS Institute, Inc, NC, USA). A *P* value of <0.025 would be considered evidence that NB2C adhesive is not inferior to the absorbable tacks. The study would be considered successful if both PP and ITT analyses on the primary efficacy endpoint showed significance at 0.025. The 95% confidence interval would be calculated for the difference in changes from baseline (screening visit) to the 6-month visit on VAS between NB2C adhesive and absorbable tacks. Tipping point analysis would also be performed to evaluate the impact of missing data.

To test the secondary outcomes and safety endpoints, a binomial noninferiority test was run using SAS Proc Freq with the Farrington-Manning method on the per-protocol set. A *P* value of <0.025 from the binomial noninferiority test would be considered evidence that NB2C adhesive is not inferior to absorbable tacks. The confidence interval on the difference between the rates would be reported, and noninferiority is indicated if the upper limit of the confidence interval is less than the noninferiority margin. Intention-to-treat analyses would be performed for the three secondary endpoints with hypothesis statements as supporting sensitivity analyses.

Planned subgroup analyses were performed for the primary endpoint with respect to hernia size (<3 or ≥3 cm), gender, age, femoral versus inguinal, direct versus indirect, primary versus recurrence, unilateral versus bilateral, TEP versus TAP, in-person versus virtual follow-up, and multifocality of the hernia.

RESULTS

Between August 2019 and December 2021, 329 patients were enrolled and 284 were randomized to NB2C adhesive or absorbable tack fixation (Fig. 2). Patient demographics and comorbidities were comparable between groups, as were the groin hernia characteristics in regards to laterality, multifocality, and recurrent nature (Table 1). Laparoscopic approach distributions (TAP/TEP) and mesh choices/sizes were similar though there were more concomitant umbilical hernias repaired in the absorbable tack arm (*P* = 0.01; Table 2). In

TABLE 2.

Operative Details

Randomization	NB2C (n = 142)	Absorbable Tacks (n = 142)	*P*
TAP	94/142 (66%)	92/142 (65%)	0.80
TEP	48/142 (34%)	50/142 (35%)	
Concomitant umbilical hernia repair	10/142 (7%)	24/142 (17%)	0.01
Other concomitant procedure	6/142 (4%)	5/142 (4%)	0.76
Mesh			
3DMax	158/195 (81%)	167/204 (82%)	0.25
3DMax Light	6/195 (3%)	2/204 (1%)	
Parietex 2D	0	2/204 (1%)	
Parietex 3D	31/195 (16%)	33/204 (16%)	
Length, in	4.3 (4.00–4.90)	4.7 (4.00–4.90)	0.97
Width, in	6.0 (6.00–6.80)	6.25 (6.00–6.80)	0.36
Mesh fixation			
Per protocol	142/142 (100%)	142/142 (100%)	1
Location, all time points			
Around the edges of the defect	87/195 (45%)	NA	NA
Over iliac vessels	113/195 (58%)	NA	NA
Other	20/195 (10%)	35/204 (17%)	0.046
Location before May 2020			
Superior mesh border	28/28 (100%)	34/34 (100%)	1
Medial over pectineal ligament	25/28 (89%)	28/34 (82%)	0.44
Medial over pubis	23/28 (82%)	24/34 (71%)	0.29
Pelvic floor	8/28 (29%)	NA	NA
Adjacent to femoral nerve	14/28 (50%)	NA	NA
Over the inferior epigastric vessels	14/28 (50%)	NA	NA
Location after May 2020			
Superomedial	162/167 (97%)	157/170 (92%)	0.06
Superolateral	156/167 (93%)	150/170 (88%)	0.10
Cooper's Ligament	146/167 (87%)	153/170 (90%)	0.45
# Mesh applications (glue or tacks)	18.5 (12.00–24.00)	5 (4.00–8.00)	<0.001
LiquiFix Fix8 volume used, g	0.23 (0.15–0.30)	NA	NA
Peritoneal closure (TAP)			
# Peritoneal applications*	20 (14.00–33.00)	9 (7.00–14.00)	<0.001
Per protocol	82/94 (87%)	84/92 (91%)	0.37
LiquiFix Fix8 volume used, g	0.25 (0.18, 0.41)	NA	NA
Inadvertant applications	1/142 (0.7%)	2/142 (1.4%)	1

Continuous variables are presented as median and interquartile range, and categorical variables are presented as percentages.

*Glue, tacks, sutures, and staples are used to close the peritoneum.

Bold values indicate statistical significance ($P < 0.05$).

regard to mesh fixation, NB2C adhesive applications were deployed over neurovascular structures where penetrating tacks are not applicable. There were no differences in opioid or nonopioid analgesic usage between groups preoperatively or postoperatively up to 1 year (Supplement 2 http://links.lww.com/AOSO/A382).

For the primary endpoint of pain difference as measured by VAS, from worst pain preoperatively to pain at 6 months after surgery, NB2C adhesive was found to be not inferior to absorbable tacks by both intention-to-treat and per-protocol analyses (Table 3). Additionally, no other time point revealed an inferior degree of pain in the adjusted per-protocol analysis (Fig. 3).

Secondary outcomes included hernia recurrence, success of mesh and peritoneal fixation, and quality of life. In regard to hernia recurrence at 6 months, there was one recurrence in the NB2C adhesive arm and 2 in the absorbable tack arm, satisfying noninferiority by intent-to-treat and per-protocol analyses (Table 3). Notably, there were no additional recurrences reported from 6 months to 1 year. While 100% of patients adhered to the randomization for mesh fixation, peritoneal fixation during TAP repairs was successful utilizing the randomization device alone in 87% of adhesive cases and in 91% of tack cases ($P = 0.37$). Details regarding adjuncts for peritoneal closure are summarized in our Consolidated Standards of Reporting Trials diagram (Fig. 2), and summarize the use of supplemental tacks, staples, or sutures to achieve adequate tissue approximation. NB2C adjuncts were required due to clogging of the device during deployment (n = 2) or inadequate tissue approximation (n = 10). Absorbable tack adjuncts were required due to either inadequate tissue approximation (n = 6) or inadequately deployed tacks due to bending of the shaft (n = 2).

Next, there were no significant differences in quality of life as measured by total CCS scores for up to 1 year (Table 3), including individual domain scores (Fig. 4A–4D). There is a statistically significant difference in CCS scores at 6 months though the difference seems both clinically negligible and is not reproduced at any further time points. Longitudinal modeling also found small differences at 2 weeks and 3 months driven by a few data points with large values, while the vast majority of values in both arms were 0 or close to 0 indicating favorable quality of life (Supplement 3 http://links.lww.com/AOSO/A383). Finally, there were no differences in rates of device or procedure-related adverse and serious AEs summarized in Table 3.

While a comprehensive list detailing AEs is provided in Supplement 4 http://links.lww.com/AOSO/A384, the novelty of the NB2C adhesive device in this operative context warrants characterization of the serious AEs either related or possibly related to the study device. These included 1 case of ilioinguinal neuralgia that began 6 months after surgery and required an outpatient nerve block along with medical therapy and a separate patient with iliohypogastric neuralgia requiring 2 inpatient admissions for medical pain control. Next, there was 1 incident of bowel obstruction where a loop of jejunum was adherent to the cecum and required laparoscopic adhesiolysis. Another patient presented 3 months after repair with a purulent fluid collection

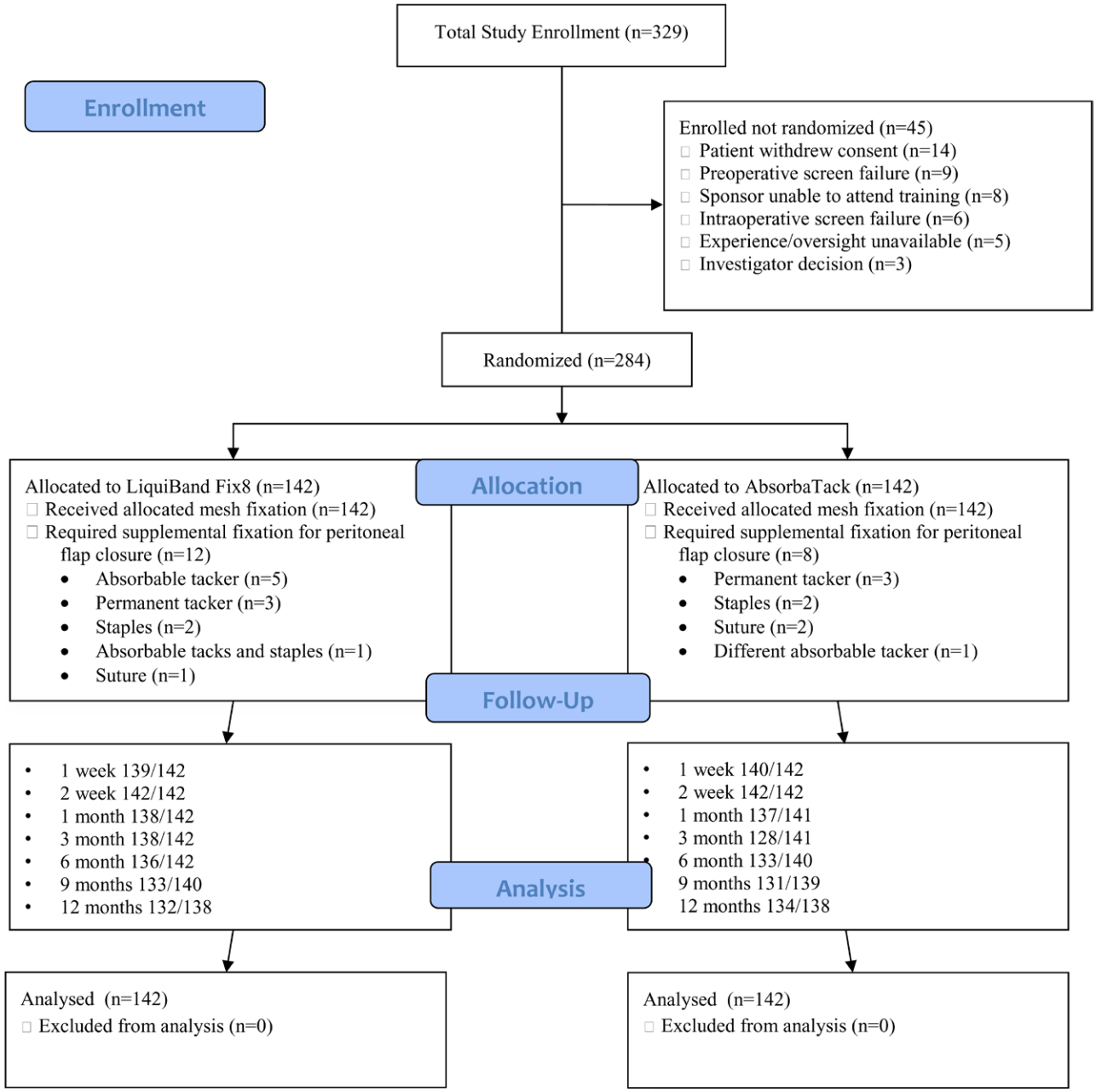

FIGURE 2. Consolidated Standards of Reporting Trials diagram.

adjacent to the mesh requiring IR drainage. Finally, one patient had a recurrence at 3 months requiring reoperation to repair it. Notably, all events were deemed "possibly related" to the device.

Finally, prespecified multivariate subgroup analyses to identify relationships with improvement in VAS (pre-op to 6 months) found no independent associations with hernia size (<3 or ≥3 cm), gender, age (<61 or ≥61), femoral versus inguinal, direct versus indirect, primary versus recurrence, unilateral versus bilateral, TEP versus TAP, in-person versus virtual follow-up, and concomitant ventral hernia repair (all $P > 0.05$) for intention-to-treat and per-protocol analyses (Supplement 5 http://links.lww.com/AOSO/A385).

DISCUSSION

For patients undergoing laparoscopic groin hernia repair with preperitoneal mesh, the NB2C adhesive device (LIQUFIX FIX8) was found to be similar to absorbable tacks in regard to pain improvement 6 months after surgery. Secondary outcomes, including additional pain scores, quality-of-life assessments, and recurrence data, were similar during the first year, as were rates of AEs. Furthermore, the experimental adhesive allowed for mesh and peritoneal fixation comparable to the tacking device (control). The NB2C adhesive device appears to be a safe and effective option for laparoscopic inguinal hernia repair that avoids the need for penetrating fixation.

The noninferiority design of the trial is the threshold for premarket approval by the FDA, whose principal interests are in the safety and efficacy of the device. Conversely, a device does need to be superior to the current standard of care in order to achieve an indication for use. In an era where most new devices—particularly in the realm of hernia repair—rely on 510k approval and do not invest in randomized clinical trials, we think that this endeavor is refreshing and commendable.

Choosing pain improvement at 6 months as a primary outcome was important, not only to confirm that NB2C adhesive

TABLE 3.

Outcomes

	Intention-to-Treat			Per Protocol		
	NB2C (n = 142)	**Absorbable Tacks (n = 142)**	***P***	**NB2C (n = 131)**	**Absorbable Tacks (n = 133)**	***P***
Change in VAS from 1 to 6 mo						
n	136	133		131	130	
Median, IQR	−4.5 (−6.8, −3.0)	−5.0 (−7.0, −3.0)		−4.7(−7.0, −3.0)	−5.0 (−7.0, −3.0)	
Mean, ±SD	−4.9 ± 2.5	5.1 ± 2.3		−4.9 ± 2.5	−5.1 ± 2.3	
Noninferiority,* difference margin 0.9, 95% CI	0.25 (−0.33 to 0.82)		0.013	0.22 (−0.36 to 0.80)		0.011
Hernia recurrence at 6 mo						
n	141	140		131	132	
Recurrences	1 (0.7%)	2 (1.4%)		1 (0.8%)	2 (1.5%)	
Noninferiority,* difference margin 10%, 95% CI	−0.7% (−3.1 to 1.7%)		<0.001	−0.8% (−3.3 to 1.8)		<0.001
Carolinas comfort scale (total), median (IQR)						
1 wk	12 (5 to 22)	13 (5 to 24)	0.75	12 (5 to 24)	12 (5 to 23)	0.92
2 wk	3 (0 to 11.5)	4 (1 to 12)	0.21	3 (0 to 12)	4 (1 to 11)	0.41
1 mo	2 (0 to 6)	1 (0 to 5)	0.98	2 (0 to 6)	1 (0 to 5)	0.97
3 mo	0 (0 to 1)	0 (0 to 2)	0.07	0 (0 to 1)	0 (0 to 2)	0.08
6 mo	0 (0 to 0)	0 (0 to 1)	0.007	0 (0 to 0)	0 (0 to 1)	0.01
9 mo	0 (0 to 0)	0 (0 to 1)	0.33	0 (0 to 0)	0 (0 to 0)	0.42
1 y	0 (0 to 0)	0 (0 to 0)	0.90	0 (0 to 0)	0 (0 to 0)	0.94
Adverse events						
Related to study device	34/142 (24%)	43/142 (30%)	0.23	32/131 (24%)	38/133 (29%)	0.45
Related to procedure	51/142 (36%)	61/142 (43%)	0.22	48/131 (37%)	56/133 (42%)	0.36
Serious adverse events						
Related to study device	5/142 (3.5%)	4/142 (2.8%)	0.73	5/131 (3.8%)	4/133 (3%)	0.72
Related to procedure	9/142 (6.3%)	10/142 (7%)	0.81	9/131 (6.9%)	9/133 (6.8%)	0.97
SAE requiring reoperation or procedure	6/142 (4.2%)	11/142 (7.7%)	0.21	6/131 (4.6%)	11/133(8.3%)	0.22

Bold values indicate <0.05. Change in VAS = multivariable linear regression adjusting for laparoscopic repair. Hernia recurrence = Farrington-Manning test. CCS = Wilcoxon rank-sum test. AEs = χ^2 test.
*Based on the noninferiority Farrington-Manning test.
IQR indicates interquartile range; SAE, significant adverse event.

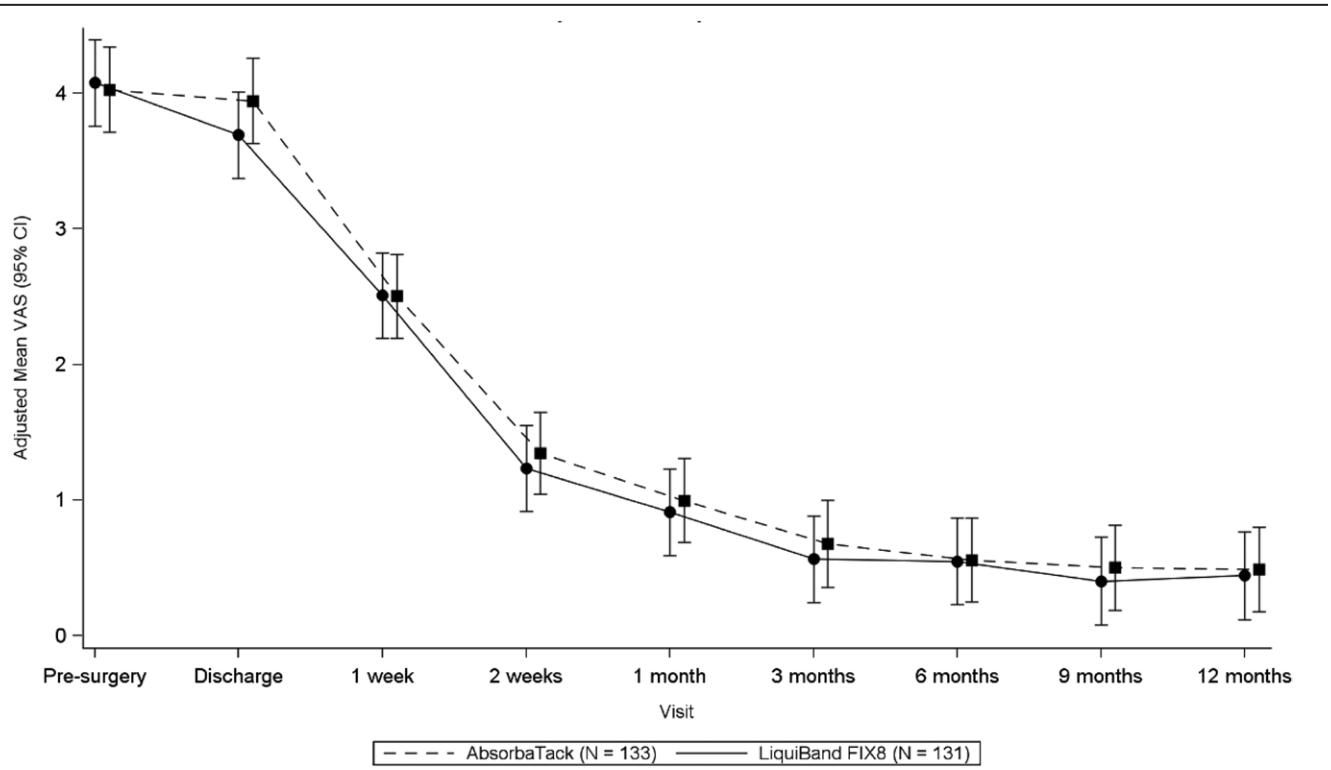

FIGURE 3. Adjusted VAS per protocol. Adjusted via a repeated measure mixed model of VAS at all standard visits adjusted for study site, laparoscopic technique, analgesic use, and other pain management.

patients could expect a similar postoperative recovery but also to capture pain scores beyond 3 months, after which pain is considered chronic. Specifically, CPIP is defined as new or different groin pain lasting 3 months after repair, and whether or not avoiding penetrating fixation is associated with less CPIP after laparoscopic inguinal hernia repair has been judiciously

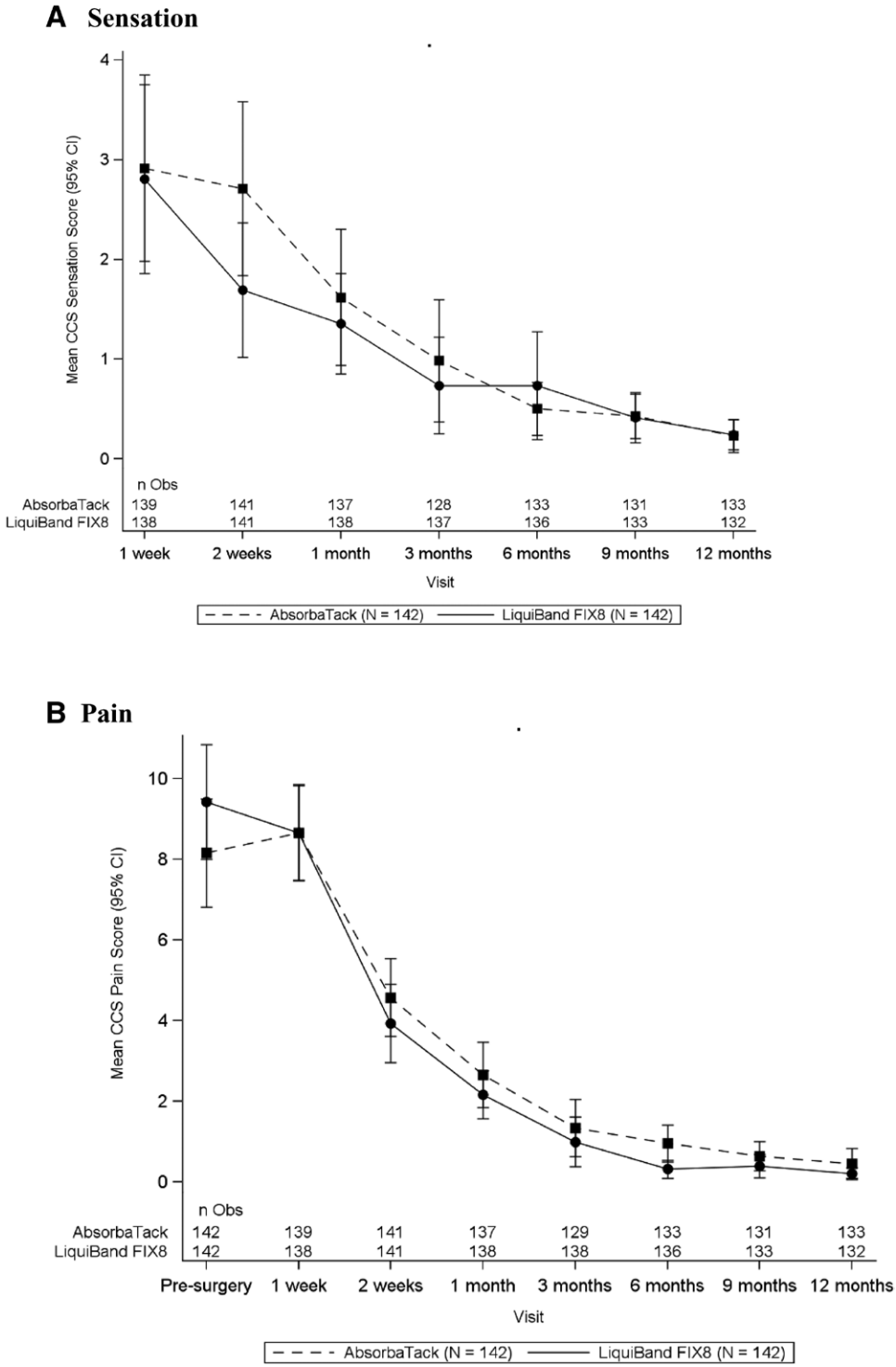

FIGURE 4. A–D, Carolinas comfort scale scores intention-to-treat.

investigated. A 2021 meta-analysis identified 15 randomized clinical trials comparing glue with mechanical mesh fixation in this setting. Thirteen of those studies reported on rates of chronic pain and found that rates of CPIP favored glue fixation (3.0% vs 7.5%; relative risk, 0.36 [95% CI, 0.19–0.69]; $P = 0.002$), particularly in the 8 homogenous patient-blinded studies (relative risk, 0.43 [95% CI, 0.27–0.86]; $P = 0.01$). Notably, the authors found no difference in the rates of CPIP when comparing the 6 trials assessing fibrin sealant versus 4 trials with cyanoacrylate.[19] While the noninferiority design of this trial was not meant to show the superiority of the adhesive, our results do not suggest that the absorbable tacks incur more acute or chronic pain, as other trials have. Whether this discrepancy is related to absorbable versus permanent tacks, the number of tacks deployed, or technical factors such as performing a more cephalad peritoneal flap (away from groin innervation) would be purely speculative. While the number of tacks used has been previously associated with CPIP, limited

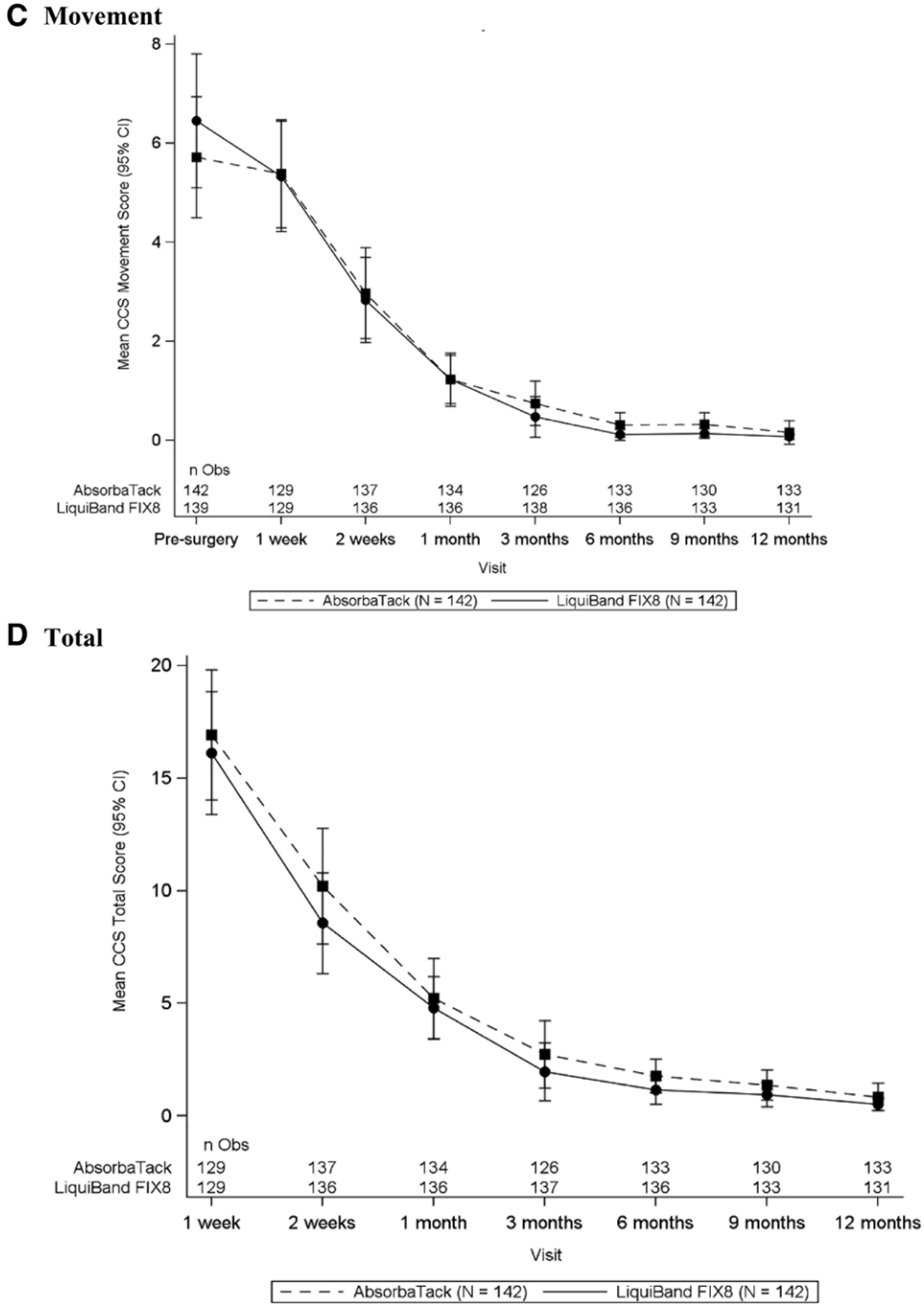

FIGURE 4. Continued

data suggest that there is no benefit of absorbable tacks over permanent in this context.[20,21] Still, many surgeons anecdotally rely on absorbable tack fixation in this context, perhaps exposing unconscious bias against permanent penetrating fixation. The absence of a difference in pain improvement between our comparison of permanent NB2C adhesive and absorbable tacks highlights an important consideration in the design and subsequent clinical interpretation of these results. Had permanent tacks been used as a control in an attempt to show the superiority of NB2C adhesive in regards to postoperative pain improvement, similar pain results would leave surgeons to wonder whether or not absorbable mechanical fixation may actually be superior to permanent adhesive. Instead, these results show that the NB2C adhesive device is at least not inferior to absorbable mechanical fixation in regards to pain improvement, and the consistency of those pain scores at 6, 9, and 12 months would suggest similar rates of CPIP as well.

Another legitimate consideration is whether any fixation is necessary during these repairs. First, it is important to mention that for TAP repairs (65% of randomized cases), even if fibrin glue or no fixation is used for mesh placement, the peritoneal flap still requires closure. While instances of mesh migration, shrinkage, and erosion certainly occur, it is fair to characterize these as rare events that have been described with and without penetrating fixation.[9,22,23] While nonpenetrating adhesive mesh fixation seems to be a reasonable compromise, a Swedish Hernia Registry Study of 25,190 laparoscopic inguinal hernia repairs found that the use of standard polypropylene

mesh without any fixation had the lowest rate of reoperation for recurrence.[24] Certainly, the size of the hernia compared to the size of the mesh placed and the adequacy of the dissection/overlap play a role in the importance of mesh fixation. However, the aforementioned registry does not record mesh size, the extent of dissection, or the reason a surgeon opted for a specific mesh/fixation combination, thus leaving room for selection bias (ie, perhaps cases without fixation were the least complex with the most adequate mesh overlap). As such, while nonfixation may be safe in some instances, those remain to be clearly defined in this data set and still do not address the problem of peritoneal closure during TAP repairs. Another important takeaway from the Swedish registry analysis—confirmed by a separate meta-analysis—is the vulnerability of lightweight mesh in regards to recurrence risk, particularly for direct defects.[25] This is an important detail in order to contemplate the role of self-fixating mesh (ie, ProGrip and Medtronic) as another option for "nonpenetrating" fixation. While ProGrip mesh offers an alternative method of nonpenetrating fixation to adhesive, it is important to recall that once the absorbable polylactic acid microhooks are resorbed at 1 year, the residual microporous polypropylene scaffold is a low-weight (38 g/m^2) material.[26] Ultimately, thoughtful consideration of the myriad options for mesh and fixation (ie, no fixation, fibrin sealant, self-fixating mesh, etc) leads surgeons to acknowledge that the mesh/NB2C adhesive arm of our trial is both highly versatile and consistent with what previous literature has identified as optimal.

Discussing the role of NB2C adhesive for minimally invasive groin hernia repair in 2024 is remiss without mentioning the robotic approach.[27] Robotic TAP allows surgeons to avoid tack fixation by using sutures to fixate the mesh and peritoneum, a task that is feasible but cumbersome laparoscopically. Randomized data from the RIVAL trial found comparable pain, quality of life, and recurrence outcomes for robotic and laparoscopic TAP repairs, which used variations of penetrating fixation—suture and permanent tacks, respectively.[28,29] As underscored by our protocol deviations for peritoneal tacks, a thin peritoneal flap can be prone to tearing with the use of penetrating fixation. While NB2C adhesive could also be applied to any robotic TAP repair as a method for nonpenetrating mesh and peritoneal fixation akin to our laparoscopic repairs, it is particularly important as an available adjunct for instances when a peritoneal flap is particularly thin and prone to tearing.

There are several limitations worth mentioning. The novelty of the adhesive device for participating surgeons may have accentuated instances where adjuncts were needed for peritoneal closure during TAP. That said, compared to a standard tracking device with which surgeons were familiar, the rate of per-protocol applications was similar between treatment arms and provides pragmatic reassurance for those anticipating adoption of the device. While COVID-19 slowed recruitment, the more dramatic impact of the pandemic was on in-person follow-up. To address this, our prespecified analysis found that virtual follow-up had no independent association with pain improvement at 6 months, our primary outcome. Next, our limited recruitment of women (5%) within the trial limits the applicability of the findings to those patients. Finally, the multicenter nature of the trial made it challenging to record the number of patients screened for entry into the study, which is important to gauge any degree of selection bias. In that same regard, the low number of intraoperative exclusions is reassuring.

CONCLUSIONS

NB2C adhesive is a reasonable option for mesh fixation and peritoneal closure during laparoscopic inguinal hernia repair.

REFERENCES

1. Arregui ME, Davis CJ, Yucel O, et al. Laparoscopic mesh repair of inguinal hernia using a preperitoneal approach: a preliminary report. *Surg Laparosc Endosc*. 1992;2:53–58.
2. Wright D, Paterson C, Scott N, et al. Five-year follow-up of patients undergoing laparoscopic or open groin hernia repair: a randomized controlled trial. *Ann Surg*. 2002;235:333–337.
3. Patterson TJ, Beck J, Currie PJ, et al. Meta-analysis of patient-reported outcomes after laparoscopic versus open inguinal hernia repair. *Br J Surg*. 2019;106:824–836.
4. Aiolfi A, Cavalli M, Ferraro SD, et al. Treatment of inguinal hernia: systematic review and updated network meta-analysis of randomized controlled trials. *Ann Surg*. 2021;274:954–961.
5. Nguyen DK, Amid PK, Chen DC. Groin pain after inguinal hernia repair. *Adv Surg*. 2016;50:203–220.
6. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618–1625.
7. Sajid MS, Ladwa N, Kalra L, et al. A meta-analysis examining the use of tacker mesh fixation versus glue mesh fixation in laparoscopic inguinal hernia repair. *Am J Surg*. 2013;206:103–111.
8. Chan MS, Teoh AY, Chan KW, et al. Randomized double-blinded prospective trial of fibrin sealant spray versus mechanical stapling in laparoscopic total extraperitoneal hernioplasty. *Ann Surg*. 2014;259:432–437.
9. Agrawal A, Avill R. Mesh migration following repair of inguinal hernia: a case report and review of literature. *Hernia*. 2006;10:79–82.
10. Goswami R, Babor M, Ojo A. Mesh erosion into caecum following laparoscopic repair of inguinal hernia (TAPP): a case report and literature review. *J Laparoendosc Adv Surg Tech A*. 2007;17:669–672.
11. Watanobe I, Miyano S, Machida M, et al. Mesh shrinkage after transabdominal preperitoneal inguinal hernia repair. *Sci Rep*. 2023;13:3894.
12. Singer AJ, Hollander JE, Valentine SM, et al. Prospective, randomized, controlled trial of tissue adhesive (2-octylcyanoacrylate) vs standard wound closure techniques for laceration repair. Stony Brook Octylcyanoacrylate Study Group. *Acad Emerg Med*. 1998;5:94–99.
13. Mittermair R, Jenic G, Kolenik R, et al. TAPP surgery with mesh fixation and peritoneal closure using n-butyl-2-cyanoacrylate (LiquiBand®FIX8TM)—initial experience. *Eur Surg*. 2016;48:110–114.
14. Wilson P, Hickey L. Laparoscopic transabdominal preperitoneal (TAPP) groin hernia repair using n-butyl-2-cyanoacrylate (Liquiband(R)Fix8) for mesh fixation and peritoneal closure: learning experience during introduction into clinical practice. *Hernia*. 2019;23:601–613.
15. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Trials*. 2010;11:32.
16. Heniford BT, Walters AL, Lincourt AE, et al. Comparison of generic versus specific quality-of-life scales for mesh hernia repairs. *J Am Coll Surg*. 2008;206:638–644.
17. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? *Acad Emerg Med*. 1998;5:1086–1090.
18. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Ann Emerg Med*. 2001;38:633–638.
19. Habib Bedwani NAR, Kelada M, Smart N, et al. Glue versus mechanical mesh fixation in laparoscopic inguinal hernia repair: meta-analysis and trial sequential analysis of randomized clinical trials. *Br J Surg*. 2021;108:14–23.
20. Koch CA, Greenlee SM, Larson DR, et al. Randomized prospective study of totally extraperitoneal inguinal hernia repair: fixation versus no fixation of mesh. *JSLS*. 2006;10:457–460.
21. Prakash PS, Wijerathne S, Salgaonkar HP, et al. The efficacy of absorbable versus non-absorbable fixation in laparoscopic totally extraperitoneal (tep) repair of large inguinal hernias. *Asian J Surg*. 2019;42:995–1000.
22. Hahnfeld LE, Nakada SY, Moon TD. Identification of microtacks in the bladder after laparoscopic pelvic surgery. *Urology*. 1999;54:162.
23. Hume RH, Bour J. Mesh migration following laparoscopic inguinal hernia repair. *J Laparoendosc Surg*. 1996;6:333–335.
24. Novik B, Sandblom G, Ansorge C, et al. Association of mesh and fixation options with reoperation risk after laparoscopic groin hernia surgery: a Swedish Hernia Registry Study of 25,190 totally extraperitoneal and transabdominal preperitoneal repairs. *J Am Coll Surg*. 2022;234:311–325.
25. Bakker WJ, Aufenacker TJ, Boschman JS, et al. Heavyweight mesh is superior to lightweight mesh in laparo-endoscopic inguinal hernia repair: a meta-analysis and trial sequential analysis of randomized controlled trials. *Ann Surg*. 2021;273:890–899.

26. Zwaans WAR, Verhagen T, Wouters L, et al. Groin pain characteristics and recurrence rates: three-year results of a randomized controlled trial comparing self-gripping progrip mesh and sutured polypropylene mesh for open inguinal hernia repair. *Ann Surg*. 2018;267:1028–1033.
27. Sheetz KH, Claflin J, Dimick JB. Trends in the adoption of robotic surgery for common surgical procedures. *JAMA Netw Open*. 2020;3:e1918911.
28. Prabhu AS, Carbonell A, Hope W, et al. Robotic inguinal vs transabdominal laparoscopic inguinal hernia repair: the RIVAL randomized clinical trial. *JAMA Surg*. 2020;155:380–387.
29. Miller BT, Prabhu AS, Petro CC, et al. Laparoscopic versus robotic inguinal hernia repair: 1- and 2-year outcomes from the RIVAL trial. *Surg Endosc*. 2023;37:723–728.