A Randomized Controlled Trial of Staple Fixation Versus N-butyl-2-cyanoacrylate Fixation in Laparoscopic Inguinal Hernia Repair

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Background: *There has been paramount concern among most surgeons over complications caused by staples in the form of pubic injury and nerve entrapment leading to chronic pain in laparoscopic inguinal hernia repair.*
Objective: *The present study aimed to compare the use of N-butyl-2-cyanoacrylate (Histoacryl®) with that of staples in fixation of mesh in totally extra peritoneal laparoscopic inguinal hernia repair in terms of acute and chronic pain, complications, and recurrence within 1 year.*
Material and Method: *60 patients were allocated into 2 groups. The same protocol of general anesthesia was applied in both groups. In the staple group, Ultrapro mesh was used to cover the myopectineal orifice and was transfixed with staples. In the glue group, Histoacryl® was sprayed to fix the mesh at the same area as in the staple group and also at the triangle of pain. Demographic data collected included fentanyl use, operation time, visual analogue pain score (VAS), chronic pain, complications and recurrence.*
Results: *Demographic data and complications showed no significant difference in the two groups. VAS in the staple group was significantly greater than that in the glue group after 24 hours (1.6 ± 1.33 vs. 2.35 ± 1.32) ($p = 0.037$). The incidence of chronic pain after 3 months and 1 year was higher in the staple group (33.0%, 33.0%, vs. 23.0%, 16.0%) ($p = 0.390, 0.360$). One patient in the staple group had a hernia recurrence eight months after the operation.*
Conclusion: *N-butyl-2 cyanoacrylate might be an alternative choice of mesh fixation in TEP since overall complications and recurrence of hernia were not significantly different compared to staple fixation.*

Keywords: *Inguinal hernia, Laparoscope, Cyanoacrylate glue, Chronic pain, Hernia repair*

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The use of minimally-invasive inguinal hernia repair results in less postoperative pain and leads to speedier recovery to normal activities than the use of open surgery[1-4]. In the past, the recurrence rate was a major outcome of concern in most studies; however, chronic pain has become a major focus in the last few years. In accordance with the original description of inguinal hernia repair by the laparoscopic totally extra peritoneal method (TEP), most surgeons secure the mesh prosthesis with staples. However, concerns have emerged about staples causing complications, such as pubic injury and nerve entrapment, leading to chronic pain[5]. Some authors have reported that good fixation of the mesh was critical for prevention of early recurrence[6]. Various alternative methods of fixation have been proposed to avoid the use of such staples including fibrin glues, acrylated adhesives and absorbable sutures[7-9]. Cyanoacrylate is licensed for external use, but many studies have reported its use in internal applications also, such as bronchopleural fistulas[10], myocardial tear[11], and inguinal hernia[8,12]. The present study aimed to compare the use of N-butyl-2-cyanoacrylate (Histoacryl®, manufactured by B. Braun) for fixing mesh in the TEP procedure with the use of staple fixation in terms of acute and chronic pain, complications, and recurrence within 1 year.

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Material and Method

During the period of October 2009-October 2010, 60 patients were enrolled in the present study after informed consent was obtained. The present study was approved by the ethics committee at Rajavithi Hospital. All patients were allocated into two groups,

the staple and the glue group, by block randomization. The exclusion criteria were patients who were under 18 years old or more than 75 years old, had bilateral groin hernia, recurrent hernia, previous lower abdominal surgery, acute or chronic pain, or had recently taken analgesic drugs. The same protocol of general anesthesia was applied in both groups to keep at $ETCO_2$ 30-35 mmHg and maintain blood pressure and pulse within 20% of patients' base line. The anesthesiologist was blinded to the type of fixation.

The operation was performed by a single surgeon as follows: a sub-umbilical incision of 1.5 cm was made and preperitoneal space was entered with finger dissection. This was followed by a balloon dissector to create more preperitoneal space. The next step was the replacement of the dissector with a 12-millimeter balloon trocar. The other two ports (5 millimeters) were located at midline 2 centimeters above the pubic symphysis and midway between the 1st and 2nd ports. CO_2 pressure was kept at 12 mmHg to open the preperitoneal space. Next, the hernia sac was identified and retracted cephalad as far as possible from the myopectineal orifice. In the staple group Ultrapro mesh (Ethicon, inc. Johnson-Johnson com) of 13 x 10 centimeters was used to cover the myopectineal orifice and was transfixed with staples (ProTack™ covidien surgical) at Cooper's ligament, transversalis fascia over iliopubic tract, and the rectus muscle. Any peritoneum tears were closed by clip or endoloop. In the glue group, Histoacryl® was sprayed to fix the mesh at the same area as in the staple group. In addition, Histoacryl® was sprayed to fix the mesh at the triangle of pain in the glue group. At the end of the operation, the foley catheter was removed and the patient was sent to the recovery room attended by an anesthetic nurse who was blinded to the fixation method.

To obtain demographic data, intraoperative fentanyl use and operation time were recorded. Patients were assessed at 4, 8, 12, 24, 36, and 48 hours postoperatively. Patients, assessor, and anesthetic nurse were blinded to randomization. Factors assessed include visual analogue pain score (VAS), analgesic requirement, complications, and postoperative analgesia provided by intravenous morphine via a patient-controlled analgesic device (IV-PCA). Two tablets of 500 mg acetaminophen were given every 6 hours to all patients, and a dose of 1.2 g clavulanate potassium and amoxicillin trihydrate was administered as prophylactic antibiotics. All patients were discharged from the hospital 48 hours after the operation. Follow-up was scheduled at the outpatient department for 3 months and 1 year after the operation to evaluate groin pain during normal daily activity and recurrence of hernia. Acetaminophen and diclofenac were given for symptomatic treatment of pain after discharge and during the follow-up period.

Statistical analysis

Categorical variables were reported as proportions and analyzed using X^2 test or Fisher's exact test. Continuous data were reported as mean $\pm$ SD and analyzed with Student's t-test. Mann-Whitney U test was used to analyze continuous data without normal distribution. Repedted measure ANOVA was used for VAS score during 48 hrs after operation. Previous data on the use of staples in hernia repair indicated that the incidence of chronic pain was 29.0%[5]. The expected incidence of chronic pain in hernia repair with N-butyl-2 cyanoacrylate glue was 5.0%. A total of 30 cases in each group was required with the power 0.7. A p-value less than 0.05 was considered statistically significant.

Results

Demographic data from the patients under study showed no significant difference in the two groups (Table 1). VAS in the staple group was greater than in the glue group significantly at 24 hours (Table 2). There were no serious complications and also no significant difference in overall complications between the two groups. Higher consumption of total IV-PCA morphine and also a higher incidence of chronic pain at 3 months and 1 year were also demonstrated in the staple group, but with no significant difference. One patient in the staple group had a hernia recurrence eight months after the operation (Table 3). A total of seven staples was used to fix the mesh in each patient in the staple group. Six and five cases of peritoneal tear, closed by endoloop, were found in the staple group and the glue group, respectively.

Discussion

Many randomized studies have been published which have reported that, when compared with open hernia repair, TEP results in reduced postoperative pain, easier return to work, and shorter hospital stay[13-15]. TEP also reduced the incidence of chronic postoperative groin pain[2,16]. It is thought that the cause of prolonged postoperative pain is nerve entrapment related to the formation of scar tissue stimulated by the mesh or tension from tissue repair[7].

The need for mesh fixation in TEP is still a controversial issue. Medial or lateral recurrence are

Table 1. Demographic data

Characteristics	Glue (n = 30)	Staple (n = 30)	p-value
Age (year)*	52.40 ± 14.95	48.27 ± 17.33	0.320
Weight (kilogram)*	61.13 ± 9.58	63.98 ± 11.44	0.330
Sex (female/male)	1/29	1/29	1.000
Operation time (minute)*	73.60 ± 34.00	63.20 ± 18.79	0.150
Type hernia [No. (%)]			
Direct	13 (43.0)	9 (30.0)	0.280
Indirect	17 (57.0)	21 (70.0)	
Intraoperative fentanyl (nanogram) *	110.57 ± 25.58	110.17 ± 26.11	0.950

* = mean ± SD

Table 2. Results of treatment VAS and morphine used

Post operation	Glue (n = 30)	Staple (n = 30)	p-value
VAS 4	3.67 ± 1.73	3.72 ± 2.03	0.919
VAS 8	3.03 ± 1.73	3.27 ± 1.72	0.603
VAS 12	2.10 ± 1.68	2.60 ± 1.61	0.245
VAS 24	1.62 ± 1.33	2.35 ± 1.32	0.037
VAS 36	1.30 ± 1.29	1.77 ± 1.33	0.137
VAS 48	0.87 ± 1.27	0.90 ± 0.92	0.908
Morphine used (milligram) *	10.02 ± 13.86	14.00 ± 12.15	0.240

VAS = visual analogue pain score at 4, 8, 12, 24, 36, 48 hours after operation (mean ± SD)
* = total morphine used during first 48 hours after operation, mean ± SD

Table 3. Results of post operation complications, chronic pain and recurrence

Results after operation	Glue (n = 30)	Staple (n = 30)	p-value
Chronic pain at 3 months [No. (%)]	7 (23.0)	10 (33.0)	0.390
Chronic pain at 1 year [No. (%)]	5 (17.0)	10 (33.0)	0.360
Recurrence at 1 year [No. (%)]	0 (0.0)	1 (3.0)	1.000
Complication [No. (%)]	4 (13.0)*	4 (13.0)[a]	1.000

* = complications in glue group 2 cases nausea, 1 case pruritus, 1 case constipation
[a] = complications in staple group 1 case seroma, 3 cases nausea

caused by the rolling up of the mesh[18,19]. Some authors have recommended fixing the mesh with staples to prevent recurrence; however, staples may cause postoperative pain and nerve injury[20,22]. An alternative method of fixation was using fibrin glue. In 1997, Chevrel[23] published his work on his use of fibrin glues in 110 incisional hernia repairs carried out since 1989. Katkhouda et al[24] were the first group to demonstrate in a porcine model that fibrin glue provided similar tensile strengths for laparoscopic fixation of hernia meshes as compared with staples. As for chronic pain, which is defined as pain or discomfort that lasts for 3 months after surgery, the incidence varied between 0 and 75 percent after open mesh repair and between 0 and 29 percent after laparoscopic repair[5,25,26]. Three types of chronic pain after herniorrhaphy have been described: somatic, neuropathic and visceral pain[5].

Several clinical studies have demonstrated a significantly lower rate of chronic pain in fibrin glue groups than that in staple groups. The incidence of chronic pain varied from 4.5% to 13.2%[27,28] and the recurrence rate was about 4.0%[29]. The prospective study reported by Boldo[30] showed that early postoperative pain was reduced with fibrin glue, and

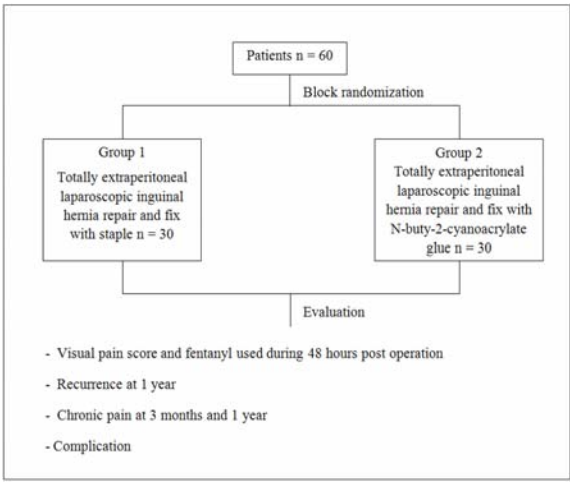

Fig. 1 Study flow chart

this finding is in clear agreement with the present study. Data on synthetic glue in mesh fixation for hernia repair in humans are scarce since most studies have been carried out on animal models[31,32]. Cynoacrylate glue polymerizes in the presence of water, joining the bonded surface in 5-6 seconds and reaching final stage in 60 seconds. Initial experience of clinical use of N-butyl-2 cyanoacrylate in TEP was reported by Jourdan et al[8] with satisfactory results. The glue was almost completely resorbed after 2 months with mild inflammation when applied to well-vascularised tissue[33]. In contrast, Fortelny et al[31] showed that this glue had still not degraded after 3 months post-operatively and also inhibited tissue integration, which occurred only in the areas of the mesh which were free of glue. More recently, N-butyl-2-cyanoacrylate tissue adhesive demonstrated its safety and efficacy in vitro and in vivo showing low cytotoxicity, genotoxicity and high adhesive properties[34-36].

Seroma formation was a common complication reported in many studies, i.e. using fibrin glue could induce inflammatory response after treatment[24]. In the present study only one case in the staple group had a seroma, and there was no recurrence in the glue group.

The one case of recurrence of hernia in the staple group was within the range of most studies on TEP repair[37,38]. The cause of recurrence was the rolling up of the lateral edge of the mesh. Operation time was longer in the glue group than in the staple group, but this was probably due to technical problems with the application device made by one of our colleagues. Further training in its use might be needed.

In the present study, the staple group seemed to show a higher incidence of chronic pain than the glue group, but with no significant difference, and this is similar to the findings of Lau[27] who compared mechanical stapling versus fibrin sealant. The cost of fibrin glue is $250 whereas cyanoacrylate glue is $35. It appears that the outcomes of using N-butyl-2-cyanoacrylate glue in the present study are comparable with those of the use of fibrin glue, which is more costly, in the Lau study. Therefore, N-butyl-2-cyanoacrylate glue might be an alternative and affordable choice. Larger sample sizes are needed to prove the statistically significant benefits of N-butyl-2-cyanoacrylate glue use in terms of chronic pain.

Conclusion

N-butyl-2 cyanoacrylate might be an alternative choice of mesh fixation in TEP since overall complications and recurrence of hernia were not significantly different compared to staple fixation.

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Potential conflicts of interest

None.

References

1. EU Hernia Trialists Collaboration. Laparoscopic compared with open methods of groin hernia repair: systematic review of randomized controlled trials. Br J Surg 2000; 87: 860-7.
2. Andersson B, Hallen M, Leveau P, Bergenfelz A, Westerdahl J. Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: a prospective randomized controlled trial. Surgery 2003; 133: 464-72.
3. Bringman S, Ramel S, Heikkinen TJ, Englund T, Westman B, Anderberg B. Tension-free inguinal hernia repair: TEP versus mesh-plug versus Lichtenstein: a prospective randomized controlled trial. Ann Surg 2003; 237: 142-7.
4. Memon MA, Cooper NJ, Memon B, Memon MI, Abrams KR. Meta-analysis of randomized clinical trials comparing open and laparoscopic inguinal hernia repair. Br J Surg 2003; 90: 1479-92.
5. Poobalan AS, Bruce J, Smith WC, King PM, Krukowski ZH, Chambers WA. A review of chronic pain after inguinal herniorrhaphy. Clin J Pain 2003; 19: 48-54.

6. Tucker JG, Wilson RA, Ramshaw BJ, Mason EM, Duncan TD, Lucas GW. Laparoscopic herniorrhaphy: technical concerns in prevention of complications and early recurrence. Am Surg 1995; 61: 36-9.
7. Golash V. Technique of suturing the mesh in laparoscopic total extra peritoneal (TEP) repair of inguinal hernia. Surgeon 2004; 2: 264-72.
8. Jourdan IC, Bailey ME. Initial experience with the use of N-butyl 2-cyanoacrylate glue for the fixation of polypropylene mesh in laparoscopic hernia repair. Surg Laparosc Endosc 1998; 8: 291-3.
9. Novik B, Hagedorn S, Mork UB, Dahlin K, Skullman S, Dalenback J. Fibrin glue for securing the mesh in laparoscopic totally extraperitoneal inguinal hernia repair: a study with a 40-month prospective follow-up period. Surg Endosc 2006; 20: 462-7.
10. Scappaticci E, Ardissone F, Ruffini E, Baldi S, Mancuso M. Postoperative bronchopleural fistula: endoscopic closure in 12 patients. Ann Thorac Surg 1994; 57: 119-22.
11. Padro JM, Mesa JM, Silvestre J, Larrea JL, Caralps JM, Cerron F, et al. Subacute cardiac rupture: repair with a sutureless technique. Ann Thorac Surg 1993; 55: 20-3.
12. Farouk R, Drew PJ, Qureshi A, Roberts AC, Duthie GS, Monson JR. Preliminary experience with butyl-2-cyanoacrylate adhesive in tension-free inguinal hernia repair. Br J Surg 1996; 83: 1100.
13. Amid PK, Shulman AG, Lichtenstein IL. Critical scrutiny of the open "tension-free" hernioplasty. Am J Surg 1993; 165: 369-71.
14. Bekavac-Beslin M, Vidovic MD, Karapandza N, Hochstadter H. Operative treatment (laparoscopic to open surgery) of early complications after laparoscopic extraperitoneal hernioplasty (TEP). Paper presented at the 6th World Congress of Endoscopic Surgery, Oral Communicationas, Posters, and Videos Rome, Italy, May 31-June 6, 1998: 913-5.
15. Tanphiphat C, Tanprayoon T, Sangsubhan C, Chatamra K. Laparoscopic vs open inguinal hernia repair. A randomized, controlled trial. Surg Endosc 1998; 12: 846-51.
16. McCormack K, Scott NW, Go PM, Ross S, Grant AM. Laparoscopic techniques versus open techniques for inguinal hernia repair. Cochrane Database Syst Rev 2003; (1): CD001785.
17. Wong J, Anvari M. Treatment of inguinodynia after laparoscopic herniorrhaphy: a combined laparoscopic and fluoroscopic approach to the removal of helical tackers. Surg Laparosc Endosc Percutan Tech 2001; 11: 148-51.
18. Deans GT, Wilson MS, Royston CM, Brough WA. Recurrent inguinal hernia after laparoscopic repair: possible cause and prevention. Br J Surg 1995; 82: 539-41.
19. Felix E, Scott S, Crafton B, Geis P, Duncan T, Sewell R, et al. Causes of recurrence after laparoscopic hernioplasty. A multicenter study. Surg Endosc 1998; 12: 226-31.
20. Andrew DR, Gregory RP, Richardson DR. Meralgia paraesthetica following laparoscopic inguinal herniorrhaphy. Br J Surg 1994; 81: 715.
21. Chevallier JM, Wind P, Lassau JP. Damage to the inguino-femoral nerves in the treatment of hernias. An anatomical hazard of traditional and laparoscopic techniques. Ann Chir 1996; 50: 767-75.
22. Stark E, Oestreich K, Wendl K, Rumstadt B, Hagmuller E. Nerve irritation after laparoscopic hernia repair. Surg Endosc 1999; 13: 878-81.
23. Chevrel JP, Rath AM. The use of fibrin glues in the surgical treatment of incisional hernias. Hernia 1997; 1: 9-14.
24. Katkhouda N, Mavor E, Friedlander MH, Mason RJ, Kiyabu M, Grant SW, et al. Use of fibrin sealant for prosthetic mesh fixation in laparoscopic extraperitoneal inguinal hernia repair. Ann Surg 2001; 233: 18-25.
25. Nienhuijs S, Staal E, Strobbe L, Rosman C, Groenewoud H, Bleichrodt R. Chronic pain after mesh repair of inguinal hernia: a systematic review. Am J Surg 2007; 194: 394-400.
26. Page B, Paterson C, Young D, O'Dwyer PJ. Pain from primary inguinal hernia and the effect of repair on pain. Br J Surg 2002; 89: 1315-8.
27. Lau H. Fibrin sealant versus mechanical stapling for mesh fixation during endoscopic extraperitoneal inguinal hernioplasty: a randomized prospective trial. Ann Surg 2005; 242: 670-5.
28. Topart P, Vandenbroucke F, Lozac'h P. Tisseel versus tack staples as mesh fixation in totally extraperitoneal laparoscopic repair of groin hernias: a retrospective analysis. Surg Endosc 2005; 19: 724-7.
29. Schwab R, Willms A, Kroger A, Becker HP. Less chronic pain following mesh fixation using a fibrin sealant in TEP inguinal hernia repair. Hernia 2006; 10: 272-7.
30. Boldo E, Armelles A, Perez de Lucia G, Martin F, Aracil JP, Miralles JM, et al. Pain after laparascopic

bilateral hernioplasty : Early results of a prospective randomized double-blind study comparing fibrin versus staples. Surg Endosc 2008; 22: 1206-9.
31. Fortelny RH, Petter-Puchner AH, Walder N, Mittermayr R, Ohlinger W, Heinze A, et al. Cyanoacrylate tissue sealant impairs tissue integration of macroporous mesh in experimental hernia repair. Surg Endosc 2007; 21: 1781-5.
32. Losi P, Burchielli S, Spiller D, Finotti V, Kull S, Briganti E, et al. Cyanoacrylate surgical glue as an alternative to suture threads for mesh fixation in hernia repair. J Surg Res 2010; 163: e53-8.
33. Pelissier P, Casoli V, Le Bail B, Martin D, Baudet J. Internal use of n-butyl 2-cyanoacrylate (Indermil) for wound closure: an experimental study. Plast Reconstr Surg 2001; 108: 1661-6.
34. Montanaro L, Arciola CR, Cenni E, Ciapetti G, Savioli F, Filippini F, et al. Cytotoxicity, blood compatibility and antimicrobial activity of two cyanoacrylate glues for surgical use. Biomaterials 2001; 22: 59-66.
35. Tebala GD, Ceriati F, Ceriati E, Vecchioli A, Nori S. The use of cyanoacrylate tissue adhesive in high-risk intestinal anastomoses. Surg Today 1995; 25: 1069-72.
36. Kukleta JF, Freytag C, Weber M. Efficiency and safety of mesh fixation in laparoscopic inguinal hernia repair using n-butyl cyanoacrylate: long-term biocompatibility in over 1,300 mesh fixations. Hernia 2012; 16: 153-62.
37. EU Hernia Trialists Collaboration. Repair of groin hernia with synthetic mesh: meta-analysis of randomized controlled trials. Ann Surg 2002; 235: 322-32.
38. Quilici PJ, Greaney EM Jr, Quilici J, Anderson S. Laparoscopic inguinal hernia repair: optimal technical variations and results in 1700 cases. Am Surg 2000; 66: 848-52.

ศึกษาผลการยึดแผ่นสังเคราะห์โดยใช้เหล็กเปรียบเทียบกับการใช้กาวยึดในการผ่าตัดไส้เลื่อนขาหนีบผ่านกล้องวีดิทัศน์

สมบูรณ์ ทรัพย์วงศ์เจริญ, กาญจนา รักษ์สกุล

***ภูมิหลัง**: การยึดแผ่นสังเคราะห์โดยใช้เหล็กยึด นำมาซึ่งปัญหาแทรกซ้อน โดยเฉพาะการเจ็บปวดเรื้อรังหลังผ่าตัด*
***วัตถุประสงค์**: การศึกษานี้มุ่งหวัง ศึกษาผลการยึดแผ่นสังเคราะห์โดยใช้เหล็ก เปรียบเทียบกับการใช้กาวยึดในการผ่าตัดไส้เลื่อน ขาหนีบผ่านกล้องวีดิทัศน์ ในแง่การเจ็บปวด, ภาวะแทรกซ้อน ภายในระยะเวลา 1 ปี*
***วัสดุและวิธีการ**: ผู้ป่วย 60 ราย แบ่งเป็น 2 กลุ่มๆ ละ 30 ราย กลุ่มแรกมีผู้ป่วยชาย 29 ราย ผู้ป่วยหญิง 1 ราย อายุเฉลี่ย 52.4 ปี ใช้กาว cyanoacrylate ยึดแผ่นสังเคราะห์ กลุ่มที่ 2 มีผู้ป่วยชาย 29 ราย ผู้ป่วยหญิง 1 ราย อายุเฉลี่ย 48.2 ปี ใช้เหล็กยึดแผ่นสังเคราะห์ โดยใช้วิธีการดมยาสลบเหมือนกันทั้ง 2 กลุ่ม เก็บข้อมูล อายุ เพศ การเจ็บปวด ภาวะแทรกซ้อน และการกลับมาเป็นใหม่ใน 1 ปี*
***ผลการศึกษา**: ในกลุ่มที่ใช้กาวพบภาวะแทรกซ้อน การกลับมาเป็นไส้เลื่อนใหม่ ไม่แตกต่างกับกลุ่มใช้เหล็กยึด แต่กลุ่มที่ใช้เหล็กยึดจะปวดมากกว่าใน 24 ชั่วโมงแรกหลังผ่าตัด แต่ความเจ็บปวดเรื้อรังไม่ต่างกันทั้ง 2 กลุ่ม*
***สรุป**: การใช้กาว N-butyl-2 cyanoacrylate อาจเป็นทางเลือกในการยึดแผ่นสังเคราะห์ในการผ่าตัดไส้เลื่อนแทนเหล็กโดยมีภาวะแทรกซ้อน การกลับมาเป็นใหม่ไม่แตกต่างกัน*