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The Effectiveness of Cyanoacrylates versus Sutures for Mesh Fixation after Lichtenstein Repair (SCyMeLi STUDY)

A Systematic Review and Meta-Analyze of Randomized Controlled Trials

Rares Trisca[1,2], Valentin Oprea[2,3]*, Mihai Toma[3,4], Carmen Elena Bucuri[2,3], Bogdan Stancu[2], Ovidiu Grad[2,3], Claudia Gherman[5]

[1]Department of Surgery, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania
[2]PhD student, Department of Surgery, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3]Department of Surgery, Constantin Papilian Emergency Clinical Military Hospital, Cluj-Napoca, Romania
[4]PhD student, George Emil Palade University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[5]Department of Surgery, Practical Abilities Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

*Corresponding author:
Valentin Oprea, M.D.
Gral Train Mosoiu Street, no 22
Cluj-Napoca, Romania
E-mail: opreacv31@gmail.com

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Rezumat

Eficiența cianoacrilaților comparativ cu suturile pentru fixarea protezei în operația Lichtenstein (studiul SCyMeLi).
Review sistematic și meta-analiza trialurilor controlate randomizate

Introducere: Durerea inghinalã cronicã postoperatorie (DICP) reprezintã o complicație frecventã dupã cura operatorie a herniilor inghinale prin procedeul Lichtenstein. Orice strategie de reducere a incidenței şi a implicațiilor acestora reprezintã un pas înainte spre rezultate postoperatorii superioare. Una dintre aceste strategii este fixarea atraumaticã a protezei cu adezivi sintetici. Pentru a evidenția efectul adezivilor sintetici comparativ cu fixarea prin suturã am realizat o meta-analizã a studiilor controlate randomizate (RCT).
Metodã: metanaliza a fost realizatã în concordanțã cu ghidurile PRISMA. Au fost selectate articolele apãrute între ianuarie 2000 şi decembrie 2021 publicate în MEDLINE, PubMed, Web of Sciences şi Google Scholars. Calitatea studiilor şi riscul de bias au fost evaluate folosind criteriile MINORS şi aplicația Cochrane de evaluare a riscului.
Results: din 269 de articole analizate am inclus în studiu 19 trialuri cu 3578 pacienți. Timpul operator a fost mai scurt (diferența medie cumulatã 6 minute; SE = 0.47; 95% CI = - 6.77 - - 4.92; t test = -12.36; p <0.0001) şi durerea inghinalã postoperatorie imediatã mai redusã ca intensitate pentru pacienții din grupul de fixare cu adeziv (2.37% vs 13.3% OR – 0.158; 95% CI = 0.064 – 0.386;

p = 0.0001). Nu au existat diferențe între grupuri în ceea ce priveşte durerea cronicã, rata de recidivã şi complicațiile plãgii.
Concluzii: fixarea cu adezivi sintetici a plasei în operația Lichtenstein pare fi alegere validã care conduce la intervenții mai puțin dureroase dar la fel de sigure în ceea ce priveşte complicațiile plãgii şi rata de recidivã.

Cuvinte cheie: hernie inghinalã, durere inghinalã cronicã postoperatorie, fixare, cianoacrilați, fire de suturã, rata de recidivã

Abstract
Background: Chronic postoperative inguinal pain (CPIP) is still the most frequent complication after open Lichtenstein repair and any strategy to reduce its incidence and implications is a step forward to better outcomes. Between the means of mesh fixation atraumatic glue fixation has been explored as such possibility. A meta-analysis of randomized controlled trials comparing the performance of cyanoacrylate glue versus sutures fixation was conducted.
Methods: the meta-analysis was conducted according to the PRISMA guidelines. Randomized controlled trials (RCTs) published between January 2000 and December 2021 were searched for in MEDLINE, PubMed, Web of Science, and Google Scholars. The quality of RCTs and the potential risk of bias were assessed using MINORS criteria and the Cochrane risk of bias tool.
Results: of 269 papers the meta-analysis was performed on 19 RCTs including 3578 patients. In the glue fixation group, the operation was shorter (mean pooled difference 6 minutes; SE = 0.47; 95% CI = - 6.77 - - 4.92; t test = -12.36; p <0.0001) and immediate postoperative pain was lower (2.37% vs 13.3%OR – 0.158; 95% CI = 0.064 – 0.386; p = 0.0001). There was no difference in terms of chronic pain, recurrence rate and wound events.
Conclusion: glue fixation of mesh in elective Lichtenstein repair of inguinal hernia seems to be a valid choice for a painful and safe procedure without increasing risk of recurrence.

Key words: inguinal hernia, chronic postoperative inguinal pain, fixation, cyanoacrylates, sutures, recurrence rate

Introduction

Inguinal hernia is one of the most common surgical condition all over the world. Its incidence and prevalence is multifactorial and complex various conditions interfere in its formation (1). The prevalence of hernias in a given population at a given time is difficult to assess and usually is underestimated. A population study is difficult to be developed in the absence of a national registry; other data sources and methodology collection are inconsistent. In the USA the current prevalence is estimated at 10% of the global population (around 32 million people). An estimated 25% of all is expected to have a hernia at a point of their lifetime and 500.000 new diagnosed inguinal hernias are reported each year (2).

The gold standard for the open repair is a mesh – based technique, Lichtenstein tension-free hernioplasty being more and more popular due to its simplicity, safety, reproducibility, and effectiveness (3). The introduction of mesh reduced hernia recurrence rates but also induced a significant level of post-operative morbidity. Among them chronic post-operative inguinal pain (CPIP) is the most frequent and constitutes an important measure of clinical

outcome. According to European Hernia Society Guidelines, the incidence of pain is variable and accounts, in its severe, invalidating forms, for 6 to 12 % of mesh repair patients (4). This shifted the research focus from recurrence to chronic pain in both open and laparoscopic hernia repair (5).

There are several factors influencing incidence of CPIP. Some of them are not under direct control of the surgeon (female gender, lower age, high preoperative pain scores, and inflammatory reaction to the mesh) but most of them are preventable (intraoperative damage to the nerves, type and technique of mesh fixation, nerve entrapment into the sutures, the weight of mesh). Despite the extremely detailed steps of the technique (6), the procedure is still blurred by endless variations and combinations especially in mesh fixation: interrupted vs continuous sutures, absorbable vs non-absorbable, self-adhering meshes, tacks, and so on. Glue fixation seems to be a viable alternative for Lichtenstein repair because of the presumed lower postoperative pain, but the results are still controversial. Existing studies, even if demonstrated real benefits, are banned by limited number of patients, by limited power, limited data on potential benefit, by combination between adhesives (synthetics and biologic), and by combination between the procedures (open and laparoscopic repairs). Biologic glues (fibrin based) are still expensive and unavailable on large scale, especially in regions with low incomes and limited medical budgets. Cyanoacrylates (CAA) (under different commercial trademarks) are the most commonly used product for mesh fixation (7). In the light of these data our goal was to determine whether CAA can reduce postoperative complications especially CPIP with no increase in recurrence rate, compared with sutures for mesh fixation. Therefore, a systematic review and a meta-analysis of the Randomized Controlled Trials (RCTs) was performed.

Search Strategy

Two independent reviewers (RT and VO) performed a structured literature search in MEDLINE, PubMed, Web of Science, and Google Scholars for randomized control trials reporting Lichtenstein hernia repair and mesh fixation with Cyanoacrylates or sutures. The search strategy was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (8). The following index terms "groin hernia" AND "Lichtenstein repair", "mesh fixation" AND "sutures" AND "Cyanoacrylates" were used to identify studies from the beginning of 2000 until December 2021. A bibliographic review of selected relevant papers was used as a secondary source for full-length articles.

Eligibility Criteria

Relevant studies published in the English language were included if they originated from a unique cohort. In the case of multiple publications from one centre, the last publication was considered comprehensive. All single arm and comparative prospective studies were included. Articles without a clear definition of the outcomes, paediatric series, non-human studies, less than 40 patient series (to avoid overestimation of the treatment effects), case reports, minimally invasive series, review articles, "How I Do It" reports, discussion papers or meta-analysis were excluded. There were also excluded papers reporting other surgical technique than Lichtenstein repair or papers with an inconsistent description of the surgical technique.

Outcome Definition

Primary outcome measurements were chronic postoperative inguinal pain (CPIP) and postoperative hernia recurrence. Chronic pain was defined as any pain appeared or persistent beyond 3 months after repair with a Visual Analogic Scale value over 3 (4). The recurrence rate was considered as the presence of a bulge under the previous incision clinically revealed after a minimum of 12 months follow-up and was documented by radiological (ultrasound,

CT scan, MRI) or any of the hernia inventory surveys. Secondary outcomes of interest were duration of operation (in minutes), wound infection (superficial), mesh/deep infection, hematoma, seroma, persisting numbness, postoperative length of stay (in days), and recovery (necessary number of day for full activity). Wound morbidity or wound events are described in *Table 1* and include Surgical Site Infections (SSI) according to CDC classification (9), Surgical Site Occurrences Content (SSO), and Surgical Site Occurrences Requiring Procedural Intervention (SSOPI). Other secondary outcomes of interest were postoperative pain rate and intensity at 1 month, 3 months 1 year or more.

Data Extraction

A data extraction form was developed as a Microsoft Excel Sheet and two authors (RT and OV) independently extracted and completed the forms. Data on the following were extracted:

1. Study information (first author, centre, year of publication);
2. Methods of the study (design, randomization, allocation concealment, blinding);
3. Participants (inclusion/exclusion criteria, enrolment dates, gender, age, sex, Body Mass Index – BMI, comorbidities, smoking status, details of hernia - location, size, onset);
4. Intervention (material of fixation);
5. Duration of follow-up in months;
6. Outcomes.

Quality and Risk of Bias Assessment

The included studies were assessed for the risk of bias by two independent ratters (RT and OV), with any disagreements resolved by consultation with a third party (CG). The risk of bias assessment was done the Cochrane Handbook for Systematic Revue Intervention (10). Since the risk of bias may not be equal for all outcomes an individual, risk analysis was performed for each outcome assessed. We classified trials at low risk of bias if none of the domains were associated with unclear risk of bias. The moderate risk of bias was assessed when one domain has unclear risk and the high risk when one of the domain has high-risk bias. The risk of bias was represented as separate columns in forest plots for individual studies and as stacked bar charts as an overview.

Two independent reviewers (MT and OG) assessed the quality of the studies according to MINORS criteria using the 12 items scale for comparative studies (11). Disagreements were resolved by consensus with a third reviewer (BC). Due to the risk of bias, it was decided that a MINORS score of at least seven was required to include the study in the meta-analysis (*Table 2*).

Table 1. Explanation of outcome measures collated in text for a uniform assessment

Term	Definition
Preoperative groin pain	Visual Analog Scale (VAS) almost immediately prior to the index operation
Duration of operation	Time from skin incision to skin closure
Acute postoperative pain	pain VAS most immediately after and during 1 week of the operation
Chronic groin pain	Groin pain persisting at least 3 months after the index operation. . VAS > 30 mm if scoring system was utilized
Recurrence	Clinical or radiologic recurrence of inguinal hernia
Surgical site occurrences requiring procedural intervention (SSOPI)	Wound opening Suture excision Percutaneous drainage Complete/partial mesh removal
Surgical site infections (SSI)	Superficial Deep Organ space
Surgical site occurrences (SSO)	Any SSI in addition to: Wound cellulitis Non-healing incisional wound Skin/soft tissue ischemia Skin/soft tissue necrosis Serous/purulent wound drainage Stitch abscesses Seroma, hematoma Infected/exposed mesh
Persisting groin numbness	Includes groin paraesthesia and dysesthesia at least 3 months after the index operation
Hospital stay	Time from the index operation to discharge
Time taken to return to normal activity	Time from the index operation to the resumption of normal daily activities, or employment where the former was unavailable

Table 2. Details of the included studies

Reference	Year	Suture (no)	Glue (no)	Outcome measures	Follow-up (months)	Suture type	Glue type	Mesh type	MINORS criteria
Matikainen (5)	2018	207	216	Pain, recurrence	1 year, 2 years	3-0 polypropylene	Histoacryl	Optilene 9/13 cm	20
Arafa (12)	2019	80	80	Pain 1 month, chronic pain, recurrence, complications	1 week, 1,6, 12 month, annually	2-0 polypropylene	Histoacryl	Polypropylene 6/11 cm	20
Dabrowiecki (13)	2012	21	20	Pain 1 month, pain 1 year, recurrence, complications, foreign body sensation	16 months	2-0 Polydioxanone (PDS)	Glubran 2	Prolene 7-10/15 cm	16
Fouda (14)	2020	20	20	Groin pain 1 month and 1 1year, recurrence, complications	1 week, 1,6, and 12 months	2-0 polypropylene	Histoacryl	Prolene 6/12 cm	20
Helbling (15)	2003	24	22	Groin pain, complications	1 month, 3 months	2-0 Polydioxanone (PDS)	Histoacryl	Vypro-II 8/14 cm	15
Hoyuela (16)	2017	182	188	Pain 1 monyh and 1 year, complications, recurrence	1 week, 1,6, 12 month, annually	2-0 polypropylene	Histoacryl	Optilene 7.5/15 cm	24
Jeyakumar (17)	2018	25	26	Pain, complications	1 month, 6 months	Not specified	Histoacryl	Not specified	16
Kim-Fuchs (18)	2012	133	131	Postoperative chronic pain, recurrence rate	3 moths, 1 and 5 years	2-0 Polydioxanone (PDS)	Histoacryl	Not specified	20
Mallikarjun (19)	2019	30	30	Postoperative pain, complications, recurrence	1month, 1 year	polypropylene	Histoacryl	Not specified	16
Matikainen (20)	2021	216	216	Chronic pain, recurrence, complications	5 years	3-0 polypropylene	Histoacryl	Optilene 9/13 cm	20
Matikainen (21)	2016	121	115	Chronic pain, foreign body sensation	7 years	3-0 polypropylene	Glubran	Optilene 9/13 cm	20
Mikhail (22)	2012	97	101	Acute, chronic pain, recurrence, complications	1, 6, 12 months	Non resorbable monofilament stiches	Glubran	Heavy weight polypropylene	16
Moren-Egea (23)	2013	20	20	Pain, complications, recurrences	15 months	2-0 polypropylene	Ifabond	Flat polypropylene mesh 7/15 cm	17
Nowobilski (24)	2004	24	22	Pain, complications, recurrences, return to work	4.7 months	3 – 0 Polyglycolic acid (Dexon)	Indermil	Not specified	15
Paajanen (25)	2011	142	144	Acute, chronic pain, foreign body sensation, complications, recurrence	1,6,12 months	3 – 0 Polyglycolic acid (Dexon)	Glubran	Optilene 9/13 cm	23
Ronka (26)	2015	207	216	Pain acute and chronic, time to return to work, complications, recurrences	1 year	2-0 Prolene	Histoacryl	Optilene 9/13 cm	17
Shen (27)	2012	55	55	Acute, chronic pain, complications, recurrence	13 moths	Not specified	Histoacryl	Not specified 7/10-13 cm	20
Tebala (28)	2015	19	26	Early and late postoperative pain, morbidity and recurrence rate	1,3, 6 months	Not specified	Cyanoacrylate	Not specified	15
Tofigh (29)	2020	30	28	Early and late postoperative pain	1,3,6, and 12 month	3-0 Prolene	N-hexyl--cyanoacrylate	Not specified	19

Statistical Analysis

Data interpretation was performed using Revue Manager (RevMan) Computer Program, version 5.4 The Cochrane Collaboration 2020. Continuous data were summarized by calculating the mean of provided measures included in the study; dichotomous data were represented as absolute numbers and percentages. Pooled proportions of the outcomes were calculated with fixed effects (FE) models in the case of non-significant heterogeneity ($p>0.1$) (Mantel – Haenszel approach) and with a random logistic regression when significant heterogeneity was present ($p<0.1$). The odds ratio (OR) with a 95% confidence interval was assessed for dichotomous outcomes while standard mean difference (SMD) was estimated for continuous outcomes. Corresponding forest plots were constructed for the pooled estimates of the described outcomes and the weight of individual studies is represented by the size of individual squares. Risk Ratio (RR) or mean differences with 95% confidence interval (CI) where calculated to evaluate the statistical difference between outcomes following mesh fixation. Heterogeneity was assessed using chi-square statistics and I^2 measure for inconsistency. Heterogeneity was not considered important when I^2 ranged between 0 and 40%, moderate between 30 and 60%, substantial between 50 and 74%, and significant between 75 and 100%. A random effect meta-regression was performed to evaluate possible patient (age, gender, Body Mass Index (BMI), diabetes, and immunosuppression) variables able to influence the outcomes. A p value below than 0.05 was considered significant for all outcomes.

Results

Study selection of the 269 studies retrieved by the electronic search, 19 (5,12-29) were deemed suitable after the selection process depicted in the PRISMA flow chart (*Fig. 1*).

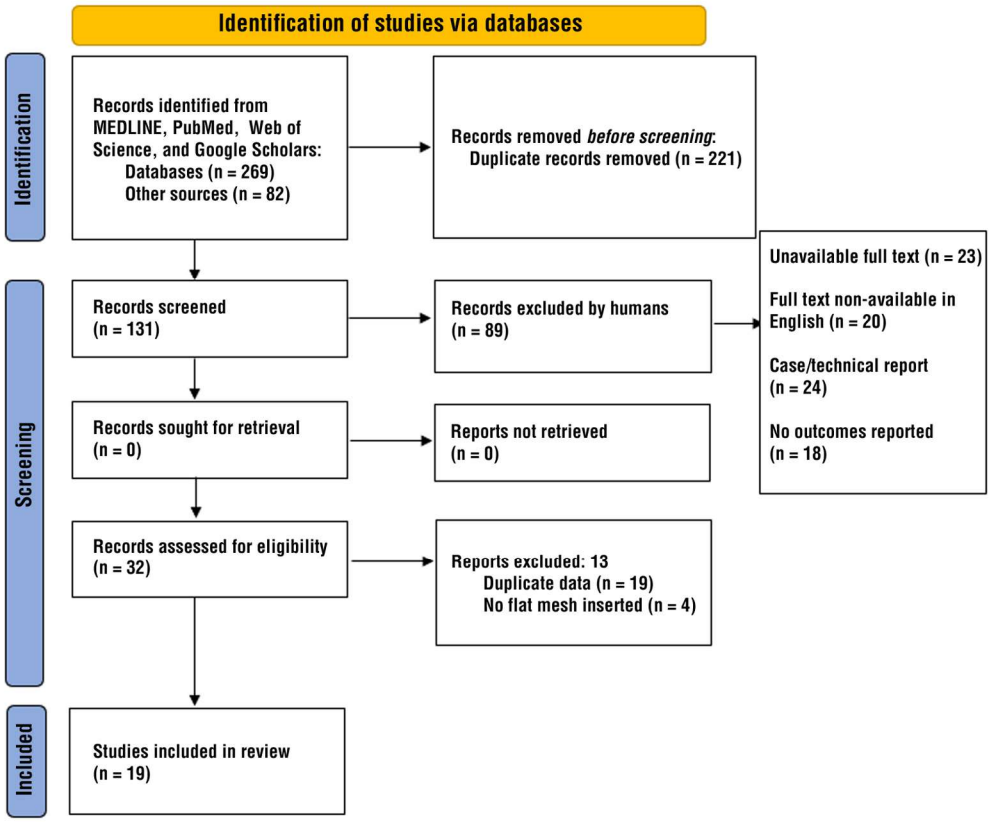


Figure 1. PRISMA flow chart for the review

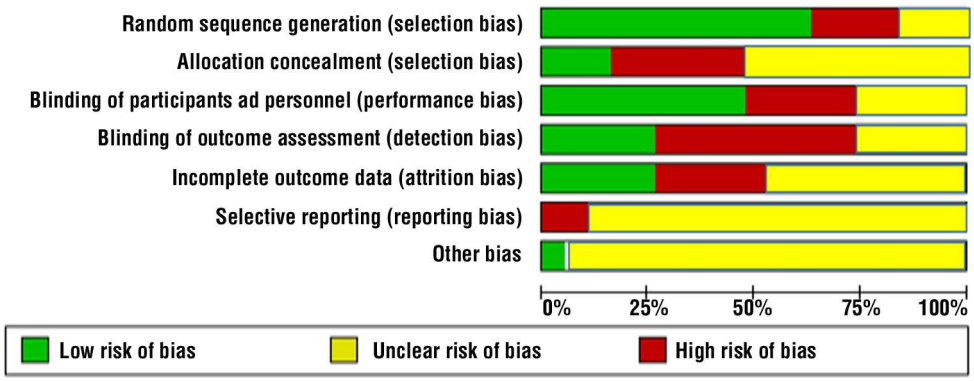


Figure 2. Authors point of view for the risk of bias evaluation

The most common reason for exclusion was the full text unavailability and the presence of only a conference abstract. This 19 RCT's included a total of 3578 patients with 1809 in the glue group and 1769 in the suture group.

The risk of bias assessment (10) is represented globally in *Fig. 2*. In our judgement, we have not found any study with low risk for bias. All of them were with high and moderate risks for random generation (high risk 75%, critical risk 18%), blinding of participants bias (moderate risk 71%, critical risk 24%), blinding of outcome and incomplete outcome data (high risk 80%, critical risk 13%).

Quality assessment only two studies showed very good methodological quality (16,25) with 23 respective 24 MINORS criteria. Most of them were of moderate quality with MINORS criteria between 22 and 19 (*Table 2*).

Baseline characteristics in total 3578 patients were included most of them being males (2633/2920 reported patients). The median of mean age as reported ranged between 19 and 67 years (aggregated median 44.13 years). Median or mean BMI (as reported) ranged from 23.2 kg/m^2 to 34.1 kg/m^2 (aggregated median 26.5 kg/m^2). Multiple comorbidities were poorly reported only in four studies (12,16,22, 23). Therefore were reported 112 patients with Chronic Obstructive Pulmonary Disease (COPD – 3.13%) and 81 diabetic patients (2.26%). Smoking patients were reported in three studies and included 239 patients (12, 14,16). Comparative pooled data for glue vs suture fixation are represented in *Table 3*.

Intra-operative details the location of the defects was described in 14 studies included in our meta-analysis (5,12-16,19-26). Direct hernia was reported for 1257 patients (39.08% of 3216) which were distributed almost equally in glue group (646) and suture group (611) (OR - 1.04; 95% CI = 0.909 – 1.20; p =0.52). There was no statistic difference between groups. Two dimensions of the defect were considered for analysis: less than 1.5 cm and more than 3 cm. Defects less or equally with 1.5 cm were reported in 10 studies and included 894 of 2477 patients (36.09%) (13,15,16,18-28). The glue group comprise 1266 patients with 458

Table 3. Comparative pooled mean values (SD) of demographic variables between groups.

Variable	Glue fixation	Suture fixation	OR (95% CI)	p
Age	45.17 ± 21.45	43.08±20.33	1.4 (0.17 – 1.53)	0.27
Gender (male)	1325/2633	1308	0.986 (0.95 – 1.005)	0.127
BMI (kg/m2)	26.43 ± 2.31	26.69 ± 2.91	0.861 (0.2 – 1.02)	0.63
Diabetes	41/313	40/309	1.01 (0.65 – 1.61)	0.95
COPD	53/417	59/409	-0.14 (-0.54 – 0.25)	0.47
Smoking	116/288	123/282	0.87 (0.62 - 1.21)	0.41

OR – odds ratio; 95% CI – 95% confidence interval; BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease.

defects of 1.5 cm compared to suture group in which 1211 patients with 436 similar defects were included (OR – 0.007; 95% CI = 0.15 – 0.17; p = 0.92). Defects with dimensions larger than 3 cm were described in 11 studies with 2918 patients (5,12,13,15,16,18,20,21,25,26). In glue fixation group were 1482 patients (with 448 hernias larger than 3 cm – 30.22%) whereas in the sutures fixation group there were 1436 patients with 432 hernias larger than 3 cm) (OR – 1.006; 95% CI = 0.85 – 1.17; p = 0.93). A large variety of polypropylene mesh were used for repair and were reported in 15 studies (5, 12-16,19-26). These were Prolene (2 studies), Vypro II (2 studies), Optilene (6 studies), ProliteUltra (1 study). In 4 studies the mesh was reported as polypropylene but without any specification of its commercial denomination. The dimensions were also variable ranging from 12/6 cm to 15/7.5 cm. There were also some variations in the type of suture used for mesh fixation; in 10 studies the used thread was 2-0 polypropylene as a running suture on the inguinal ligament and as an interrupted suture on the internal oblique fascia. 3-0 polyglycolic acid (Dexon) was used in 2 studies in the same manner, while 2-0 polydioxanone was used in 2 studies. Regarding the glue group fixation N-butyl-2cyanoacrylate (Glubran, Histoacryl, and Indermiel) was used in 17 reports in a usual dosage of 0.5 ml. In the rest of the reports, N-hexyl – cyanoacrylate (Ifabond) was used. Median or mean operative time as reported ranged between 32.43 and 79 minutes (aggregated median 44.69 minutes) and was reported as outcome in 14 studies for 3195 patients (5,12, 14,16-18,20,21,23-28). Patients with glue fixation (1614 – 50.51%) have a pooled operative time of 41.7 ± 12.62 minutes comparing with 47.61 ± 14.09 minutes for patients with mesh sutures fixation (SE = 0.47; 95% CI = 6.77 – 4.92; t test = -12.36; p <0.0001). Hetero-geneity was extremely high I^2 = 91% despite the significant statistical difference (*Fig. 3*).

1 – Year recurrence only six studies under-

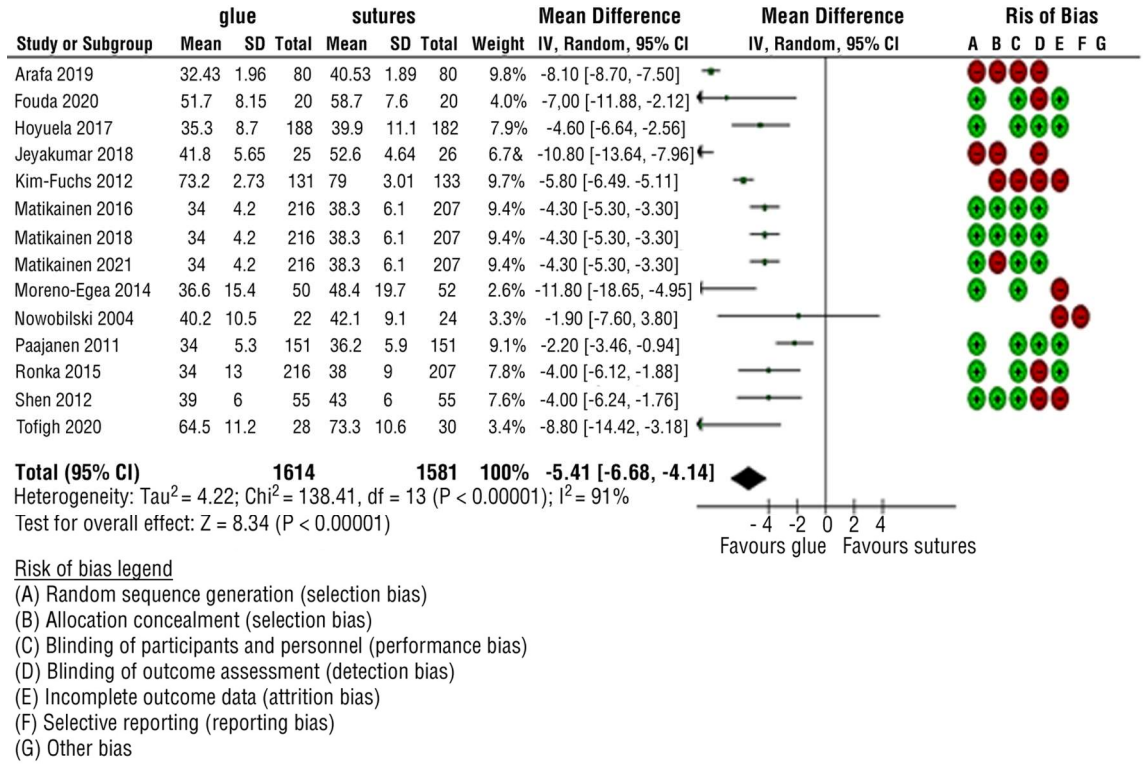


Figure 3. Forest plot showing difference in duration of operation between glue and sutured mesh. A random effect model was used. Mean differences are charted with 95% confidence interval (significant difference favours glue fixation SE = 0.47; 95% CI = - 6.77 - - 4.92; t test = -12.36; p <0.0001).

went meta-analysis for recurrence (12,18,23,25, 26,28). Seventeen events were reported of 1280 included patients with an incidence of 1.32%. There was no heterogeneity among the studies [$\chi^2 = 0.71$, df = 3 (p = 0.87), $I^2 = 0\%$]. Using the random effect model, there was no significant difference between groups in reporting recurrence rate (seven events of 647 glue patients vs 10 events of 633 patients; OR – 0.68; 95% CI = 0.25 – 1.80; p = 0.43) (*Fig. 4*). The rate of one – year recurrence varied substantially between the studies and ranged from zero to 5%. There was a difference in the duration of follow-up, and completeness of follow-up data not shown. We found only one study reporting long-term recurrence rate (7 years) with an adequate follow-up which reporting 5 recurrences (4.3%) for glue patients and three (2.5%) recurrent hernias for sutures group (21).

Postoperative Pain

One – month pain: only three studies reported one – month postoperative pain and underwent meta-analysis (12,15,25). This includes 37 events on 486 patients (7.61%). No significant heterogeneity among the studies was identified. In glue group only six patients reported significant pain (2.37%) whereas in the sutures group 31 were included (13.3%). The difference was statistically significant (OR – 0.158; 95% CI = 0.064 – 0.386; p = 0.0001) (*Fig. 5*).

Chronic postoperative inguinal pain was reported in nine studies included in the meta-analysis (5,12,20-22,25,26-28). The pooled estimated incidence was 7.66% and varied among studies between 2.12% and 17.83%. Overall, 91 events in 2491 patients were reported and were distributed almost equally: 96 of 1270 in the glue patients and 95 of 1221 in the suture patients group; there was no significant difference among the groups (OR – 0.96; 95% CI = 0.72 – 1.30; p = 0.835) (*Fig. 6*). A moderate heterogeneity between studies ($I^2 = 51\%$; $\chi^2 = 18.29$, df = 8 (p = 0.02)) was identified.

Wound Complications

Seroma was reported in seven studies, which underwent meta-analysis (12,14,16,18,19,26, 28) and included 1362 patients. The incidence varied among studies between 0.54 and 12.5%; the pooled estimated incidence was 3.1% (41 events). In glue group of patients the pooled reported seroma rate was lower (19 events in 691 patients) than for the suture group (22

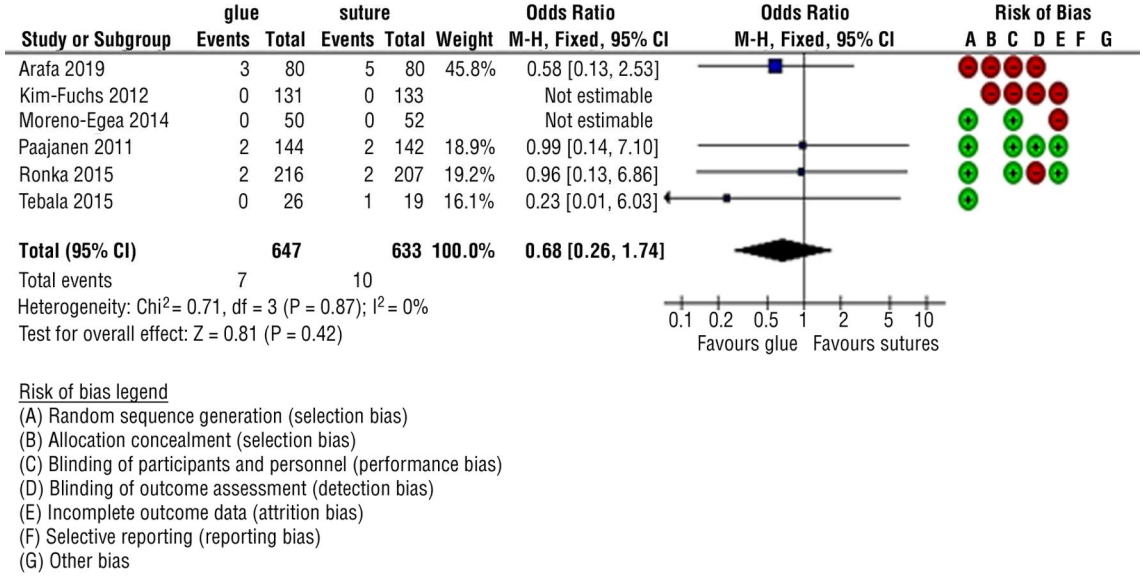


Figure 4. Forrest plot comparing 1 year hernia recurrence following glue and suture fixation of mesh. A random effect model was used. Odds ratios are charted with 95% confidence interval (OR – 0.68; 95% CI = 0.25 – 1.80; p = 0.43)

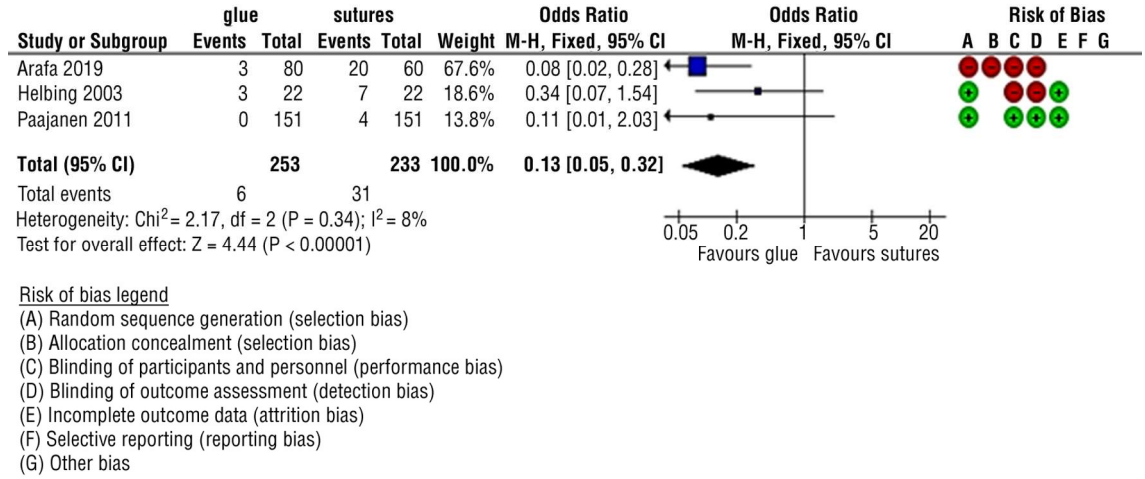


Figure 5. Forrest plot comparing early postoperative pain (1-month) following glue and suture fixation of mesh. A random effect model was used. Odds ratios are charted with 95% confidence interval (significant difference favours glue fixation OR – 0.158; 95% CI = 0.064 – 0.386; p = 0.0001)

events for 671 patients) but the difference was not statistically significant (OR – 0.83; 95% CI = 0.44 – 1.55; p = 0.56). There was no heterogeneity among the reported studies (*Fig. 7*).

Hematoma was reported in eight studies and has had a pooled reported rate of 5.57% (12,15,16,18,23,25-27). Using the random effect model, we found no difference between glue patients (42 events in 893 patients) and suture patients (57 of 884) (OR – 0.716; 95%CI = 0.47 – 1.078; p = 0.1103). No reported heterogeneity among reported studies (*Fig. 8*).

Surgical site infections the meta-analysis included 950 patients reported in six studies (12,14-16,23,25). The pooled incidence was 1.89% (18 events) and varied among studies between 0.98 and 2.5%. There was no heterogeneity among studied groups ($\chi^2 = 2.39$; df = 5 (p =0.79; I2 = 0%). Even if the pooled incidence was higher in glue patients (11 events for 441

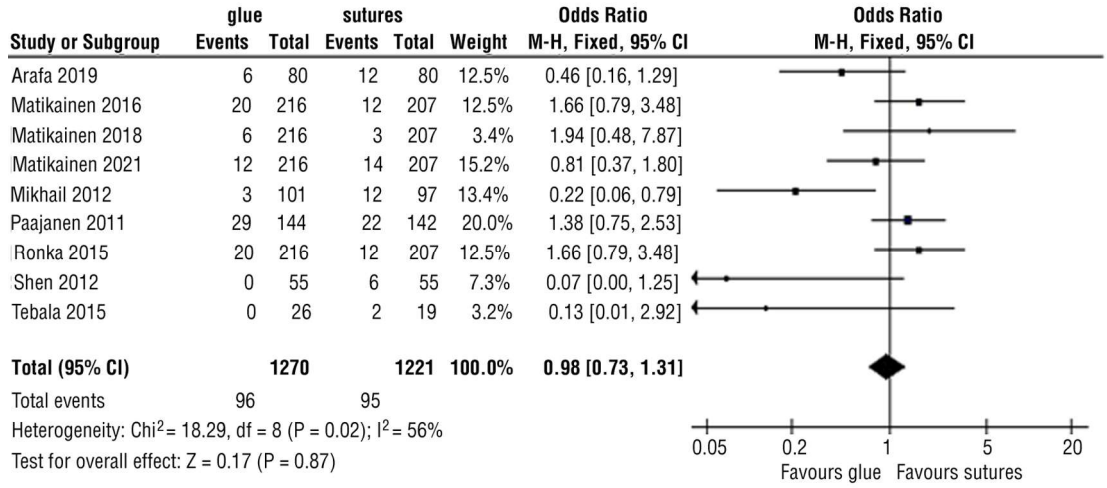


Figure 6. Forrest plot comparing chronic postoperative inguinal pain (1-year) following glue and suture fixation of mesh. A random effect model was used. Odds ratios are charted with 95% confidence interval (no difference between groups OR – 0.96; 95% CI = 0.72 – 1.30; p = 0.835)

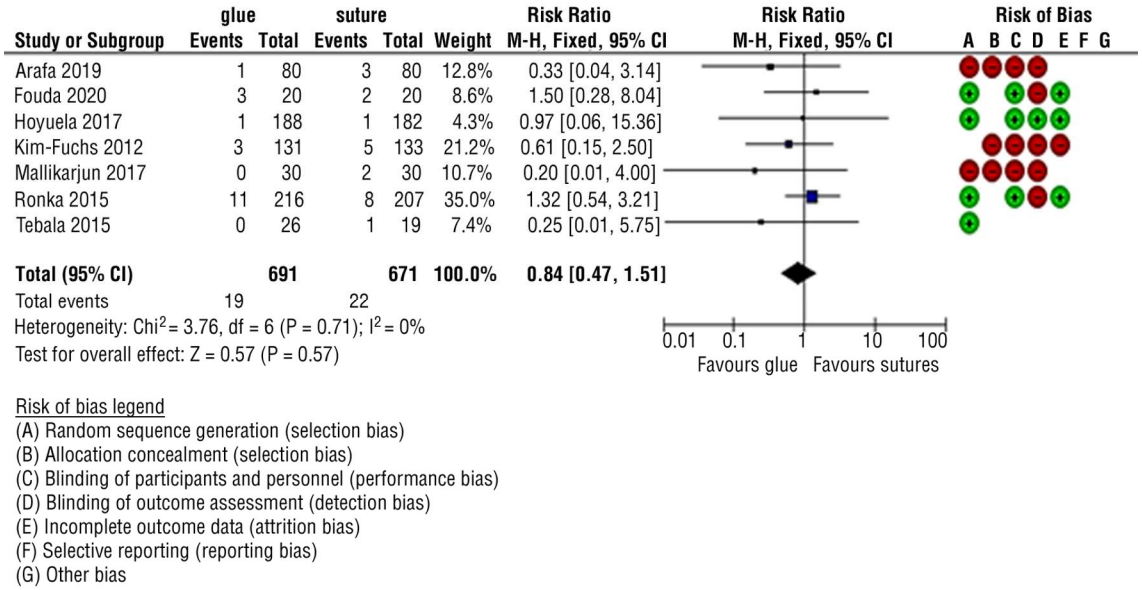


Figure 7. Forrest plot comparing seroma rate following glue and suture fixation of mesh. A random effect model was used. Risk ratios are charted with 95% confidence interval (OR – 0.83; 95% CI = 0.44 – 1.55; p = 0.56 no statistical difference)

reported patients – 2.49%) than in suture patients group (seven events for 509 patients – 1.37%) the random effect model showed no difference between groups (OR – 1.83; 95% CI = 0.70 – 4.77; p = 0.213). No identified heterogeneity between groups (*Fig. 9*).

Length of hospital stay was reported in six studies but in two was less than 24 hours so they were not included and only four underwent meta- analysis (13,15,18,27). It was

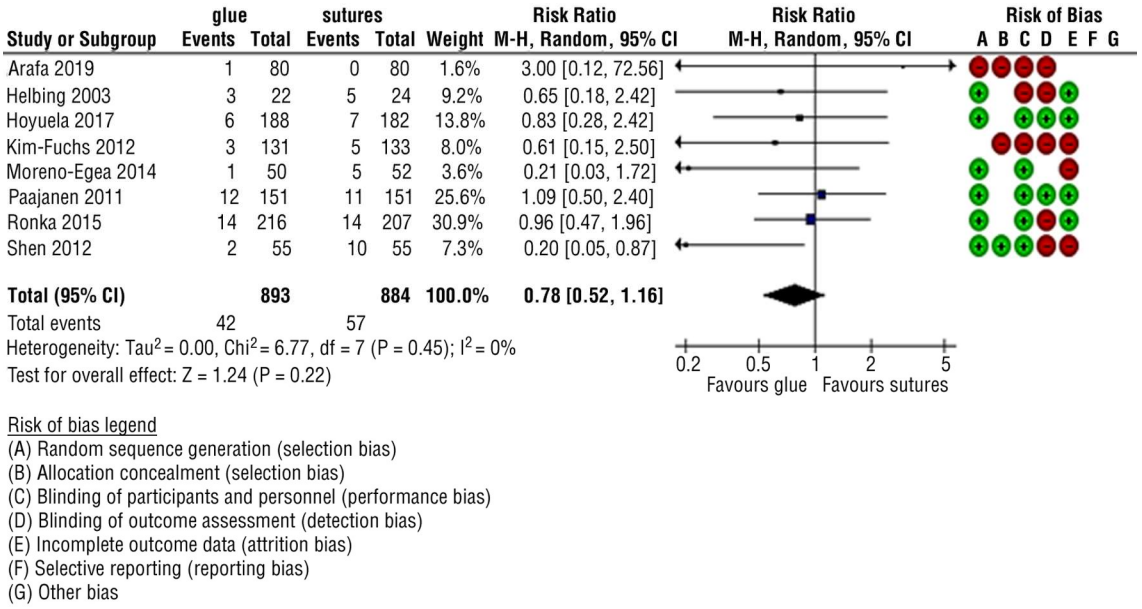


Figure 8. Forrest plot comparing hematoma rate following glue and suture fixation of mesh. A random effect model was used. Risk ratios are charted with 95% confidence interval (no significant difference between groups OR – 0.716; 95%CI = 0.47 – 1.078; p = 0.1103)

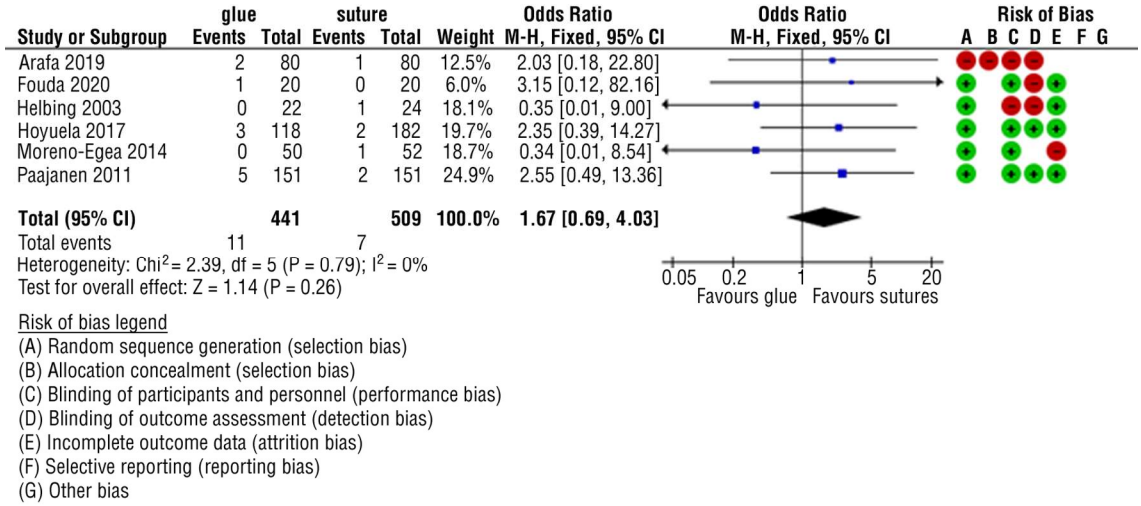


Figure 9. Forrest plot comparing surgical site infections rate following glue and suture fixation of mesh. A random effect model was used. Risk ratios are charted with 95% confidence interval (no significant difference identified between groups OR – 1.83; 95% CI = 0.70 – 4.77; p = 0.213)

reported as a mean and varied from two to 3.4 days (aggregated mean 2.68 ± 0.68 days). Patients with glue fixation had a pooled hospital stay of 2.68 ± 0.79 compared 2.94 for patients with sutures fixation. The random effect model showed a significant statistical difference (SE = 0.0675; 95% CI = - 0.39 - 0.12; t-Test = -3.86; p = 0.0001) but with an increased heterogeneity (χ^2 = 14.11; df 3 (p = 0.003); I^2=79%) (*Fig. 10*).

Follow-up expressed as mean, ranged between 4.7 and 160 months with an aggregated pooled value of 28.94 ± 44.51 months. Eleven studies met the criteria to undergo meta-analysis (14,16,18,20,22-28) and included 2118 patients. Patients had almost equal periods of follow up (29.15 ± 45.93 for glue group vs 28.73 ± 45.28 months); the difference was insignificant (SE = 1.98; 95% CI = -3.46 – 4.30; p = 0.83).

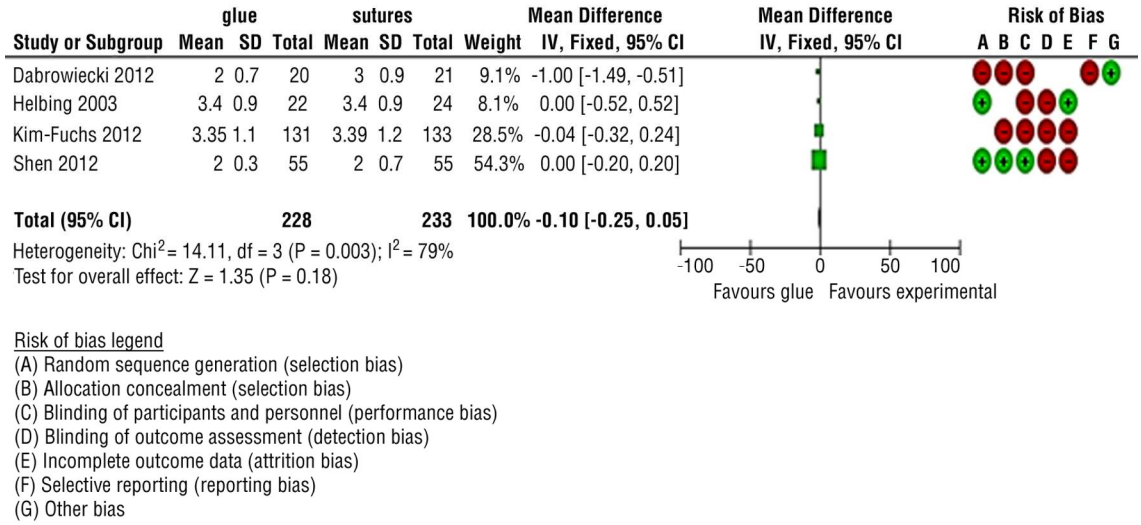


Figure 10. Forrest plot comparing length of hospital stay following glue and suture fixation of mesh. A random effect model was used. Mean difference ratios are charted with 95% confidence interval

Discussion

There were at least 6 systematic reviews and meta-analysis published in the last 10 years searching for the effectiveness of glue versus suture fixation of the mesh in Lichtenstein hernia repair (7,30-34). All of them mixed the results of mesh fixation with synthetic and biologic glues which somehow it is not correct due to the different physicochemical properties in terms of degradation and power of fixation. As inguinal hernia repair is often associated with CPIP, even modest improvements in clinical outcomes would have a significant medical and economic impact (7). Until now, despite of a large amount of research there is no consensus regarding which method of fixation is better.

This systematic review and meta-analysis is focused on the short-term consequences of mesh fixation with cyanoacrylates compared with suture fixation in open tension free Lichtenstein hernia repair. To complete last meta-analyse of Sun et al more studies and almost a double number of patients were included to exclude this concerns.

Compared to fixation with sutures, our review suggests that hernia repair can benefit more from glue fixation only for operative time (shorter with a pooled mean of 6 minutes), early postoperative pain (1 month), and length of hospital stay (which somehow is superfluous because more frequent hernia is repair as day case procedure). There were no differences between glue and suture fixation of mesh in terms of hernia recurrence, postoperative wound events, and CPIP. There were heterogeneity among the studies in terms of duration of surgery, SSI rate, and length of hospital stay. Despite the use of random effects model the interpretation of the results requires some caution.

Our compared groups showed no difference in the baseline characteristics in terms of age, sex, female sex, or preoperative groin pain. This is a relevant finding and in association with the reduction of early postoperative pain seems to be an important factor of chronic postoperative pain by avoiding suture-related nerve entrapment or nerve compression by a folded mesh (35-37). As the intensity of acute postoperative pain highly correlates with the risk of developing CPIP, it is most likely that only patients with intraoperative nerve damage will suffer this complication (38). As a direct consequence, surgeons must be trained to perfectly know the nervous groin anatomy, to identify and preserve the nerves and to correctly manage a damaged nerve (35). This strategy has been shown to reduce the incidence of CPIP from 21.6% to 5.5% (39). The use of light mesh in Lichtenstein repair has also shown reduced chronic pain as shown in Sajid's et al Meta-analyse (40). Unfortunately, we cannot identify during our analysis how surgeons handled the nerves during procedure and how postoperative pain was, whether acute or chronic, influenced by that.

NBCA is a synthetic cyanoacrylic adhesive which polymerizes exothermically in the presence of water and gradually absorbed (41). Can reach an adhesive strength of up to 11 N/cm^2 or 1120 cm H_2O (27). Physicochemical properties vary depending on the length of their alkyl chain which determines degradation speed. Ideal synthetic glues (biocompatible, fast – acting, easily applied, and economical) are long acting derivate (butyl, hexyl or octyl) (41, 42). They also have haemostatic and antibacterial effect. The adhesive effect can be compromised by local condition: excess fat, presence of blood and large wounds. There is no toxicity and presumed inflammatory reaction (32,41).

Our review is not without limitations. Analysing RCTs with limited number of included patients can be considered a serious publication bias with a huge impact upon the quality of the results. There is a clinical high heterogeneity among studies regarding patient' population, comorbidities, the description, definition, and evaluation (quantitative and qualitative) of pain. The absence of important details regarding the surgical procedure (especially nerve handling) can be considered another publication bias and this impacts the correct evaluation of pain and of the factors

influencing it. Functional outcomes (Quality of Life and daily activities) are reported sporadically and incompletely and therefore, they cannot be included in the review.

Another shortcoming is the quality of the included studies. This is low and moderate according to MINORS criteria for RCTs. Only Hoyuela and Paajanen report high quality trial. Most of them have biased assessment end-points, high percentage of lost from follow-up patients and no prospective size calculation. This calculation can be critical for all studies. According to the number of patients required to demonstrate a 50% Risk Ratio difference with a baseline recurrence rate of 2%, with a power of 80% and with a significance level of 95% would be at least 4534!!! (43).

There is also a lack of complete data reporting on postoperative complications so, these cannot be pooled and compared. There was little information on hernia size and location. Various types of glues, sutures and meshes were used which limited comparability. Last, but not least follow-up, was 1 year for almost all studies and this is an important drawback because there is no realistic evaluation of the real recurrence rate. It is well known that 50% of recurrences are diagnosed around 4 years after the primary procedure (44). Only two studies (Fucks and Matikainen) reported data on recurrence after five respective 7 years but with an important amount of lost patients. The cost – benefit analysis is reported only in one study which revealed a reduction of expenses with the use of glue (22).

Conclusions

Considering all these limitations, our meta-analysis suggests that glue fixation is superior to suture fixation in Lichtenstein repair in terms of duration of operation and acute postoperative pain. Glue fixation was not apparently associated with increased rates of 1-year recurrence, wound events and prolonged hospital stay. Glue can change the paradigm of mesh fixation in open hernia repair if future studies will standardize the assessment of acute and chronic postoperative pain focusing on long-term outcomes.

Author's Contributions

RT; VO, CG: Study design, data collection, data analysis, writing, final approval of the manuscript. MT, CEB, BS, OG: Study design, data analysis, review of article, final approval of the manuscript

Conflict of Interest

None to declare for all authors.

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