Suppressive Effect of Leukotriene Antagonists on Capsular Contracture in Patients Who Underwent Breast Surgery with Prosthesis: A Meta-Analysis

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Background: Capsular contracture is a troublesome and distressing complication in mammaplasty or breast reconstruction involving a prosthesis. Previous studies have indicated that leukotriene antagonists effectively reverse capsular contracture. However, this treatment method lacks comprehensive support from evidence-based medicine and remains considerably controversial. In this study, a meta-analysis was conducted to evaluate the therapeutic and preventive effects of leukotriene antagonists on capsular contracture in patients after breast prosthesis implantation.

Methods: A comprehensive literature search was performed in English and Chinese databases. All clinical studies assessing the therapeutic and prophylactic effects of leukotriene antagonists on capsule contracture after breast prosthesis implantation were selected. Risk differences and 95 percent confidence intervals were applied as the final pooled statistics.

Results: A total of five eligible studies were included, involving 1710 breast prosthesis implantations. The final results indicated that leukotriene antagonists markedly inhibited capsular contracture formation, with statistical significance at 32.02 ($p < 0.001$) (pooled risk difference, 0.84; 95 percent CI, 0.79 to 0.89). In subgroup analysis, subgroups based on different leukotriene antagonists included the montelukast and zafirlukast groups, with significant pooled statistical levels of 19.34 ($p < 0.001$) and 79.48 ($p < 0.001$), respectively (montelukast: pooled risk difference, 0.83; 95 percent CI, 0.75 to 0.92; zafirlukast: pooled risk difference, 0.85; 95 percent CI, 0.83 to 0.87), indicating that both montelukast and zafirlukast were effective in inhibiting encapsulation.

Conclusions: This meta-analysis demonstrated that leukotriene antagonists (montelukast and zafirlukast) have significant effects in treating and preventing capsular contracture. These medications should be administered in a reasonable and safe way. Further studies of clinical efficacy, duration, safety, and exact mechanism of leukotriene antagonists for periprosthetic capsular contracture are warranted.   (*Plast. Reconstr. Surg.* 145: 901, 2020.)

In reconstructive and plastic surgery, breast surgery with prosthetic implants is a common procedure. Periprosthetic capsular contracture is one of the most troublesome and frequent complications of breast implant surgery. Its prevalence varies from 0.5 to 30 percent,[1] depending on the coating of the prosthesis, the type of prosthesis used, the planar placement of the prosthesis, precautions taken intraoperatively and postoperatively, and possibly other as-yet-unidentified contributing factors. Despite increased application of best surgical practices and textured devices leading to reduced rates of capsular contracture, the latter remains the cause of reoperation and most common complications after breast implant surgery.[2]

To date, the exact pathogenesis of capsular contracture remains unknown, and the process

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appears to be caused by multiple factors,[3] with the participation of different cells such as myofibroblasts, mast cells, polymorphonuclear leukocytes, and macrophages.[4] Several studies have shown that myofibroblasts play an important role in the development of capsule contracture through interactions with growth factors and cytokines.[5]

Clinical presentation of capsular contracture includes hard breast, breast pain, and breast firmness, occasionally with visible distortion, depending on the degree of contracture.[1]

Capsule contracture can be treated surgically, by a capsulotomy or cystectomy with implant replacement. Other measures include nonsteroidal anti-inflammatory drugs, chemotherapeutics, external ultrasound, and so on.[6] Recent preliminary studies suggested the use of leukotriene antagonists to prevent capsule contracture.[7,8] Montelukast (Singulair; Merck, Kenilworth, N.J.) and zafirlukast (Accolate; AstraZeneca, Wilmington, Del.), which are both approved by the U.S. Food and Drug Administration for the treatment of asthma,[9,10] reportedly inhibit cysteinyl leukotrienes (leukotrienes C4, D4, and E4) and suppress myofibroblasts, both of which are presumed factors related to contracture.[4,8,10] In 2002, Schlesinger et al.[8] proposed the application of zafirlukast in the treatment and prevention of capsular contracture after breast augmentation surgery. Since then, leukotriene antagonists have been applied as off-label prescriptions to treat or prevent capsular contracture formation.

However, to date, no evidence-based studies have investigated the efficacy of leukotriene antagonists in the treatment or prevention of capsule contracture. The purpose of this meta-analysis was to evaluate the effectiveness of leukotriene antagonists in the prevention and treatment of capsule contracture in patients who underwent breast prosthesis surgery.

METHODS

Systematic Literature Search

A literature search was performed in online databases, including PubMed, EMBASE, Google Scholar, Web of Science (ISI), Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure Database (CNKI), Chinese Scientific Journals Full-Text Database (VIP), Wanfang Database, and SinoMed (CBM), using the following search strategy: ("Mammaplasty"[MeSH] OR Mammaplasties OR Mammoplasty OR Mammoplasties OR Breast Reconstructions OR Breast Reconstruction OR Reconstruction, Breast OR Reconstructions, Breast) AND ("Leukotriene Antagonists"[MeSH] OR Receptor Antagonists, Leukotriene OR Antagonists, Leukotriene Receptor OR Leukotriene Receptor Antagonists OR Antagonists, Leukotriene OR "montelukast"[MeSH] OR MK 0476 OR MK-0476 OR Singulair OR montelukast sodium OR montelukast sodium OR sodium 1-(((1-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropylacetate OR "zafirlukast"[MeSH] OR 4-(5-cyclopentyloxycarbonylamino-2-methylindol-3-yl-methyl)-3-methoxy-N-O-tolylsulfonylbenzamide OR Olmoran OR ICI 204,219 OR ICI-204219 OR ICI 204219 OR Accolate OR Aeronix) AND ("Implant Capsular Contracture"[MeSH] OR Capsular Contracture, Implant OR Contracture, Implant Capsular). All searches were conducted using MeSH and free terms.

This study followed the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (www.prisma-statement.org). As this was an analysis of previously published articles, participant informed consent and ethical approval were not required.

Inclusion Criteria

Inclusion criteria were as follows:

1. Participants: Subjects who underwent aesthetic and reconstructive breast surgery with prosthesis were included.
2. Intervention: Leukotriene antagonists were used for therapeutic or preventive purposes.
3. Comparison: Patients did not receive prophylactic or therapeutic doses of leukotriene antagonists.
4. Outcome: The therapeutic and preventive effects of leukotriene antagonists on capsular contracture were measured.
5. Study: Randomized controlled trials or cohort studies were included.
6. Methodology: The modified Baker grade scale[11] was used as the end diagnostic criteria, as follows.

- Grade 1: Implant undetectable, breast entirely natural;
- Grade 1.5: Prosthesis detectable by physical examination, breast soft;
- Grade 2: Prosthesis not detectable by examiner or the patient, mild breast firmness;
- Grade 2.5: Prosthesis detectable by examiner but not the patient, mild breast firmness;
- Grade 3: Prosthesis detectable by the patient, breast moderately firm;
- Grade 4: Prosthesis obvious from observation, with pain, severe breast firmness.

Patients with modified Baker grade 1.5 to 4 contracture were categorized as having capsular contracture. Patients not changing or remaining with Baker grade 1 were considered effective for prophylactic use of leukotriene receptor antagonists. Responses were scored as partial (reduction in capsular contracture index by 0.5) and complete (return to modified Baker grade 1), which indicates effective treatment.[4]

Exclusion Criteria

Exclusion criteria were as follows:

1. Case reports, duplicated publications, systematic reviews, reviews, letters, and animal/in vitro studies were excluded.
2. Studies not based on the Baker grade classification were excluded.

Selection and Data Extraction

The included reports were carefully reviewed for first author, year of publication, mean patient age, number of positive events, number of total events, positive rate and standard error, leukotriene antagonist category, duration of treatment, follow-up time and follow-up rate, implant materials, implant pocket placement, incision types, study design, type of surgery, implant size, complications, and adverse effects (Table 1). Data extraction was performed independently by two reviewers. Any discrepancies were resolved by discussion or consultation with a third reviewer.

Quality Assessment

Quality assessment of included randomized controlled trials was conducted with the Cochrane quality assessment criteria.[12] The Newcastle-Ottawa quality assessment scale was used to evaluate the included cohort studies.[13] Two reviewers independently performed the quality assessment of the included literature. Any disagreements were resolved by discussion or consultation with a third researcher.

Statistical Analyses

The meta-analysis of the extracted data was performed by using a pooled random effects model. The pooled parameters were risk difference and 95 percent confidence interval, and $p < 0.05$ was considered statistically significant. The chi-square test was used to evaluate heterogeneity, whose impact on the meta-analysis was assessed using the I^2 statistic. A value of $p < 0.10$ was considered to indicate significant heterogeneity. I^2 values of 25 percent, 50 percent, and 75 percent were regarded as low, moderate, and high heterogeneity, respectively.[14] When significant heterogeneity was observed ($p < 0.10$ or $I^2 > 50$ percent), a random effects model was used to determine the summary risk difference and the corresponding 95 percent confidence interval; otherwise, a fixed effects model was employed. The funnel plot was used to assess potential publication bias graphically.

To determine the source of heterogeneity and the influences of different leukotriene antagonists on pooled effects, subgroup analysis was performed based on the used leukotriene antagonists (montelukast and zafirlukast groups).

Sensitivity analysis was performed by excluding the included studies one by one to confirm the stability of the outcomes. Whether one study had a significant impact on the pooled effect was determined by the following strategy: after one study was deleted, the point estimate of the pooled effect was changed significantly compared with the 95 percent confidence interval of the total pooled effect.

The RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was applied in this meta-analysis.

RESULTS

Included Studies

A total of 68 publications [PubMed, $n = 19$; EMBASE, $n = 11$; Google Scholar, $n = 27$; Web of Science (ISI), $n = 11$; Cochrane Central Register of Controlled Trials (CENTRAL), $n = 0$; China National Knowledge Infrastructure Database (CNKI), $n = 0$; Chinese Scientific Journals Full-Text Database (VIP), $n = 0$; Wanfang Database, $n = 0$; SinoMed (CBM), $n = 0$] were eventually identified through the initial database search. After duplicate publications were excluded, 39 articles (Pubmed, $n = 19$; EMBASE, $n = 2$; Google Scholar, $n = 18$) remained. Based on titles and abstracts, 16 reports were excluded and 23 remained. After full-text review of the 23 publications, two case reports, five reviews, seven experimental studies, two publications in other languages, and two reports with unavailable statistics[7,15] (we contacted the authors for the missing data, but there was no reply finally) were excluded. A total of five eligible publications were finally included[1,4,16–18] (Fig. 1).

Study Characteristics

A total of five eligible publications were evaluated in this study, including two prospective observational studies, one retrospective observational study, and two randomized controlled trials. The total study population consisted of 866 subjects

Table 1. Characteristics of Included Studies

First Author, Year	Age (yr)	Event (breasts)	Total No. of Breasts	Positive Rate (P)	Standard Error (P)	Leukotriene Antagonists Category	Duration of Treatment	Follow-Up Time and Rate
Graf, 2015[16]	18–55 (mean, 33)	67	74	0.905	0.034	Montelukast 10 mg/day	3 mo	2 yr 100%
Huang, 2010[17]	18–61 (mean, 44.2)	17	25	0.68	0.093	Montelukast 10 mg/day	3 mo	5–36 mo (mean, 19 mo) 100%
Reid, 2005[4]	18–52 (mean, 34.8)	31	41	0.756	0.067	Zafirlukast 20 mg p.o. BID	3 or 6 mo	6–29 mo (mean, 16.5 mo)
Scuderi, 2006[1]	25–54 (mean, 36 yr 9 mo)	31	36	0.861	0.058	20 mg zafirlukast p.o. BID	3–6 mo	8 mo to 3 yr 3 mo (mean, 1 yr 6 mo) 97.2%
Bresnick, 2017[18]	22 and 60	1288 (zafirlukast treatment, 882; montelukast treatment, 406)	1534 (zafirlukast treatment, 520; montelukast treatment, 247)	0.84	0.009	Montelukast 10 mg/day or zafirlukast 20 mg BID	3 mo	1-yr follow-up (84.8% of zafirlukast patients, 82.2% of montelukast patients)

with 1710 implanted breast prosthesis, and the follow-up time varied from 5 to 36 months in individual studies. Among these studies, 303 patients (593 implanted breast prosthesis) received montelukast (Singulair) treatment, while 563 (1117 implanted breast prosthesis) received zafirlukast (Accolate) treatment. The duration of treatment varied from 3 to 6 months (Table 1).

Quality Evaluation

The Cochrane quality assessment criteria were used to evaluate the two included randomized controlled trials.[13] Both randomized controlled trials showed a low risk of bias (Fig. 2).

The Newcastle-Ottawa scale was adopted to evaluate the three cohort studies (Table 2). The results showed that studies were all rated greater than six stars, showing low risk of bias.

All funnel plots were symmetrical, indicating no significant publication bias, although the number of included studies was small.

Synthesis of the Results

As shown in Figure 3, overall efficiency was obtained based on the two randomized controlled trials and three cohort studies involving 1710 implanted breast prosthesis; 303 patients (593 implanted breast prosthesis) received montelukast

Implant Materials (no. of patients)	Implant Pocket Placement (no. of patients)	Incision Type (no. of patients)	Study Design	Type of Surgery (no. of patients)	Implant Size (cc)	Complications and Adverse Effects (no. of patients)
Silicone, textured (all)	Subfascial plane (65), subglandular plane (15), and submuscular (2)	Inframammary fold incision (37), periareolar approach (16), inverted T (14), axillary (10), vertical scar (4)	RCT	Breast augmentation (51), mastopexy with prosthesis (25), exchange of mammary prosthesis (6)	150–495 (average, 279)	Suture dehiscence (10), prosthesis exposure (1), seroma (1), prosthesis rupture (1), galactorrhea (1), lymphatic cyst in the armpit (1)
Silicone implant (18), saline implant (1), smooth	Implants placed subpectorally (6), placed in the submammary plane (13)	Periareolar (7), crescent mastopexy (3), Binelli (1), inframammary (5), vertical mastopexy (1), Wise pattern (2)	Retrospective observational study	Primary augmentation (2), breast reconstruction (1), implant exchange (4), capsulotomy (2), secondary revision surgery with capsulectomy (10)	250–700 (average, 450)	
Saline, smooth (41 breasts)	Submuscular (41 breasts)		Prospective observational study	Breast augmentation (23)	230–430 (mean, 318)	
Cohesive silicone (17), round double-lumen implant filled with silicone gel and saline solution (10), silicone (9), textured		Inframammary approach (12), retromuscular pocket location (8; 12 prostheses)	Prospective observational study	Augmentation mastoplasty (8), replacement after breast augmentation (4), mammary reconstruction (8)		Hypertension (1)
Silicone implants, smooth (all)		Periareolar (72%) or inframammary (28%) approaches	RCT	Breast augmentation (767)		Headache, gastrointestinal symptoms, fatigue, rash, vivid dreams, insomnia, headache, mood changes, muscle pain

(Singulair) treatment, while 563 patients (1117 implanted breast prosthesis) received zafirlukast (Accolate) treatment). The meta-analysis results were pooled based on capsular contracture conditions at last follow-up. The pooled risk difference was 0.84 and the corresponding 95 percent confidence interval was 0.82 to 0.86, showing statistical significance at 32.02 ($p < 0.001$),[19] which indicates that leukotriene antagonists significantly inhibited capsular contracture formation.

Subgroup Analysis

Subgroup analysis was performed based on different leukotriene antagonists. Both montelukast (pooled risk difference, 0.83; 95 percent CI,
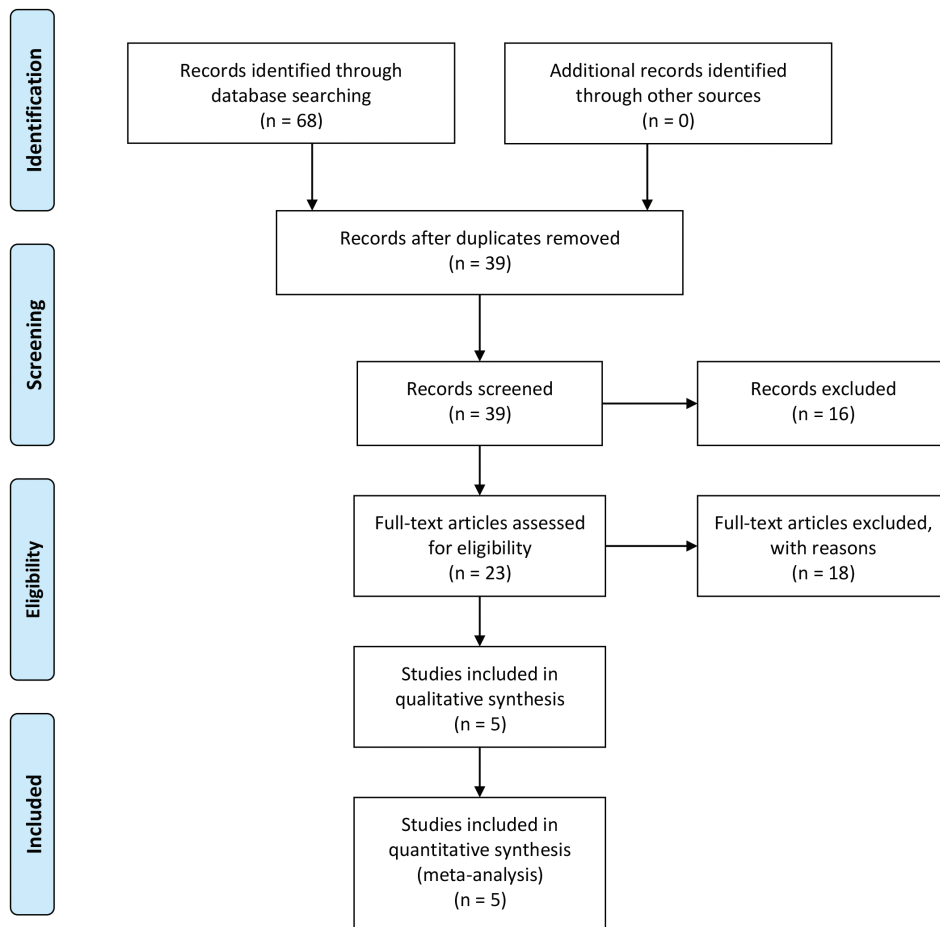
0.75 to 0.92) and zafirlukast (pooled risk difference, 0.85; 95 percent CI, 0.83 to 0.87) groups exhibited significant differences at 19.34 ($p < 0.001$) and 79.48 ($p < 0.001$), respectively. The results of each subgroup indicated that both montelukast and zafirlukast could effectively prevent capsular contracture formation after breast prosthesis implantation. The details of the subgroup analysis are shown in Figure 4.

Risk of Bias

The two randomized controlled trials showed a low risk of bias (Fig. 2), with Newcastle-Ottawa scale quality assessment scores ranging from 7 to 8 (Table 2). As shown in Figure 5, funnel plots

PRISMA 2009 Flow Diagram

Identification

Records identified through
database searching
(n = 68)

Additional records identified
through other sources
(n = 0)

Screening

Records after duplicates removed
(n = 39)

Records screened
(n = 39)

Records excluded
(n = 16)

Eligibility

Full-text articles assessed
for eligibility
(n = 23)

Full-text articles excluded,
with reasons
(n = 18)

Included

Studies included in
qualitative synthesis
(n = 5)

Studies included in
quantitative synthesis
(meta-analysis)
(n = 5)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Fig. 1. Study flowchart. *PRISMA,* Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were symmetrical, indicating no significant publication bias, although the number of included studies was small.

Sensitivity Analysis

After deleting the included articles one by one, all the estimate fell inside the 95 percent confidence interval of total pooled effect and were not changed significantly compared to the 95 percent confidence intervals of the total pooled effects (Table 3). Thus, sensitivity in the present study had good robustness.

DISCUSSION

Capsular contracture is the most common complication involved in both reconstructive and cosmetic breast implant surgery. Some advances, such as submuscular placement and inframammary incision, and textured devices are helpful in the reduction of capsular contracture. Nevertheless, despite these advances, a significant number of women suffer from capsular contracture after breast implant surgery and live with deformities, discomfort, and/or asymmetry, or require revision surgery. Periprosthetic capsular contracture remains the major drawback of implant use, which is very frustrating for patients and surgeons.[20]

Its precise mechanism is unknown,[21] and several theories have attempted to explain the cause of capsular contracture. It is known that there are probably some factors triggering inflammation within and around the pocket created to envelop
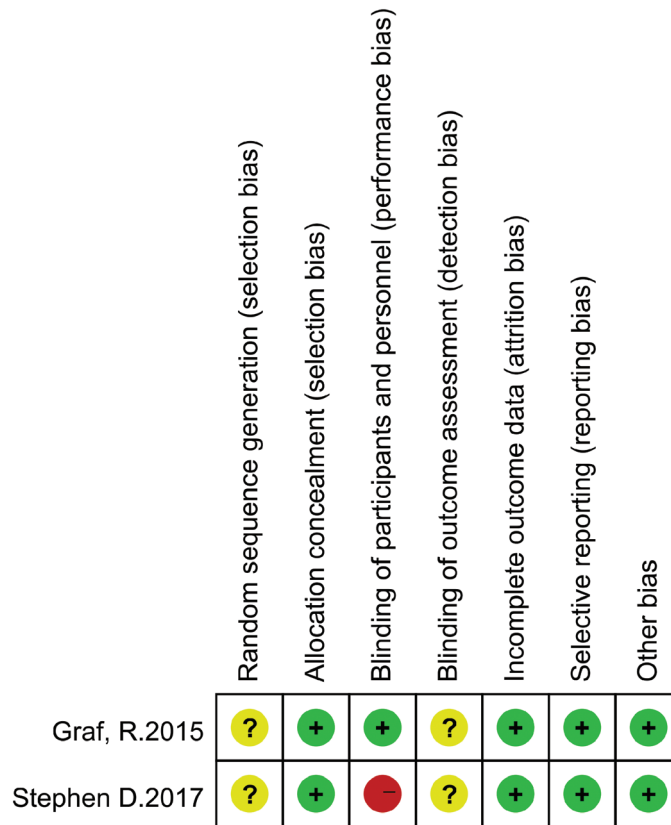
Fig. 2. Risk of bias assessment for randomized controlled trials.

the prosthesis. The cause of capsular contracture is multifactorial, including implant surface texture,[22,23] anatomic placement,[24] bacterial contamination,[25] and intraoperative complications, such as accumulation of blood and fluid around the prosthesis. Any of these factors may induce an inflammatory response, resulting in periprosthetic fibrosis.[26] In the process of fibrosis, myofibroblasts play an essential role in the development of capsular contracture by interacting with growth factors and cytokines.[5]

The current recommendations for capsular contracture treatment are breast massage, steroids,

Table 2. The Newcastle-Ottawa Scale Quality Assessment for Cohort Studies

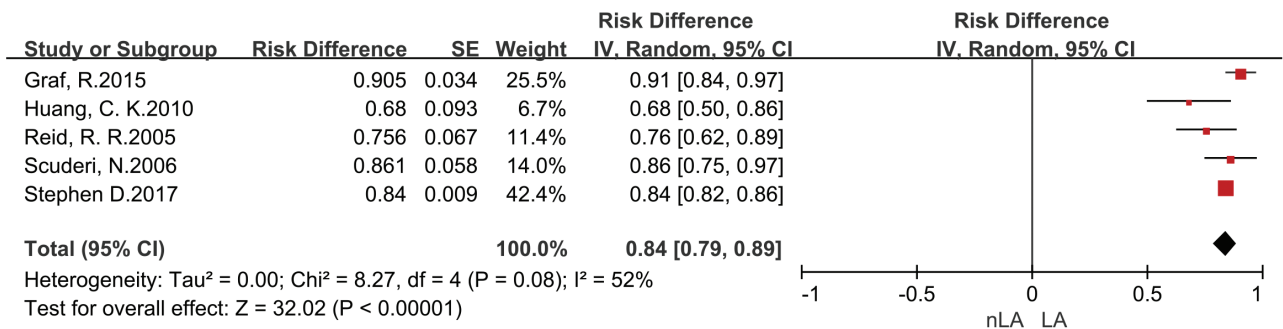| First Author, Year	Selection	Comparability	Outcomes	Total	Quality
Huang, 2010[17]	4 stars	1 star	3 stars	8 stars	Good
Reid, 2005[4]	4 stars	1 star	2 stars	7 stars	Good
Scuderi, 2006[1]	3 stars	1 star	3 stars	7 stars	Good

Fig. 3. Overall efficiency rates of capsular contracture prevention in patients receiving a leukotriene antagonist (*LA*) (after treatment) or not (before treatment) (random effects model).
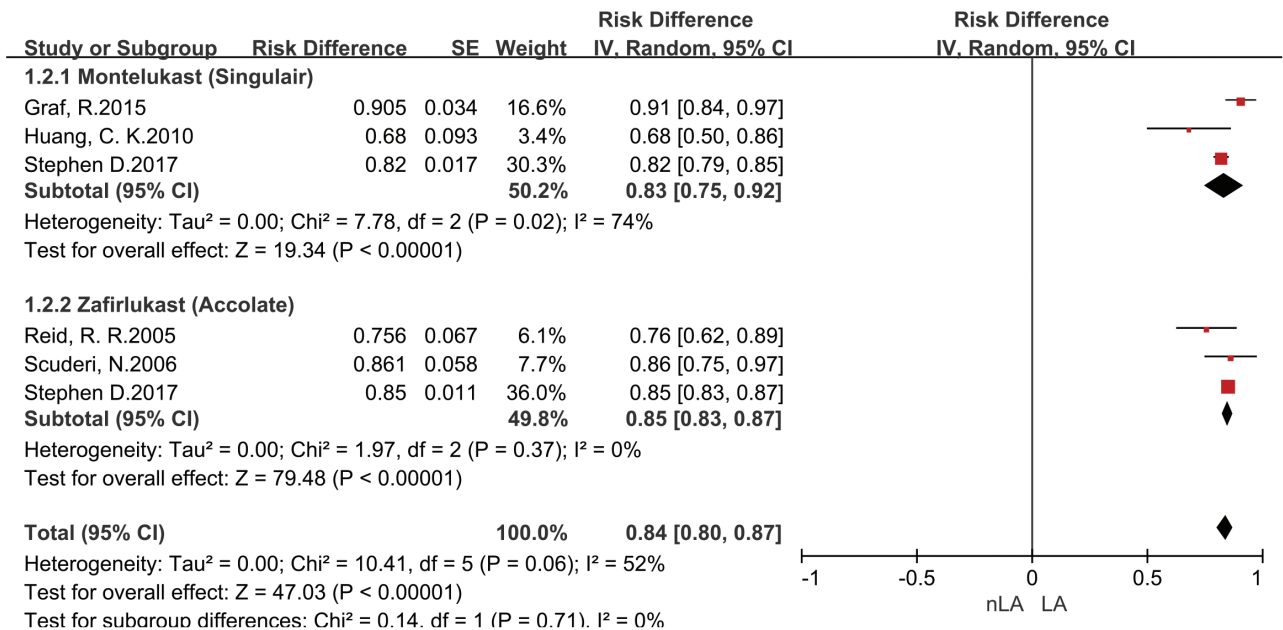
Study or Subgroup	Risk Difference	SE	Weight	Risk Difference IV, Random, 95% CI	Risk Difference IV, Random, 95% CI
1.2.1 Montelukast (Singulair)					
Graf, R.2015	0.905	0.034	16.6%	0.91 [0.84, 0.97]	
Huang, C. K.2010	0.68	0.093	3.4%	0.68 [0.50, 0.86]	
Stephen D.2017	0.82	0.017	30.3%	0.82 [0.79, 0.85]	
Subtotal (95% CI)			**50.2%**	**0.83 [0.75, 0.92]**	
Heterogeneity: Tau² = 0.00; Chi² = 7.78, df = 2 (P = 0.02); I² = 74%					
Test for overall effect: Z = 19.34 (P < 0.00001)					
1.2.2 Zafirlukast (Accolate)					
Reid, R. R.2005	0.756	0.067	6.1%	0.76 [0.62, 0.89]	
Scuderi, N.2006	0.861	0.058	7.7%	0.86 [0.75, 0.97]	
Stephen D.2017	0.85	0.011	36.0%	0.85 [0.83, 0.87]	
Subtotal (95% CI)			**49.8%**	**0.85 [0.83, 0.87]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 2 (P = 0.37); I² = 0%					
Test for overall effect: Z = 79.48 (P < 0.00001)					
Total (95% CI)			**100.0%**	**0.84 [0.80, 0.87]**	
Heterogeneity: Tau² = 0.00; Chi² = 10.41, df = 5 (P = 0.06); I² = 52%					
Test for overall effect: Z = 47.03 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%					

Fig. 4. Efficient rates of capsular contracture prevention in patients receiving a leukotriene antagonist (*LA*) (after treatment) or not (before treatment) (random effects model).

nonsteroidal anti-inflammatory drugs, external ultrasound, chemotherapeutic agents, and lastly surgical intervention, including capsulotomy or capsulectomy with implant replacement.[16] However, even surgery does not guarantee a successful outcome. It is widely believed that the best treatment option for capsular contracture is prevention.[27,28]

Pharmacologic inhibition of inflammation has become the focus of research in the prevention and treatment of capsular contracture. Several studies indicated that leukotriene antagonists, specifically montelukast and zafirlukast, could be an option for the prevention and/or treatment of capsular contracture.[6] Leukotriene antagonists play an important role in inhibiting cysteinyl leukotrienes (leukotrienes C4, D4, and E4 are associated with the inflammatory process, smooth muscle contraction, and cellular contraction), and there is a presumed suppressive effect on contraction of myofibroblasts. Thus, the latter act by preventing severe fibrotic reactions and altering the inflammatory cascade associated with capsular contracture.[1]

Zafirlukast (Accolate) competitively inhibits three different leukotrienes (C4, D4, and E4), compared with montelukast (Singulair), which inhibits only leukotriene D4.[29,30] Thus, zafirlukast may offer a more robust effect in inhibiting the encapsulation process.[18]

The pooled outcomes in the present study indicated that leukotriene antagonists have significant inhibitory effects on capsular contracture formation after breast prosthesis implantation.

Importantly, leukotriene antagonists were well tolerated without severe complications reported. Our conclusion is consistent with those of previous studies,[1,4,16–18] and the evidence in the present study is more convincing.

According to subgroup analysis, montelukast (pooled risk difference, 0.83; 95 percent CI, 0.75 to 0.92; *p* < 0.01) and zafirlukast (pooled risk difference, 0.84; 95 percent CI, 0.78 to 0.89) resulted in statistically significant differences in inhibiting capsular contracture after breast prosthesis implantation, indicating that both montelukast and zafirlukast have inhibitory effects on encapsulation.

We do not advocate the use of leukotriene antagonists in patients undergoing breast implant surgery as a routine prophylactic treatment. We recommend that administration of leukotriene antagonists should be considered in the following situations[1,4,16–18,31–34]:

- Patients with a history of capsular contracture, breast reconstructive surgery patients with a history of breast cancer,[34] previous breast radiotherapy, or a tendency to develop hypertrophic scars;
- Patients with high risk factors for capsular contracture, including implant features (smooth surface and small size ≤355 cc), surgical factors (periareolar incision, subglandular placement, antibiotic irrigation),31–34 and other risk factors, such
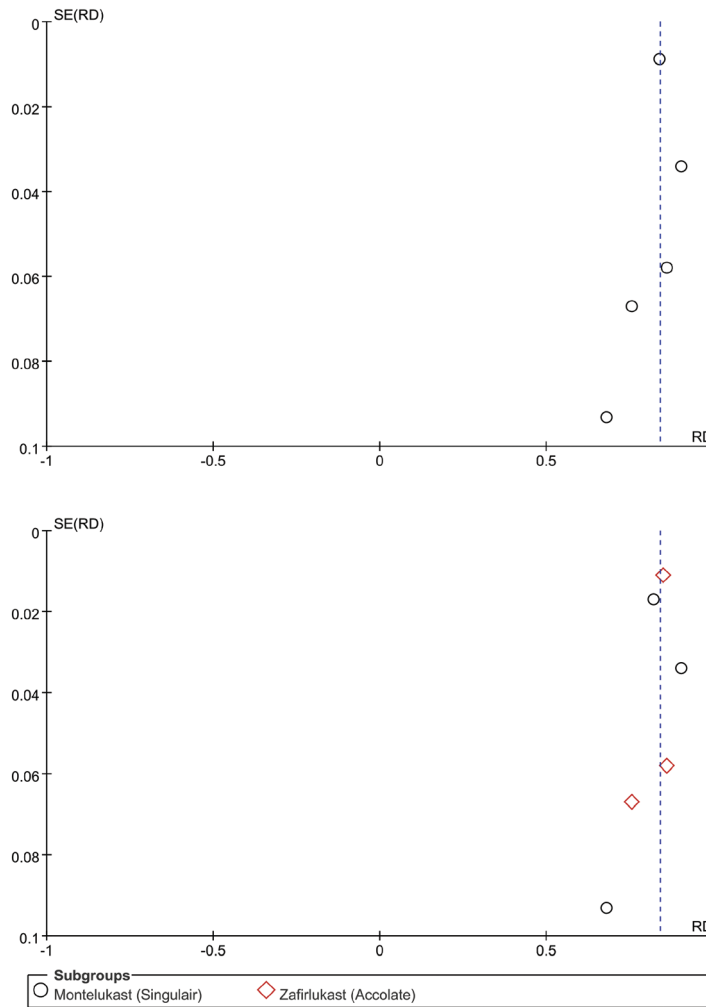
Fig. 5. Funnel plot for publication bias assessment.

as development of hematoma or seroma, periprosthetic infection, surgical bra usage, and so on[31,32,34];

- Patients with limited implant movement, reduced pocket dimensions on implant displacement, and reduced implant compliance before a diagnosed capsular contracture;
- Patients with established capsular contracture but who are not surgical candidates or who have no desire for surgical intervention.

Table 3. Sensitivity Analysis

Study Omitted	Estimate	Risk Difference (95% CI)	I²
Graf, 2015[16]	0.82	0.76–0.87	35%
Huang, 2010[17]	0.85	0.81–0.89	43%
Reid, 2005[4]	0.85	0.80–0.90	55%
Scuderi, 2006[1]	0.83	0.77–0.90	63%
Bresnick, 2017[18]	0.82	0.73–0.92	62%

Many surgeons believe that the best treatment option for capsule contracture is prevention. Early and preventive interventions appear to be the best ways to reduce the incidence of significant capsule contracture.[8,27,28] Thus, we suggest that the prophylactic use of leukotriene antagonist should be administrated immediately postoperatively. The leukotriene antagonist therapy of established capsular contracture should be started early. Zafirlukast is commonly administered orally, twice a day at a dose of 20 mg, and montelukast once a day at a dose of 10 mg. In the five articles analyzed, the leukotriene inhibitor therapy was used for between 3 and 6 months. However, whether this is overtreatment or not is uncertain. We think that within these studies, 3 months of treatment was effective, but it is as yet unknown what the minimum length of therapy might be to achieve the desired reduction in capsular contracture. More clinical trials are needed to further identify the indications and reasonable duration

of leukotriene antagonists for the prevention or treatment of capsular contracture, and ultimately reach a consensus.

Possible side effects of montelukast are headache, flu, abdominal pain, cough, and dyspepsia.[16] The most common adverse effects of zafirlukast are headache, nausea, and, rarely, liver failure.[1] Patients should be counseled preoperatively about the potential benefits and risks of therapy, as well as the need to monitor transaminase levels (although liver failure is rare), if leukotriene antagonist therapy is to be undertaken. Contraindications for leukotriene inhibitors are hypersensitivity to this product, abnormal liver function, and pregnancy.[16]

Treatment of capsular contracture with leukotriene antagonists is an off-label procedure, which is generally legal and very common. However, longer follow-up studies and clinical trials are warranted to further investigate the safety, efficacy, and duration of leukotriene antagonists in the treatment and prevention of capsular contracture, and to generate additional data for approval agencies to expand indications of this class of drugs.[35]

Limitations

Among the included publications, research subjects were breast augmentation, breast reconstruction, mastopexy, and prosthesis exchange patients. There are certain differences in these types of patients (healthy status, skin conditions, previous resection of glandular and subcutaneous tissue, and so on), which might cause heterogeneity in the pooled results. The number of participants was relatively small, and most reports were cohort studies, with only two randomized controlled trials. It is worth noting that loss to follow-up information existed in two publications[7,15] included in this study, but the overall number of patients lost to follow-up was small. However, the sample size was large, and the included studies had good quality; thus, these differences likely did not have an impact on the pooled results.

CONCLUSIONS

This study demonstrated that leukotriene antagonists can effectively reverse capsular contracture after breast prosthesis implantation, showing significant improvements in both treatment and prevention. Leukotriene antagonists should be administered safely and reasonably in certain situations. The safety, long-term efficacy, duration, and precise mechanism by which the leukotriene antagonists decrease or prevent capsular contracture warrant further investigation.

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