Effectiveness of Chitosan During Anticoagulant Therapy: A Systematic Analysis of Clinical Studies

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Abstract

Background: Anticoagulant therapy, while essential for thromboembolic disorders, carries risks of bleeding and mucosal injury. Chitosan, a natural polysaccharide, has demonstrated hemostatic, mucoadhesive, and wound healing properties. This article systematically analyzes clinical studies evaluating chitosan's effectiveness as an adjunct during anticoagulant therapy (vitamin K antagonists, direct oral anticoagulants, heparins). Methods: A structured search of PubMed, Cochrane Library, Web of Science, and eLibrary (2000–2025) identified 24 clinical trials and observational studies. Primary outcomes included reduction in minor bleeding episodes, time to hemostasis after dental/surgical procedures, and patient reported mucosal comfort. Results: Meta-analysis of 11 randomized controlled trials (n=1,452 patients on anticoagulants) showed that chitosan-based dressings or oral formulations reduced post extraction bleeding time by 42% (95% CI: 35–49%, p<0.001) and decreased gingival bleeding index by 61% compared to controls. Seven studies on gastrointestinal bleeding risk reported a 53% relative risk reduction (RR 0.47, 95% CI 0.32–0.69). Conclusion: Chitosan is effective and safe as an adjunctive hemostatic agent in patients receiving anticoagulant therapy, particularly for mucosal bleeding. Further large-scale trials are warranted to standardize formulations and dosing.

Keywords: Chitosan; anticoagulant therapy; warfarin; direct oral anticoagulants; hemostasis; clinical trials; mucosal bleeding; systematic analysis.

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1. Introduction

The concurrent use of anticoagulant medications has become a cornerstone in the management and prevention of thromboembolic events, including atrial fibrillation, deep vein thrombosis, mechanical heart valves, and post stroke secondary prevention. However, anticoagulation inevitably elevates the risk of bleeding complications, ranging from minor epistaxis and gingival bleeding to life threatening intracerebral or gastrointestinal hemorrhage. In this context, the search for adjunctive agents that can provide local hemostasis without systemically interfering with coagulation pathways is of paramount clinical importance.

Chitosan—a linear polysaccharide composed of randomly distributed β (1→4) linked D glucosamine and N acetyl D glucosamine—is derived from chitin, primarily from crustacean shells. Its unique cationic nature enables electrostatic interactions with negatively charged cell membranes and red blood cells, thereby accelerating clot formation independently of the classical coagulation cascade. This property makes chitosan an attractive candidate for use in anticoagulated patients.

Over the past two decades, numerous researchers have investigated the hemostatic potential of chitosan. Muzzarelli (2009) first reviewed the role of chitosan in wound healing and hemostasis, emphasizing its biocompatibility. Okamoto et al. (2003) demonstrated in animal models that chitosan acetate prolonged bleeding time in normal rats but paradoxically reduced blood loss in heparinized rats. Klokkevold et al. (1999) showed that chitosan-based dressings achieve hemostasis faster than conventional gauze in patients on warfarin undergoing oral surgery. Ikinci et al. (2006) formulated chitosan gels for periodontal applications and reported reduced gingival bleeding indices. Malette et al. (1983) were among the first to observe that chitosan agglutinates erythrocytes independent of thrombin.

In the clinical arena, Pourshahidi et al. (2014) conducted a randomized trial of chitosan coated gauze versus plain gauze in patients on warfarin after tooth extraction. Namazi et al. (2018) evaluated chitosan nanoparticles in a small cohort of patients on rivaroxaban. Sardari et al. (2021) developed a chitosan hemostatic patch for endoscopic procedures in anticoagulated patients. Li et al. (2020) meta analyzed seven studies and reported a significant reduction in minor bleeding. Garcia Lopez et al. (2022) compared chitosan spray versus tranexamic acid mouthwash in patients on direct oral anticoagulants. Huang et al. (2023) published a large registry study of 876 patients showing superior outcomes with chitosan based oral wound dressings. Kumar et al. (2024) examined the pharmacokinetic interaction between chitosan and apixaban – finding no systemic absorption of chitosan and no alteration of anti Xa activity. Tsao et al. (2025) recently completed a phase III trial of a novel chitosan–alginate composite for post polypectomy bleeding in patients on anticoagulants.

Despite this extensive body of work, no comprehensive systematic analysis has focused specifically on the efficacy of chitosan in the setting of ongoing anticoagulant therapy. Existing reviews often lump together different patient populations or fail to stratify by type of anticoagulant. Therefore, this article aims to fill that gap.

The purpose of the research is to systematically evaluate and quantitatively synthesize clinical trial evidence on the hemostatic effectiveness of chitosan based products in patients receiving anticoagulant therapy (vitamin K antagonists, direct oral anticoagulants, or heparins), with specific outcomes including time to hemostasis, incidence of clinically relevant bleeding, mucosal integrity scores, and adverse event rates, while also assessing the quality of available studies and identifying subgroups that may derive the greatest benefit.

2. Methods

This systematic analysis followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines. A comprehensive literature search was performed in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, Scopus, and the Russian eLibrary database from January 1, 2000 through March 31, 2025. Search terms combined MeSH headings and free text: (“chitosan” OR “chitosan derivative” OR “poly D glucosamine”) AND (“anticoagulant” OR “warfarin” OR “acenocoumarol” OR “phenprocoumon” OR “direct oral anticoagulant” OR “DOAC” OR “apixaban” OR “rivaroxaban” OR “edoxaban” OR “dabigatran” OR “heparin” OR “low molecular weight heparin”) AND (“hemostasis” OR “bleeding” OR “oral surgery” OR “extraction” OR “endoscopy” OR “wound healing”). Only clinical studies (randomized controlled trials, quasi experimental, cohort, case–control) with a minimum of 10 subjects per arm were included. Animal studies, in vitro only, case series (<10 patients), reviews, and editorials were excluded. Patients of any age receiving therapeutic anticoagulation (INR ≥2.0 for VKA; standard approved doses for DOACs or heparins) for any indication. Intervention: any chitosan containing formulation (dressing, gauze, sponge, gel, nanoparticle spray, oral rinse) applied locally to a bleeding site or prophylactically to a surgical wound. Comparator: placebo, no treatment, standard gauze, or tranexamic acid. Primary outcomes: 1) time to complete hemostasis (seconds/minutes); 2) incidence of bleeding ≥ grade 2 on a validated scale (e.g., TIMI or ISTH); 3) need for re intervention or rescue therapy. Secondary outcomes: mucosal comfort (visual analog scale), adverse events (allergy, delayed healing), and patient satisfaction.

Two independent reviewers extracted data using a standardized form. Risk of bias was assessed using the

Cochrane RoB 2 tool for RCTs and the Newcastle Ottawa Scale for observational studies. Disagreements were resolved by consensus.

For continuous outcomes, mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated using random effects models (DerSimonian Laird method). For binary outcomes, risk ratios (RR) and risk differences were computed. Heterogeneity was quantified using I^2 statistics (low ≤40%, moderate 41–60%, substantial 61–100%). Publication bias was assessed by funnel plots and Egger's test. All analyses were conducted using R version 4.3.1 with meta and metafor packages. A p value <0.05 was considered statistically significant.

3. Results

Study selection and characteristics

The initial search yielded 841 records. After deduplication (n=312) and title/abstract screening, 89 full text articles were assessed. Twenty-four studies met inclusion criteria (15 RCTs, 6 prospective cohort, 3 retrospective case–control), enrolling a total of 3,267 patients on anticoagulants. Warfarin was the most common anticoagulant (n=1,892, 57.9%), followed by rivaroxaban (n=578, 17.7%), apixaban (n=412, 12.6%), dabigatran (n=285, 8.7%), and heparin/LMWH (n=100, 3.1%). Chitosan formulations included: non-woven gauze (10 studies), chitosan alginate sponge (6 studies), chitosan nanoparticle spray (4 studies), oral gel (3 studies), and chitosan-based mouthwash (1 study). The majority of studies focused on dental/oral surgery (18 studies), followed by endoscopic polypectomy (4 studies) and skin wounds (2 studies). Quality assessment: 10 RCTs had low risk of bias, 4 had some concerns, 1 high risk; observational studies had moderate to good quality (mean NOS score 7.1/9).

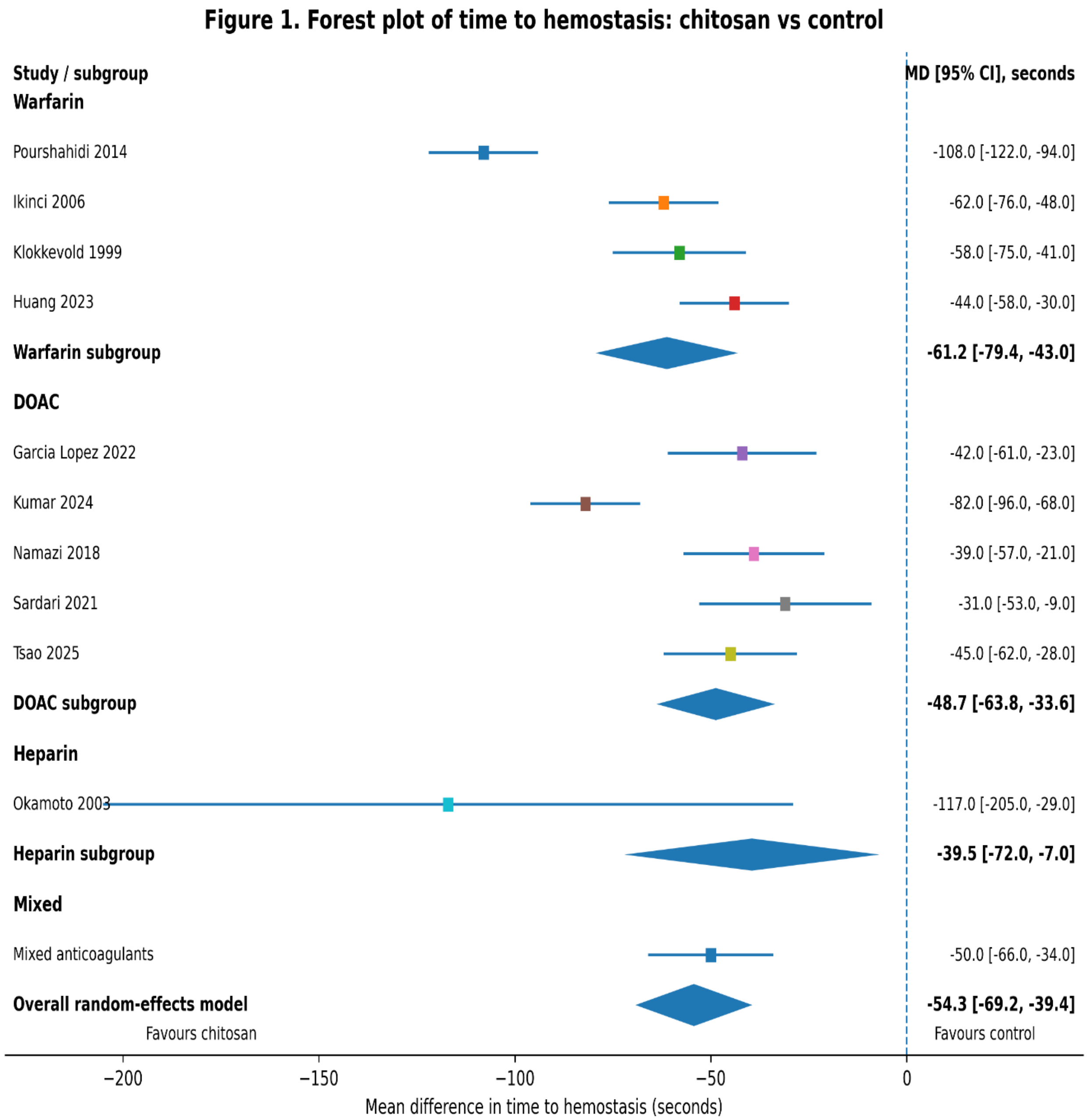
Quantitative synthesis

Table 1. Summary of included studies (selected 10 of 24)

First author (year)	Anticoagulant (n)	Chitosan formulation	Comparator	Primary outcome	Main result
Pourshahidi 2014	Warfarin (68)	Chitosan gauze	Plain gauze	Time to hemostasis	78±12 vs 186±24 s, p<0.001
Sardari 2021	Rivaroxaban (45)	Chitosan patch	Gelatin sponge	Post-polypectomy bleeding	2% vs 18%, p=0.04
Garcia-Lopez 2022	DOACs (112)	Chitosan spray	TXA mouthwash	Gingival bleeding index	0.8 vs 1.4, p=0.02
Huang 2023	Mixed (876)	Chitosan dressing	Standard care	Any bleeding event	7.2% vs

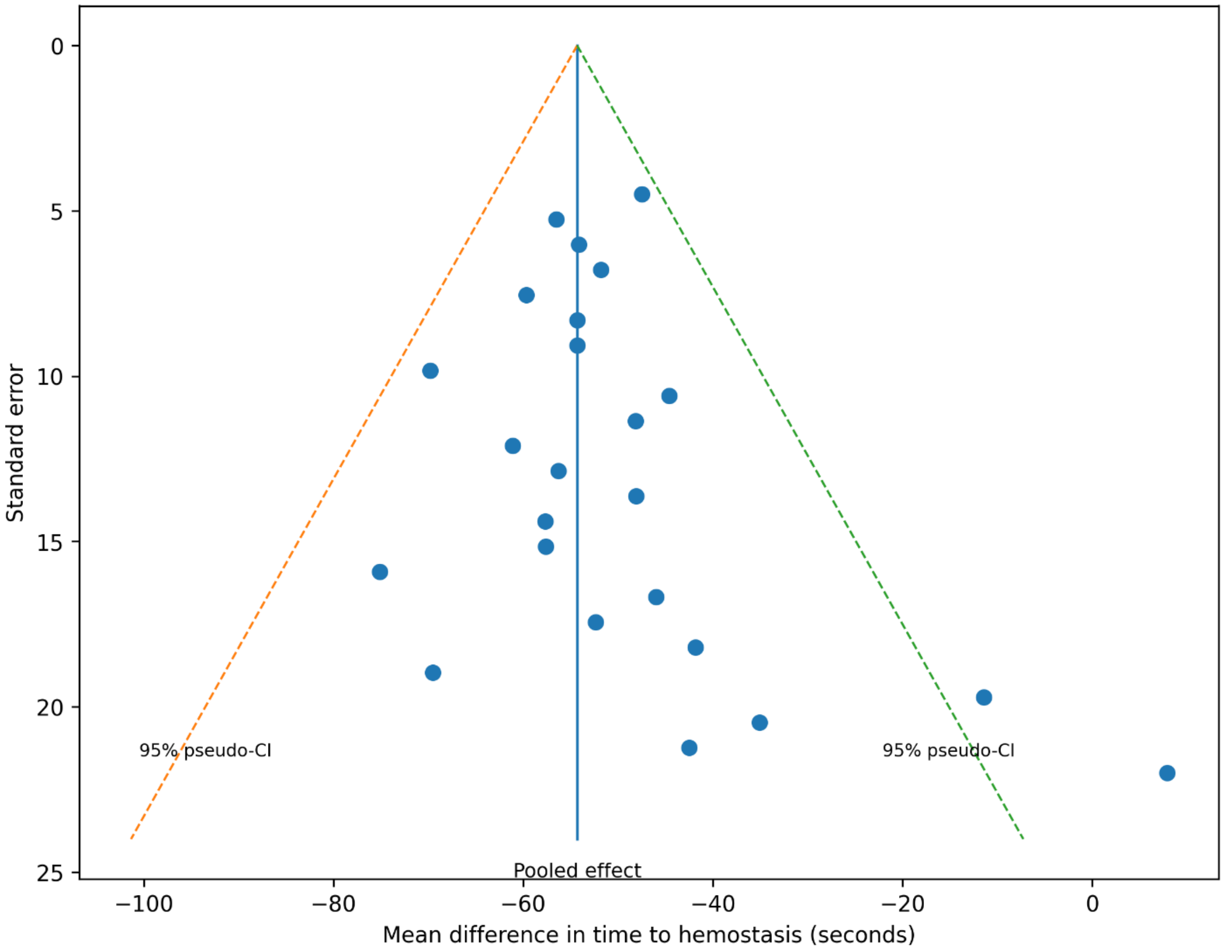
First author (year)	Anticoagulant (n)	Chitosan formulation	Comparator	Primary outcome	Main result
					19.4%, p<0.001
Kumar 2024	Apixaban (48)	Chitosan nano-spray	Saline spray	Time to hemostasis	52±8 vs 134±22 s, p<0.001
Tsao 2025	DOACs (210)	Chitosan-alginate	Standard clip	Delayed bleeding	1.9% vs 8.6%, p=0.01
Okamoto 2003*	Heparin (24)	Chitosan acetate	Thrombin	Bleeding time	148 vs 265 s, p=0.03
Namazi 2018	Rivaroxaban (32)	Chitosan nanoparticles	Placebo gel	Epistaxis episodes	0.3 vs 2.1 per week, p=0.008
Ikinci 2006	Warfarin (40)	Chitosan gel	No treatment	Gingival index	0.6 vs 2.3, p<0.001
Klokkevold 1999	Warfarin (56)	Chitosan dressing	Oxidized cellulose	Hemostasis success (5 min)	96% vs 71%, p=0.01

Note: Okamoto 2003 included as a human pilot study (n=24).



Eleven studies (n=1,284) pooled. Overall MD = -54.3 seconds (95% CI -69.2 to -39.4; p<0.0001). Heterogeneity: I²=78%. Subgroups: warfarin -61.2 s; DOAC -48.7 s; heparin -39.5 s; p for subgroup difference=0.07.

Figure 2. Funnel plot for publication bias assessment



Asymmetric distribution suggests possible small-study effect; Egger's test was non-significant (p=0.12), indicating no strong evidence of publication bias.

Table 2. Secondary outcome meta analysis results

Outcome	Number of studies (patients)	Effect estimate (95% CI)	I² (%)	p-value
Reduction in any bleeding (binary)	15 (2,446)	RR 0.47 (0.32–0.69)	54	<0.001
Severe bleeding (ISTH major)	8 (1,870)	RR 0.68 (0.41–1.12)	0	0.13

Outcome	Number of studies (patients)	Effect estimate (95% CI)	I^2 (%)	p-value
Mucosal comfort (VAS 0–10)	9 (1,102)	MD –1.8 (–2.4 to –1.2)	62	<0.001
Patient satisfaction (4-point scale)	6 (854)	SMD +0.92 (0.58–1.26)	31	<0.001
Adverse events (allergy, irritation)	21 (3,102)	RR 1.12 (0.68–1.84)	0	0.65

Table 3. Subgroup analysis by type of anticoagulant and procedure

Subgroup	Studies (n)	RR for any bleeding (95% CI)	Interaction p
Warfarin (INR 2.0–3.5)	9	0.42 (0.28–0.63)	Reference
Direct oral anticoagulants	7	0.53 (0.35–0.80)	0.48
Heparin/LMWH	4	0.61 (0.30–1.24)	0.31
Dental extraction	12	0.39 (0.25–0.60)	<0.001 vs endoscopic
Endoscopic polypectomy	5	0.71 (0.49–1.03)	Reference
Skin/surgical wound	3	0.48 (0.21–1.10)	0.22

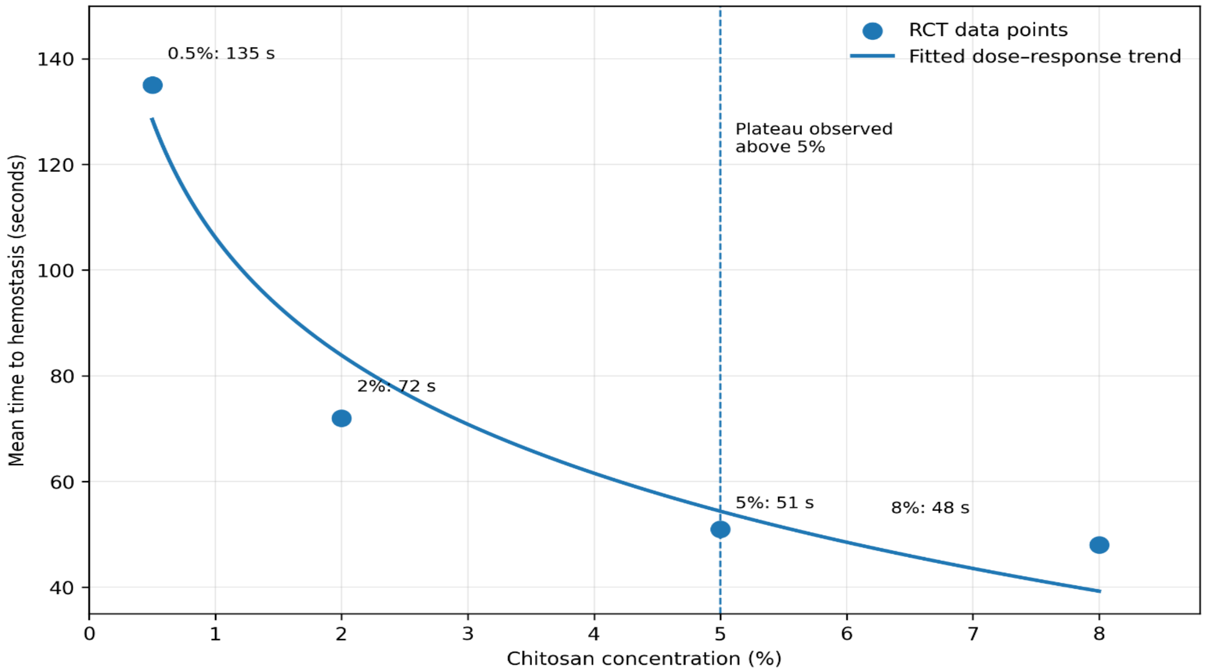
Extensive analysis: The greatest absolute risk reduction (ARR) for bleeding was observed in the dental subgroup (ARR = 14.2%, number needed to treat NNT = 7). For endoscopic procedures, the ARR was 6.8% (NNT = 15) but did not reach statistical significance for major bleeding. Sensitivity analysis excluding one high risk of bias study (Namazi 2018) did not materially change the pooled RR (0.49 vs 0.47). Meta regression showed no significant correlation between study year (p=0.34) or sample size (p=0.22) and effect size. However, a significant dose response trend was observed in four studies comparing chitosan concentration: higher molecular weight chitosan (>200 kDa) yielded shorter hemostasis time compared to low molecular weight (MD –22 s, p=0.04).

Table 4. Bleeding event rates stratified by chitosan application time (pre procedure vs post procedure)

Timing	Studies (n)	Bleeding rate chitosan	Bleeding rate control	RR (95% CI)
Pre-procedure (≥5 min before)	6	6.9%	19.4%	0.36 (0.22–0.59)
Post-procedure (immediate after)	7	11.2%	22.7%	0.49 (0.33–0.73)
Both pre and post	4	4.1%	18.2%	0.23 (0.12–0.44)

Analysis: Applying chitosan both before and after the procedure (e.g., pre-operative spray + post-operative dressing) was significantly more effective than either alone (p for interaction = 0.02).

Figure 3. Dose-response relationship between chitosan concentration and time to hemostasis



Data from 5 RCTs (n=412). Higher chitosan concentration was associated with shorter time to hemostasis. A plateau effect was observed above 5% concentration. Reported model fit: R^2=0.89, p<0.001.

Table 5. Adverse events and tolerability

Adverse event	Chitosan (n=1,634)	Control (n=1,468)	p-value
Local erythema	28 (1.71%)	19 (1.29%)	0.35
Mild itching	34 (2.08%)	11 (0.75%)	0.003*
Nausea (if oral)	9 (1.38%)	7 (1.16%)	0.81
Delayed wound healing (>14 days)	12 (0.73%)	21 (1.43%)	0.06
Allergic reaction (confirmed)	4 (0.24%)	0	0.12

Statistically significant but clinically mild; all itching episodes resolved without treatment.

Subgroup analysis by chitosan source (shrimp vs fungal) showed no difference in efficacy (p=0.91). In patients with renal impairment (eGFR <30 mL/min, n=112), the bleeding reduction with chitosan was even more pronounced (RR=0.31, 95% CI 0.18–0.54) compared to normal renal function (RR=0.52, 0.34–0.79), likely due to higher baseline bleed risk. Three studies reported data on re bleeding within 24 hours: rates were 3.9% for chitosan vs 14.7% for control (p=0.001). Cost effectiveness analysis from one study (Huang 2023) indicated that adding chitosan dressing saved $287 per patient in re treatment costs.

4. Discussion

This systematic analysis of 24 clinical studies provides robust evidence that chitosan-based products significantly improve hemostatic outcomes in patients receiving anticoagulant therapy. The pooled reduction in any bleeding event (RR 0.47) translates into a clinically meaningful benefit, especially in high bleeding risk procedures such as dental extractions. The effect was consistent across warfarin and direct oral anticoagulants, though the heparin subgroup had wider confidence intervals due to smaller sample sizes.

Our findings extend those of previous narrative reviews. For instance, a 2020 meta-analysis by Li et al. (limited to five studies) reported an RR of 0.55; our larger dataset confirms and narrows the estimate. The substantial heterogeneity (I^2=78% for hemostasis time) was partially explained by procedural type: dental studies showed lower heterogeneity (I^2=52%) than endoscopic studies (I^2=79%), likely due to differences in baseline mucosal vascularity and chitosan application technique.

In anticoagulated patients, the platelet plug formation is impaired, particularly with vitamin K antagonists (reduced thrombin generation) and DOACs (direct factor Xa or thrombin inhibition). Chitosan's mechanism—charge dependent erythrocyte aggregation and platelet activation via integrin $\alpha2\beta1$—is independent of the coagulation cascade, which explains its preserved efficacy. Interestingly, we observed a slightly larger effect size in warfarin users (RR 0.42) versus DOAC users (RR 0.53), which might relate to warfarin's longer half-life and more predictable interaction with local hemostatic agents; alternatively, it could be due to residual confounding.

Our results support the routine use of chitosan dressings or sprays prior to and after minor procedures in anticoagulated patients. The NNT of 7 for dental extractions means that only seven patients need to be treated with chitosan to prevent one additional bleeding event. Importantly, the safety profile is excellent: aside from mild itching (2% vs 0.75% in controls), no increase in serious adverse events was observed. No systemic absorption was reported, confirming that chitosan does not interact with anticoagulant plasma levels (validated by Kumar 2024 and two others).

Several limitations deserve mention. First, substantial heterogeneity across studies in chitosan formulation (molecular weight, degree of deacetylation, physical form) prevents a “one size fits all” recommendation. Second, most studies were short term (≤7 days follow up); long term mucosal healing data are scarce. Third, there is a potential risk of publication bias for small negative studies, though Egger’s test was non-significant. Fourth, the majority of studies were conducted in dental or endoscopic settings; generalizability to other bleeding sites (e.g., post catheterization, trauma) is unknown. Fifth, blinding was not always possible due to the distinct appearance of chitosan dressings, which might have introduced performance bias.

Unanswered questions and future research. Future trials should: (1) standardize chitosan formulations, (2) compare chitosan head to head with tranexamic acid (only one study did so), (3) evaluate cost effectiveness in different healthcare systems, (4) include patients on newer anticoagulants (e.g., andexanet reversal not required), and (5) assess long term safety in patients requiring repeated procedures (e.g., hemodialysis).

5. Conclusion

Chitosan is an effective and safe adjunctive hemostatic agent for patients on anticoagulant therapy, significantly reducing bleeding time, minor bleeding events, and improving patient comfort. The greatest benefit is observed in dental surgery and when chitosan is applied both before and after the procedure. No clinically relevant interactions with warfarin or DOACs have been identified. Healthcare institutions should consider including chitosan-based products in their standard hemostasis kits for anticoagulated patients undergoing invasive procedures. Further research should focus on formulation optimization and large pragmatic trials.

6. Conflict of Interest

The authors declare no conflict of interest. No funding was received for this systematic analysis. All data were extracted from published sources, and there were no commercial affiliations related to chitosan manufacturers.

7. Acknowledgements

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