Topical hemostatic therapies for endoscopic treatment of nonvariceal GI bleeding

Reading the RCT evidence with the right nuance

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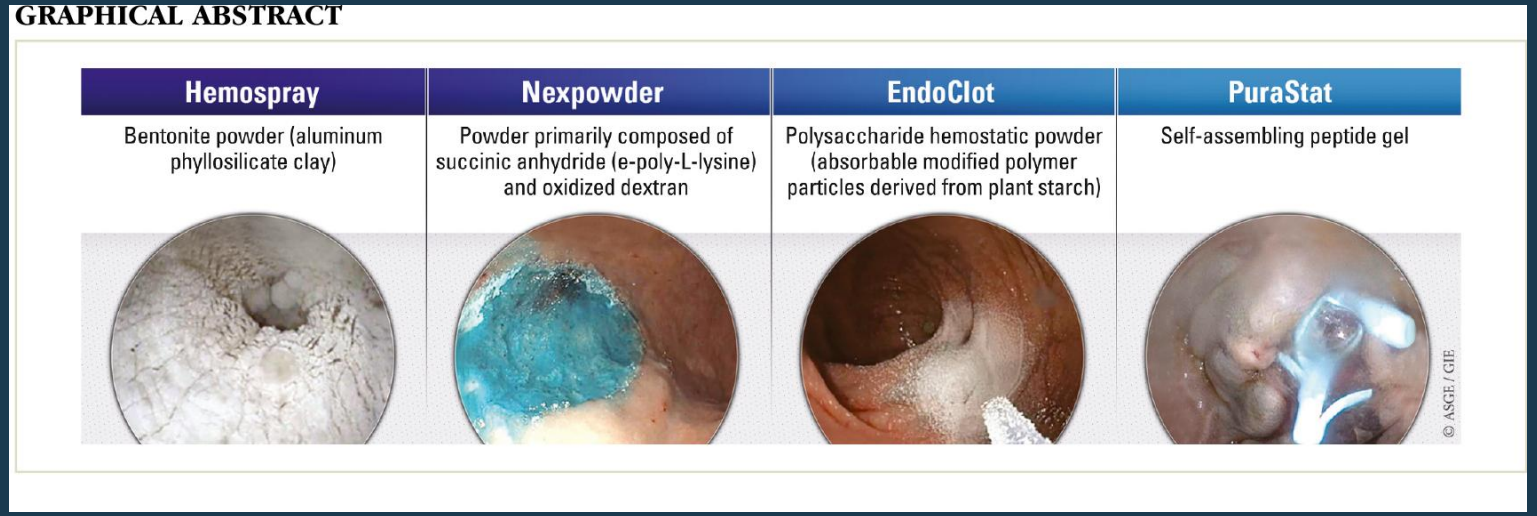
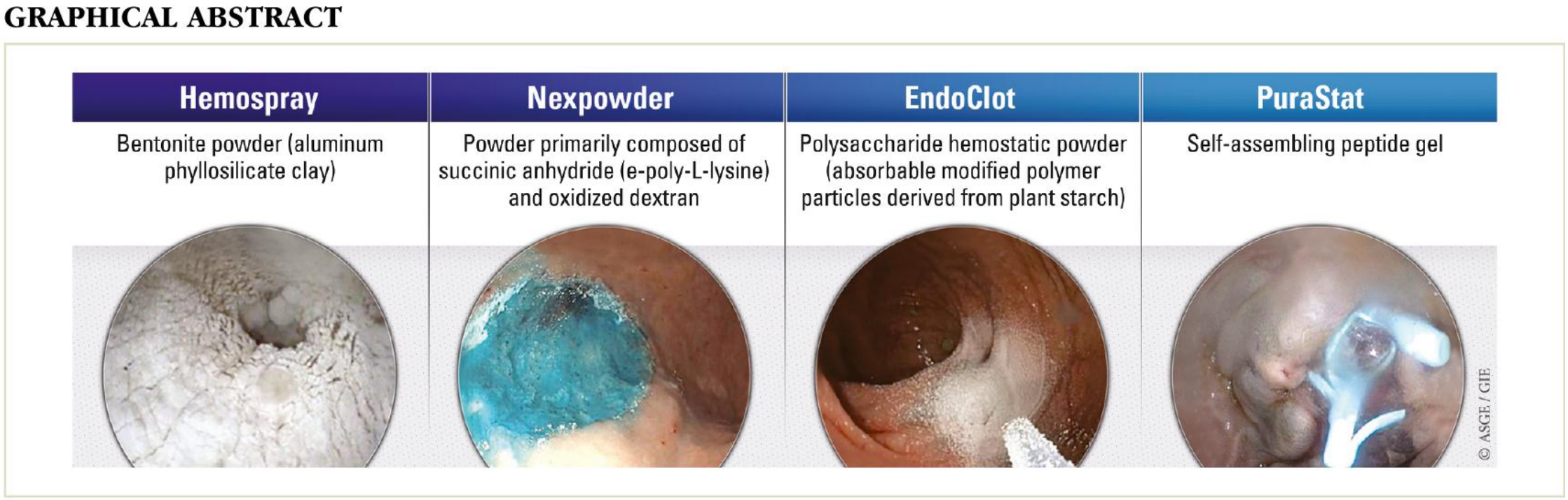


Graphical abstract: four topical hemostatic agents

Hemospray · Nexpowder · EndoClot · PuraStat



Review focus

- 4 FDA-approved topical agents for nonvariceal GIB
- Key question: are they superior or at least noninferior to conventional endoscopic therapy?
- RCTs are prioritized because observational studies mix different bleeding causes, settings, and treatment roles.

Graphical abstract reproduced from Laine L. Gastrointest Endosc. 2026;103:1112–1120.

Before the evidence: how to read the RCTs

Original Table 1 preserved: blinding, endpoint definition, and analysis strategy frame the interpretation of every agent-specific trial that follows.

Blinding
Double-blind if possible (generally not possible for endoscopic therapy)
If double-blind not possible, blind those involved in subsequent care of participants, management decisions, and study functions (eg, recording and analyzing data)
Careful definition of inclusion/exclusion criteria
Overt symptoms of GIB
Outpatient vs inpatient at the time bleeding began
Timing of endoscopy (eg, within 24-36 hours of presentation)
Type(s) of bleeding lesions and Forrest class (train investigators to ensure better agreement on Forrest classification)
Screening log listing participants not enrolled and key characteristics
Allows assessment of the generalizability of the population enrolled in the study
Predefine end points and definitions
Primary end point: further bleeding at 7 days (some use 30 days), defined as persistent or recurrent bleeding. This end point overcomes problems in dealing with rescue therapy/crossover in patients whose bleeding was not controlled with study-assigned therapy
Key secondary end point: mortality at 30 days
Other potential end points: initial hemostasis, subsequent urgent intervention (endoscopy, interventional radiology, and surgery), transfusion, hospital stay, cost, adverse events
Standardize study endoscopic therapies
Define therapies to be used and methods of application; train investigators
Independent blinded adjudication of end points
Reduces bias that occurs when on-site investigators adjudicate end points
Data analysis
Predefine sample size based on assumptions regarding primary end point results with intervention and comparator - Superiority: estimate difference in favor of intervention based on available data and clinical judgment (difference must be clinically meaningful) - Noninferiority: choose noninferiority margin (defined as a difference that would be considered not unacceptably worse) for intervention vs comparator that is clinically reasonable and maintains at least 50% of the benefit of the comparator over no endoscopic therapy
Predefine population for analysis (intent-to-treat and/or per protocol) - Choose the most conservative analysis (one less likely to be biased in favor of the new intervention) - Superiority study: intent-to-treat - Noninferiority study: per-protocol should always be included

GIB, GI bleeding.

1. Blinding is inherently limited

The endoscopist knows the assigned therapy. Treatment “vigor,” subsequent care, and outcome adjudication can therefore be biased.

2. Use “further bleeding”

Persistent bleeding + recurrent bleeding gives a more faithful estimate of overall hemostatic efficacy than either endpoint alone.

3. Analysis differs by hypothesis

Superiority: ITT is conservative. Noninferiority: per-protocol should always be included because crossover/nonadherence can falsely favor equivalence.

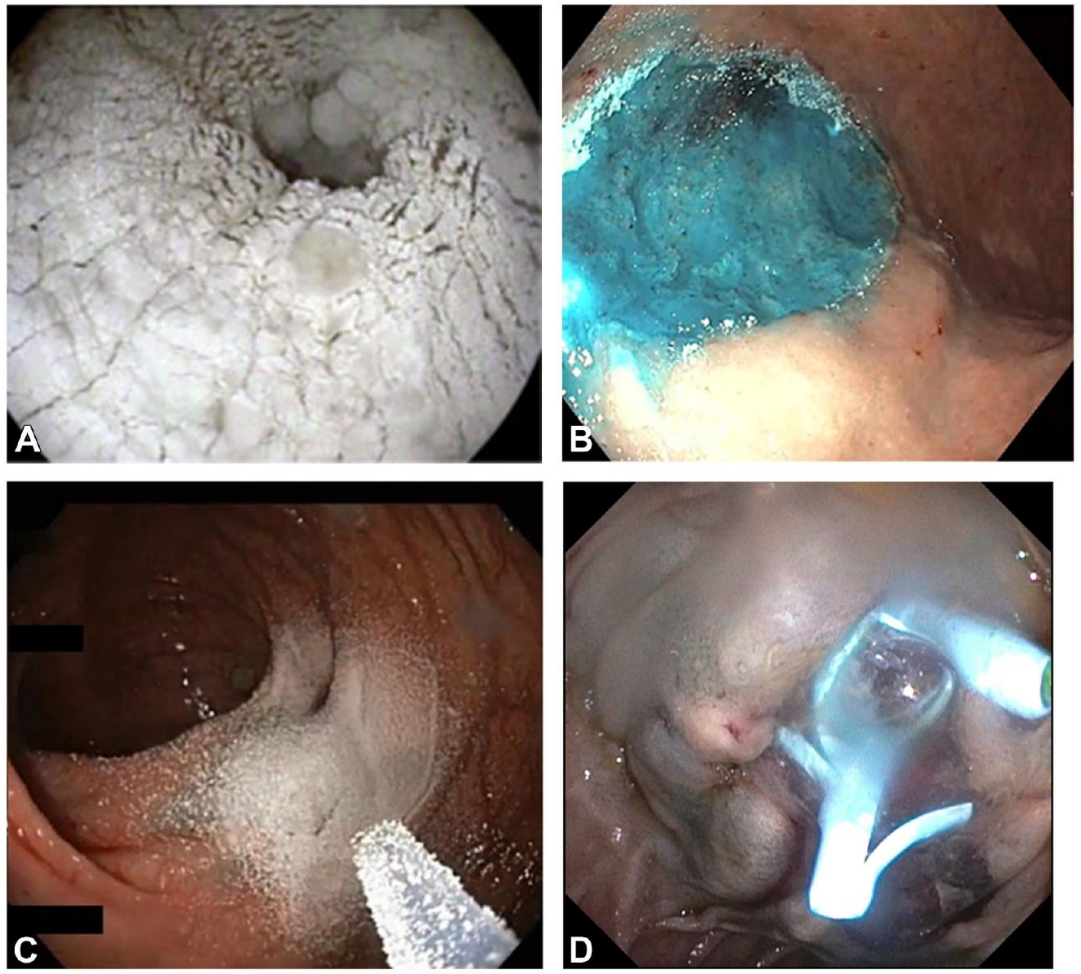
4. A 10% NI margin is debatable

Statistically noninferior does not automatically mean clinically equivalent. The review explicitly questions whether 25% vs 15% further bleeding would be acceptable.

Original Table 1 excerpt from Laine L. Gastrointest Endosc. 2026;103:1112–1120.

Four agents, four evidence profiles

The materials look similar at the bedside, but their mechanisms, delivery systems, and evidence bases are not interchangeable.



mospray (Cook Medical, Bloomington, Ind, USA) applied over diffusely bleeding portal hypertensive gastropathy.[4] **B,** Nex olis, Minn, USA) (with characteristic *blue color*) applied over endoscopic submucosal dissection defect.[5] **C,** EndoClot (Ol

Hemospray

Bentonite powder. Absorbs water on blood contact → mechanical barrier/tamponade + concentration of clotting factors. Best RCT evidence.

Nexpowder

Adhesive hydrogel forms with moisture; blood is not required. Strong adjunctive RCT, but no RCT as standalone primary therapy.

EndoClot

Plant-starch polysaccharide powder. Interpretation of the key ulcer RCT is limited by epinephrine in both arms and outcome design.

PuraStat

Self-assembling peptide gel. Evidence is mainly procedural (ESD/EMR); acute nonprocedural GIB still lacks a comparative RCT.

Figure 1 reproduced from Laine L. Gastrointest Endosc. 2026;103:1112–1120.

Hemospray: the pivotal noninferiority RCT (n = 224)

The important result is 30-day further bleeding — not just immediate hemostasis.

TABLE 2. Randomized noninferiority trial comparing Hemospray* with conventional endoscopic therapy in actively bleeding nonvariceal upper GI bleeding[3]

Outcome	Hemospray (*n* = 111)	Standard (*n* = 113)	Difference (95% CI)
30-day further bleeding			
All patients	11 (10%)	21 (19%)	−9% (−17% to 0.5%)
Ulcer	8/68 (12%)	11/68 (16%)	−4% (−16% to 7%)
Tumor	3/29 (10%)	6/13 (46%)	−36% (−63% to 9%)
Dieulafoy	0/6	3/16 (19%)	−19% (−51% to 13%)
Spurting	1/9 (11%)	5/12 (42%)	−31% (−70% to 8%)
Oozing	10/102 (10%)	16/101 (16%)	−6% (−15% to 3%)
Initial hemostasis	108 (97%)	102 (90%)	7% (1%-13%)
Treatment for further bleeding	10 (9%)	12 (11%)	−2% (−9% to 6%)
Death	14 (13%)	14 (12%)	0.2% (−8% to 9%)

*Cook Medical, Bloomington, Ind, USA.

Primary endpoint

NI was met

30-day further bleeding: 10% vs 19%. Difference -9% (95% CI -17% to 0.5%).
The upper CI bound stayed below the +10% NI margin.

Do not call it superiority

The trial was designed for noninferiority. The point estimate favored Hemospray, but the correct primary conclusion is noninferiority.

Subgroups: hypothesis-generating

Tumor and spurting rows look impressive, but numbers are small. Avoid overclaiming subgroup superiority.

Original Table 2. Lau JYW, et al. Ann Intern Med. 2022;175:171–178. Interpretation follows Laine 2026 review.

Hemospray in malignant tumor bleeding: a particularly attractive niche

The meta-analysis suggests better immediate control, while the conventional meta-analytic estimate for 30-day further bleeding remains imprecise.

TABLE 3. Meta-analysis of 4 randomized trials comparing Hemospray* with conventional endoscopic therapy for malignancy-related GI bleeding[13]

Outcome	Risk ratio (95% CI)	Absolute effect (95% CI)
30-d further bleeding	0.31 (0.08-1.23)	−29.6% (−39.4% to 9.9%)
Failure to achieve hemostasis	0.10 (0.03-0.37)	−23.1% (−24.9% to −16.2%)
30-d recurrent bleeding	0.50 (0.14-1.77)	−11.9% (−20.5% to 18.3%)
Days of hospitalization	–	4.28 (−0.27% to 8.82)
Units of blood transfused	–	−0.09 (−0.93 to 0.74)
Adverse events	1.27 (0.83-1.94)	5.3% (−3.3 to 18.3%)
6-mo mortality	0.94 (0.69-1.29)	−2.3% (−11.8 to 11.0%)

–, Not computable.

30-day further bleeding

RR 0.31, but 95% CI 0.08–1.23 crosses 1. The conventional meta-analysis alone does not prove a significant reduction.

Initial hemostasis

Failure to achieve hemostasis RR 0.10 (0.03–0.37): this is the clearest statistically significant signal in Table 3.

Why the review is still positive

Individual-patient-data meta-analysis of 3 RCTs found lower persistent bleeding (OR 0.02) and 30-day recurrent bleeding (OR 0.28). This is why recent guidance is favorable in malignant bleeding.

Original Table 3 from Laine 2026 review; malignancy RCT meta-analysis discussed in the article.

Nexpowder: strong adjunctive evidence — but only after standard hemostasis

This is not a trial of Nexpowder as initial monotherapy.

TABLE 4. Randomized trial comparing Nexpowder* versus no endoscopic treatment after successful conventional endoscopic therapy in 341 patients with nonvariceal upper GI bleeding (317 with ulcers) and active bleeding or nonbleeding visible vessels[23]

Outcome	Nexpowder (N = 173)	Control (N = 168)
Recurrent bleeding		
All patients (3 d)	5 (2.9%)	19 (11.3)
Ulcers (3 d)	5/167 (3.0%)	18/150 (12.0%)
All patients (30 d)	12 (7.0%)	31 (18.8%)
Ulcers (30 d)	12/167 (7.2%)	29/150 (19.3%)
Treatment for recurrent bleeding (3 d)	3 (1.7%)	14 (8.3%)

$P < .006$ for all comparisons.
*Medtronic, Minneapolis, Minn, USA.

Adjunctive therapy only

Clear recurrence reduction

After successful conventional hemostasis, recurrent bleeding was lower at both 3 days (2.9% vs 11.3%) and 30 days (7.0% vs 18.8%).

What this trial cannot answer

Because every patient first achieved hemostasis conventionally, it does not establish Nexpowder as a standalone primary hemostatic therapy.

Clinical interpretation

Think “rebleeding prevention after successful hemostasis,” not “replacement for standard therapy.”

Original Table 4. Shin J, et al. Gut. 2025;74:1821–1827. Interpretation follows Laine 2026 review.

EndoClot: the key RCT is harder to interpret than the headline numbers suggest

The apparent 87.6% initial-hemostasis rate is not the cleanest estimate of immediate efficacy.

TABLE 5. Randomized trial comparing EndoClot* and conventional endoscopic therapy after epinephrine injection in both study arms for bleeding ulcers (Forrest Ia/b, IIa/b)[26]

Outcome	EndoClot (n = 105)	Conventional (n = 111)
Initial hemostasis†		
All patients	92 (87.6%)	96 (86.5%)
Forrest Ia/b	35/48 (72.9%)	30/37 (81.1%)
Forrest IIa	36/36 (100%)	51/59 (86.4%)
Forrest IIb	21/21 (100%)	15/15 (100%)
Recurrent bleeding		
7 d	6/102 (5.9%)	4/108 (3.7%)
30 d	8/102 (7.8%)	10/108 (9.3%)

*Olympus, Center Valley, Pa, USA.
†Primary outcome (all with failed hemostasis had alternate endoscopic therapy).

Confounding #1: epinephrine

Both groups received epinephrine before EndoClot or conventional therapy. That prevents an independent assessment of EndoClot's immediate effect.

Confounding #2: nonbleeding lesions

Including Forrest IIa/IIb inflates "initial hemostasis." Among actively bleeding patients only, initial hemostasis was ~73% with EndoClot vs ~81% conventional.

Bottom line

Rebleeding rates were low and similar, but the trial design makes it difficult to conclude that EndoClot independently matches standard therapy for initial control.

Original Table 5. Jung DH, et al. Clin Gastroenterol Hepatol. 2023;21:2844–2853. Interpretation follows Laine 2026 review.

PuraStat: procedural hemostasis evidence ≠ acute nonprocedural GIB evidence

This distinction is easy to miss because the product is visually attractive and technically easy to apply.

What has been studied

- ESD intraprocedural bleeding: 2 RCTs
- Prophylactic use after EMR: 1 RCT
- Reduced use of electrocoagulation during ESD in some studies

What was not improved

- No reduction in delayed post-ESD bleeding in the cited RCTs
- No benefit in post-EMR bleeding in the prophylactic RCT

The key evidence gap

No RCT has compared PuraStat with standard endoscopic therapy for acute nonprocedural GIB.

Therefore, procedural bleeding data should not be extrapolated to acute ulcer/tumor bleeding.

Evidence status: useful procedural gel with practical advantages, but acute nonprocedural GIB remains an evidence gap.

Subramaniam S, et al. Endoscopy. 2021;53:27–35; Uraoka T, et al. Am J Gastroenterol. 2023;118:276–283; Drews J, et al. Gut. 2025;74:1103–1111.

Original Table 6: same category, very different levels of evidence

The original summary table is preserved; the labels on the right are the practical evidence hierarchy emphasized by this review.

TABLE 6. Summary of topical hemostatic agents approved for endoscopic treatment of nonvariceal GIB

	Hemospray	Nexpowder	EndoClot	PuraStat
Hemostatic material	Bentonite powder (aluminum phyllosilicate clay)	Powder primarily composed of succinic anhydride (Ɛ-poly-L-lysine) and oxidized dextran	Polysaccharide hemostatic powder (absorbable modified polymer particles derived from plant starch)	Self-assembling peptide gel
Refrigeration required	No	No	No	Yes
Application mechanism	Bursts of CO_2 from a pressurized cartridge	Air pump	Air compressor	Syringe
Efficacy for nonvariceal GIB based on RCTs	Noninferior to conventional therapies for further bleeding and superior for initial hemostasis—especially for malignant tumor bleeding	Reduces recurrent bleeding after successful endoscopic hemostasis with conventional endoscopic therapy, but no RCT has studied its use as initial therapy	Uncertain because interpretation of the single RCT is limited by the use of epinephrine in both study arms and study's reporting of outcomes. EndoClot results were not different from conventional therapy, but its initial hemostasis rate for active bleeding was relatively low at 73%	No RCT data for patients presenting with acute GIB Two RCTs for treatment of intraprocedural bleeding during ESD showed addition of PuraStat to monopolar electro-coagulation vs electro-coagulation alone reduced the use of electrocoagulation during ESD but did not reduce post-ESD bleeding
FDA-approved for active spurting bleeding (Forrest Ia)	Yes	Yes	No	No
Side effects	Rare catheter or channel clogging, adherence of the endoscope to the mucosa High-pressure CO_2 is suggested as a cause of minor abdominal pain and as a theoretical risk for perforation	Expect less catheter clogging than Hemospray and fewer side effects related to insufflation	Expect less catheter clogging than Hemospray and fewer side effects related to insufflation	Should not have issues that powders may have with clogging or insufflation of CO_2 or air
List price	$2750	$895	$1883 (3 g)*, $2897 (5 g)	$1034†
Potential contract prices[6]	$1500-$2500	$750	$1200 (3 g); $1500 (5 g)	$650-$750

ESD, Endoscopic submucosal dissection; *FDA*, Food and Drug Administration; *GIB*, GI bleeding; *RCT*, randomized controlled trial.
*Based on the list price of the kit with 2 applications (3 g) and a reusable air compressor (list price is $2318 for 3 g EndoClot powder alone)

Original Table 6 and summary/conclusions from Laine L. Gastrointest Endosc. 2026;103:1112–1120.

Hemospray — strongest evidence for initial active GIB

Nexpowder — good adjunctive evidence, not primary monotherapy

EndoClot — RCT signal limited by design / confounding

PuraStat — no comparative RCT for acute nonprocedural GIB

Author's overall conclusion

Among currently available topical agents, Hemospray has the clearest evidence to support initial treatment of active nonvariceal GIB.

Fellow take-home: 4 nuances not to miss

1. **Approval does not mean equivalent clinical evidence. All four topical agents are available/approved, but the quality and clinical context of supporting evidence differ substantially**

2. **RCT evidence should drive interpretation.**
   Hemospray and Nexpowder have the strongest randomized evidence for active GI bleeding

3. **The optimal role differs by bleeding scenario**

4. **Choose the agent according to both evidence and indication**

Based on Laine L. Topical hemostatic therapies for endoscopic treatment of nonvariceal gastrointestinal bleeding. Gastrointest Endosc. 2026;103:1112–1120.