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The Effects of Lysine Analogs During Pelvic Surgery: A Systematic Review and Meta-Analysis

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ABSTRACT

Pelvic vasculature is complex and inconsistent while pelvic bones impede access to pelvic organs. These anatomical characteristics render pelvic surgery inherently difficult, and some of these procedures are frequently associated with blood loss that necessitates blood transfusion. The aim of this study was to review the literature on the use of lysine analogs to prevent bleeding and blood transfusion during pelvic surgery. The objective of this study was to assess the safety and efficacy of lysine analogs during pelvic surgery. A systematic literature search was performed using Medline, Cochrane Register of Clinical Trials, Embase, and the reference lists of relevant articles. Randomized controlled trials or observational cohort studies comparing a lysine analog to placebo or standard care were included. Outcomes collected were blood transfusion, blood loss, thromboembolic adverse events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), nonthromboembolic adverse events, and death. There were no language limitations. Fifty-six articles reported on 68 comparisons between a lysine analog and an inactive comparator, involving a total of 7244 patients published between 1961 and 2013. Thirty-nine studies evaluated urologic procedures, and 21 evaluated gynecologic procedures. Thirty-six studies (60%) were published before 1980. Of the 43 randomized comparisons, only 30 (44%) had a score of 3 or higher on Jadad's 5-point scale of methodological quality. Among randomized trials, lysine analogs reduced the risk of blood transfusion (pooled odds ratio [OR], 0.47; 95% confidence interval [CI], 0.35-0.64) and blood loss (pooled OR, 0.22; 95% CI, 0.18-0.27). There was a small statistically insignificant increased risk of thromboembolic events (pooled OR, 1.07; 95% CI, 0.72-1.59) and no-thrombotic serious adverse events (pooled OR, 1.11; 95% CI, 0.67-1.83). In the 17 randomized trials published since the year 2000, only 6 thrombotic events were reported, 4 of which occurred in the placebo arm. Lysine analogs did not increase risk of death (pooled OR, 0.91; 95% CI, 0.34-2.48). These results are significant as they indicate that lysine analogs significantly reduce blood loss and blood transfusion during pelvic surgery. Although there does not appear to be a large increase in the risk of thromboembolic and nonthrombotic adverse events, more data are required to definitively assess these outcomes. Based on this review, lysine analogs during pelvic surgery seem to reduce bleeding and blood transfusion requirements. Although there does not seem to be a significant risk of adverse effects, larger studies would help clarify risks, if any, associated with lysine analog use.

Pelvic vasculature is complex and inconsistent while pelvic bones impede access to pelvic organs. These anatomical characteristics render pelvic surgery inherently difficult, and some of these procedures are frequently associated with blood loss that necessitates blood transfusion [1]. For example, perioperative blood transfusion is performed in 26% to 55% of radical cystectomy procedures [2,3] and approximately 10% of radical prostatectomy procedures [4,5].

Lysine analogs are synthetic derivatives of the amino acid lysine that reversibly block lysine binding sites on plasminogen molecules [6]. Through this mechanism, these drugs inhibit conversion of plasminogen to plasmin and thus prevent breakdown of blood clots (fibrinolysis). Lysine analogs are used predominantly during cardiac surgery but have been studied in orthopedic surgery [7] and trauma patients [8]. In most of these

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studies, reduction of blood loss was observed, and adverse events were minor or infrequent.

There are clear anatomical and procedural differences between cardiac, orthopedic, and pelvic surgery. Pelvic surgery patients may have different diseases and predilection for adverse events such as deep vein thrombosis [9]. In a recent survey of urologists, lysine analogs were infrequently used, primarily because of lack of knowledge about the drugs and concerns regarding safety [10]. Therefore, summarizing the current evidence of lysine analogs during pelvic surgery will address potential knowledge and evidence gaps. The objective of this systematic review was to summarize the evidence on lysine analogs during pelvic surgery.

Patients and Methods

This review was based on a nonregistered protocol that was agreed upon by the principal investigators (Appendix A). This study was partly funded by an unrestricted grant from Hoffman-Roche.

Information Source and Search

Structured strategies were designed and run in Ovid databases: Medline and Cochrane Register of Clinical Trials (with and without Dickersin's filter for randomized trials [11]: Appendix B) as well as Embase (with SIGN randomized trials filter) [12]. Those databases were searched from inception through March 19, 2013. A more basic strategy was used in Google Scholar to locate publications from nonindexed periodicals, up to July 12, 2013.

Eligibility Criteria, Study Selection, and Data Abstraction

Full-text published reports of clinical studies that enrolled human patients undergoing pelvic surgery were included. Studies were eligible if they reported administration of a lysine analog (aminocaproic acid [ACA], tranexamic acid [TXA], or para-aminomethylbenzoic acid [PAMBA]) for a digestive, urogenital, neurovascular, or integumentary surgical procedure for any nontraumatic indication. Study designs involving prospective data collection were eligible, provided they featured at least 1 inactive comparator (placebo control or standard of care) and they reported quantitative clinical data. Studies that used historical referent groups were excluded. All types of surgical approaches (open, laparoscopic, or endoscopic) and surgical techniques (excision, transplantation, or reconstruction) were eligible. There was no restriction based on treatment indication, sample size, age, sex, geography, publication date, or language.

Digital titles and abstracts from search outputs were screened and full-text versions of potentially eligible studies were reviewed. Reference lists of included manuscripts were also screened to identify additional articles. All stages of selection were performed independently by 2 trained reviewers who consensually reconciled disagreements based on the predetermined criteria. Interpretation services were obtained for publications in languages other than English or French.

Reviewers independently performed data extraction using standardized electronic forms; disagreements were consensually reconciled. A third reviewer systematically verified items extracted for completeness, accuracy, and coherence. When contradictory data statements were encountered, we used information in tables/figures over the text, and those from the full text were used over

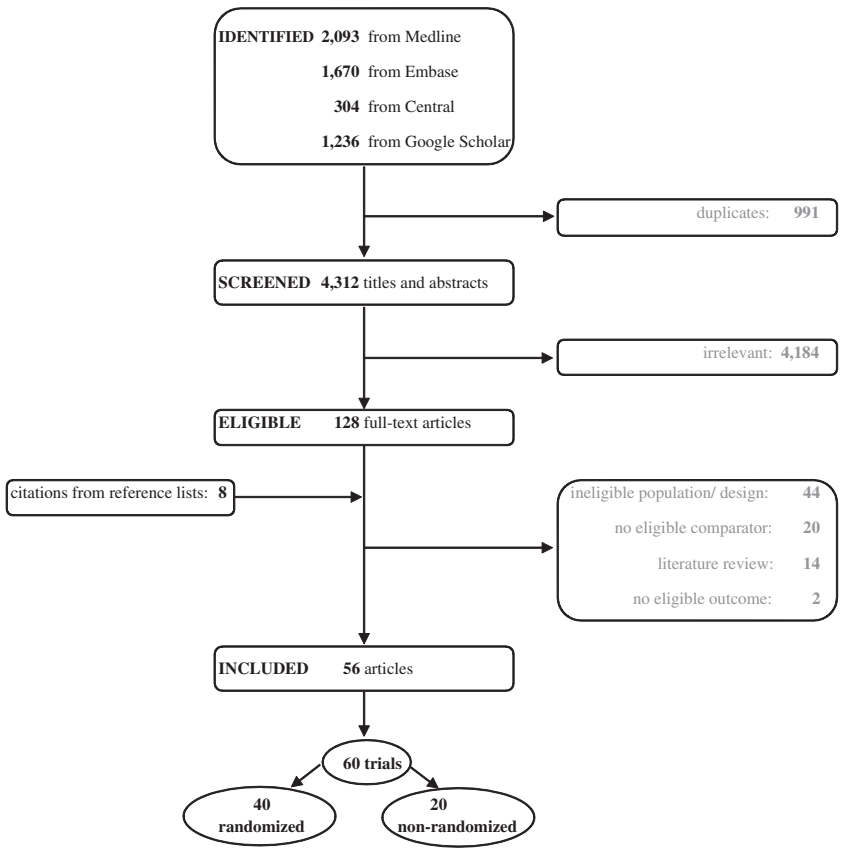

Fig 1. Selection flow diagram.