AEJ ANESTHESIA EJOURNAL
Volume 6 - No. 3 2018

Prophylaxis and Treatment of Hereditary Angioedema With Fresh Frozen Plasma: A Synthesis and Narrative Review

Meredith Mosier, RN, BSN, RRNA[1]
J. Dru Riddle, PhD, DNP, CRNA[2]

Affiliation:

1. School of Nurse Anesthesia Texas Christian University, Fort Worth, TX. The author was a student at the time of writing.

2. Assistant Professor of Professional Practice, School of Nurse Anesthesia Harris College of Nursing and Health Sciences, Texas Christian University, Fort Worth, TX

Funding/Conflict of Interest Disclosure:
None

KEYWORDS: angioedema, fresh frozen plasma, surgery

Abstract

Patients with angioedema who experience an acute exacerbation may die if their symptoms are not treated promptly. Airway compromise can occur if proper precautions are not taken. Surgical patients with hereditary angioedema should undergo prophylactic treatment before surgical procedures to decrease the risk of an exacerbation. A literature search was performed using the Embase (Elsevier), CINAHL (EBSCO), Health Source: Nursing/Academic Edition (EBSCO), and MEDLINE (National Library of Medicine) databases. Six articles were found that discussed administration of fresh frozen plasma (FFP) for treatment or prophylaxis against angioedema exacerbations. Synthesis of the evidence suggests that use of FFP as a sole prophylaxis or treatment for angioedema is inappropriate. FFP can be used as part of a multimodal treatment plan for prophylaxis against angioedema if a C1 esterase inhibitor is not available.

INTRODUCTION

Rapid intervention by a skilled team of clinicians is required when angioedema occurs in the operative setting. Hereditary angioedema (HAE), acquired angioedema (AAE), and angiotensin-converting enzyme (ACE) inhibitor-induced angioedema are 3 types of bradykinin-mediated angioedema.[1] Patients susceptible to bradykinin-mediated angioedema may experience a precipitating event before an acute episode occurs.[1] Airway instrumentation, upper airway trauma resulting from airway instrumentation, surgery, and psychologic or physiologic stress experienced by the patient may precipitate an exacerbation of angioedema.[1] However, exacerbations can also occur in the absence of a triggering event.[1] Patients at risk for bradykinin-mediated angioedema are susceptible to airway compromise during or immediately after surgery. For susceptible patients, anesthetists should anticipate an exacerbation resulting in potential airway compromise. If a patient undergoing surgery is known or suspected to be at risk for bradykinin-mediated angioedema, prophylactic measures can be taken.[2] Pharmacologic prophylactic options include fresh frozen plasma (FFP), C1 esterase inhibitor (C1-INH), and androgen therapy.[1]

The present review aimed to answer the PICO question, In patients with a known history of or suspected susceptibility to HAE, does the administration of FFP compared with no infusion of FFP affect the occurrence or severity of angioedema postoperatively? This synthesis presents search strategies for the topic and reviews 6 articles (Appendix A) pertaining to the above PICO question.

SEARCH METHODOLOGY

Two structured searches were conducted. The Embase database (Elsevier) was searched by using the search terms "fresh frozen plasma," "angioneurotic edema," and "anesthesia" combined with the Boolean operator "AND." The search was limited to articles published between 2000 and 2016. Twenty-three articles were retrieved and 3 were selected for analysis.[1,3,4] The second search was conducted of the CINAHL (EBSCO), Health Source: Nursing/Academic Edition (EBSCO), and MEDLINE (National Library of Medicine) databases within the EBSCOhost platform search engine. The search terms "angioedema," "fresh frozen plasma," and "surgery" were combined with the Boolean operator "AND." This search was limited to articles in English and retrieved 16 results. Three articles were selected for review.[5,6,7] In total, 6 articles were selected that best related to the stated PICO question. The selected articles were classified according to the Joanna Briggs Institute Levels of Evidence.[8] A PRISMA flow diagram of the search is shown in Appendix B.[9]

REVIEW OF THE LITERATURE

Limited quality research exists regarding FFP prophylaxis against an acute HAE episode during the operative course. HAE is an uncommon condition and, if an exacerbation occurs, it can be life-threatening.[7] The rarity and severity of HAE exacerbations make opportunities to conduct clinical trials almost nonexistent. The existent body of research therefore consists of case studies. Two retrospective chart reviews, 1 expert opinion article, and 3 case reports were selected as the best evidence for inclusion.

Macbeth et al reviewed the medical records of 24 patients with bradykinin-mediated angioedema who received general anesthesia.[1] The researchers searched for evidence of prior airway compromise, frequency of angioedema episodes, prophylactic treatment before surgery, and perioperative management. They also conducted a literature search of the MEDLINE database and located 19 case reports and 2 case series that described patients with angioedema who underwent general anesthesia. Macbeth et al included data from the results of their database search in their discussion.

We classified Macbeth et al's study as a level of evidence 3.b cohort study.[8] Although Macbeth et al[1] analyzed the largest amount of data compared with the other articles included here, their work had some weaknesses. The authors occasionally arrived at conclusions through speculation. For example, they speculated that, although the complication risk for patients who did not receive prophylaxis was low at 5.7%, using prophylaxis would further reduce the incidence of angioedema perioperatively.[1] They also proposed that infusions of FFP could exacerbate an acute episode of angioedema because of the additional complement components FFP contains besides C1-INH. No source was cited to support this claim and it was stated that, because FFP contains complement components, it should be used as prophylaxis before surgery if no other treatment option is available.[1]

Prematta and colleagues[5] reviewed the medical records of all patients from their institution who were diagnosed with HAE and received FFP from their institution's blood bank. Twenty-three cases were compiled. Only 2 of these cases involved the use of FFP as prophylaxis before surgery. These 2 patients did not have an acute HAE exacerbation postoperatively and the authors concluded that FFP is an effective treatment for surgical prophylaxis against HAE. The authors identified weaknesses in their review and pointed out that no control group existed. Thus, there was no way to be certain that infusions of FFP prevented an HAE exacerbation. The amount of FFP administered to each patient was not consistent. The number and timing of doses varied among the patients discussed in the review. We classified this retrospective study as a level of evidence 3.b cohort study.[8]

Szema and colleagues[3] authored guidelines for the preoperative and intraoperative management of patients with HAE. This article was a level 5.b expert consensus.[8] The authors used literature retrieved from PUBMED to construct the guidelines.[3] They suggested giving 3 units each day before a surgical procedure and checking serum C1 and C4 esterase inhibitor levels after the first and second doses. The authors suggested transfusing 2 units of FFP intraoperatively. Recommendations were graded based on the strength of supporting evidence. Recommendations based on evidence from randomized controlled trials (RCTs) were not provided because no RCTs were located.

Shick et al[6] wrote a case study, level of evidence 4.d,[8] concerning a patient with HAE who underwent coronary artery bypass grafting (CABG). The patient's care team determined that CABG without cardiopulmonary bypass (off-pump CABG, or OP-CABG) would be most appropriate.[6] The care team chose this technique in an effort to minimize the risk of activation of complement cascade. The patient was given 2 units of FFP before incision and 2 units of FFP intraoperatively. The patient was later extubated in the intensive care unit (ICU) without complication and discharged home 6 days after admission. Several measures were taken to prevent an acute exacerbation of HAE during the operative period, including an increased danazol dose preoperatively, use of the OP-CABG technique, and infusions of FFP.[6] The patient was also premedicated with intravenous doses of diphenhydramine, ranitidine, and hydrocortisone. These drugs have shown little benefit in patients with HAE suffering an acute exacerbation.[1] The role of FFP infusion as prophylaxis against an acute HAE exacerbation cannot be absolutely determined from the evidence contained in the study.

Mihailovic et al[4] authored a case study that described a patient with HAE who underwent CABG on cardiopulmonary bypass. We assigned the study a level of evidence 4.d.[8] The patient was prescribed danazol 3 days preoperatively. On the day of surgery, the patient received 2 doses of FFP 2 hours preoperatively and received 4 doses of FFP before successful extubation in the ICU.[4] The authors also used other prophylactic methods in addition to infusions of FFP. They reported that infusions of FFP raised the patient's plasma levels of C1-INH and were instrumental in preventing an HAE exacerbation. However, FFP cannot be solely credited for preventing the exacerbation, and the extent that FFP contributed to prophylaxis cannot be determined when other prophylactic measures are taken.

A case study written by Cifuentes and colleagues[7] examined FFP as a treatment option for exacerbation of angioedema. The researchers reported the case of a patient with undiagnosed HAE who underwent orthognathic surgery.[7] The authors reported that the patient developed severe facial and upper airway edema on postoperative day 1. The patient was emergently intubated and received 2 units of FFP as a treatment for angioedema. The patient experienced a 10% reduction in edema 12 to 14 hours after the infusion and remained intubated for 24 hours. Subsequently,

the patient was extubated without complication and discharged 2 weeks later. This case did not describe the prophylactic use of FFP, but it did describe a rare scenario that may be encountered in the surgical arena.

SYNTHESIS

The research studies reviewed are inconclusive related to the value of FFP in HAE prophylaxis because in all cases the investigators used multiple prophylactics. We did not identify any clinical trials investigating the effect of FFP on HAE. Administration of FFP as a treatment for acute exacerbations does not lend itself to clinical trial studies because occurrences are rare. When signs and symptoms of HAE occur, the situation is acute and requires immediate, multimodal prophylactic measures to treat the condition. The use of FFP as the sole treatment in a clinical trial or withholding FFP to establish a placebo group is not appropriate. HAE can be life-threatening, so when signs and symptoms appear, multiple therapeutic techniques should be used. Patients in the cases studied received other prophylactic measures besides FFP infusions, including attenuated androgens, histamine antagonists, and corticosteroids.

It has been determined that HAE exacerbations result from deficiency of C1-INH and subsequent overproduction of bradykinin.[1] The overproduction of bradykinin may lead to vascular permeability and HAE exacerbation.[1] Researchers have concluded that exogenous C1-INH is a valuable component in treatment and prophylaxis against HAE exacerbations. The Food and Drug Administration approved Cinryze (complement C1 esterase inhibitor) in 2008 for use as a routine prophylaxis against HAE,[3] but the drug is not widely available. Because FFP is more readily available at hospitals in the United States than exogenous C1-INH, FFP has become a mainstay of treatment to be administered in conjunction with additional prophylactic measures.

CONCLUSION

The information presented represents the best evidence available concerning the use of prophylactic FFP to prevent HAE exacerbations. The PICO question, In patients with a known history of or suspected susceptibility to HAE, does the administration of FFP compared with no infusion of FFP affect the occurrence or severity of angioedema postoperatively, cannot be definitively answered. All the above studies included prophylactic measures such as administration of danzolol preoperatively, administration of antifibrinolytics, or administration of antihistamines in addition to FFP. The effect of administration of FFP without additional prophylactic measures on the occurrence or severity of angioedema cannot be determined from the evidence cited.

Acknowledgments

This review was conducted in partial fulfillment of the requirements for the Doctor of Nursing Practice degree at the School of Nurse Anesthesia at Texas Christian University.

REFERENCES

1. MacBeth LS, Volcheck GW, Sprung J, Weingarten TN. Preoperative course in patients with hereditary or acquired angioedema. *J Clin Anesth*. 2016;34:385-391. doi:10.1016/j.jclinane. 2016.05.010.
2. Levy JH, Freiberger DJ, Roback J. Hereditary angioedema: current and emerging treatment options. *Anesth Analg*. 2010;110(5):1271-1280. doi:10.1213/ANE.0b013e3181d7ac98.
3. Szema AM, Paz G, Merriam L, Stellaccio F, Jen J. Modern preoperative and intraoperative management of hereditary angioedema. *Allergy Asthma Proc.* 2009;30:338–342. doi:10.2500/aap.2009.30.3225.
4. Mihailovic S, Volas L, Arezina Mihailovic A. Hereditary angioedema type II: perioperative management of coronary artery bypass graft surgery: 4AP2-2. *Eur J Anaesthesiol.* 2012;29:55.
5. Prematta M, Gibbs JG, Pratt EL, Stoughton TR Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2007;98(4):383-388. doi:10.1016/S1081-1206(10)60886-1.
6. Shick V, Sanchala V, McGoldrick K, Tartaglia JJ, Nelson J, Fleisher AJ. Perioperative management of a patient with hereditary angioedema during off-pump coronary artery bypass graft surgery. *J Clin Anesth*. 2010;22(4):282-284. doi:10.1016/j.jclinane.2009.04.007.
7. Cifuentes J, Palisson F, Valladares S, Jerez D. Life-threatening complications following orthognathic surgery in a patient with undiagnosed hereditary angioedema. *J Oral Maxillofac Surg*. 2013;71(4):e185-e188. doi:10.1016/j.joms.2012.11.023.
8. Levels of Evidence and Grades of Recommendation Working Party. New JBI levels of evidence. The Joanna Briggs Institute Web site. http://joannabriggs.org/assets/docs/approach/ JBI-Levels-of-evidence_2014.pdf. Published October 2013. Accessed April 20, 2016.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097. doi:10.1371/journal.pmed1000097.

Summary of Key Points

Hereditary angioedema (HAE) is a rare disease but can have life-threatening consequences when an exacerbation occurs. Situations in which patients with HAE are at risk for an exacerbation include airway instrumentation, upper airway trauma resulting from airway instrumentation, and psychologic or physiologic stress experienced by the patient. Knowledge of treatment options is paramount for anesthesia providers.

- Angioedema requires rapid intervention, including securing the airway and pharmacologic interventions to decrease severity of angioedema.
- Prophylaxis should be considered in patients with HAE undergoing surgery.
- HAE exacerbations result from deficiency of C1 esterase inhibitor (C1-INH) and subsequent overproduction of bradykinin.
- FFP contains C1-INH.
- FFP may have some value in treating or preventing HAE exacerbations if the FDA-approved complement C1 esterase inhibitor (Cinryze) is not available.

Appendix A: Annotated Bibliography Table				
Author and Year	**Joanna Briggs Institute Level of Evidence**	**Methodology**	**No. of Subjects**	**Major Findings, Conclusions**
Prematta et al, 2007	3.B Cohort Study	Reviewed literature and patient records to evaluate efficacy of FFP in treatment or prophylaxis of HAE exacerbation.	N=23 case reports of FFP being used as treatment or prophylaxis for HAE	FFP does not worsen acute exacerbation of HAE. FFP is an effective surgical prophylaxis agent and treatment for acute exacerbations.
MacBeth et al, 2016	3.B Cohort Study	Retrospective review of medical records and review of published case reports of patients with bradykinin-mediated angioedema who underwent general anesthesia with airway manipulation.	N=24 medical records of patients who had bradykinin-mediated angioedema and received general anesthesia	Plasma-derived C1-INH should be administered 1 hour before surgery and repeated daily after a major procedure until there is no remaining risk for exacerbation. FFP should be used only if no other treatment option is available.
Szema et al, 2009	5.B Expert Consensus	Reviewed literature regarding airway management and angioedema etiology and prophylaxis. Developed guidelines for managing patients with HAE preoperatively and intraoperatively.	None stated	Preoperative protocol for management of patients with hereditary angioedema developed.
Mihailovic et al, 2012	4.D Case Study	One case was presented involving a patient with HAE undergoing CABG surgery. Patient did not develop angioedema postoperatively.	N=1	Patient was successfully extubated without exacerbation of HAE. Patient received danazol 200 mg twice a day preoperatively, 2 doses of FFP preoperatively, and 4 doses of FFP after surgery and before extubation.
Shick et al, 2010	4.D Case Study	One case was presented concerning a patient with HAE undergoing off-pump CABG surgery. This patient did not develop angioedema postoperatively.	N=1	The patient received 2 units of FFP before incision and 2 additional units of FFP intraoperatively. Patient received other prophylactic treatment measures as well. The patient was successfully extubated in the intensive care unit.
Cifuentes et al, 2013	4.D Case Study	One case was presented involving a patient with undiagnosed HAE who underwent orthognathic surgery and developed facial and airway edema.	N=1	The patient developed severe facial and upper airway edema on postoperative day 1 that required endotracheal intubation. The patient's edema improved after administration of FFP, and the patient was discharged from the hospital 2 weeks after extubation.

Abbreviations: C1-INH, C1 esterase inhibitor; CABG, coronary artery bypass grafting; FFP, fresh frozen plasma; HAE, hereditary angioedema.

PRISMA 2009 Flow Diagram