

AWARD NUMBER: W81XWH-14-2-0177

TITLE: Topical Application of Tranexamic Acid to Reduce Blood Loss During Complex Combat-Related Spine Trauma Surgery

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REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY) October 2015		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 30 Sep 2014 - 29 Sep 2015	
4. TITLE AND SUBTITLE Topical Application of Tranexamic Acid to Reduce Blood Loss During Complex Combat-Related Spine Trauma Surgery				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-2-0177	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Lehman, Ronald A., MD Messer, Zachary M., MPH				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Columbia University Medical Center: 5141 Broadway, 3 Field West 022, New York, NY 10034; Harborview Medical Center: 325 9th Avenue, Seattle, WA 98104; Henry M. Jackson Foundation: 6720A Rockledge Drive, Suite 100, Bethesda Maryland 20817; Rothman				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Shortly after IRB approval was obtained at Washington University, the PI, Dr. Ronald Lehman, transferred to Columbia University. No other study-related procedures have taken place, as the transfer of the grant continues to be processed. Two issues have slowed the completion of this transfer. First, Columbia University does not encounter patients that meet inclusion criteria at nearly the same volume as the original institution. Thus, new sub-sites needed to be added to ensure that recruitment would follow the time course described in the statement of work. Second, over the course of the transfer, it was discovered that one of the sub-sites originally listed had applied for a grant in direct competition to this one. Subsequently, that site was removed from the grant and a replacement was needed to cover the associated loss in anticipated patient enrollment. We apologize for this delay, and have every anticipation that the transfer application will be submitted shortly and successfully.					
15. SUBJECT TERMS Spine; Tranexamic Acid; Perioperative blood loss; Trauma; Antifibrinolytic; Postoperative drain output; Allogenic transfusion; Hemorrhage; Spinal injuries; Back injuries; Wounds					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES 11	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER (Include area code)

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1. **INTRODUCTION:** The purpose of this prospective, randomized, double-blind, placebo-controlled study is to study the role and cost-effectiveness of topical tranexamic acid as a therapeutic tool, applied intraoperatively into the surgical wound for five minutes before closure, to reduce perioperative blood loss in patients undergoing surgery for complex combat-related and civilian spine trauma.
2. **KEYWORDS:** Spine; Tranexamic acid; Perioperative blood loss; Trauma; Antifibrinolytic; Postoperative drain output; Allogenic transfusion; Hemorrhage; Spinal injuries; Back injuries; Wounds
3. **OVERALL PROJECT SUMMARY:** Shortly after IRB approval was obtained at Washington University, the PI, Dr. Ronald Lehman, transferred to Columbia University. No other study-related procedures have taken place, as the transfer of the grant continues to be processed. Two issues have slowed the completion of this transfer. First, Columbia University does not encounter patients that meet inclusion criteria at nearly the same volume as the original institution. Thus, new sub-sites needed to be added to ensure that recruitment would follow the time course described in the statement of work. Second, over the course of the transfer, it was discovered that one of the sub-sites originally listed had applied for a grant in direct competition to this one. Subsequently, that site was removed from the grant and a replacement was needed to cover the associated loss in anticipated patient enrollment. We apologize for this delay, and have every anticipation that the transfer application will be submitted shortly and successfully.

Below, please find the original aims and tasks as outlined in the original statement of work, along with percent completions and explanatory text as needed.

IRB HUC submission/review/approval (February – July 2014)

Task 1. Submit clinical protocol to Walter Reed National Military Medical Center IRB for review and approval, to be completed by WRNMMC PI. (February – July 2014)

Completed, although insufficient as lead site has changed. IRB approval at Columbia University is 50% complete.

Task 2. Submit clinical protocol to the Thomas Jefferson University Medical Center and Washington University in St. Louis Medical Center IRB for review and approval, to be completed by each sites PI. (February – July 2014) *Not completed, as the lead site and sub-sites have changed. The IRB requires an up-to-date list of all sites on a multi-center trial, thus this was on hold and will resume as soon as the transfer is complete and Columbia University IRB approval is obtained. In addition, Washington University is no longer part of this study.*

Task 3. Submit clinical protocol to the Department of Defense (DoD) Human Research Protection Office for review and approval, to be completed by Project PI. (February – July 2014) *100% Completed, though updates will be submitted once the transfer application is complete.*

Task 4. An IND application will be submitted to the FDA for review and approval, to be completed by Project PI (February – July 2014) *100% complete. The IND is in good order, and the FDA has been made aware of the project status and provided with all necessary documentation.*

Specific Aim 1: Evaluate the efficacy of topical tranexamic acid to reduce perioperative blood loss and allogenic transfusion requirements. *0% completed for all tasks below. No patients have been recruited due to the aforementioned issues, thus, no evaluation of tranexamic acid's effectiveness could be performed. In addition, Walter Reed and Washington University are no longer part of this project.*

Task 1. Recruit military combat casualties and civilian patients after high-energy trauma that have sustained thoracic or lumbar spinal column with or without neurologic deficit requiring surgical fixation when they are admitted to each institution within 21 days of injury; complete screening procedures. **(August 2014 – July 2016)**

1a) WRNMMC will enroll a minimum of twenty-six (26) military patients to complete task 1, with a quarterly enrollment target of 3 to 4 patients per quarter.

1b) Washington University will enroll a minimum of 176 patients, with a quarterly enrollment target of 22 patients per quarter in Year 1 and Year 2.

1c) Thomas Jefferson University will enroll a minimum of 50 patients, with a quarterly enrollment target of 6 to 7 patients per quarter.

1d) The PI or AI will perform a complete evaluation of the patient, including clinical examination and review of imaging studies, documenting in the medical record per standard of care a complete neurologic examination using the ASIA impairment scale, and the location and severity/pattern of spinal column injury. The surgeon investigator will obtain informed consent for the surgical procedure.

1e) Research coordinators will identify patients with spinal column injuries requiring surgical intervention and will perform an interview to determine if the patient meets inclusion or exclusion criteria. The research coordinator will review the study goals and consent form with the patient and family, when applicable.

1d) When a patient with a spinal column injury requiring surgical fixation demonstrates interest in the clinical study, the research coordinator will provide education material, discuss the details of the study, and then allow privacy and time to allow decision making for up to 72 hours after recruitment or if surgical intervention is required earlier up to the morning of surgery.

1e) Screening blood laboratory specimens will be drawn after patient recruitment and consent is obtained to determine eligibility for the study and for pre-operative planning to evaluate baseline complete blood count, complete metabolic panel to evaluate renal and hepatic function and electrolyte balance, and coagulation panel to evaluate for pre-existing coagulopathy.

1f) Patients will complete clinical outcome surveys to determine baseline, pre-intervention/baseline outcome scores.

Task 2. Randomization and Intervention. **(August 2014 – July 2016)** *0% completed for all tasks below. No patients have been recruited, randomized, or participated in interventions.*

2a) On the morning of surgery, the patient will be randomized and a sealed envelope carrying the randomization information will be taken to the research pharmacist to prepare the study medication.

2b) Patients will be taken to the operating room for planned surgical intervention, and the study medication will be applied per protocol.

Task 3. Patient follow-up and Study termination (**August 2014 – July 2018**) *0% completed for all tasks below, due to aforementioned situation.*

3a) Research coordinators will obtain patient data at 1 hour post-op in the recovery area, ensuring laboratory specimens are drawn and sent for processing. Data will be recorded every morning on POD#1 through POD#4 by the research coordinator regarding drain output, laboratory values, VAS pain scale, and neurologic examination using the ASIA impairment scale.

3b) Research coordinators will schedule and ensure appropriate patient follow-up after discharge from the hospital at Week 2, Week 16, Year 1 and Year 2 post-operative visits. At each follow-up visit, clinical outcome surveys will be completed, and radiographs will be taken at Week 16, Year 1 and Year 2 post-operative visits.

3c) Each site principal investigator and research coordinator will be responsible for submitting annual interim report, and to report any adverse events during the follow-up period.

3d) Study termination will occur two-years after final subject enrollment. Each site principal investigator and research coordinator will be responsible for appropriately closing out the study at their local IRB and providing final study summaries/reports. All hardcopy documents and information stored on electronic devices will be stored for 2 years and then destroyed.

Specific Aim 2: Determine the effect of topical tranexamic acid on the rate of surgical site infection *0% completed for all tasks below. No patients have been recruited due to the aforementioned situation.*

Task 1. Patient follow-up (**August 2014 – July 2018**)

1a) Research coordinators will be responsible for documenting the occurrence of deep surgical site infection at each follow-up visit

1b) If deep surgical site infection is treated by a non-study surgeon at another institution, the non-study surgeon will be contacted and the research coordinator will request complete medical records regarding the patient's treatment course for deep surgical site infection.

Specific Aim 3: Evaluate the safety and systemic absorption following topical application of tranexamic acid in a surgical wound *0% completed for all tasks below. No patients have been recruited due to the aforementioned situation.*

Task 1. Patient follow-up (**August 2014 – July 2018**)

1a) Research coordinators will ensure plasma tranexamic level laboratory specimens are drawn within 1 hour post-op in the recovery area and then sent for processing.

1b) Patients will have screening duplex ultrasound of bilateral lower extremities on POD#3. Research coordinators will be responsible for documenting the occurrence of deep vein thrombosis or pulmonary embolism at each follow-up visit

1c) If deep vein thrombosis or pulmonary embolisms is treated by a non-study physician at another institution, the non-study physician will be contacted and the research coordinator will request complete medical records regarding the patient's treatment course.

Specific Aim 4: Evaluate patient health-related quality of life outcomes measures and perform a cost analysis based on and determined the use of tranexamic acid for blood loss management and prevention of surgical site infection *0% completed for all tasks below. No patients have been recruited due to the aforementioned situation.*

Task 1. Data analysis (August 2018 – October 2018)

1a) After patient enrollment, research coordinators will collect completed patient health-related quality of life questionnaires/surveys (SF-36 and ODI), these will be collected again at the 16 week, 1 year and 2 year follow-up clinic visits.

1b) After termination of the study, the biostatistician will perform cost analysis using regressive and normative methods to establish a decision model of cost resulting from use of topical tranexamic acid with posterior spinal fusion surgery in complex spine trauma surgery.

- 4. KEY RESEARCH ACCOMPLISHMENTS:** Nothing to report.
- 5. CONCLUSION:** Nothing to report.
- 6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:** Nothing to report.
- 7. INVENTIONS, PATENTS AND LICENSES:** Nothing to report.
- 8. REPORTABLE OUTCOMES:** Nothing to report.
- 9. OTHER ACHIEVEMENTS:** Nothing to report.
- 10. REFERENCES:**

1. Schwarzkopf R, Chung C, Park JJ, Walsh M, Spivak JM, Steiger D. Effects of perioperative blood product use on surgical site infection following thoracic and lumbar spinal surgery. *Spine (Phila Pa 1976)*. Feb 1 2010;35(3):340-346.
2. Llewelyn CA, Taylor RS, Todd AA, Stevens W, Murphy MF, Williamson LM. The effect of universal leukoreduction on postoperative infections and length of hospital stay in elective orthopedic and cardiac surgery. *Transfusion*. Apr 2004;44(4):489-500.
3. Triulzi DJ, Vanek K, Ryan DH, Blumberg N. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion*. Jul-Aug 1992;32(6):517-524.
4. Sitges-Serra A, Insenser JJ, Membrilla E. Blood transfusions and postoperative infections in patients undergoing elective surgery. *Surg Infect (Larchmt)*. 2006;7 Suppl 2:S33-35.
5. Lehman RA, Jr. Military contributions to spine care. *Spine J*. Sep 2012;12(9):727-728.
6. Blair JA, Patzkowski JC, Schoenfeld AJ, et al. Spinal column injuries among Americans in the global war on terrorism. *J Bone Joint Surg Am*. Sep 19 2012;94(18):e135(131-139).
7. Lehman RA, Jr., Huddleston P, Yaszemski M. Axial spine injuries in the current conflicts in Iraq and Afghanistan. *J Am Acad Orthop Surg*. 2012;20 Suppl 1:S13-17.
8. Kang DG, Lehman RA, Jr., Carragee EJ. Wartime spine injuries: understanding the improvised explosive device and biophysics of blast trauma. *Spine J*. Sep 2012;12(9):849-857.
9. Possley DR, Blair JA, Freedman BA, Schoenfeld AJ, Lehman RA, Hsu JR. The effect of vehicle protection on spine injuries in military conflict. *Spine J*. Sep 2012;12(9):843-848.
10. Possley DR, Blair JA, Schoenfeld AJ, Lehman RA, Hsu JR. Complications associated with military spine injuries. *Spine J*. Sep 2012;12(9):756-761.

11. Blair JA, Possley DR, Petfield JL, Schoenfeld AJ, Lehman RA, Hsu JR. Military penetrating spine injuries compared with blunt. *Spine J.* Sep 2012;12(9):762-768.
12. Patzkowski JC, Blair JA, Schoenfeld AJ, Lehman RA, Hsu JR. Multiple associated injuries are common with spine fractures during war. *Spine J.* Sep 2012;12(9):791-797.
13. Blair JA, Patzkowski JC, Schoenfeld AJ, et al. Are spine injuries sustained in battle truly different? *Spine J.* Sep 2012;12(9):824-829.
14. Schoenfeld AJ, Lehman RA, Jr., Hsu JR. Evaluation and management of combat-related spinal injuries: a review based on recent experiences. *Spine J.* Sep 2012;12(9):817-823.
15. Kang DG, Lehman RA, Jr. Spine immobilization: prehospitalization to final destination. *J Surg Orthop Adv.* Spring 2011;20(1):2-7.
16. Lehman RA, Jr., Kang DG, Bellabarba C. A new classification for complex lumbosacral injuries. *Spine J.* Jul 2012;12(7):612-628.
17. Kang DG, Cody JP, Lehman RA, Jr. Open lumbosacral spine fractures with thecal sac ligation after combat blast trauma. *Spine J.* Sep 2012;12(9):867-868.
18. Dworak TC, Kang DG, Lehman RA, Jr. Combat-related L3 fracture treated with L2-L4 posterior spinal fusion complicated by multidrug-resistant acinetobacter infection. *Spine J.* Sep 2012;12(9):864-866.
19. Kang DG, Cody JP, Lehman RA, Jr. Combat-related lumbopelvic dissociation treated with L4 to ilium posterior fusion. *Spine J.* Sep 2012;12(9):860-861.
20. Kang DG, Dworak TC, Lehman RA, Jr. Combat-related L5 burst fracture treated with L4-S1 posterior spinal fusion. *Spine J.* Sep 2012;12(9):862-863.
21. Cody JP, Kang DG, Lehman RA, Jr. Combat-related lumbopelvic dissociation treated with percutaneous sacroiliac screw placement. *Spine J.* Sep 2012;12(9):858-859.
22. Lehman RA, Jr., Paik H, Eckel TT, Helgeson MD, Cooper PB, Bellabarba C. Low lumbar burst fractures: a unique fracture mechanism sustained in our current overseas conflicts. *Spine J.* Sep 2012;12(9):784-790.
23. Helgeson MD, Lehman RA, Jr., Cooper P, Frisch M, Andersen RC, Bellabarba C. Retrospective review of lumbosacral dissociations in blast injuries. *Spine (Phila Pa 1976).* Apr 1 2011;36(7):E469-475.
24. Risberg B. The response of the fibrinolytic system in trauma. *Acta Chir Scand Suppl.* 1985;522:245-271.
25. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am.* Nov 3 2010;92(15):2503-2513.
26. Smorgick Y, Baker KC, Bachison CC, Herkowitz HN, Montgomery DM, Fischgrund JS. Hidden blood loss during posterior spine fusion surgery. *Spine J.* Mar 21 2013.
27. Baldus CR, Bridwell KH, Lenke LG, Okubadejo GO. Can we safely reduce blood loss during lumbar pedicle subtraction osteotomy procedures using tranexamic acid or aprotinin? A comparative study with controls. *Spine (Phila Pa 1976).* Jan 15 2010;35(2):235-239.
28. Elgafy H, Bransford RJ, McGuire RA, Dettori JR, Fischer D. Blood loss in major spine surgery: are there effective measures to decrease massive hemorrhage in major spine fusion surgery? *Spine (Phila Pa 1976).* Apr 20 2010;35(9 Suppl):S47-56.
29. Tse EY, Cheung WY, Ng KF, Luk KD. Reducing perioperative blood loss and allogeneic blood transfusion in patients undergoing major spine surgery. *J Bone Joint Surg Am.* Jul 6 2011;93(13):1268-1277.
30. Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology.* Nov 2006;105(5):1034-1046.

31. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thromb Res.* Mar 2009;123(5):687-696.
32. Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS One.* 2013;8(2):e55436.
33. Gill JB, Chin Y, Levin A, Feng D. The use of antifibrinolytic agents in spine surgery. A meta-analysis. *J Bone Joint Surg Am.* Nov 2008;90(11):2399-2407.
34. De Bonis M, Cavaliere F, Alessandrini F, et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *J Thorac Cardiovasc Surg.* Mar 2000;119(3):575-580.
35. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. *Can J Anaesth.* Mar 2009;56(3):202-212.
36. Georgiou C, Neofytou K, Demetriades D. Local and systemic hemostatics as an adjunct to control bleeding in trauma. *Am Surg.* Feb 2013;79(2):180-187.
37. Ipema HJ, Tanzi MG. Use of topical tranexamic acid or aminocaproic acid to prevent bleeding after major surgical procedures. *Ann Pharmacother.* Jan 2012;46(1):97-107.
38. Krohn CD, Sorensen R, Lange JE, Riise R, Bjornsen S, Brosstad F. Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. *Eur J Surg Suppl.* Jul 2003(588):57-61.
39. Molloy DO, Archbold HA, Ogonda L, McConway J, Wilson RK, Beverland DE. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: a prospective, randomised controlled trial. *J Bone Joint Surg Br.* Mar 2007;89(3):306-309.
40. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. *J Am Acad Orthop Surg.* Mar 2010;18(3):132-138.
41. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. *Br J Anaesth.* May 2003;90(5):596-599.
42. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery.* Feb 1962;51(2):224-232.
43. FDA. FDA Approved Drug Products, Cyklokapron Label and Approval History. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019281s031lbl.pdf. Accessed on 7 Jul 2014.
44. World Health Organization. WHO Model List of Essential Medicines, 17th List, March 2011. <http://www.who.int/medicines/publications/essentialmedicines/en/>. Accessed 2013 Jul 7.
45. Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. *N Engl J Med.* Mar 30 1989;320(13):840-843.
46. Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L. Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. *J Cardiothorac Surg.* 2009;4:25.
47. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. *J Clin Pathol Suppl (R Coll Pathol).* 1980;14:41-47.
48. Ahlberg A, Eriksson O, Kjellman H. Diffusion of tranexamic acid to the joint. *Acta Orthop Scand.* Oct 1976;47(5):486-488.

49. Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F. Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. *Anesthesiology*. Apr 2005;102(4):727-732.
50. Vaccaro AR, Lehman RA, Jr., Hurlbert RJ, et al. A new classification of thoracolumbar injuries: the importance of injury morphology, the integrity of the posterior ligamentous complex, and neurologic status. *Spine (Phila Pa 1976)*. Oct 15 2005;30(20):2325-2333.
51. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology*. Jul 2006;105(1):198-208.
52. Freedman J, Luke K, Monga N, et al. A provincial program of blood conservation: The Ontario Transfusion Coordinators (ONTraC). *Transfus Apher Sci*. Nov 2005;33(3):343-349.
53. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. Feb 11 1999;340(6):409-417.
54. Blood transfusion and the anaesthetists: red cell transfusion 2. London: The Association of Anaesthetists of Great Britain and Ireland; 2008.
55. Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. *Transfusion*. Jan 2005;45(1):103-110.
56. Kuriyan M, Carson JL. Anemia and clinical outcomes. *Anesthesiol Clin North America*. Jun 2005;23(2):315-325, vii.
57. Carson JL, Terrin ML, Jay M. Anemia and postoperative rehabilitation. *Can J Anaesth*. Jun-Jul 2003;50(6 Suppl):S60-64.
58. Diamond PT, Conaway MR, Mody SH, Bhirangi K. Influence of hemoglobin levels on inpatient rehabilitation outcomes after total knee arthroplasty. *J Arthroplasty*. Aug 2006;21(5):636-641.

11. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

NOTE:

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