

# The Use of Preoperative Epoetin- $\alpha$ in Revision Hip Arthroplasty

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**Abstract:** *Purpose:* To evaluate the efficacy of preoperative epoetin- $\alpha$  on the revision hip arthroplasty patient. We hypothesized that epoetin- $\alpha$  will reduce blood transfusion. A pertinent review of the literature is provided.

*Methods:* Forty-six patients were retrospectively reviewed. Sixteen patients received epoetin- $\alpha$ . Patients were case matched by age, preoperative hemoglobin, surgery, gender, and BMI. The clinical triggers for blood transfusion during or after the procedure were determined based on peri- and postoperative hemoglobin levels, ASA score, and/or clinical symptoms consistent with anemia. Blood salvage was not used.

*Results:* Blood transfusion and length of stay were decreased in the epoetin- $\alpha$  group. Hemoglobin in the intervention group increased from 12.0 to 14.5, preoperatively. Patients who received epoetin- $\alpha$  were 0.78 (RR=0.225) times as likely to receive a transfusion. Number Needed to Treat (NNT) to avoid one allogeneic transfusion was 1.84. Age, Gender, BMI, ASA, total and hidden blood loss, preoperative Iron supplements, preop Hct, preop PLT, PT, PTT, and INR were similar. One (6.0%) patient developed an uncomplicated deep venous thrombosis in the intervention group.

*Conclusions:* The mildly anemic revision hip arthroplasty patient is at increased risk for transfusion. Epoetin- $\alpha$  increased preoperative hemoglobin counts and reduced transfusions in this study; it also decreased patient length of hospital stay likely allowing for an earlier readiness to resume normal activities and/or meet short-term milestones. A randomized study to evaluate the direct and indirect costs of such a treatment methodology in the mildly anemic revision patient may be warranted.

**Keywords:** Anemia, orthopedic surgery, autologous blood donation, blood transfusion, epoetin- $\alpha$ , revision total hip arthroplasty.

## INTRODUCTION

Revision hip arthroplasty is associated with increased transfusion needs [1]. A typical patient loses 4.0 g/dL, and receives three units [2] – such units have been of allogeneic or of autologous origin. However, both treatment modalities can lead to significant clinical morbidity.

Preoperative autologous donation has been used to prevent allogeneic transfusions. However, recent studies found that it may be less efficacious than anticipated. For instance, it can induce anemia, and thus may not be indicated when baseline hemoglobin levels ( $\leq 13.0$  g/dl) are low [3]. In contrast, recent studies suggest that the primary hip arthroplasty patient may benefit from preoperative epoetin- $\alpha$  more so than autologous donation [4]. Lastly, epoetin- $\alpha$  was efficacious in numerous fields of medicine and surgery; one of which was orthopaedic trauma [5]. To the knowledge of

these authors, there has been one study that evaluated the use of preoperative epoetin- $\alpha$  in the revision hip patient [6].

The purpose of this study is to assess the effect of preoperative epoetin- $\alpha$  injection on the mildly anemic patient - a population thought to hold a four-fold and fifteen-fold transfusion rate increase over those with levels between 13.0-15.0g/dl and  $>15$ g/dl, respectively [7, 8]. Our hypothesis is that epoetin- $\alpha$  injection will reduce transfusions. A pertinent review of the literature is provided.

## METHODS

Following Institutional Review Board (IRB) approval, we performed this retrospective analysis. Between January 2007 and May 2010 there were 46 patients who met our inclusion and exclusion criteria. All of our patients received revision hip surgery for prosthesis wear out and/or loosening. All surgical procedures were elective. The following cases were excluded from the study: control subjects with pre-operative hemoglobin values less than 10 g/dL or greater than 13g/dL, patients with hematological diseases or coagulation disorders, a prior history of deep

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venous thrombosis or pulmonary embolus, and subjects who received a postoperative drain. We termed patients with a hemoglobin level at or below 13g/dL and at or above 10g/dL mildly anemic.

For initial hemoglobin levels (obtained a month prior to surgery)  $>13\text{g/dL}$  and  $\leq 14\text{g/dL}$ , a pre-operative autologous collection was offered. When a hemoglobin level was  $\geq 10$  and  $\leq 13\text{ g/dL}$ , then three weekly doses of epoetin- $\alpha$  were considered. All risks associated with epoetin- $\alpha$  use were discussed. Patients that did not receive epoetin- $\alpha$  treatment were patient matched according to age, gender, body mass index, and ASA score. All patients were offered oral multi-vitamins, vitamin B12, folic acid, and iron.

The preoperative work-up, surgical technique, anesthesia, and postoperative management of patients in both groups were identical. All surgeries were completed under combined spinal-epidural anesthesia. A hardinge approach utilizing the old incision was performed on all patients. All THAs were non-cemented. Neither cell saver nor drains were used - at our institution, it is not a routine practice to utilize drains during THA without an indication. Through 4-weeks postop, proper anticoagulant (either oral warfarin or subcutaneous enoxaparin) was administered to the patient. The target INR for all patients was 2.0-2.5. The first dose of prophylactic antibiotic (1 gram IV cefazolin or vancomycin for allergic patients) was administered within one hour prior to incision and then continued for the first 24 hours after surgery. The clinical triggers for blood transfusion during or after the procedure were determined based on an intraoperative hemoglobin level  $\leq 8$ , or symptoms consistent with anemia.

We used a chi-square test for the proportions of cases receiving blood, and Student's *t*-test and Chi-square for comparing the continuous and categorical variables, respectively. For the statistical analysis, version 18 of PASW<sup>®</sup> Statistics (SPSS Inc., an IBM Company Headquarters, Chicago, Illinois) was used. A  $p < 0.05$  was considered statistically significant.

## RESULTS

The demographic data for the two cohorts are reported in Table 1. The records of 46 patients were reviewed, and no difference was found in demographic data between cohorts for age, gender, ASA, or BMI. There were no differences in patient blood values for preoperative PT, PTT, INR, or platelet count ( $p > 0.05$ ).

The average postoperative total blood loss (TBL), hidden blood loss (HBL), and calculated blood loss (CBL) are provided in Table 2. The average estimated blood loss was lower in the group of patients receiving epoetin- $\alpha$  ( $p = 0.019$ ). There was no difference in the median estimated blood loss. There was no difference in the average quantity of transfused blood.

The average use of 2.88 doses of epoetin- $\alpha$  decreased the number of patients requiring transfusion. The discharge hemoglobin was higher in the intervention group. At the time of hospital admission the mean hemoglobin level was higher in the epoetin- $\alpha$  group. The mean duration of surgery was similar for both cohorts. There was a shorter length of hospital stay for patients who received epoetin- $\alpha$  (Table 2).

**Table 1. Demographic Data for Hip Revision Patients**

Characteristic	Epoetin- $\alpha$	Control	p-Value
Age (y)	70.7	74.1	0.349
BMI (kg/m <sup>2</sup> )	28.8	26.8	0.249
ASA score (no.)	2.56	2.70	0.404
INR	1.33	1.39	0.966
Platelet count (per mm <sup>3</sup> )	242,000	242,590	0.777
Sg Duration (min)	79.2	92.0	0.145
Length of Stay (days)	3.33	4.28	0.046

The index revision surgery was defined as any procedure in which at least acetabular, femoral, or liner/head components were exchanged. In the epoetin- $\alpha$  cohort, 12 (75%) patients had an acetabular revision. Three patients (18.8%) had a liner/head exchange, and 1 (6.3%) had a femoral component revision. In the control cohort, 21 (75%) of patients had an acetabular revision. Six patients had a liner/head exchange (21.4%), and 2 had a femoral revision (3.6%) (Table 3).

There was a single cardiovascular complication in this cohort. One of the patients in the intervention group (epoetin- $\alpha$ ) developed an uncomplicated deep venous thrombosis diagnosed by ultrasound. The patient was treated as an outpatient. No further complications were noted.

In the epoetin- $\alpha$  group, 17.6% of the patients (3 of 17) required blood transfusion. This was significantly lower than the control group where 75.8% of the patients (22 of 29) received at least one unit of blood ( $p = 0.0003$ ) (Table 2). The relative risk of the epoetin- $\alpha$  treatment regimen was 0.225 (0.176/0.719). Number Needed to Treat (NNT) to avoid one allogeneic transfusion was 1.84 ( $1/(0.719-0.176)$ ) (Table 2).

## DISCUSSION

While preoperative epoetin- $\alpha$  injection has been shown to reduce peri- [9] and postoperative transfusions in primary hip replacements, there has been one report, to the knowledge of these authors, of its effect on the revision hip patient [6]. Our patients who received epoetin- $\alpha$  were transfused less, had an elevated preoperative and discharge hemoglobin level, and a shorter hospital length of stay. Patients who received epoetin- $\alpha$  were 0.78 (RR=0.225) times as likely to receive a transfusion. Number Needed to Treat (NNT) to avoid one allogeneic transfusion was 1.84. There was one blood-related study cohort complication of deep venous thrombosis (6.0%) in a patient that was not transfused.

Noordin *et al.* studied revision THA patients. They noted that the transfusion rate for epoetin- $\alpha$  was no different than for a matched control group. However, not only did Noordin *et al.* use a different epoetin- $\alpha$  drug regimen, dose schedule, and study inclusion criteria, but they also used a control cohort that consisted of emergent surgery for periprosthetic fractures or infections. Additionally, their study group patients had a lower ASA score as well as a decreased rate of comorbidities than their blood utilization program patients [6]. Our study differs because we patient-matched our

**Table 2. Blood Data for Hip Revision Study Patients**

Characteristic	Epoetin- $\alpha$	Control	p-value
Average epoetin- $\alpha$ dose 40,000u	2.88*	0	Na
#Epoetin- $\alpha$ effect on Hb (g/dL)	12.0 to 14.5	Na	0.002
Hb at Sg (g/dL)	14.0	12.0	<0.001
Hb on discharge (g/dL)	10.1	9.39	0.016
Transfusion (%)	17.6	71.9	<0.001
Average transfusion (mL)	333	335	0.981
Mean Total Blood Loss (mL)	1176	1047	0.424
Mean Hidden Blood Loss (mL)	1065	1178	0.534
Median Total Blood Loss (mL)	1118	1059	Na
Median Hidden Blood Loss (mL)	1064	1145	Na
Average transfused (mL)	333	335	0.981
Mean Estimated Blood Loss (mL)	189 Range:50-500cc	338 Range:50-850cc	0.019
Median Estimated Blood Loss (mL)	150	200	

\*Two of sixteen patients missed a preoperative dose for an unspecified reason.

‡ Only pts with pre-injection CBC performed at our institution.

cohorts (age, BMI, gender, ASA) to decrease the inherent design flaws of a retrospective study. As such, we believe this study suggests that epoetin- $\alpha$  may be an efficacious option to reduce blood transfusions in the revision hip arthroplasty patient [10, 11].

**Table 3. Components for Hip Revision Study Patients**

Component Revisions	Epoetin- $\alpha$ (Total=16)	Controls (Total=28)
Acetabular revisions	12 (75%) 1 (8.3%) transfused	21 (75%) 19 (90%) transfused
Femoral component revisions	1 (6.3%) 0 transfused	1 (3.6%) 0 transfused
Liner/head exchange	3 (18.8%) 2 (66.7%) transfused	6 (21.4%) 1 (16.6%) transfused

Moonen *et al.* [4] conducted a randomized trial that compared two cohorts of 50 patients each with mild anemia ( $10 \geq \text{Hb} \leq 13 \text{g/dL}$ ) who underwent either primary total hip or knee arthroplasty. The group randomized to receive a preoperative epoetin- $\alpha$  injection had a decreased blood transfusion frequency; however, the cost of the epoetin- $\alpha$  intervention exceeded that of the autologous re-transfused blood group. Another randomized trial by Slappendel *et al.* [12] evaluated 695 patients with preoperative hemoglobin values of 10–13 g/dL who underwent elective orthopedic surgery – of which 113 patients had rheumatoid arthritis (RA). Their randomized cohorts consisted of either preoperative epoetin- $\alpha$  injection with standard care or standard care alone. They concluded that RA patients benefitted from preoperative epoetin- $\alpha$  treatment in combination with iron supplementation.

Gonzalez-Porras *et al.* [13] studied 305 patients who either underwent elective THA or TKA. The patients were

individually assigned to one of five strategies: (1) no pre-operative intervention; (2) oral iron therapy; (3) intravenous iron therapy; (4) recombinant human epoetin- $\alpha$  with intravenous iron; and, (5) pre-operative autologous donation plus oral iron. They noted that preoperative autologous donation caused a reduction in hemoglobin levels. Furthermore, a multivariate subgroup analysis designed to evaluate postoperative transfusion risk factors determined that decreased weight and/or preoperative hemoglobin levels as well as the lack of a blood protocol strategy independently increased transfusion needs [13].

Garvin *et al.* found blood loss was greater for revision THA femoral components than for acetabular in 147 patients [14]. Furthermore, Zarin *et al.* found that when femoral and acetabular components were revised together blood loss was highest; whereas either component revised alone had no difference [15]. Our study was not powered for such an analysis, but we identified for our controls that 90% of revised acetabular components required a transfusion, whereas for our study patients 8.3% of acetabular components required one.

Our study demonstrated that three weekly doses of 40,000 units of epoetin- $\alpha$  increased preoperative hemoglobin levels. Furthermore, for every 1.84 patients treated with epoetin- $\alpha$ , we were able to prevent one transfusion. We also believe that epoetin- $\alpha$  may be a more patient friendly and cost-effective treatment option for preoperative anemia [16]. For example, predonation of autologous blood can be an inefficient process since approximately 40-56% of it may be wasted [17, 18]. It also carries a risk for compartment syndrome, contamination, febrile and/or septic reactions, clerical error, and inflammatory processes [19]. Furthermore, it is known to induce a phlebotomy related anemia [3]. Therefore, we try to avoid its use.

Moonen *et al.* [4] reported that epoetin- $\alpha$  injection, supplemented by ferrofumarate tablets, increased the cost per

patient when compared with a re-transfusion system. Their result was based on a direct cost analysis in Euros. However, the scarcity of and risk associated with allogeneic blood, potential transfusion error, administrative cost of testing, storing, and transfusing blood also need to be considered in an analysis. Furthermore, length of stay and patient satisfaction, among others should be considered. We recommend pre-op iron, folic acid, vitamin B12, and multivitamin use to all our patients undergoing elective surgery.

According to Sehat KR *et al*, there may be hidden blood loss into the soft tissue and joint of an arthroplasty patient. We did not detect a difference, but our study was likely not powered to do so; however, our average total and hidden blood losses were elevated when compared to the primary THA patient [20]. Importantly, the total and hidden blood loss is not a perfect measure; a part of its flaw is that the estimated blood loss intra- and postoperatively is a subjective measure based off a non-standardized process. One study presented their results utilizing the median value for total and hidden blood loss due to the numerous outliers present [21]. Therefore, we found it difficult to compare our blood loss results to those published. However, one interesting finding derived from such calculations is that a total hip arthroplasty has a lower hidden blood loss than total knee arthroplasty [20]. The change in hemoglobin from pre- to postoperatively in our study cohort was 12 to 14.5g/dL. Such a change was similar to those recorded by Sehat KR *et al*. who noted that a THA without re-infusion had a change of 3.3 g/dL and 2.8 g/dL with re-infusion. These authors consider this to be clinically significant since postoperative hemoglobin levels have been shown to correlate with patient readiness to resume normal activities after elective arthroplasty. Furthermore, it is known that short-term milestones are reached more rapidly if patients participate in inpatient rehabilitation immediately after surgery [22].

There is a thought that epoetin- $\alpha$  may increase the occurrence of cardiovascular system side effects. However, there are also studies that link the drug with an anti-apoptotic activity that in preclinical and small clinical studies has been shown to protect cells from hypoxic and ischemic events [23-25]. It is possible that the anti-apoptotic activity of it may improve or prevent the outcome of an adverse event. However, cancer and chronic renal failure trial patients had an increased risk of thrombotic complications and death [26-28]. Our protocol for epoetin- $\alpha$  administration had one blood-related complication. One patient developed an uncomplicated deep venous thrombosis (6%). It is standard in our orthopedic practice to transfuse patients based on anemic symptoms, or a hemoglobin count less than 8. All patients received the same postoperative treatment course that consisted of anti-thromboprophylaxis, early ambulation, and physical therapy. Additionally, no study patient had an ischemic event.

There were limitations to our study. The patient enrollment in the epoetin- $\alpha$  program was strictly voluntary, and the retrospective nature of our analysis invites the possibility of a confounding variable; however, we patient-matched on age, gender, BMI, ASA score, and procedure. Also, our study patients, on average, used more supplements preoperatively. Therefore, it is possible that we captured the

effect of not only epoetin- $\alpha$  but also the vitamins; however, it is unlikely that the difference had a true clinical effect. Although estimated blood loss (EBL) was significantly different between our cohorts, we believe it was due to a few outliers present in the control group. Furthermore, the median estimated blood loss in the study and control groups were 150 and 200ml, respectively. Our series included a consecutive group of patients that received epoetin- $\alpha$ . Additionally, spinal anesthesia is thought to decrease perioperative loss when compared to general anesthesia [29]. Most of our patients underwent spinal anesthesia, but a few required general. Also, we did not include patients with a prior thromboembolic history because they are inherently at increased risk of clotting. Lastly, the trigger for transfusions is generally physician dependent. To account for this, we included cases performed by two surgeons only who have similar transfusion triggers as stated previously.

In conclusion, the present study demonstrates that the mildly anemic revision hip arthroplasty patient is at increased risk for transfusion. It also may suggest that epoetin- $\alpha$  could decrease the need for blood transfusion and/or decrease the length of hospital stay for the mildly anemic patient allowing earlier return to normal activities and/or to meet short-term milestones [22]. A randomized study to evaluate the direct and indirect costs of such a treatment methodology in the mildly anemic revision hip patient may be warranted.

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#### CONFLICT OF INTEREST

Declared none.

#### REFERENCES

- [1] Bridgens J, Evans C, Dobson P, Hamer A. Intraoperative red blood-cell salvage in revision hip surgery. A case-matched study. *Clin Orthop Relat Res* 2007; 89(2): 270-5.
- [2] Callaghan JJ, O'Rourke MR, Liu SS. Blood management: issues and options. *J Arthroplasty* 2005; 20: 51-4.
- [3] Pierson JL, Hannon TJ, Earles DR. A blood-conservation algorithm to reduce blood transfusions after total hip and knee arthroplasty. *J Bone Joint Surg Am* 2004; 86-A(7): 1512-8.
- [4] Moonen AF, Thomassen BJ, Knoors NT, van Os JJ, Verburg AD, Pilot P. Pre-operative injections of epoetin-alpha versus post-operative retransfusion of autologous shed blood in total hip and knee replacement: a prospective randomised clinical trial. *J Bone Joint Surg Br* 2008; 90(8): 1079-83.
- [5] Wilson J, Yao G, Raftery J, *et al*. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007; 11(13): 1-220.
- [6] Noordin S, Waters TS, Garbuz DS, Duncan CP, Masri BA. Tranexamic acid reduces allogenic transfusion in revision hip arthroplasty. *Clin Orthop Relat Res* 2011; 469(2): 541-6.
- [7] Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. *J Bone Joint Surg* 1999; 81(1): 2-10.
- [8] Salido JA, Marin LA, Gomez LA, Zorrilla P, Martinez C. Preoperative hemoglobin levels and the need for transfusion after prosthetic hip and knee surgery: analysis of predictive factors. *J Bone Joint Surg* 2002; 84(2): 216-20.
- [9] Laupacis A, Fergusson D. Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Transfus Med (Oxford, England)* 1998; 8(4): 309-17.
- [10] de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. Baseline hemoglobin as a predictor of risk of transfusion and

- response to Epoetin alfa in orthopedic surgery patients. *Am J Orthop* (Belle Mead NJ) 1996; 25(8): 533-42.
- [11] Faris PM, Ritter MA, Abels RI. The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American Erythropoietin Study Group. *J Bone Joint Surg Am* 1996; 78(1): 62-72.
- [12] Slappendel R, Weber EW, Hemon YJ, *et al.* Patients with and without rheumatoid arthritis benefit equally from preoperative epoetin-alpha treatment. *Acta Orthop* 2006; 77(4): 677-83.
- [13] Gonzalez-Porras JR, Colado E, Conde MP, Lopez T, Nieto MJ, Corral M. An individualized pre-operative blood saving protocol can increase pre-operative haemoglobin levels and reduce the need for transfusion in elective total hip or knee arthroplasty. *Transfus Med* 2009; 19(1): 35-42.
- [14] Garvin KL, Feschuk CA, Sekundiak TD, Lyden ER. Blood salvage and allogenic transfusion needs in revision hip arthroplasty. *Clin Orthop Relat Res* 2005; 441: 205-9.
- [15] Zarin J, Grosvenor D, Schurman D, Goodman S. Efficacy of intraoperative blood collection and reinfusion in revision total hip arthroplasty. *J Bone Joint Surg* 2003; 85(11): 2147-51.
- [16] Faris PM, Ritter MA. Epoetin alfa. A bloodless approach for the treatment of perioperative anemia. *Clin Orthop Relat Res* 1998; (357): 60-7.
- [17] Billote D, Glisson S, Green D, Wixson R. A prospective, randomized study of preoperative autologous donation for hip replacement surgery. *J Bone Joint Surg Am* 2002; 84(8): 1299-304.
- [18] Hatzidakis A, Mendlick M, Mckillip T, Reddy R, Garvin KL. Preoperative autologous donation for total joint arthroplasty: an analysis of risk factors for allogenic transfusion. *J Bone Joint Surg Am* 2000; 82(1): 89-100.
- [19] Woronoff-Lemsi MC, Arveux P, Limat S, Morel P, Le Pen C, Cahn JY. Erythropoietin and preoperative autologous blood donation in the prevention of hepatitis C infection: necessity or luxury? *Transfusion* 1999; 39(9): 933-7.
- [20] Sehat K, Evans R, Newman J. Hidden blood loss following hip and knee arthroplasty: correct management of blood loss should take hidden loss into account. *J Bone Joint Surg Br* 2004; 86(4): 561-5.
- [21] Liu X, Zhang X, Chen Y, Wang Q, Jiang Y, Zeng B. Hidden blood loss after total hip arthroplasty. *J Arthroplasty* 2011; 26(7): 1100-5.
- [22] Munin MC, Rudy TE, Glynn NW, Crossett LS, Rubash HE. Early inpatient rehabilitation after elective hip and knee arthroplasty. *JAMA* 1998; 279(11): 847-52.
- [23] Coleman T, Brines M. Science review: Recombinant human erythropoietin in critical illness: a role beyond anemia? *Crit Care* 2004; 8(5): 337-41.
- [24] Maiese K, Li F, Chong ZZ. New avenues of exploration for erythropoietin. *JAMA* 2005; 293(1): 90-5.
- [25] Brines M, Cerami A. Discovering erythropoietin's extra-hematopoietic functions: biology and clinical promise. *Kidney Int* 2006; 70(2): 246-50.
- [26] Henke M, Laszig R, Rube C, *et al.* Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003; 362(9392): 1255-60.
- [27] Leyland-Jones B, Semiglazov V, Pawlicki M, *et al.* Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005; 23(25): 5960-72.
- [28] Bohlius J, Wilson J, Seidenfeld J, *et al.* Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 2006; 98(10): 708-14.
- [29] Juelsgaard P, Larsen UT, Sørensen JV, Madsen F, Soballe K. Hypotensive epidural anesthesia in total knee replacement without tourniquet: reduced blood loss and transfusion. *Reg Anesth Pain Med* 2001; 26(2): 105-10.

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