G. Gasparini · P. Papaleo · P. Pola · S. Cerciello ·
E. Pola · C. Fabbriani

Local infusion of norepinephrine reduces blood losses and need of transfusion in total knee arthroplasty

Received: 21 November 2005 / Accepted: 29 November 2005 / Published online: 7 March 2006
© Springer-Verlag 2006

Abstract Blood loss after total knee arthroplasty (TKA) is often associated with cardiovascular complications and a high transfusion rate of allogenic blood. In our study we focused our attention on developing a new intra-surgical procedure that appears safe, easy to perform and effective in the reduction of bleeding in TKA. We evaluated 84 patients who underwent TKA and met our inclusion criteria; they were assigned to two groups: 55 controls in which a saline solution was used to wash the surgical field before tourniquet release, and a second group of 29 patients, in which a saline solution containing a low dose of norepinephrine was locally applied before tourniquet release. The local administration of a low dose of norepinephrine has induced a significant reduction of perioperative blood loss and blood transfusion requirements; in addition, this method was characterised by the absence of complications or adverse effects. In conclusion, our data suggest that intraoperative local administration of a low dose of norepinephrine could represent an effective and safe method of reducing blood loss and preventing blood transfusions in patients with TKA.

Résumé Les pertes sanguines après prothèse totale du genou sont souvent associées avec des complications cardio-vasculaires et nécessitent un pourcentage important de transfusions sanguines. Nous avons développé pour notre étude une technique chirurgicale destinée à réduire les saignements dans les prothèses totales du genou. Nous avons inclus 84 patients qui ont bénéficié d'une prothèse totale du genou. Nous les avons divisés en deux groupes: un groupe contrôle de 55 patients pour lesquels une solution saline a été utilisée pour laver le champ opératoire avant le lever du garrot et un second groupe de 29 patients pour lequel une solution saline contenant une faible dose de norépinéphrine a été localement appliquée avant l'ablation du garrot. L'administration locale d'une petite dose de norépinéphrine a entraîné une réduction significative du saignement péri-opératoire et de la nécessité de transfusion sanguine. Cette méthode n'a entraîné aucune complication. Conclusion, ces données nous incitent à suggérer que l'administration locale de deux petites doses de norépinéphrine représente une méthode de réduction du saignement et de prévention de la transfusion sanguine dans la mise en place d'une prothèse totale du genou.

G. Gasparini · S. Cerciello · E. Pola · C. Fabbriani
Department of Orthopedics, A. Gemelli University Hospital,
Università Cattolica del Sacro Cuore School of Medicine,
Rome, Italy

P. Papaleo · P. Pola
Department of Medicine, A. Gemelli University Hospital,
Università Cattolica del Sacro Cuore School of Medicine,
Rome, Italy

P. Papaleo (✉)
Istituto di Patologia Speciale Medica e Semeiotica Medica,
A. Gemelli University Hospital,
L.go A. Gemelli 8,
00168 Rome, Italy
e-mail: pieropapaleo@yahoo.it
Tel.: +39-06-30154846
Fax: +39-06-35500486

Introduction

Blood loss in total knee arthroplasty (TKA) is a major issue in orthopaedic surgery. Extensive blood loss during and after TKA is associated with a high risk of, in particular, cardiovascular complications, and a high transfusion rate of allogenic blood [4]. Furthermore, allogenic blood transfusion increases the risk of immunological and non-immunological adverse effects for patients, including postoperative infections and disease transmission, and increases medical costs [2–4]. For these reasons various methods to reduce blood loss, such as postoperative autotransfusion [9], the use of a femoral intramedullary plug [6] and intravenous administration of tranexamic acid [1, 10] have been proposed.

Recently, drainage clamping combined with infusion of an epinephrine solution has been advocated to reduce post-

operative blood loss [8, 11]. Although this method reduced blood loss, it is associated with complications, such as delayed wound healing with skin edge necrosis, haematoma and deep venous thrombosis.

Thus, we focused our attention on developing a new intra-surgical procedure based on the local infusion of a norepinephrine solution without drainage clamping in patients undergoing TKA.

Materials and methods

From January to December 2004, 150 consecutive primary cemented TKA were performed in the Department of Orthopaedics at the Catholic University of the Sacred Heart School of Medicine. We excluded patients with bleeding disorders or previous open knee surgery. Eighty four patients satisfied these criteria. All operations were performed by the same senior surgeon, always using the same posterior stabilised cemented implant and never performing patellar replacement. Under general anaesthesia, a pneumatic tourniquet was applied to each patient. The arthrotomy was performed through a midline skin incision and a medial parapatellar capsular incision.

Patients were assigned to two groups: one control group of 55 patients, in which after cementation of the components a saline solution was used to wash the surgical field before tourniquet release, and a second group of 29 patients, in which a saline solution containing a low dose of norepinephrine (dilution 1:200,000) was locally applied before tourniquet release. The surgeon was blinded to the nature of the irrigant. Lateral release was performed on three knees in each group. The tourniquet was released intraoperatively after cementing the prosthesis; haemostasis was achieved with electrocoagulation and the application of bone wax to the pin holes. At the end of the operation a 14-CH drainage was inserted into the knee joint. Elastic compression dressing was also applied. Drainage was removed 48 h after operation. Continuous passive motion was initiated on the first postoperative day. Low molecular weight heparin (enoxaparin, 4,000 IU) was administered subcutaneously 12 h before surgery and once a day for 45 days postoperatively.

Table 1 Demographic and clinical characteristics of the study population

Characteristic	Statistic
Number of patients	84
Age* (years)	71.1±6.1
Male:female ratio	17/67
Number of patients with hypertension	33
BMI*	29.1±4.3
Preoperative Hb level (g/dl)*	13.2±1.3
Preoperative Ht (%)*	40.14±3.9
Number of patients with blood transfusion	30

*Mean and standard deviation

Table 2 Demographic and clinical characteristics of the patients who underwent total knee arthroplasty (TKA) with local administration of norepinephrine

	Norepinephrine	Controls	<i>p</i> value
Number of patients	29	55	
Age (years)*	70.3±6.1	71.5±6.2	0.4
Male:female ratio	5/24	12/43	0.7
Number of patients with hypertension	14	19	0.4
BMI*	28.6±3.2	29.2±4.7	0.6
Preoperative Hb level (g/dl)*	13.1±1.1	13.2±1.4	0.5
Preoperative Ht (%)*	40±3.4	40.2±4.2	0.8
Hb level (g/dl) on the first day after surgery	10.1±1.4	9.7±1.3	0.2
Ht (%) on the first day after surgery	30.5±4.1	29.2±4.2	0.2

*Mean and standard deviation

Haemoglobin (Hb) and haematocrit (Ht) were determined preoperatively and on postoperative days one, three and five. Total blood loss was calculated as the sum of perioperative (intraoperative plus six hours after operation) and postoperative (the amount of blood collected at 48 h in the drainage bottle, starting six hours after operation). We also measured the decrease in haemoglobin and haematocrit for each patient, calculated as the difference between preoperative and postoperative values on the first day after surgery. Patients were transfused only if haemoglobin levels decreased to <7 g/dl.

Table 3 Blood loss, decrement of haemoglobin (Hb) level and haematocrit (Ht), and blood transfusion in patients who underwent TKA with local administration of norepinephrine

	Norepinephrine	Controls	<i>p</i> value
Perioperative blood loss*	405.7±251.1	620±351.4	0.01
Blood loss at 24 h*	307.2±166	455.2±209.7	0.001
Blood loss at 48 h*	436.8±198.1	632.3±247.9	0.0005
Total blood loss*	821.9±270.8	1,270.8±394.5	<0.0001
Difference between preoperative Hb and Hb on the first day after surgery*	2.9±1	3.5±1	0.01
Difference between preoperative Ht and Ht on the first day after surgery*	9.4±3.3	11.5±4.9	0.054
Number of patients with blood transfusion	6	24	0.03

*Mean and standard deviation

Statistical analysis was performed using Student's *t* test for interval data and the Chi-squared test with Fisher's exact test for categorical data. *p* values <0.05 and the powers of the *t*-test >80% were considered significant.

Results

The demographic and clinical characteristics of the whole study population are described in Table 1.

The demographic and clinical characteristics of the two study groups are presented in Table 2. The mean age was 70.3 ± 6.1 years for the study group, and 71.5 ± 6.2 for the control group ($p=0.4$). The male:female ratio was 5:24 and 12:43 respectively ($p=0.7$); 14 and 19 patients suffered from hypertension in the two groups ($p=0.4$), while the body mass index (BMI) was $28, 6 \pm 3.2$ for the study patients and 29.2 ± 4.7 for the controls ($p=0.6$). The average Hb level measured before surgery was 13.1 ± 1.1 and 13.2 ± 1.4 ($p=0.5$), while the preoperative Ht (%) was 40.3 ± 3.4 and 40.2 ± 4.2 respectively ($p=0.8$). None of the parameters studied showed any statistically significant differences between the two groups before surgery.

Evaluation of blood loss showed significant differences between the two groups, as shown in Table 3. In particular, perioperative blood loss was 405.7 ± 251.1 in patients who underwent TKA with local administration of norepinephrine and 620 ± 351.4 ($p=0.01$) in control patients; blood loss at 24 h was 307.2 ± 166 and 455.2 ± 209.7 ($p=0.001$) respectively, while the amount at 48 h was 436.8 ± 198.1 for the study group and 632.3 ± 247.9 for the controls ($p=0.0005$). Total blood loss, calculated as the sum of perioperative blood loss and the amount blood loss at 48 h was 821.9 ± 270.8 and $1,270.8 \pm 394.5$ ($p=0.0000$) respectively.

Also, the difference between preoperative Hb level and its postoperative value on the first day after surgery showed statistical significance: 2.9 ± 1 in the study patients and 3.5 ± 1 in the controls ($p=0.01$). Furthermore, allogenic blood transfusion was necessary significantly more often in the control group compared with in the norepinephrine group: 24 patients and six patients respectively ($p=0.03$). No complications were observed in either of the groups regarding deep venous thrombosis and skin edge necrosis.

Discussion

Over the last few decades various methods have been proposed to reduce perioperative blood loss and to prevent the need for blood transfusion in patients undergoing TKA. Indeed, bleeding during and after TKA is often associated with cardiovascular complications and a high transfusion rate of allogenic blood [4]. Recently, drainage clamping, associated with epinephrine solution infusion, has been shown to be effective at reducing blood loss. However, this method is not completely free from complications: some authors reported delayed wound healing with skin edge necrosis and haematomata (with a return to the operating room in some instances), deep venous thrombosis, or

sometimes severe bleeding through the wound, requiring dressing reinforcement and temporary clamping of the drainage [7, 11].

In our study local administration of saline solution containing a low dose of norepinephrine has induced a significant reduction of perioperative blood loss compared with the administration of saline solution alone. Hb and Ht level reduction on the first postoperative day in the norepinephrine group was less than in the control group and this difference was statistically significant. This method was characterised by the absence of complications and adverse reactions. When norepinephrine was added to the saline solution, there was a greater haemostatic effect compared with the saline solution alone. The efficacy of norepinephrine is related to the peak of blood flow that is normally present for 20–30 min after tourniquet release [5]. The local infusion of norepinephrine before releasing the tourniquet induces contraction of peripheral vessels, with a reduction of this peak. Moreover, norepinephrine is a platelet-stimulating agent since it causes aggregation of human platelets through α_2 -adrenoceptors [12]. These actions may explain the efficacy of this drug at reducing perioperative (contraction of peripheral vessels) and postoperative (haemostatic effect) blood loss.

Blood transfusion requirement was significantly different in the two groups: in fact only six patients in the norepinephrine group required allogenic blood transfusion compared with 24 patients in the control group. Since allogenic blood transfusion increases the risk of immunological and non-immunological adverse effects for the patients and increases medical costs [2, 4], intraoperative use of norepinephrine should be considered as an effective method of preventing these severe complications and reducing the cost of blood management in knee replacement surgery.

This is the first study in which the reduction of blood loss and allogenic blood transfusion requirements in TKA have been achieved by the simple expedient of local administration of norepinephrine. The method is shown to be safe and easy to perform.

References

1. Benoni G, Fredin H (1996) Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br* 78:434–440
2. Borghi B, Casati A (2000) Incidence and risk factors for allogenic blood transfusion during major joint replacement using an integrated autotransfusion regimen. The Rizzoli Study Group on Orthopaedic Anaesthesia. *Eur J Anaesthesiol* 17:411–417
3. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP (1999) Transfusion medicine. Second of two parts—blood conservation. *N Engl J Med* 340:525–533
4. Juelsgaard P, Moller M, Larsen U (2002) Preoperative Acute Normovolaemic Hemodilution (ANH) in combination with Hypotensive Epidural Anaesthesia (HEA) during knee arthroplasty surgery. No effect on transfusion rate. A randomized controlled trial. *BMC Anesthesiol* 2:1

5. Larson J, Lewis DH, Liljedhal S-O, Lofstrom JB (1977) Early biomechanical and hemodynamic changes after operation in a bloodless field. *Eur Surg Res* 9:311
6. Raut VV, Stone MH, Wroblewski BM (1993) Reduction of postoperative blood loss after press-fit condylar knee arthroplasty with use of a femoral intramedullary plug. *J Bone Joint Surg Am* 75:1356–1357
7. Ritter MA, Keating EM, Faris PM (1994) Closed wound drainage in total hip or total knee replacement. A prospective, randomized study. *J Bone Joint Surg Am* 76:35–38
8. Ryu J, Sakamoto A, Honda, Saito S (1997) The postoperative drain clamping method for hemostasis in total knee arthroplasty: reducing postoperative bleeding in total knee arthroplasty. *Bull Hosp Jt Dis* 56:251–254
9. Thomas D, Wareham K, Cohen D, Hutchings H (2001) Autologous blood transfusion in total knee replacement surgery. *Br J Anaesth* 86:669–673
10. Veien M, Sorensen JV, Madsen F, Juelsgaard P (2002) Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. *Acta Anaesthesiol Scand* 46:1206–1211
11. Yamada K, Imaizumi T, Uemura M, Takada N, Kim Y (2001) Comparison between 1-hour and 24-hour drain clamping using diluted epinephrine solution after total knee arthroplasty. *J Arthroplasty* 16:458–462
12. Yun-Choi HS, Park KM, Pyo MK (2000) Epinephrine induced platelet aggregation in rat platelet-rich plasma. *Thromb Res* 100:511–518