Pre-operative injections of epoetin-α versus post-operative retransfusion of autologous shed blood in total hip and knee replacement

A PROSPECTIVE RANDOMISED CLINICAL TRIAL

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This prospective randomised clinical trial evaluated the effect of alternatives for allogeneic blood transfusions after total hip replacement and total knee replacement in patients with pre-operative haemoglobin levels between 10.0 g/dl and 13.0 g/dl. A total of 100 patients were randomly allocated to the Eprex (pre-operative injections of epoetin) or Bellovac groups (post-operative retransfusion of shed blood). Allogeneic blood transfusions were administered according to hospital policy.

In the Eprex group, 4% of the patients (two patients) received at least one allogeneic blood transfusion. In the Bellovac group, where a mean 216 ml (0 to 700) shed blood was retransfused, 28% (14 patients) required the allogeneic transfusion (p = 0.002). When comparing Eprex with Bellovac in total hip replacement, the percentages were 7% (two of 30 patients) and 30% (nine of 30 patients) (p = 0.047) respectively, whereas in total knee replacement, the percentages were 0% (0 of 20 patients) and 25% (five of 20 patients) respectively (p = 0.042).

Pre-operative epoetin injections are more effective but more costly in reducing the need for allogeneic blood transfusions in mildly anaemic patients than post-operative retransfusion of autologous blood.

Operations for major joint replacement frequently require blood transfusion. The potential risks involved have stimulated the search for alternatives, such as pre-operative injections of epoetin-α and post-operative cell saving. In spite of algorithms to reduce allogeneic blood transfusions, it is not known which intervention or combination of measures is most successful. Pre-operative injections of epoetin-α have been shown to reduce the need for allogeneic blood transfusion by increasing the pre-operative haemoglobin (Hb) level in patients whose baseline level lay between 10.0 g/dl and 13.0 g/dl. One prospective randomised study showed that only 12% of patients treated with injections of epoetin-α received at least one blood transfusion, compared with 46% in the control group. Post-operative retransfusions with autologous blood have been shown to reduce the requirements for allogeneic transfusion in patients who did not have pre-operative anaemia. A prospective randomised study concluded that patients treated with a post-operative cell-saving system had a significant reduction in transfusions of allogeneic blood compared with controls, as evidenced by an absolute risk reduction from 19% to 6%. However, in that study, all patients had pre-operative Hb levels between 13.0 g/dl and 14.5 g/dl.

After a Pubmed search (MeSH terms Blood Transfusion, Autologous, Erythropoietin, Recombinant) we found no randomised studies which compared pre-operative injections of epoetin and post-operative cell saving. We therefore carried out a prospective randomised trial designed to evaluate the the use of a relatively cheap post-operative retransfusion system in patients with pre-operative Hb levels between 10.0 g/dl and 13.0 g/dl, compared with using expensive pre-operative injections of epoetin-α. Our aim was to compare the differences in the need for allogeneic blood transfusions in both groups.

Patients and Methods

Between June 2006 and October 2007, all patients scheduled for elective total hip replacement (THR) or total knee replacement (TKR) for primary osteoarthritis (OA) with a pre-operative Hb level between 10.0 g/dl and 13.0 g/dl were selected for the trial. Patients with haematological diseases, coagulation disorders, or with known malignancy or infection were excluded. Informed consent was obtained, and the study was approved by the local hospital ethics committee.
A total of 100 patients were enrolled and all were randomly allocated to the Eprex or Bellovac groups by block randomisation and sealed envelopes which were labelled with a consecutive case number from 1 to 100. Patients in the Eprex group received 40 000 IU of epoetin-α (Eprex, Janssen-Cilag BV, Tilburg, The Netherlands) in each injection. Four subcutaneous injections were given weekly, beginning three weeks before with the final injection immediately after operation. The injections were supported by supplementary oral iron (ferrofumerate 200 mg three times daily), beginning three days before the first injection and finishing the day before operation.

To prevent bias, a retransfusion system (Bellovac ABT, AstraTech AB, Mölndal, Sweden) was employed in both groups, but only those in the Bellovac group had an autologous retransfusion. At the end of the operation a deep drain was connected to the retransfusion system after closure of the wound. This system comprises a suction bellows connected to a transfusion bag with a 40 μm filter. The filtered blood was returned either when the bag was full (500 ml) or six hours post-operatively. The amount of blood collected and retransfused was recorded.

Patients undergoing THR received an ABG-II system (Stryker Netherlands, Waardenburg, The Netherlands), cemented or uncemented depending on their age and bone quality. Those undergoing TKR received a cemented Vanguard prosthesis (Biomet, Dordrecht, The Netherlands). The operations were done by five different surgeons, all experienced in joint replacement. In TKR, a tourniquet was used and was released after wound closure.

Patients on anticoagulants (acenocoumarol or acetylsalicylate) stopped these five days before the operation. All patients received low molecular weight heparin for thromboembolic prophylaxis, starting after surgery and continuing for six weeks.
In order to evaluate the increase in Hb levels caused by injections of epoetin-α, the Hb levels in the Eprex group were measured on the day of admission. As part of the routine pre-operative investigations, Hb levels in the Bellovac group were also obtained on the day of admission. After operation the Hb levels were measured on the first and third days in both groups.

Allogeneic blood transfusions were administered according to hospital policy (Table I). Post-operatively, the anaesthetist determined the Hb transfusion trigger, depending on the American Society of Anesthesiologists (ASA) classification and the course of the operation. The anaesthetist was independent but not blinded, as all prescribed medications, including epoetin-α and ferrofumerate, were recorded. The pre-operative Hb levels were different in the two groups, thereby making blinding difficult. All allogeneic blood transfusions and complications were recorded according to the classification of Parvizi et al. The rehabilitation programme conformed to a standard policy, with discharge from hospital planned for five days after operation. The length of follow-up varied from two to 18 months.

Before the study, a sample size calculation was performed based on retrospective data. A reduction of 10% in allogeneic blood transfusions by using a retransfusion system in patients with a pre-operative Hb level between 10.0 g/dl and 13.0 g/dl, compared with controls from the past, was considered to be the smallest clinical difference. With the α level set to 0.05 and the power at 0.80, it was calculated that 50 patients were needed in each group. The results were analysed statistically using Fisher’s exact test for testing the proportions of those receiving allogeneic blood transfusions. All other continuous variables were analysed with Student’s t-test. A p-value < 0.05 was considered significant. Patients were evaluated according to the intention-to-treat principle.

**Results**

Of the 50 patients in each group (Table II), all were ASA grades 2 or 3 and there were no statistical differences between the groups in terms of age, gender, height, weight, pre-operative Hb level, type of surgery or post-operative transfusion trigger.

There was one failure of inclusion in a patient randomly assigned to the Eprex group who received pre-operative injections of epoetin-α and then a post-operative retransfusion of 400 ml. One patient in the Eprex group suffered a thrombosis in the superior sagittal sinus with an Hb level of 15.6 g/dl after the second injection of epoetin-α. No further epoetin injections were administered and the operation was postponed for six months until the patient had recovered completely. Both patients were evaluated according to the intention-to-treat principle.

Primary THR was performed in 60 patients and primary TKR in 40. In most cases (84 patients, 84%) spinal anaesthesia was used. The remainder had general anaesthesia. The intra-operative blood loss was similar in both groups, being 395 ml in the Eprex and 381 ml in the Bellovac group (NS). This was not statistically significant (p = 0.75).

The mean transfusion triggers in the Eprex and Bellovac groups were 8.5 g/dl (8.1 to 9.7) and 8.7 g/dl (8.1 to 9.7) respectively (Table II). A mean of 216 ml (0 to 700) were retransfused in the Bellovac group, 131 ml (0 to 500) in THR and 341 ml (0 to 700) in TKR. In one patient, retransfusion was not carried out as the quality of shed blood was considered dubious owing to premature discon-

<table>
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<th>Table III. Cost comparison per patient in Euros</th>
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<td><strong>Eprex group</strong></td>
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<td>Epoetin-α injections</td>
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<td>Total costs per patient</td>
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Graph showing the level of haemoglobin (Hb) in both groups pre-operatively and at one and three days post-operatively (* indicates statistical significance).
nection of the drain to the collection bag. This patient was included according to the intention-to-treat principle.

In the Eprex group two patients (4%) received at least one allogeneic blood transfusion, compared with 14 (28%) in the Bellovac group (p = 0.002). When comparing Eprex with Bellovac in THR, these results were 7% (2 of 30) and 30% (9 of 30), respectively (p = 0.047), whereas in TKR they were 0% and 25% (5 of 20) (p = 0.042). The number of units of erythrocyte concentrates per transfused patient was 1.5 (3/2) in the Eprex group and 1.4 (20/14) in the Bellovac group. None of the patients randomly assigned to the Bellovac group with a post-operative transfusion trigger of 8.1 g/dl needed allogeneic blood. The costs of treatment in both groups and the costs of allogeneic transfusions are presented in Table III.

The pre-operative levels of Hb were a mean of 12.4 g/dl (10.6 to 13.0) in the Eprex group and 12.4 g/dl (10.8 to 13.0) in the Bellovac group (Fig. 1). The Hb level immediately before operation after the injections in the Eprex group increased by a mean of 2.5 g/dl to 14.9 g/dl (13.0 to 16.6). On the first day after operation the mean Hb level had decreased to 11.4 g/dl (9.0 to 13.8) in the Eprex group and to 9.7 g/dl (7.6 to 12.1) in the Bellovac group. By the third day the levels had decreased to 11.2 g/dl (8.4 to 13.7) in the Eprex group and to 9.5 g/dl (7.2 to 11.1) in the Bellovac group. These reductions were significantly different between the groups on the first (p = 0.011) and third (p = 0.012) days after operation.

The incidence of clinical complications was similar between the groups (Table IV). Four patients in the Eprex group and five in the Bellovac had haematomas and prolonged wound discharge. In the latter group one patient with a superficial wound infection needed debridement without removal of the prosthesis.

Discussion

Most hospitals use restrictive transfusion triggers because they are aware of the risks and complications of allogeneic blood. In addition, other interventions to reduce the use of allogeneic blood are in use, and it is not known which is the most successful. Post-operative cell saving using a retransfusion system is relatively inexpensive, whereas pre-operative injections of epoetin-α are approximately 15 times more expensive. Changing treatment from injections of epoetin to cell saving in patients with pre-operative Hb levels between 10.0 g/dl and 13.0 g/dl would reduce the cost to the health system. Although its efficacy has already been demonstrated in patients without pre-operative anaemia, the effectiveness of a retransfusion system in patients with mild anaemia before operation can be disputed. The analysis of the costs showed that in such patients the use of injections of epoetin supported by ferrofumerate tablets increased the cost per patient compared with the retransfusion system. Although this was only based on direct costs, actual comparisons of cost-effectiveness between the groups is hardly possible, as the indirect costs were not measured.

In this study, 28% of patients in the Bellovac group needed allogeneic blood, compared with 46% of the control group in the study of Weber et al. Comparing these results, the absolute risk reduction would be 18%. Although some patients in the Bellovac group still needed allogeneic transfusions, their reduction of these was probably due to the retransfusion of shed blood. Our absolute risk reduction in allogeneic blood transfusion of injections of epoetin compared with post-operative cell saving was 24%. Thus, in every 4.2 patients treated with pre-operative injections of epoetin-α, one allogeneic transfusion was prevented compared with treatment with a retransfusion system.
The average amount of retransfused shed blood (216 ml) in the Bellovac group was small compared with published values.\(^5,6,15\) A possible confounding factor is the position of the drain. Some of our surgeons preferred the subfascial position in THR, which appeared to influence the amount of collectable blood compared with placement in the joint. Therefore, retransfusion of different amounts of shed blood may influence the increase in the systemic post-operative Hb level and hence the need for allogeneic transfusion. More studies are needed in this respect.

Both options for allogeneic transfusion involved complications. In the Eprex group a patient with an Hb level of 15.6 g/dl after the second injection of epoetin suffered thrombosis of the superior sagittal sinus. This serious event raised the question whether epoetin was related to thromboembolic complications, in line with suggestions that such problems might arise from an additional influence on coagulation activation.\(^16,17\) However, other studies, including large randomised clinical trials, observed no differences in adverse events between epoetin and controls.\(^5,6,18,19\) Hence, the thromboembolic complication in our patient, although recognised in the literature, could not be proven to be related.

Patients with pre-operative Hb levels > 14.5 g/dl have less chance of receiving allogeneic blood than do mildly anaemic patients with a pre-operative Hb < 13.0 g/dl.\(^20\) Treating these patients enhances the level of Hb. In our study, the average increase in Hb was 2.5 g/dl to an absolute of 14.0 g/dl, agreeing with earlier reports.\(^2,4\) After primary THR and TKR the mean total blood loss to the third post-operative day causes a fall in Hb of approximately 3.0 g/dl.\(^21\)

The average reduction in Hb in patients in our Eprex group was 3.5 g/dl on day 1 and 3.7 g/dl on day 3, compared with the pre-operative level. Severe blood loss was needed before an allogeneic blood transfusion was given. Conversely, in the Bellovac group, the average reduction in Hb was 2.7 g/dl and 2.9 g/dl, respectively. Because the post-operative levels of Hb were significantly lower, less blood loss was needed before allogeneic blood was given to these patients. Our finding that none of the Bellovac patients with a post-operative transfusion trigger of 8.1 g/dl needed allogeneic transfusion may imply that, being even more restrictive, fewer patients in the Bellovac group would need allogeneic blood. Therefore, further randomised trials on this topic are justified.

In conclusion, pre-operative injections of epoetin are more effective in reducing the need for allogeneic blood transfusions in mildly anaemic patients with pre-operative Hb levels of 10.0 g/dl to 13.0 g/dl compared with post-operative retransfusion of autologous shed blood in major joint arthroplasty, but are more expensive.

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References