Patient Pain and Blood Management in Total Hip and Knee Arthroplasty

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Chapter 1

Introduction and research questions

The number of hip (THA) and knee (TKA) arthroplasties performed in the Netherlands is still rising. During the first five years of the Dutch LROI database (2007-2011) 105,455 primary hip arthroplasties and 79,272 primary knee arthroplasties were registered.[1] As of June 2014 about 150,000 TKA and 200,000 THA are registered. The projected increase until 2020 in prevalence of hip and knee arthroplasties will have important ramifications with regard to the number of joint arthroplasties expected and the subsequent increase in health care costs.[2]

Health care costs are expanding and in all areas solutions are being sought to decrease the national burden of health care. The changes of the last decennia in daily orthopaedic practice, especially the increase in not only the number of total joint arthroplasties, but also in faster postoperative rehabilitation is considerable. The introduction of fast-track surgery by means of clinical pathways for elective joint arthroplasties has reduced sin ome part the in-hospital inefficiency. Furthermore, techniques for reducing 'surgical stress' made a large change in the postoperative rehabilitation program.[3] After surgical injury the body responds with profound changes in neural, endocrine and metabolic systems in addition to alterations in organ functions.[4-6] These changes represent an universally conserved cellular defence mechanism of the body, but the stress-induced changes in postoperative organ function may also be implicated in the development of postoperative complications.[5,7] Both pain and blood management are important issues, in order to reduce this surgical stress response, which could counteract fast postoperative rehabilitation.

PAIN MANAGEMENT

In the last decades the focus in pain management was on the prevention of side effects, such as drowsiness or nausea. The implemented analgesia regime to enhance faster postoperative recovery and reduce morbidity to the patient was achieved with a multimodal approach.[8,9] This approach should minimize stimuli at each nervous level (central and peripheral) and limit activation of the central nervous system. The use of a variety of medications at relatively low doses takes advantage of multiple pain modulators. Thus, the medication addresses several different steps along the pain pathway, which results in lower narcotic use and therefore fewer side effects that interfere with mobilisation.

Pre-emptive analgesia is a pillar in this concept, the medication is given before the surgical injury takes place, in order to block the transmission to the nervous system as early as possible.[10-12] Better pain control and fewer side effects are present than when a single modality (i.e. opioids) is used.[10-12] Although there is still debate on the concept of

pre-emptive analgesia, more local analgesia techniques in THA and TKA were introduced in addition to the current gold standards of locoregional anaesthesia such as spinal or epidural.[13] The beneficial effects of a femoral nerve block or local infiltration analgesia (LIA) in TKA have been widely studied in recent years.[14-17] Different mixtures (content of the technique, composition of the LIA solution) and types of local infiltration (with or without catheter and its placement) are used around the world.[15,18] Since LIA in THA and TKA has great effects on postoperative rehabilitation, it will also have implications on perioperative patient blood management. The impact of high-volume local infiltrations on the collection of shed blood for autologous blood transfusion is unknown.

BLOOD MANAGEMENT

Total hip and knee arthroplasty surgery have significant perioperative blood loss; the combined visible and invisible blood loss is reported to be 1500 mL on average.[19,20] This blood loss eventually causes a decrease in the postoperative haemoglobin (Hb) level of approximately 3 g/dL.[19] Therefore blood transfusions are frequently reported after this type of surgery. Nevertheless, a large variation in perioperative transfusion rates have been reported, with up to 69% of patients being transfused, depending mainly on the used transfusion policy.[21]

During the last two decades great efforts have been made to change the practice of a liberal blood transfusion policy to a more restrictive policy.[22-24] The awareness that the HIV and hepatitis virus could be transmitted through allogeneic blood transfusions in the early 1980's changed the attitude of both physicians as well as the public to the inherent risks of allogeneic blood. This also stimulated the emerging of a new discipline: 'Transfusion Medicine'.[25]

The restrictive blood transfusion policy, i.e. awareness and a strict transfusion trigger (the so-called 4-5-6 (mmol/L) rule that is currently advised in the Netherlands) has led to a decrease in allogeneic blood transfusions by 30-40% in THA and TKA.[26,27] Next to a restrictive blood transfusion policy several techniques for reducing the need for allogeneic blood transfusions became available. Alternatives for an allogeneic blood transfusion can be subdivided in two main groups: non-pharmaceutical interventions and pharmaceutical interventions.[28,29]

The non-pharmaceutical interventions consist of preoperative autologous donation, peri-operative normovolaemic haemodilution, the use of a perioperative cell saver or post-operative autologous blood retransfusion devices

The pharmaceutical interventions comprise the pre-operative use of erythropoietin with (or without) iron supplementation, the perioperative use of anti-fibrinolytics such as tranexamic acid or fibrin glue.

Although we see a clear downward trend in transfusion needs, still many controversies are present about both the clinical effectiveness and the cost effectiveness of these alternatives. Although there is an awareness of transfusion medicine nowadays, the optimal algorithm for using these transfusion alternatives remains unclear. In addition, reported effects of many transfusion alternatives differ extensively leading to questions on methodology quality of PBM trials. Guyatt and co-workers developed several guidelines on this topic of quality assessment.[30-32] Especially in surgical randomised clinical trials, bias is to a great extent determined by absence of concealment of allocation, blinding of patients (where possible) and outcome assessors and lost to follow-up.[33-35] Evaluation of the quality of blood management trials comprises the second part of this thesis.

SCOPE OF THE THESIS

Evaluation of postoperative patient pain management (PPM) and patient blood management (PBM) in elective total knee and total hip arthroplasty:

– Patient Pain Management (PPM)
  - Postoperative analgesia in TKA patients with a more local technique, a femoralis block. What is an optimal dose in patients for an equipoise between pain and sufficient strength for postoperative rehabilitation (**chapter 2**)
  - Patient safety in presence of local infiltration analgesia (LIA) and autologous blood reinfusion devices in total knee arthroplasty (**chapter 3, 4**)
– Patient Blood Management (PBM)
  - An evaluation of two different transfusion alternatives was carried out in patients with specific haemoglobin values (**chapter 5**)
  - A cost calculation for erythropoietin alpha in daily practice was made based on the cost saving data in literature and transfusion figures from two large teaching hospitals (**chapter 6**)
  - Transfusion of shed blood collected with an autologous blood transfusion device is possible within 6 hours postoperative. Is there a difference in efficacy and an additional value of an autologous transfusion device (**chapter 7**)

- A new intra- and postoperative cell saving device was tested in revision and primary THA with the hypothesis that it would reduce allogeneic blood transfusions in the postoperative phase (**chapter 8**)

– Two methodological aspects in PBM trials were investigated. Firstly, the aspect of blinding is important in the conduct of a clinical trial but is it also important to be blind for study results when evaluating risk of bias (**chapter 9**). Secondly, the heterogeneity in drainage trials is investigated because transfusion figures divers significantly. Which variables are of additional value when transfusion trials are being compared (**chapter 10**).

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Chapter 2

Femoral nerve block using ropivacaine 0.025%, 0.05% and 0.1%: effects on the rehabilitation programmes following total knee arthroplasty: a pilot study

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ABSTRACT

Femoral nerve blockade is recommended for analgesia following total knee arthroplasty. Following implementation of this type of postoperative analgesia in our hospital we found that active mobilization the day after surgery, may be difficult due to insufficient quadriceps muscle strength. We therefore designed a pilot study comparing the effect of ropivacaine 0.1%, 0.05% or 0.025% on the patient's postoperative rehabilitation and analgesia. Three groups of 12 patients received bolus doses of ropivacaine via their femoral nerve catheters for postoperative analgesia. The ability to actively mobilize, quadriceps muscle strength, pain VAS-scores and patient's satisfaction were measured during the first three postoperative days. There were no significant differences in the patient's ability to actively mobilize and the pain VAS-scores. The overall satisfaction of the patients with the pain treatment was significantly better (p=0.049) in the 0.1% compared with the 0.025% group. This pilot study demonstrated no advantage associated with the use of a ropivacaine concentration less than 0.1%.

INTRODUCTION

Adequate postoperative pain control is important for rapid and optimal rehabilitation following total knee arthroplasty (TKA).[1] A multimodal approach for postoperative pain management that reduces nociception at a local, spinal and cerebral level is recommended, because it achieves better pain control and less side effects than when a single modality (i.e. opioids) is used.[2-3] In recent years several studies have indicated the beneficial effect of a femoral nerve blockade as part of a multimodal analgesia regime on postoperative pain and passive joint function following TKA.[4-6] However, after incorporation of a femoral nerve catheter for bolus doses of 10 mL ropivacaine 0.1% in our postoperative pain protocol for TKA we received feedback from the nurses and physiotherapists that although analgesia appeared to be improved, a greater number of patients were unable to mobilize (i.e. walk) the day following surgery due to inadequate quadriceps muscle strength and diminished proprioception (i.e. sensation of joint position). Femoral nerve blockade produces a motor and sensory block of the anterior thigh muscles, i.e. quadriceps femoris, pectineous muscle, iliopsoas muscle and sartorius muscle and the skin on the anteromedial aspect of the thigh and knee. These factors may cause decreased muscle power and diminished proprioception and therefore interfere with the fast-track rehabilitation programme after TKA used in our institution. In this programme, patients are mobilised the morning after surgery and they follow an active rehabilitation schedule, which enables patients to be discharged home on the morning of the 5th postoperative day.

On the assumption that decreasing the concentration of ropivacaine used for femoral nerve blockade may improve the patient's ability to follow the fast-track rehabilitation programme after TKA, we designed a pilot study using 0.1%, 0.05% or 0.025% ropivacaine bolus doses postoperatively. The purpose of this pilot study was to identify an optimal concentration of ropivacaine that provides good analgesia and patient's satisfaction following TKA, whilst not interfering with the active mobilisation program.

METHODS

The local Ethical Committee approved the study. Patients scheduled for TKA, aged between 18-80 years, without allergic or other contra-indications to the medication used in this study, were selected. Eligible patients, received verbal and written information on the study. One week before the scheduled surgery the patients gave written informed consent.

Approximately 1hr prior to surgery the attending anaesthetist inserted a perineural femoral catheter (Pajunk with stimulating tip, Plastimed Benelux B.V., Velserbroek, The Netherlands) and administered 20 mL ropivacaine 0.2% using this catheter. Following confirmation of correct catheter position by the loss of skin sensibility and quadriceps weakness, 36 patients were randomly allocated, by the use of sealed envelopes, to one of three equally sized groups (i.e. 0.1%, 0.05% or 0.025% ropivacaine). The ward received blinded study medication for the postoperative bolus injections of ropivacaine in a 100 mL bottle with only the patient's name and study number on it. Patients and investigators were blinded to the concentration of ropivacaine administered in the bolus injections on the ward.

Patients had the option of either general anaesthesia or spinal analgesia. Patients preferring general anaesthesia received propofol 1.5-2.5 $mg.kg^{-1}$ and fentanyl 0.02 $mg.kg^{-1}$ for induction. Atracurium 0.3-0.5 $mg.kg^{-1}$ was used to facilitate tracheal intubation. The patients' lungs were mechanically ventilated using oxygen (40-60%) in air and sevoflurane at an end-tidal concentration of approximately 1.8%. At the discretion of the anaesthetist additional doses of fentanyl could be administered to suppress responses of the patient indicating inadequate anaesthesia. For spinal analgesia 15-20 mg bupivacaine 0.5% was administered at the interspace L2-3 or L3-4 using a 27-gauge 3.5-inch Whitacre spinal needle and a midline approach with the patient in a sitting position.

During the study period all patients received acetaminophen 1g four times daily, starting approximately 1hr before surgery and celecoxib 200 mg once daily, started in the recovery room. On arrival in the recovery room a continuous infusion of ropivacaine 0.1% $5mL.h^{-1}$ via the femoral catheter was started and was infused until 06.00 the following morning to ensure good analgesia during the first night after surgery. At 06.00 the infusion was discontinued and the patients received bolus injections of 10 mL ropivacaine at a concentration according to their study group (i.e. 0.1%, 0.05% or 0.025%). Four bolus injections were given on fixed times, i.e. first postoperative day at 06.00 (after discontinuation of the continuous infusion), 11.00 (after mobilisation by the physiotherapist) and 22.00 and the second postoperative day at 06.00, to achieve a basic level of analgesia together with the acetaminophen and celecoxib. Apart from these fixed bolus injections, extra 10 mL doses of ropivacaine with a minimum time interval between doses of 30 min were given on patient request. If two consecutive doses of ropivacaine did not achieve adequate pain relief, 15 mg piritramide intramuscularly was administered as rescue medication. In the morning of the third postoperative day the femoral catheter was removed.

One week before the scheduled surgery basic measurements of pain (VAS, a 100 mm horizontal line with the words 'no pain' at the left and 'worst possible pain' on the right) and quadriceps muscle strength were performed. Quadriceps muscle strength was measured by the physiotherapist using two methods: a qualitative measurement using a 6-point numerical rating scale (MRC scale[7], Table 1) and a quantitative method for knee extension using a hand-held isometric force dynamometer (microFET2®, Hoggan Health Industries Inc., USA). The quantitative measurements of quadriceps muscle strength during the study were reported as a percentage of the baseline measurements 1 week before surgery.

Table 1 Qualitative 6-point rating of quadriceps muscle strength (MRC)[7]

Level	Grading
0	No muscle action
1	Flicker of movement
2	Unable to overcome gravity
3	Able to overcome gravity
4	Able to overcome gravity and moderate resistance
5	Assessor unable to manually overcome the muscle power

Qualitative 6-point rating of quadriceps muscle strength

In the first two postoperative days the physiotherapist visited the patients at approximately 10.00 and 14.30, the third day at 10.00 and the fourth day at 14.30 to measure the muscle strength and to determine if the patient had adequate muscle strength and sufficient proprioception to safely start the active training program. If patients had a MRC <3 or an inadequate sense of joint position they were not allowed to walk but followed a training programme in bed. At these time points the physiotherapist also tested the patient's ability to passively flex the operated knee ≥90°. The rehabilitation programme after TKA, used in our institution, aimed at the rapid achievement of a functional level of recovery that enables patients to leave the hospital on the fifth postoperative day. The minimal discharge criteria were 40m walking with two crutches and ascending and descending stairs consisting of 12 steps using one crutch and the handrail.

During the physiotherapy visits the patients recorded a pain VAS score at rest and on flexion of the knee in a diary. They also recorded a daily satisfaction score with the pain treatment (VAS, on a 100 mm horizontal line for satisfaction with the words 'extremely dissatisfied' at the left and 'excellent' on the right) for the first three postoperative days. The nursing staff recorded the use of rescue medication (piritramide) in the diary.

Statistics

Our primary aim was to reduce the number of patients not able to participate in active mobilisation due to insufficient muscle power defined as a MRC score <3, while still maintaining an adequate pain relief. Previous testing indicated a mean (SD) MRC of 2.2 (1.02) the day after surgery while using ropivacaine 0.1%. A sample size of 12 per group was calculated to detect a clinical relevant increase of the mean MRC of 1.5 between the groups at a two-sided 0.05 significant level with a power of 80%.

Data are presented as mean ± SD, median with interquartile ranges (IQR), numbers or percentages. Student's *t*-test was used for comparison of the means of continuous variables. One-way analysis of variance (ANOVA) was used for ordinal data (e.g. VAS-scores, patient's satisfaction with pain therapy), if indicated followed by a Kruskal-Wallis test. Categorical data (e.g. ASA physical status, type of anaesthesia) were analysed using chi-squared test with Yates correction or two-tailed Fisher's exact test where appropriate. A *p*-value <0.05 was considered statistically significant.

RESULTS

The groups were comparable for gender, age, body mass index, ASA physical status and type of anaesthesia (Table 2). Table 3 shows the qualitative and quantitative measurements of quadriceps muscle strength in the operated leg and the patient's ability to flex the knee. There were no significant differences in the number of patients per group with permission (MRC ≥3) to active mobilise during the study period. In fact, more patients in the group 0.1% were able to mobilise on the first postoperative day (0.1%: 0.05%: 0.025% = 7: 6: 5, NS).

Table 2 Demographic and anaesthetic characteristics

Group	0.025%	0.05%	0.1%
n (male/female)	12 (4/8)	12 (5/7)	12 (4/8)
Age (years)	68.5 (4.9)	68.3 (8.3)	71.5 (8.6)
Body mass index	28.3 (4.7)	29.9 (6.0)	29.1 (4.3)
ASA physical status I/II	4/8	2/10	5/7
Spinal/general	11/1	11/1	11/1

Data presented as mean (SD) or frequency data

Table 3 Measurements of quadriceps muscle strength and flexion of the knee

	Group	0.025%	0.05%	0.1%
Day 1				
10.00	MRC	2 (2-2.3)	3 (2-3)	2 (1.8-3)
	%	15 (22)	10 (15)	11 (13)
14.30	MRC	2.5 (2-3)	3 (2-3)	3 (2-3.3)
	%	21 (25)	22 (18)	23 (21)
Flexion	>90°	3/12	2/12	1/12
Day 2				
10.00	MRC	2.5 (2-3)	3 (2-3)	3 (2.8-3)
	%	11 (12)	16 (14)	30 (28)*
14.30	MRC	3 (2-3)	3 (2.5-3)	3 (2-3.3)
	%	21 (25)	25 (25)	30 (29)
Flexion	>90°	4/12	7/12	10/12*
Day 3				
10.00	MRC	3 (3-3)	3 (3-3)	3 (3-4)
	%	24 (19)	29 (19)	33 (25)
Flexion	>90°	7/12	8/12	10/12
Day 4				
14.30	MRC	3.5 (3-4)	3 (3-3.8)	3.5 (3-4)
	%	31 (20)	36 (31)	35 (21)
Flexion	>90°	8/12	10/12	12/12

*Difference between 0.025% group and 0.1 group significant (p<0.04)
Qualitative measurements (MRC, median (IQR)), quantative measurements (expressed as mean % (SD) of the measurement 1 week before the surgery). Flexion is the number of patients with a passive range of motion of the operated knee >90°/total number of patients.

By the end of the third postoperative day all patients had permission to walk with a walking frame. The quantitative strength measurements in the operated leg declined sharply from the pre-operative values in all groups on the first postoperative day and recovered only partially (31-36%) (Table 3) in the days until discharge from the hospital. Apart from the first measurement (10.00) (Table 3) on the second day there were no significant differences in the quantitative power measurements between the groups. Except for the measurement at 10.00 on the first postoperative day (r=0.63, p=0.01), the Pearson correlation between the qualitative and quantitative strength measurements on the other data collection points was poor and not significant (r=0.20-0.26). From day 2 more patients in group 0.1% had a passive range of motion of the operated knee >90° compared with the other two groups. All patients in group 0.1% reached this milestone in the rehabilitation programme on the fourth postoperative day (Table 3). The difference in knee flexion between group 0.1% and

0.025% was significant on the second postoperative day. All patients achieved the discharge criteria on the fourth postoperative day and went home the following morning.
There were no significant differences in the median VAS scores for pain in rest and during flexion of the knee and the median VAS score for patient's satisfaction with the pain treatment between the groups on the separate data collection points (Table 4).

Table 4 Median (IQR) VAS pain score in rest (VAS_R) and knee flexion (VAS_M) and patient's daily satisfaction with the pain treatment (VAS_S, 0 = poor and 100 is excellent)

	Group	0.025%	0.05%	0.1%
1 week preop				
	VAS_R	6 (5-42)	4 (3-7)	5 (4-17)
	VAS_M	7 (6-37)	9 (3-35)	5 (2-52)
Day 1				
10.00	VAS_R	36 (12-46)	40 (25-47)	34 (21-44)
	VAS_M	38 (26-58)	41 (25-50)	36 (23-47)
	VAS_S	37 (20-75)	66 (54-73)	58 (46-81)
14.30	VAS_R	17 (5-43)	11 (7-29)	13 (9-17)
	VAS_M	29 (10-48)	27 (14-35)	22 (14-30)
Day 2				
10.00	VAS_R	31 (17-46)	20 (16-27)	22 (10-48)
	VAS_M	37 (24-46)	40 (24-71)	37 (20-64)
	VAS_S	45 (26-78)	70 (51-79)	79 (70-90)
14.30	VAS_R	10 (5-15)	10 (5-21)	15 (7-17)
	VAS_M	26 (19-35)	39 (18-60)	28 (24-43)
Day 3				
10.00	VAS_R	11 (9-20)	15 (9-23)	12 (7-36)
	VAS_M	24 (16-46)	20 (11-43)	38 (22-49)
	VAS_S	70 (40-90)	73 (63-82)	83 (64-86)
Day 4				
	VAS_R	10 (4-21)	16 (8-19)	15 (9-42)
	VAS_M	24 (13-34)	42 (17-55)	25 (11-58)

There were no significant differences between the groups in VAS pain scores. VAS_S over the whole study period (day 1-3) was significantly better in group 0.1% compared to group 0.025% (ANOVA, p=0.049).

However, the overall patient's satisfaction was consistently better in the group 0.1%. Measured over the entire study period (day 1-3) this difference was significant compared with the group 0.025% (Table 4). Moreover, the median number of extra bolus doses ropivacaine on request of the patient tended to be higher in the 0.025% group (NS, Table 5) and the mean decrease of the VAS score 30 min after the bolus injection was significantly

lower compared with the 0.1% group. Also the median (IQR) number of rescue piritramide injections were higher in patients of the 0.025% group compared with the 0.1% group, although this difference did not reach statistical significance (p=0.056).

Table 5 Number of extra bolus doses ropivacaine, decrease in VAS pain scores 30 min after a bolus dose of ropivacaine and the number of rescue piritramide injections during the study

Group	0.025%	0.05%	0.1%	*p* (0.025% vs 0.1%)
Extra bolus doses	10 (6-11)	6 (4-11)	6 (5-8)	NS
Decrease VAS pain	8 (11.7)	13 (13.3)	16 (15.9)	0.01
Piritramide injections	2 (1-4)	0 (0-2)	1 (1-1)	0.056

The number of extra bolus doses ropivacaine presented as median (IQR), the decrease in VAS pain scores 30 min after a bolus dose of ropivacaine presented as mean (SD) and the median (IQR) number of rescue piritramide injections during the study (day 1-3).

DISCUSSION

In recent years several studies have indicated the beneficial effect of femoral nerve blockade on analgesia and the rehabilitation programme following TKA.[4-6,8-10] The principal aim of these studies was to detect improvement of postoperative pain control, reduction of opioid use and the associated side effects after TKA.

Although quadriceps muscle weakness is often mentioned as a potential disadvantage for early ambulation of the patient[2,3,5,11], most studies do not comment further on this since their rehabilitation programmes in the first postoperative days were mostly in bed using a continuous passive motion machine and active walking was postponed until the second or third postoperative day or even later.[4-6,8-10] Salinas et al. also using the microFET® dynamometer, reported a quantitative decrease in quadriceps motor strength to 6 ± 16% from baseline motor strength in 17 healthy volunteers who had a continuous femoral block with ropivacaine 0.2% 10 mL.h^{-1} for 4 hours and an initial bolus injection of 10 mL lidocaine 1%.[1] Eight hours after stopping the infusion they had recovered only to 58 ± 40% of their baseline power. Apart from the femoral nerve block itself, TKA surgery has a significant negative effect on quadriceps muscle strength of the operated leg.[5,12] In 14 consecutive patients after TKA without a postoperative regional technique in our institution the mean (SD) muscle strength in the operated leg declined to 33% (18) the day after surgery and recovered to 54% (30) on the fourth postoperative day (B.J.W. Thomassen, unpublished data). In the present study quantitative strength measurements declined to 15-23% of the baseline on the first postoperative day and recovered to 31-36% the day before discharge

(Table 3). There were no apparent differences in quantitative muscle strength between the groups and no indication of higher values in the groups with a lower concentration of ropivacaine that might become significant if we had included more patients in our study.

Barrington et al. using the same 6-point rating scale for qualitative muscle strength measurement as in our study (Table 1), reported that only 6 of 53 patients had a score ≥3 on the first day after TKA in their femoral nerve block group using bupivacaine 0.2% at 0.1 $mL.kg^{-1}.h^{-1}$ with a PCA bolus of 0.05 $mL.kg^{-1}$.[5] They also found significantly greater quadriceps muscle blockade in their femoral nerve blockade group on the second postoperative day compared with the group of patients with epidural analgesia with a continuous infusion of ropivacaine 0.2% plus fentanyl. In the present study there were no significant differences in qualitative muscle strength measurements between the groups. However, this study was designed to detect a substantial difference in qualitative strength measurements and lacked the power to find smaller but probably clinically less relevant differences. The median qualitative strength score in all groups ranged between 2 and 3 (Table 3) on the first postoperative day and consequently only half of the patients had permission to actively mobilise with a walking frame that day. However, all patients with a slow start at ambulation made up the difference in the days thereafter and met the discharge criteria by the end of the fourth postoperative day.

In this study we used a qualitative 6 point rating scale (Table 1) and a quantitative (isometric muscle force dynamometer) method to evaluate quadriceps muscle strength and found a poor correlation between these two measurements. Zaric et al. in a study with epidural ropivacaine in 30 healthy volunteers also observed that qualitative strength measurements (modified 4-point Bromage scale) decreased far less and later than expected on basis of the quantitative measurements and at the recovery of the Bromage score from grade 1 to 0, only 22-40% of the muscle force for knee extension, assessed by the quantitative method, had recovered.[13] However, they did find a close relationship between the sensory blockade (pinprick) and the quantitative strength measurements. Although the use of force dynamometry allows for more precise quadriceps strength measurements, than the normally used qualitative rating scale, caution in the interpretation of early postoperative measurements after TKA is warranted, because maximal isometric quadriceps contraction may be painful in the first postoperative days and lead to erroneously low values.[11,13,14]

There were no significant differences between the groups in the VAS pain scores at rest and during flexion of the knee (Table 4). However, the patients in the 0.025% group tended to use more piritramide rescue medication and the VAS scores for satisfaction with the pain treatment were significantly better in the 0.1% group (Table 4). In view of the fact

that all patients met the discharge criteria on the end of the fourth postoperative day, although several of them could not participate in the active mobilisation (i.e. walking) in the first postoperative days, we consider to investigate the effect of a higher ropivacaine concentration (i.e. 0.15%, 0.2%) on our fast track rehabilitation programme, as these concentrations were reported as superior for analgesia and may not lead to a longer hospital stay.[6,10]

In conclusion, this pilot study indicated no apparent advantage in decreasing the concentration of ropivacaine administered as bolus injections via the femoral nerve catheter below 0.1% on the patient's ability to actively participate in the rehabilitation programme after TKA. In fact, the lowest studied concentration (i.e. 0.025%) resulted in a lower patient's satisfaction with the pain treatment, while not improving recovery after TKA.

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Chapter 3

Safety of retransfusing shed blood after local infiltration analgesia in total knee arthroplasty

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ABSTRACT

We investigated the safety of LIA (local infiltration analgesia) combined with retransfusion of drained blood. Total knee arthroplasty patients received two peri-articular injections during surgery followed by continuous infusion, both with ropivacaine (567 mg). Ropivacaine plasma concentrations were determined in blood samples taken at 0, 3, 6 and 24 hours postoperatively. The collected shed blood was not retransfused, instead retransfusion was modelled by estimating the cumulative plasma concentrations at 6 hours postoperative. Total and unbound ropivacaine plasma concentrations ranged respectively from 0.08 to 1.9 mg/L and 0.003 to 0.11 mg/L. An average of 13.1 ± 3.7 mg unbound ropivacaine would have been returned to the patient. The estimated cumulative ropivacaine plasma levels showed that instant retransfusion would have led to plasma levels below 0.26 mg/L. It appears to be safe to transfuse autologous blood in combination with LIA. However, before drawing definite conclusions formal measurement of actual concentrations is required.

INTRODUCTION

Recovery after total knee arthroplasty (TKA) is hampered by postoperative pain when not adequately dealt with.[20] A multimodal approach that reduces nociception is recommended to achieve maximum efficacy in pain control. As part of a 'multimodal approach' local infiltration technique with local anaesthetics, local infiltration analgesia (LIA), has been introduced. Large case series have been performed with satisfactory results for pain relief and despite the high volume, the frequency of side effects of the local infiltration techniques was low.[13,17]

Several LIA variations have been described in the last decades, with different routes of administration, types of anaesthetics, and the combination of intra-operative infiltrations with postoperative catheters. At the moment there is non-uniformity with regard to the preferred technique. Kohan and Kerr described their LIA technique using a catheter for postoperative single-shot local anaesthetic administration after 15 to 20 hours.[13] Bianconi et al. favoured the LIA technique when compared to systemic analgesia because of less postoperative pain, opioid use reduction and shorter hospital stay.[3]

Several authors have studied the effectiveness of autologous retransfusion drains. Moonen et al. and Cheng et al. found a reduction in allogeneic blood transfusions in knee- and hip arthroplasty.[7,16] However, Amin et al. and Abuzakuk et al. found no effect of retransfusion drains.[1,2] Despite the discussion about the effectiveness of wound drains in general, in our hospital, as in many clinics worldwide retransfusion of drained blood is still standard care and independent of the haemoglobin level in many hospitals.

A combination of LIA and retransfusion of shed blood involves the risk of reinfusing potentially high concentrations of local anaesthetics. Ropivacaine (Naropin®, AstraZeneca) is most frequently used in LIA, because of its enhanced safety profile compared to other long-acting local anaesthetics.[12,25] Parker et al. reported the safe combination of both techniques in case of single shot LIA. However, no continuous wound catheter was present and no unbound ropivacaine plasma concentrations were analysed.[19-20] Most of the plasma binding of local anaesthetics is due to association with α-1-acid glycoprotein (AAG). In this case, unbound ropivacaine plasma concentration interacts with receptors to produce pharmacological or toxicological effects after systemic administration. That is why the unbound ropivacaine plasma concentration is of particular importance since side effects and complications are largely attributable to this fraction.

This study was designed to determine ropivacaine plasma concentrations in the patient and in shed blood after local (continuous) infiltration and to estimate cumulative ropivacaine plasma concentrations assuming retransfusion of shed blood.

METHODS

This experimental prospective study protocol was approved by the local Medical Ethics Committee (CCMO no. NL25137.098.08) and registered in the Dutch trial registry (NTR1784). After written informed consent had been obtained, twenty primary TKA patients were enrolled in the study. Inclusion criteria were age from 18 till 90 years, ASA 1-2, haemoglobin (Hb) levels above 7.5 mmol/L and normal renal function (Modified diet in renal disease equation (MDRD)) value above 48 mL/min. Before surgery two intravenous cannulae were inserted into a vein of both arms, one for routine monitoring of the patient during surgery and one (controlateral side) in order to obtain blood samples. All patients received lumbar spinal anaesthesia with 15 mg bupivacaine 0.5%. Two orthopaedic surgeons performed the operations according to standard procedure. Cemented cruciate retaining components (PFC Sigma, DePuy, Johnson&Johnson) were placed and patella resurfacing was done when necessary.

A solution consisting of 50 mL ropivacaine 0.75% (=375 mg) (AstraZeneca, Sweden), 50 mL NaCl 0.9% and 0.5 mL of 1:1000 epinephrine was injected in the peri-articular tissues. The solution was equally divided in two 50 mL syringes and injected with 22 gauge spinal needles. Before placement of the final implants the posterior capsule and deep peri-articular tissues were infiltrated with the first syringe. The second syringe was used to infiltrate the synovium of the suprapatellar pouch, quadriceps and patellar tendons and subcutaneous tissue surrounding the incision.

Additionally, near the end of the operation the Solace™ Infusion System (Apex medical, San Diego) was inserted and connected. This single use elastomeric type pump was filled with 270 mL ropivacaine 0.2% without epinephrine, which was attached to two small catheters, each producing 2 mL/h, which were placed intraarticular and subfascial. A total of 96 mL ropivacaine 0.2% (=192 mg) was infused during the first 24 hours after surgery.

Furthermore, a Bellovac autologous blood transfusion (ABT) drain (AstraTech, Sweden) was placed intra-articularly.

Blood samples were taken at the conclusion of surgery (T=0) before the Solace infusion system and drain were opened and 3, 6 and 24 hours after the first sample. At 6 hours, the drain was disconnected and two samples were taken out of the blood bag: one before and

one after passage through the filter cascade. Shed blood was not returned to the patient. The 6-hour sampling time was taken because this is the maximum time allowed for blood collection in autologous retransfusion drains.

All samples were centrifuged at 3000 rpm for 10 minutes and plasma was stored at minus 80 degrees Celsius. The wound drain and Solace infusion catheters were removed after 24 hours.

During hospitalisation haemoglobin levels (Hb) were measured preoperatively and post-operatively on day 1 and 3.

Analyses

Total and unbound ropivacaine concentrations were measured with liquid chromatography-mass spectrometry (LC-MSMS, Agilent Technologies 6410 Triple Quad).[4] The accuracy and intermediate precision of these analyses were respectively 2.2-4.4% and 2.0-2.9%.

The free ratio of ropivacaine for each patient (Psfr) was calculated by dividing the unbound concentration by the total concentration.

Subsequently we modelled the theoretical maximum unbound ropivacaine plasma concentration if the shed blood would have been instantly returned to the patient. We estimated circulating plasma volume per patient according to the formulae of Lemmens et al.[15] and the patient specific haematocrit (preoperative) values. Next, we estimated the theoretical maximum unbound ropivacaine plasma concentration as follows:

((Rbel x Vbel x $Psfr_6$) + (Rpl_6 x pat specific circulating plasma volume)) / (pat specific circulating plasma volume + Vbel). (Rbel = unbound ropivacaine concentration in mg/L in the retransfusion device after blood passage through the filter cascade, Vbel = volume of shed blood in L, $Psfr_6$ = patient specific free ratio of ropivacaine at 6 hours postoperatively, Rpl_6 = unbound ropivacaine plasma concentration in mg/L at 6 hours postoperatively)

In this calculation we assume that a part of the unbound ropivacaine in the shed blood will instantly bind to AAG upon retransfusion. $Psfr_6$ determines the amount of ropivacaine remaining unbound.

Statistics

The continuous data are presented as the number of subjects, mean, standard deviation (SD), minimum and maximum values, and categorical data expressed as frequencies and percentages. Normally distributed data are presented as mean ± SD; in case of non-normal distribution median and range are used.

Spearman's correlations were calculated to examine a potential relationship between patients' characteristics (age, BMI and renal clearance) and ropivacaine concentrations in plasma. Data were analysed using SPSS 17.0 (SPSS for Windows, Chicago: SPSS Inc.).

RESULTS

Twenty consecutive eligible patients undergoing elective TKA were enrolled in the study (Table 1). The first and second local analgesia block were given respectively 43 and 63 minutes (on average) after start of surgery (SD: 10 min). The catheter for continuous infusion was unclamped 57 minutes (SD: 11 min) after the first block was given. The first sample was taken 34 minutes (SD: 9 min) after the second intraoperative injection.

Table 1 Patient demographic data

	Mean ± SD (range)
Age (years)	71.3 ± 7.5 (58-84)
Body Mass Index (kg/m^2)	27.1 ± 3.5 (21-37)
Renal clearance (MDRD) (mL/min)	69.7 ± 11.8 (48-86)
Male / female	15 (75%) / 5 (25%)
ASA classification (1/2)	4 (20%) / 16 (80%)
Left / right	7 (35%) / 13 (65%)
Patella resurfacing (yes/no)	11 (55%) / 9 (45%)

MDRD = modification of diet in renal diseases
ASA = American Society of Anaesthesiologists

Mean total and unbound ropivacaine plasma concentrations are shown in Table 2, on average the free fraction of ropivacaine was 4.8% (SD: 0.7%).
The plasma values at 6 hours postoperatively ranged for total ropivacaine from 0.54 to 1.69 mg/L and unbound ropivacaine 0.03-0.11 mg/L at 6 hours postoperatively. The C_{max} (peak concentration) of the total ropivacaine plasma concentration was 1.89 mg/L found at 24 hours postoperatively, for unbound ropivacaine plasma concentration C_{max} was 0.11 mg/L at 6 hours postoperatively. Both values were found in different patients. The C_{max} for the total ropivacaine plasma concentration was found in 13 patients at 24 hours postoperatively, others had their maximum at 3 hours (n=2) and 6 hours (n=5) postoperatively. The C_{max} for unbound ropivacaine plasma concentration was found in half of the patients at 6 hours, 5 patients had C_{max} at 3 hours and 5 patients at 24 hours postoperatively.

A negative correlation was found between age and BMI (r=-0.458) and the differences in C_{max} time points. Furthermore, no significant relationship was found between the time window, the single-shots and the sampling points.

The median shed blood volume was 600 mL (range: 303-869 mL). In one case the exact amount could not be measured, the missing value was imputed from the mean volume of the shed blood in all other patients, which was 591 mL.

There was a small difference in the total and unbound ropivacaine concentration before and after filtration of the shed blood, respectively 33.05 vs. 32.7 mg/L for the total concentration. We used the filtered total ropivacaine concentration for modelling the cumulative concentration; because the filtered shed blood would be returned to the patient.

The ropivacaine concentrations in shed blood were much higher in comparison to the plasma levels. The unbound ropivacaine fraction (mean ± SD) in shed blood (68.8 ± 4.6%) was higher as compared to plasma (4.8 ± 1.1%).

When the shed blood would have been returned to the patient an average of 13.1 ± 3.7 mg (range: 6.2-18 mg) unbound ropivacaine would have been administered intravenously.

We estimated the cumulative ropivacaine plasma concentration when the shed blood would have been returned to the patient. This model showed a mean unbound ropivacaine plasma concentration after retransfusion of the shed blood of 0.26 ± 0.11 mg/L (range: 0.12-0.58 mg/L).

Haemoglobin levels showed the expected decrease during the first postoperative days in all patients. The average pre-operative Hb value was 9.1 mmol/L (SD: 0.5 mmol/L), on day 1 and 3 Hb values were respectively 6.9 mmol/L (SD: 0.6 mmol/L) and 6.6 mmol/L (SD: 0.8 mmol/L). None of the patients received an allogeneic blood transfusion.

Table 2 Total and unbound ropivacaine concentrations in plasma and shed blood

	Unbound	Total	Fraction
T0	0.014 ± 0.009 (0.003-0.036)	0.302 ± 0.177 (0.078-0.698)	4.5 ± 0.6 (3.1-5.3)
T3	0.042 ± 0.019 (0.019-0.086)	0.798 ± 0.254 (0.448-1.434)	5.1 ± 0.9 (3.3-7.1)
T6	0.050 ± 0.022 (0.025-0.105)	0.888 ± 0.299 (0.539-1.689)	5.8 ± 2.2 (3.4-12.6)
T24	0.040 ± 0.015 (0.017-0.078)	1.028 ± 0.328 (0.467-1.886)	3.9 ± 0.6 (2.7-5.1)
ABT before	23.05 ± 5.72 (11.95-32.69)	33.049 ± 6.539 (18.445-41.773)	69.1 ± 4.7 (62.2-78.5)
ABT after	22.61 ± 5.72 (10.33-31.87)	32.69 ± 6.777 (16.385-41.300)	68.5 ± 4.5 (59.9-77.2)

Unbound and total values are shown in mg/L as mean ± SD (range). The fraction is unbound concentration in % of the total concentration. Values under timepoints (T) 0, 3, 6 and 24 hours represents plasma.
ABT (Autologous Blood Transfusion) before and after represents shed blood before and after filtration.

DISCUSSION

LIA is a relatively simple technique where significant opiate sparing effects have been described.[9,11] The combination with a retransfusion drain is performed in several hospitals however questions were raised with respect to its safety. Before addressing efficacy we need to examine the issues of safety. We combined these two modalities with special focus on the unbound ropivacaine plasma concentration, since the unbound fraction is mainly responsible for systemic toxicity. We expected that the cumulative modelled unbound ropivacaine plasma concentration at 6 hours postoperatively would be well below the threshold for systemic toxicity stated by Knudsen et al.[14] They performed a study on healthy volunteers receiving ropivacaine intravenously. Based on the arterial sampling a threshold for CNS (central nervous system) toxicity is apparent at mean (min-max) unbound ropivacaine plasma concentration in the order of 0.56 mg/L (range: 0.34-0.85 mg/L).[14] Without retransfusion we found unbound ropivacaine plasma concentrations of 0.05 ± 0.02 mg/L (95% CI: 0.04-0.06 mg/L) at 6 hours postoperative.

It is important to base the safe limits on the unbound ropivacaine plasma concentrations since this concentration is related to systemic pharmacodynamic effects and toxicity. Two studies used LIA intraoperatively with ropivacaine in dose up to 400 mg generating unbound ropivacaine plasma concentrations well below the threshold for systemic toxicity. [6,8,14]

Four studies have so far been published where shed blood has been collected postoperatively and analysed for ropivacaine content.[4,10,18,21] In these studies, the total amount of ropivacaine in the shed blood collected was found to be low, <27 mg, in comparison to doses used in regional anaesthesia. In one of these studies doses up to 490 mg were used.[21] In our study we found a maximum total ropivacaine concentration in shed blood of 41.3 mg. The reason for this slightly higher value might be explained by our study design. We started the postoperative wound infusion immediately after the end of surgery in difference with all the other published studies where the wound infusion started after six hours, e.g after finalisation of drain blood collection.

No investigation has so far been published measuring the change in unbound ropivacaine following retransfusion of shed blood. However, in one study the change in total ropivacaine was measured.[18] The estimated mean maximum dose of ropivacaine reinfused, obtained from the product of drain volume and concentration, was approximately 1.3 mg (range: 0.4-2.6 mg). The mean total ropivacaine plasma concentration increased slightly, 0.03 µg/mL, from 0.79 µg/mL to a mean value of 0.82 µg/mL after completion of retransfusion.[18] In our study the total amount of ropivacaine in shed blood was 32.7 mg

(range: 16.4-41.3 mg). Considering a worst case scenario where shed blood with 41.3 mg ropivacaine would be reinfused our values would be 32 times (41.3/1.3) higher than by Parker et al.[18] Theoretically this would with our study results generate a blood level increase of total ropivacaine with 32 x 0.03 mg = 0.95 mg/L, when the shed blood had been reinfused.

The major determinant of systemic toxicity in local anaesthetics is the unbound concentration in plasma. It is known that AAG, the protein responsible for ropivacaine binding, has high inter- and intra-individual variability and therefore concentrations and binding capacity can largely differ over time and between patients. Furthermore, AAG concentrations are influenced by surgery, myocardial infarction and inflammatory processes.[24] Essving et al noted that even though the total plasma concentration showed increasing values, the free fraction decreases with time.[8] This is in line with the fact that ropivacaine is mainly bound to AAG. The AAG availability has been associated with an increase in the protein binding of ropivacaine during long-term infusion after surgery.[5,23] This is also seen in our study were the mean unbound ropivacaine fraction decreases after 24 hours. In our study mean unbound ropivacaine fraction was 4.8% in the included ASA I and II patients. This is lower than reported by Knudsen et al., which may be explained by the fact that our patients had more co-morbidity.[14]

In two previously published studies the unbound ropivacaine fraction was measured.[4,8] The unbound ropivacaine fraction in the different studies varied between 2.2 and 8.8%. In our study we found unbound ropivacaine fraction in plasma at six hours to be 5.8% (range: 3.4-12.6%). Applying the highest fraction on the theoretically generated total plasma level increase of 0.95 mg/L would generate unbound ropivacaine, if reinfused, of 12.6% x 0.95 mg/L = 0.12 mg/L. Adding this maximum calculated increase to the highest reported unbound ropivacaine plasma concentration generates a maximum unbound ropivacaine plasma concentration of 0.105 + 0.12 = 0.225 mg/L, a concentration well below the threshold for systemic toxicity of 0.56 mg/L.[14] Also the model we used with all specific data from each patient (e.g. plasma volume, shed blood volume and free fraction) showed a mean unbound ropivacaine plasma concentration after retransfusion of the shed blood of 0.26 ± 0.11 mg/L (range: 0.12-0.58 mg/L). In both models we assume instant retransfusion and instant binding. In daily practice however, an erythrocyte concentrate is normally reinfused in half an hour or more, so even lower unbound ropivacaine values are likely.

Regarding the shed blood collected, the median total drainage loss of 600 mL was similar to the reported amounts in the study of Vendittoli et al.[22] Vendittoli et al. noted that drainage

loss was not significantly different between patients with single morphine consumption or in combination with peri-articular infiltration.[22]

In conclusion, data so far indicate that intraoperative local infiltration analgesia with ropivacaine for hip and knee arthroplasty can safely be combined with autologous blood reinfusion, even if a postoperative ropivacaine wound infusion at low rates starts directly after the end of surgery. Nonetheless, the safety issues have to be warranted by actual administration of the shed blood collected.

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Chapter 4

Safety of blood reinfusion after local infiltration analgesia with ropivacaine in total knee arthroplasty

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ABSTRACT

The authors hypothesized that it is safe to combine local infiltration analgesia (LIA) in total knee arthroplasty (TKA) with a retransfusion drain since ropivacaine concentrations would not exceed the arterial toxicity threshold concentrations of 4.3 mg/L for total and 0.56 mg/L for unbound ropivacaine.

Twenty-two patients scheduled for primary TKA were included. During surgery three peri-articular injections with ropivacaine (300mg) were given. Plasma and shed blood samples were taken at 0, 1, 3, 6, 7 and 24 hours postoperatively.

At 6 hours postoperatively, the total ropivacaine plasma concentration ranged from 0.26 to 1.53 mg/L and unbound ropivacaine from 0.03 to 0.12 mg/L. At 7 hours, the total ropivacaine plasma concentration ranged from 0.19 to 1.71 mg/L and unbound ropivacaine from 0.02 to 0.09 mg/L. In the collected shed blood, a total of 0.27 to 12.8 mg (median 3.73 mg) unbound ropivacaine was present. Reinfusion would lead to an addition of 3.73 mg (median) unbound ropivacaine that would be reinfused into the patient. The calculated (modelled) estimation regarding the maximum unbound ropivacaine plasma concentration showed a median value of 0.114 mg/L (IQR: 0.09, 0.12 mg/L). All concentrations were well below reported toxicity thresholds.

The combination of LIA and reinfusion presented herein are considered safe. However, differences in pain protocol lead to changes in the safety evaluation. Compared with previous studies, the technique of administration is of greater importance for the effect on unbound ropivacaine because of unknown mechanisms.

INTRODUCTION

As part of a multimodal approach, local infiltration anaesthesia (LIA) has been introduced. Large case series have been described with satisfactory results for pain relief and despite the high concentration, side effects of local infiltration techniques occur infrequently.[1,2]
The combination of LIA with autologous blood transfusion, that is postoperatively giving back the patient's own blood collected in a transfusion bag during the first 6 hours after surgery, might lead to infusion of considerable amounts of local anaesthetics. In this respect, continuous infusion issues, plasma concentrations and toxicity are clinical pharmacological issues that have to be considered in the safety evaluation of intra-operative local infiltration techniques with ropivacaine in hip and knee arthroplasty combined with autologous blood transfusion.
In plasma, ropivacaine is mainly bound to α-1-acid glycoprotein (AAG) which is an acute-phase protein whose concentration has been shown to increase in response to surgical stress.[3] As ropivacaine is eliminated by hepatic metabolism, with an intermediate to low extraction ratio, its rate of elimination should, theoretically, depend on the unbound ropivacaine concentration in plasma.[4-6] The total plasma clearance is expected to vary with changes in the unbound fraction, i.e. a postoperative increase in the AAG concentration will decrease the free fraction (due to increased protein binding), which will decrease the total clearance and result in a relative increase in total plasma concentrations.[6,7] This is important, as it is the unbound plasma concentration that is related to systemic pharmacodynamic effects and toxicity. Since the rate of diffusion across a membrane is proportional to the unbound drug concentration, the rapid appearance of systemic central nervous system and cardiovascular toxicity of local anaesthetics is determined by the unbound concentration as opposed to the total plasma drug concentration.
Only six small studies have been published about (possible) reinfusion following total knee arthroplasty (TKA) with LIA using ropivacaine.[8-13] Hitherto, reinfusion was studied in two studies with different doses (200 mg vs. 150 mg), additional bolus injections (twice vs. none) and even other comparators such as tourniquet usage and hip and knee arthroplasty.[9,10]
The aim of this study was to determine the safety of LIA in combination with a retransfusion drain. Total ropivacaine plasma concentrations should not exceed 4.3 mg/L (arterial) as these are associated with toxicity; as for the unbound ropivacaine plasma concentrations – supposing a protein binding of 87% – concentrations greater than 0.56 mg/L (arterial) are associated with toxicity.[14] Since protein binding may vary considerably between and within

subjects, we measured total and unbound ropivacaine plasma concentrations as well as ropivacaine concentrations in the retransfusion device.

METHODS

Our regional ethical committee approved the study (CCMO no. NL33364.098.10) and the trial was registered in the Dutch trial registry (NTR2677). Patients planned for a primary TKA with preoperative haemoglobin (Hb) concentrations above 7.5 mmol/L were eligible for participation in the study. Other inclusion criteria were age between 18 and 90 years, American Society of Anaesthesiologists (ASA) classification 1 or 2, lumbar spinal anaesthesia (L2-3 or L3-4 level with 3 mL of bupivacaine 0.5%), an estimated GFR with the modification of diet in renal disease (MDRD) formula >48mL/min. Patients gave their informed consent after having received oral and written information.

An intravenous cannula was inserted into a vein of each arm, one for routine monitoring of the patient during surgery and one (antecubital) in order to obtain blood samples. One orthopaedic surgeon performed all operations according to standard procedure. Cemented cruciate retaining components (PFC Sigma, DePuy, Johnson&Johnson, Warsaw, IN) were placed and patella resurfacing was done when necessary. A tourniquet was used during surgery which was inflated to 300 mmHg. Tourniquet was released after skin closure and compressive bandaging. Peroperative and postoperative surveillance of the patient was performed by routine cardiac monitoring which took place for at least 3 hours after surgery. Three syringes each containing 50 mL ropivacaine 0.2% (Fresenius Kabi, Hamburg, Germany) and 0.33 mg epinephrine were injected with an 18-gauge spinal needle. Before placement of the final implants the posterior capsule and deep peri-articular tissues were infiltrated with the first syringe. The second syringe was used to infiltrate the capsule and the borders of the incised quadriceps and patellar tendons, infra-patellar ligament and possible remnants of the fat pad. The third syringe was used to infiltrate the subcutaneous layer around skin incision.

At the end of surgery an autologous blood transfusion (ABT) drain (Bellovac ABT, AstraTech, Mölndal, Sweden) was placed intra-articular in the knee joint. The drain was opened at the recovery unit after the first blood sample was taken (T=0). At 1, 3, 6, 7 and 24 hours after the first sample another blood sample was taken from the patient. At 1, 3 and 6 hours the drainage bag was disconnected, volume noted and a sample was taken. All samples were drawn with EDTA tubes and samples were centrifuged at 3000 rpm for 10 minutes, plasma

samples were then stored at -70°C until LC-MSMS analysis. The Bellovac ABT drain was removed after 24 hours.

A standardised pain therapy protocol was used (Table 1). The Visual Analog Scale (VAS) for pain was asked before blood samples were taken.

Table 1 Pain treatment protocol

Before surgery (~2 hours)
600 mg Gabapentin
200 mg Celecoxib
During surgery
1000 mg Acetaminophen (IV)
4 mg Ondansetron (IV)
Infiltration of 150 mL ropivacaine 2 mg/mL / 1 mg/mL epinephrine
4 hours after surgery
1000 mg Acetaminophen (oral)
8 hours after surgery
300 mg Gabapentin
1000 mg Acetaminophen (oral)
Day 1 after surgery
300 mg Gabapentin
200 mg Celecoxib
1000 mg, 4 times daily Acetaminophen (oral)
Following days
200 mg, once daily Celecoxib (till 2 weeks postoperative)
1000 mg, 4 times daily Acetaminophen (oral)
Escape medication
200 mg, once daily Celecoxib
1000 mg, 4 times daily Piritramide (IM)
4 mg, 2 times daily Ondansetron (IV) (except for surgery day)

IM = intramuscular, IV = intravenous
Escape medication is taken in case a patient experiences to much pain (VAS > 4)

Analyses

The main analyses of this study consisted of total and unbound ropivacaine plasma concentrations in the different patients' and shed blood samples. Ropivacaine concentrations were measured with liquid chromatography-tandem mass spectrometry (LC-MSMS, Agilent Technologies 6410 Triple Quad, Agilent, Amstelveen, Netherlands).[8]

The accuracy of the ropivacaine analyses was 2.2-4.4% and intermediate precision was 2.0-2.9%.[12]

The free ratio of ropivacaine for each patient was calculated by dividing the unbound ropivacaine plasma concentration by the total ropivacaine plasma concentration of the different samples (Psff = patient specific free fraction).

Subsequently, the theoretical maximum unbound ropivacaine plasma concentration was modelled if the blood from the retransfusion device would have been instantly returned to the patient. Circulating plasma volume per patient was estimated according to the blood volume formulae of Lemmens et al., patient specific (preoperative) haematocrit value and body weight.[15] Next, the theoretical maximum unbound ropivacaine plasma concentration was estimated as follows:

((Rbel x Vbel x $Psff_6$) + (Rpl_6 x pat specific circulating plasma volume)) / (pat specific circulating plasma volume + Vbel). (Rbel = unbound ropivacaine plasma concentration in mg/L in the retransfusion device after blood passage through the filter cascade, Vbel = volume of shed blood in L, $Psff_6$ = patient specific free fraction of ropivacaine at 6 hours postoperatively, Rpl_6 = unbound ropivacaine plasma concentration in mg/L at 6 hours postoperatively).

In this calculation the assumption that most of the unbound ropivacaine present in the blood collected in the retransfusion device would instantly bind to plasma protein upon reinfusion was made.

Pharmacokinetic analysis

Individual pharmacokinetic parameters for ropivacaine were calculated with the MW/Pharm pharmacokinetic software package (version 3.70, Medi/Ware, Netherlands). MW/Pharm consists of Bayesian modelling software and uses an 'a priori' population pharmacokinetic model.[16] Using Bayesian techniques the model was fitted to the measured ropivacaine data. 'A priori' pharmacokinetic parameters were taken from our previous study[12] and consisted of an one-compartment open model with a metabolic clearance (CLm) of 11 ± 5.98 L/h, fraction excreted unchanged in the urine (fr) of 1%, volume of distribution 0.5099 ± 0.3674 L/kg LBMc, (LBMc is Lean Body Mass corrected), absorption constant from the site of injection 0.0313 ± 0.0114 h^{-1} and a lag time until absorption of 0.1267 ± 0.1364 h. When modelling the data, the fraction excreted unchanged was fixed to the literature value of 0.01 because of lack of data on renal elimination.[17]

Statistics

Continuous data are presented as the number of subjects, mean, standard deviation, minimum and maximum concentrations. Categorical data expressed as frequencies and percentages. Data were tested for normality. Normally distributed data are presented as mean ± standard deviation; in case of a non-normal distribution median and inter-quartile range (IQR) was used.

Data were analysed using SPSS 17.0 (SPSS for Windows, SPSS Inc. Chicago, IL, USA).

RESULTS

A total of 24 consecutive patients were enrolled in the study, 22 patients were included in the final analysis. Two patients were excluded because no blood samples could be drawn. The average age was 67.7 ± 9.8 years, body mass index (BMI) was 27.8 ± 3.4 kg/m^2. The majority of patients was male (59%) and were operated upon the right knee (64%) with patella resurfacing in 9 cases (41%). Eighty-six percent of the patients had American Society of Anaesthesiologist (ASA) classification 2, eGFR ranged between 63 and 109 mL/min (average 81.5 mL/min). The average length of hospital stay was 3.69 ± 0.98 days. The three LIA blocks were given on average respectively 47, 66 and 76 minutes after start of surgery. The first sample was taken 50 minutes (SD: 9 min) after the first intra-operative injection.

Table 2 Total and unbound ropivacaine concentrations in plasma

	Unbound	Total	Fraction
T=0	0.009 (0.006-0.013)	0.106 (0.081-0.192)	6.498 (5.596-8.288)
T=1	0.016 (0.014-0.022)	0.269 (0.209-0.375)	6.581 (5.762-7.544)
T=3	0.032 (0.027-0.043)	0.466 (0.428-0.609)	6.791 (5.870-7.432)
T=6	0.043 (0.036-0.050)	0.585 (0.455-0.663)	7.538 (6.208-9.272)
T=7	0.045 (0.003-0.062)	0.593 (0.189-1.708)	7.560 (6.706-9.622)
T=24	0.024 (0.017-0.039)	0.433 (0.278-0.578)	6.195 (4.777-7.094)

Unbound and total values are shown in mg/L as median (IQR), fraction is unbound concentration in % of the total concentration.

Mean total and unbound ropivacaine plasma concentrations are shown in Tables 2 and 3. The plasma concentrations 6 and 7 hours postoperatively are important for the potential reinfusion of shed blood. Plasma concentrations 6 hours postoperatively ranged from 0.26 to 1.53 mg/L for total ropivacaine and from 0.03 to 0.12 mg/L for unbound ropivacaine. At 7 hours the concentrations were 0.19 to 1.71 mg/L for total ropivacaine and 0.02 to

0.09 mg/L for unbound ropivacaine. Lowest total and unbound ropivacaine plasma concentrations were found in patient 20 at T=0 and were respectively 0.023 and 0.003 mg/L. In the same person the highest concentrations were found in shed blood at T=1, 141.98 mg/L for total ropivacaine and 111.49 mg/L for unbound ropivacaine. The highest unbound ropivacaine plasma concentration was found at T=6 (0.12 mg/L) and the highest total ropivacaine plasma concentration was 1.80 mg/L (at T=24), both in the same person.
The time points where patients reached peak concentrations varied widely. For total ropivacaine peak plasma concentrations were reached at 3 hours (8 patients), 6 hours (5 patients), 7 hours (5 patients) and 24 hours (4 patients). The unbound ropivacaine plasma concentrations reached their peak at 3 hours (6 patients), at 6 hours (7 patients), at 7 hours (7 patients) and 2 patients at 24 hours.

Table 3 Total and unbound ropivacaine concentrations in shed blood

	Volume	Unbound	Total	Fraction
T=1 ABT	100 (60-225)	15.793 (9.634-24.666)	27.462 (18.996-42.725)	57.731 (54.214-59.762)
T=3 ABT	190 (100-250)	3.772 (2.237-8.083)	9.751 (7.963-17.317)	39.969 (28.046-46.052)
T=6 ABT	200 (100-234)	2.774 (1.269-3.380)	8.049 (5.373-9.551)	31.841 (22.445-36.939)

Volume presented in mL. Unbound and total values are shown in mg/L as median (IQR), fraction is unbound concentration as % of the total concentration.

The median of postoperative shed blood volume was the sum of the 4 time points (1, 3, 6 and 24 hours postoperative) and was 707 mL (IQR: 403, 909 mL). The median of postoperative shed blood (collected blood until 6 hours postoperative) that would be returned to the patient was 463 mL (IQR: 306, 669 mL).
When the shed blood would have been returned to the patient, the volume and concentrations collected during the first 6 hours are important (Table 3). In the cumulative collected shed blood from the first 6 hours a total of 0.27 to 12.8 mg (median 3.73 mg) unbound ropivacaine was present. The median unbound amount per time point (1, 3 and 6 hours postoperatively) was, respectively, 2.18 mg (IQR: 1.21, 3.51 mg), 0.73 mg (IQR: 0.36, 1.4 mg) and 0.44 mg (IQR: 0.15, 0.69 mg). The amount of blood collected was quite equal during these time points but unbound ropivacaine concentrations decreased significantly from T=1 to T=3 and T=6. Reinfusion would lead to an addition of 3.73 mg (median) unbound ropivacaine to the patient's blood.

The calculated (modelled) estimation, assuming reinfusion, regarding the maximum unbound ropivacaine plasma concentration showed a median value of 0.11 mg/L (IQR: 0.09, 0.12 mg/L).

Pharmacokinetic analyses are presented in Table 4. Mean metabolic clearance in the pharmacokinetic analyses was, 12.41 ± 6.32 L/h. The Ka and Tlag were 0.05 ± 0.11 hr and 0.16 ± 0.11 hr respectively. The volume of distribution for ropivacaine averaged 0.61 ± 0.36 L/kg.

Table 4 Pharmacokinetic data

Patient no	CLm (L/h)	Vd (L/kg)	Ka (hr)	Tlag (hr)
1	12.03	0.17	0.02	0.06
2	10.45	0.55	0.04	0.27
3	23.85	0.65	0.05	0.11
4	25.05	1.31	0.53	0.15
5	22.54	0.32	0.02	0.19
6	12.4	0.74	0.041	0.21
7	22.46	0.76	0.04	0.44
8	10.06	1.25	0.03	0.10
9	3.45	0.37	0.04	0.03
10	6.07	0.51	0.04	0.13
11	10.76	0.27	0.03	0.04
12	9.03	0.17	0.02	0.06
13	7.55	0.97	0.03	0.22
14	9.49	0.88	0.03	0.15
15	7.97	0.19	0.02	0.23
16	5.25	0.48	0.04	0.12
17	19.68	0.24	0.04	0.37
18	14.29	0.62	0.03	0.08
19	14	0.39	0.03	0.19
20	9.73	1.37	0.02	0.34
21	8.07	0.58	0.03	0.06
22	8.93	0.75	0.03	0.04
Mean ± SD	12.41 ± 6.32	0.61 ± 0.36	0.05 ± 0.11	0.16 ± 0.11
Variance	50.91	59.44	197.78	69.26

CLm = metabolic clearance. Vd = volume of distribution. Ka = absorption rate intramuscular. Tlag = time till absorption. Renal elimination was fixed at a literature value of 0.01 of the creatinine clearance.[17]

Routine cardiac monitoring peroperative and 3 hours postoperatively did not show any remarkable changes that could be addressed to ropivacaine toxicity. None of the patients experienced any adverse events attributable to the LIA procedure during hospitalisation

and until 6 weeks postoperative. Furthermore, no non-specific adverse events, such as headache, were experienced by the patients during and after the procedure.
Additionally, the VAS scores were good for all patients. The first two patients with too much pain (VAS >4) were reported at 3 hours postoperative. The patients that reported too much pain at the following time points were successfully treated with the escape medication mentioned in the pain protocol.

DISCUSSION

There is sufficient evidence that LIA is safe and can reduce postoperative pain following TKA.[18] We studied the safety of LIA in combination with a retransfusion drain. Total and unbound concentrations of ropivacaine were used as surrogate parameters for safety. The individual unbound ropivacaine plasma concentrations at 6 hours postoperative are below the published arterial toxicity threshold of 0.56 mg/L, and no cardiac symptoms related to ropivacaine or other adverse effects were observed in all patients studied.[14] Cardiac symptoms of ropivacaine toxicity were measured by peroperative and postoperative surveillance of the patient, monitoring took place for at least 3 hours after surgery.
If we should add 3.73 mg unbound ropivacaine (via shed blood) and assume instant binding, unbound ropivacaine plasma concentrations would rise by a median of 0.11 mg/L. Also the maximum unbound ropivacaine plasma concentration (0.44 mg/L) does not exceed the toxic threshold especially if we take into account the elimination of ropivacaine between 6 and 7 hours postoperative.
We previously performed a similar study with a slightly different design. In the former study patients received LIA with two syringes of 50 mL ropivacaine 0.375% and continuous infiltration after surgery during the next 24 hours. Plasma samples were taken at the same time points, excluding T=1 and T=7 and shed blood was only collected at 6 hours postoperative.[12] The sample handling, laboratory and ropivacaine analysis were performed by the same persons and the same validated analytical technique, only some samples were stored longer than others which is inherent to the inclusion of eligible patients. Also the pharmacokinetic data analysis was performed by the same person with the same software. However, both studies revealed some contradictions which could not be explained by difference in study design alone.
The mean free fraction in the current study (7.3%) was higher than the population average of 5% and even significantly higher than the 4.8% in the former study.[12] This difference could not be explained by the included patients, because both patient groups were equal

in co-morbidity, ASA classification and medication usage. In the former study, continuous infusion was given in the first 24 hours postoperative which could lead to saturation of AAG. It is known that AAG, the protein responsible for ropivacaine binding, has high inter- and intra-individual variability and therefore concentrations and binding capacity can largely differ over time and between patients. Furthermore, AAG concentrations are influenced by surgery, myocardial infarction and inflammatory processes.[3] In the study by Essving et al. it is noted that even though the total plasma concentration showed increasing concentrations, the free fraction decrease with time.[19] This is in line with the fact that ropivacaine is mainly bound to AAG, and AAG availability has been associated with an increase in the protein binding of ropivacaine during long-term infusion after surgery.[7,20] This is also seen in both studies performed, where the mean unbound ropivacaine fraction decreased after 24 hours.

Secondly, the unbound and total ropivacaine concentrations at T=0 were lower in the current study despite the higher concentration of ropivacaine given at that time point (300 mg versus 150 mg). The fluid management during surgery showed no differences between both studies. In the former study an average of 1300 mL (median 1500 mL) was given, in the current study an average of 1227 mL (median 1250 mL) was infiltrated perioperatively. All patients received intravenous Sodium chloride and Ringers solution. Also the intraoperative sedation (propofol) beside the spinal anaesthesia during surgery could potentially explain the differences between the two groups. The intravenously given fat emulsion (vehicle for propofol) is prone to absorb ropivacaine.[21] However, in both groups the same number of patients, 14 versus 13 respectively in the current and former study group received propofol infusion (same dose) during surgery.

Thirdly, we had expected that the ropivacaine concentrations in the shed blood would be much lower because no continuous infusion with ropivacaine was given in the current study. But the median unbound concentrations differed only 1.8 mg per litre in shed blood between the two studies.

The pharmacokinetic data analyses had some remarkable findings. The metabolic clearance was much lower than expected, 12.4 L/hr (13.6 L/hr previous study) compared to the 26 L/hr as expected from literature. The volume of distribution of ropivacaine (0.61 L/kg current and 0.63 L/kg previous study) was comparable with literature value (0.67 L/kg).[17] The lower absorption rates were to be expected because the injection site was intra-articular and intramuscular and furthermore ropivacaine was combined with epinephrine which causes a contraction of the blood vessels which leads to slower release from the injection site.

There is not much data to compare our results with, the studies that focus on ropivacaine infusion and injection site do not focus on specific pharmacokinetics and pharmacodynamics. Two studies focus on the pain intensity after intra- versus extraarticular continuous infusion.[22,23] One study has shown that after synovial procedures, where an extensive raw surface is created, there is an increased absorption of bupivacaine. Furthermore tourniquet inflation seems to reduce absorption, however longer tourniquet ischemia may lead to enhanced post-ischemic reperfusion with enhanced systemic absorption. In our studies no differences in tourniquet inflation and duration was seen. Cederholm et al. investigated the different concentrations of ropivacaine in combination with or without epinephrine on the skin blood flow.[24] They found a reduction of skin blood flow compared to saline. This reduction was more pronounced with lower concentrations of ropivacaine (<0.5%: tested 1%, 0.5%, 0.375%, 0.125% and 0.063%). All the above factors except for the concentrations in the LIA injections were equal, 0.375% in 100 mL (375 mg) and 0.2% in 150 mL (300 mg) in both studies.

Six other small studies have so far been published where blood has been collected postoperatively in wound drains and analysed for ropivacaine.[8-13] The ropivacaine doses for LIA ranged between 150 and 400 mg. Only in three studies shed blood was returned to the patients after LIA with ropivacaine. In comparison with the other studies the total ropivacaine amount in shed blood found in the current study was higher (median 8.2 mg, range: 1.3-19.5 mg) than in the other studies (range: 0.28-7 mg). The only other study that looked at unbound ropivacaine concentrations had a lower unbound ropivacaine plasma concentration (<0.038 mg/L) than the 0.043 mg/L unbound ropivacaine in the current study without reinfusion. The mean calculated unbound plasma concentration after potential reinfusion was 0.11 mg/L. This is remarkable because our ropivacaine concentrations in shed blood (range: 0.27-12.8 mg) are comparable with the ranges found by Breindahl et al. (range: 0.49-7.2 mg), but our plasma concentrations are much higher.[9] Also, no explanation could be found when comparing study data in which the same retransfusion systems are being compared.

Furthermore, it is quite extraordinary that the unbound ropivacaine plasma concentration that is related to systemic pharmacodynamic effects and toxicity is scarcely measured in studies, because total and unbound concentrations are related to each other.

Limitations of our study include the assumption of reinfusion that has not actually been performed out of safety considerations. Also this study has no large groups of patients studied and furthermore pain protocols were not completely comparable with the first study

performed. Additionally to the performed laboratory analysis actual AAG concentrations would have give us more insight in the apparent anomalies in free-fraction.

Conclusion

Based on unbound ropivacaine concentrations and the absence of signs of ropivacaine related cardiotoxicity, the combination of LIA and reinfusion presented herein can be considered as safe. However, as seen in the comparison of this study with the former study performed by this same group, differences in pain protocol lead to unexplainable changes in the pharmacokinetic evaluation. The mode of administration is of greater importance than expected which is difficult to explain because of an unknown gradient/hydrostatic effect in the human body. The pharmacokinetic analysis showed that the results are unpredictable because they depend upon unknown variables.

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Chapter 5

Preoperative injections of epoetin alpha versus postoperative retransfusion of autologous shed blood in total hip and knee replacement

A prospective randomised clinical trial

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ABSTRACT

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 preoperative 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 (postoperative 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 mL) 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).

Preoperative epoetin injections are more effective but more costly in reducing the need for allogeneic blood transfusions in mildly anaemic patients than postoperative retransfusion of autologous blood.

INTRODUCTION

Operations for major joint replacement frequently require blood transfusion. The potential risks involved have stimulated the search for alternatives, such as preoperative injections of epoetin alpha and postoperative cell saving.[1-8] In spite of algorithms to reduce allogeneic blood transfusions,it is not known which intervention or combination of measures is most successful.[9]

Preoperative injections of epoetin alpha have been shown to reduce the need for allogeneic blood transfusion by increasing the preoperative haemoglobin (Hb) level in patients whose baseline lay between 10.0 g/dL and 13.0 g/dL.[2,4] One prospective randomised study[4] showed that only 12% of patients treated with injections of epoetin alpha received at least one blood transfusion, compared with 46% in the control group. Postoperative retransfusions with autologous blood have been shown to reduce the requirements for allogeneic transfusion in patients who did not have preoperative anaemia. A prospective randomised study concluded that patients treated with a postoperative cell saving system had a significant reduction in transfusions of allogeneic blood compared with controls,[7] as evidenced by an absolute risk reduction from 19% to 6%. However, in that study, all patients had preoperative 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 preoperative injections of epoetin and postoperative cell saving.[10] We therefore carried out a prospective randomised trial designed to evaluate the use of a relatively cheap postoperative retransfusion system in patients with preoperative Hb levels between 10.0 g/dL and 13.0 g/dL, compared with using expensive preoperative injections of epoetin alpha. Our aim was to compare the differences in the need for allogeneic blood transfusions in both groups.

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 preoperative 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 alpha (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 (500mL) or six hours postoperatively. The amount of blood collected and retransfused was recorded.

Patients undergoing THR received an ABG-II system (Stryker, 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). Five different surgeons, all experienced in joint replacement, did the operations. 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 alpha, the Hb levels in the Eprex group were measured on the day of admission. As part of the routine preoperative 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 1). Postoperatively, the anaesthetist determined the Hb transfusion trigger, depending on the American Society of Anaesthesiologists (ASA) classification and the course of the operation.[11] The anaesthesiologist was independent but not blinded, as all prescribed medications, including epoetin alpha and ferrofumerate, were recorded. The preoperative 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.[12] 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 preoperative 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.

Table 1 Transfusion triggers

		Number op patients	
Haemoglobin level (g/dL)	**ASA score**	**Eprex group**	**Bellovac group**
8.1	ASA 2, 1	25	17
8.9	ASA 3, 2 #	17	26
9.7	ASA 4, 3 ##	8	7

ASA, American Society of Anesthesiologist[11]

= significant blood loss during surgery (>500 mL); ## = minor complications during surgery for example, temporary deflections on electrocardiogram

RESULTS

Of the 50 patients in each group (Table 2), 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 postoperative transfusion trigger.

Table 2 Patient and surgical characteristics

Characteristic	Eprex group (n=50)	Bellovac group (n=50)
Age (years)	73 (49-88)	75 (59-88)
Gender (male/female)	9 / 41	6 / 44
Height (cm)	164 (150-176)	163 (154-174)
Weight (kg)	71 (53-101)	76 (51-106)
Preoperative Hb at screening (g/dL)	12.4 (10.6-13.0)	12.4 (10.8-13.0)
Type of surgery (THR / TKR)	30 / 20	30 / 20
Type of THR (uncemented/hybrid/cemented)	8 / 6 / 17	7 / 7 / 16
Type of anaesthesia (spinal / general)	43 / 7	41 / 9
Postoperative transfusion trigger (g/dL)	8.5 (8.1-9.7)	8.7 (8.1-9.7)

Data are reported as mean (range). THR = total hip replacement; TKR = total knee replacement. There were no significant differences between both groups.

There was one failure of inclusion in a patient randomly assigned to the Eprex group who received preoperative injections of epoetin alpha and then a postoperative 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 alpha. 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 patients. 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 (p=0.75).

The mean transfusion triggers in the Eprex and Bellovac groups were 8.5 g/dL (range: 8.1-9.7 g/dL) and 8.7 g/dL (range: 8.1-9.7 g/dL) respectively (Table 2). A mean of 216 mL (range: 0-700 mL) were retransfused in the Bellovac group, 131 mL (range: 0-500 mL) 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 disconnection of the drain to the collection bag. This patient was included according to the intention-to-treat principle.

Table 3 Cost comparison per patient in Euro's

	Eprex group	**Bellovac group**
Epoetin alpha injections	1,831.68	None
Ferrofumerate tablets	302.22	None
Bellovac ABT retransfusion system	None	84.70
Allogeneic blood transfusion	12.04	80.24
Total costs per patient	**2,145.94**	**164.94**

Data are reported as costs per patient in both groups. The costs of the used treatment were based on the recommended prices of the manufacturers. The cost of allogeneic blood per patient was based on the percentage of patients receiving allogeneic blood combined with the number of units erythrocyte concentrates transfused per patient. The cost of one erythrocyte concentrate was € 200.60.

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 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 postoperative 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 3.

Table 4 Clinical complications

Complication	Eprex group (n=50)	Bellovac group (n=50)
Systemic major		
Cerebral thrombosis in the sagittal sinus	1 (2)	
Perforated sigmoid colon		1 (2)
Systemic minor		
Nausea	1 (2)	1 (2)
Diabetes mellitus instability		1 (2)
Urinary retention	1 (2)	
Urinary track infection	1 (2)	
Local major		
Peri-prosthetic fracture		1 (2)
Local minor		
Haematoma	1 (2)	2 (4)
Prolonged wound discharge	3 (6)	3 (6)
Superficial wound infection		1 (2)
Total	8 (16)	10 (20)

Data are reported as number (%) of patients with complications in both groups. The one patient in the Bellovac group with a "Local major" complication includes a patient with a periprosthetic fracture due to a fall one month after primary THR. A revision of the stem was performed. There were no significant differences between both groups.

The preoperative levels of Hb were a mean of 12.4 g/dL (range: 10.6-13.0 g/dL) in the Eprex group and 12.4 g/dL (range: 10.8-13.0 g/dL) in the Bellovac group (Figure 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 (range: 13.0-16.6 g/dL). On the first day after operation the mean Hb level had decreased to 11.4 g/dL (range: 9.0-13.8 g/dL) in the Eprex group and to 9.7 g/dL (range: 7.6-12.1 g/dL) in the Bellovac group. By the third day the levels had decreased to 11.2 g/dL (range: 8.4-13.7 g/dL) in the Eprex group and to 9.5 g/dL (range: 7.2-11.1 g/dL) 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 4). Four patients in the Eprex 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.

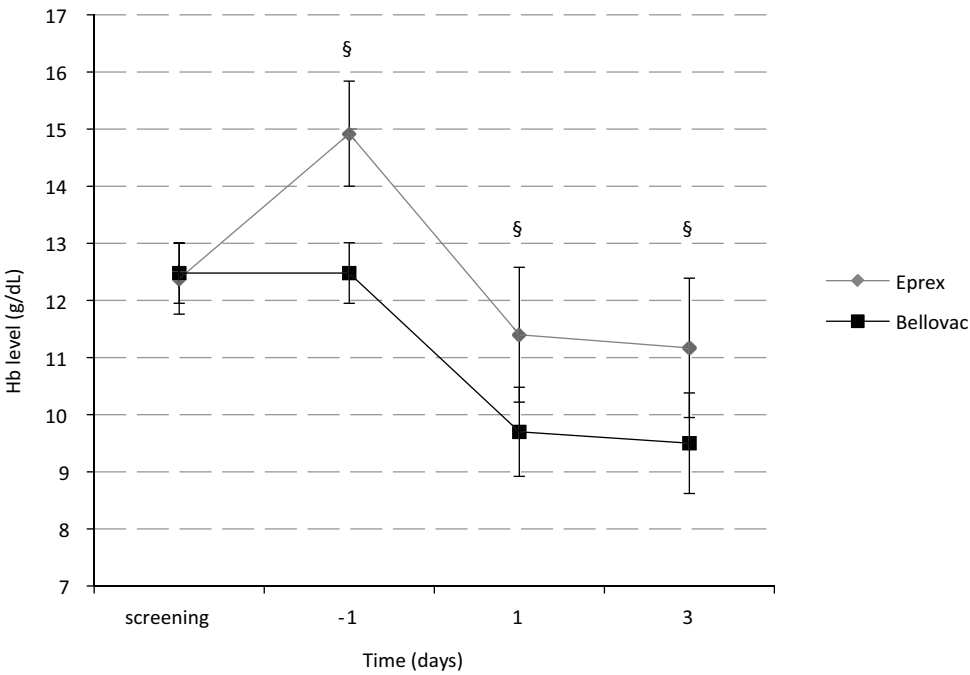

Figure 1 Perioperative Hb level

The level of haemoglobin (Hb) in both groups preoperatively and at one and three days postoperatively, § indicates statistical significance.

DISCUSSION

Most hospitals use restrictive transfusion triggers because they are aware of the risks and complications of allogeneic blood.[13,14] In addition, other interventions to reduce the use of allogeneic blood are in use, and it is not known which is the most successful.[1-8] Postoperative cell saving using a retransfusion system is relatively inexpensive, whereas preoperative injections of epoetin alpha are approximately 15 times more expensive.[5-8] Changing treatment from injections of epoetin to cell saving in patients with preoperative 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 preoperative anaemia, the effectiveness of a retransfusion system in patients with mild anaemia before operation can be disputed.[6-8] The analysis of the costs showed that in such patients the use of injections of epoetin supported by ferrofumerate tablets increased the cost per patients 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.[4] Comparing these results, the absolute risk reduction would be 18%. Although some patients in the Bellovac group still needed allogeneic blood 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 postoperative cell saving is 24%. Thus, in every 4.2 patients treated with preoperative injections of epoetin alpha, 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 postoperative 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.[2,4,18,19] Hence, the thromboembolic complication in our patient, although recognised in the literature, could not be proven to be related.

Patients with preoperative Hb levels >14.5 g/dL have less chance of receiving allogeneic blood than do mildly anaemic patients with a preoperative 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 14.9 g/dL, agreeing with earlier reports.[2,4] After primary THR and TKR the mean total blood loss to the third postoperative 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 preoperative level. Severe blood loss was needed before an allogeneic blood transfusions 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 postoperative

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 postoperative 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, preoperative injections of epoetin are more effective in reducing the need for allogeneic blood transfusions in mildly anaemic patients with preoperative Hb levels of 10.0 g/dL to 13.0 g/dL compared with postoperative retransfusion of autologous shed blood in major joint arthroplasty, but are more expensive.

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Chapter 6

Allogeneic blood indicator is not unambiguous

Easy manipulation of transfusion indicator by hospitals

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ABSTRACT

Hospitals were critized in many ways (medical care and patient safety), so different stakeholders jointly started the project 'Zichtbare Zorg Ziekenhuizen' (ZZZ; 'Visible Care Hospitals'). This project has developed indicator sets for over eighty disorders. The goal of this project was to collect data from hospitals in a uniform manner. Transfusion of allogeneic blood is one of the indicators that provides information about the quality of actual hip- and knee replacement surgery and the treatment around it. However, there exists a flaw in the system that needs to be further discussed. Namely, hospitals can positively influence this indicator without having to bear the costs of the investments.

INTRODUCTION

Annually different quality lists are presented that rank hospitals by the level of care offered. These lists are different regarding ranking because each list has its own parameters for scoring quality of care. To create more uniformity the project 'Zichtbare Zorg Ziekenhuizen' (ZZZ; 'Visible Care Hospitals') was initiated. The aim of the ZZZ is to gather quality information from hospitals in a standardized format to allow for a comparison of quality of care to be made. ZZZ strives to collect the information through one channel and to support the hospitals in this action through the same organisation. The indicator sets of ZZZ are composed of the following parties: Consumers' Union, The Health Care Inspectorate (IGZ), The Dutch Federation of University Medical Centres (NFU), The Federation of Patients and Consumer Organisations in the Netherlands (NPCF), The Dutch Federation of Hospitals (NVZ), The Dutch Nurses and Carers (V&VN), The Council of Medical Physicians (OMS), The Association of Health Care Insurers (ZN) and the scientific professional associations.

Human mistakes

ZZZ's main goal is to give insight into the quality of treatment of 80 disorders. In 2010, twenty-three disorders had a so-called indicator set. In 2011, twenty-two new indicator sets were developed. All these sets are based on medical guidelines and comprise the complete treatment process. For orthopaedic surgery the indicator sets 'total hip and knee arthroplasty' have existed for some years already (in 2011 divided in two different sets) and different steps of the treatment process are visualized in these sets.[1,2] The following indicators are defined: complication registry, Dutch Arthroplasty Register, deep infections, preoperative antibiotic prophylaxis, preoperative thrombosis prophylaxis, and allogeneic blood transfusions. Allogeneic blood transfusions are part of this set due to the risks associated with allogeneic blood transfusions. Possible risks include: Hepatitis, HIV/AIDS, transfer of infectious diseases and also human mistakes by administration of blood products.[3] A part of patients is not possible to exclude, despite all efforts for extensive and better precautions. Besides that, an allogeneic blood transfusion could have a negative influence on the immune system. Several methods have been introduced to decrease the use of allogeneic blood transfusions. In 2004 the Dutch homologous blood transfusion guidelines were developed. The introduction of a stricter indication regime for allogeneic blood transfusion, the so-called 4-5-6 rules (the numbers indicate haemoglobin (Hb) levels in mmol/L), had an important revolutionary effect. The indications for allogeneic blood transfusions are very clear. The health status of the patient, ASA classification (American

Society of Anaesthesiologists) and cardiopulmonal changes due to the surgery are taken into account.

Blood saving techniques

Besides a restrictive blood regime other blood-saving techniques are possible in joint arthroplasties. Important features to account for during surgery include careful haemostasis and maintaining patients' normothermia. Before surgery, autologous blood donation is possible and patients with a moderate anaemia (Hb $\leq$ 8.1 mmol/L) could be treated with erythropoietin alpha (epo). During surgery, cell saving (washed and unwashed systems) and fibrin glue are possibilities. Furthermore, after surgery blood loss could be measured in the first six hours after surgery and retransfused to the patient. These measures are all part of the DRG (Diagnosis-related group, in Dutch DBC: diagnosis treatment combination). Hospitals have to make their own decisions regarding cost-effectiveness of various blood saving techniques. Erythropoietin alpha treatment is an exception because the treatment costs are part of the extramural care. The treatment consists of four injections with a total price of €1440,-. This treatment option in fact, leads to an omission in the indicator. Hence hospitals could positively influence the indicator allogeneic blood transfusions without being responsible for the costs.

Calculation example

To illustrate the discrepancy above we analysed data from two large teaching hospitals. We retrospectively analysed collected data about allogeneic blood transfusions in primary total hip and knee arthroplasties, operated during 2008 or 2009. A total of 2077 joint arthroplasties (1189 total hip arthroplasties and 888 total knee arthroplasties) were performed. In this group 249 patients (12%) received an allogeneic blood transfusion. We checked if the allogeneic blood transfusions were given correctly in combination with another blood saving technique (if applicable). The transfusions were identified as 'incorrect', 'possible incorrect' and 'correct'. This classification followed the 4-5-6 rule in combination with patients' health status, Hb level of transfusion, number of bags transfused, increase in Hb level and patients' complaints.

In 78 percent the allogeneic blood transfusion was given correctly, possible incorrect in 16% of the cases and 5% was incorrectly given. These figures indicate that continuous training, education and refreshment courses have an additional value to minimize the amount of allogeneic blood transfusions.

Four injections

Depending on preoperative Hb values we determined if patients were eligible for receiving erythropoietin alpha preoperatively to reduce the number of allogeneic blood transfusions. Of the 249 patients, 165 patients (66%) would receive erythropoietin alpha if this was standard practice in these hospitals. Thus, patients with a haemoglobin level below 8.2 mmol/L should receive four erythropoietin alpha injections. On average, one in five has a haemoglobin level below 8.2 mmol/L. In our case, this would lead to 415 indications for erythropoietin alpha. Erythropoietin alpha is currently offered by Janssen-Cilag and Sandoz. If standard practice this should cost €598.000,- for the patient cohort under investigation.
Research has concluded that after erythropoietin alpha treatment the incidence of allogeneic blood transfusion should decrease by 75 percent.[4] In our case, the preoperative moderate anaemic patients with an allogeneic blood transfusion would decrease from 165 to 41 patients. Theoretically, we could have reduced the amount of allogeneic blood transfusions from 249 to 125 patients if erythropoietin alpha injections were standard practice in these hospitals. Not all allogeneic blood transfusions can be prevented, so the costs for these transfusions should be added to the sum of the erythropoietin alpha treatment.
The costs for allogeneic blood transfusions are €53.550,-, for 125 patients who receive an average of 2.1 packed cells (€204,- per packed cell). The total costs would be €651.550,-. In the current situation, where erythropoietin alpha is not the standard of care, the costs would be lower, €106.672,- (249 patients with an average of 2.1 packed cells multiplied by €204,-). If erythropoietin alpha would be introduced as standard treatment of care the costs would be increase by factor 6.

Dubious validity

Indicators have led to more unambiguous reporting of health care quality. Transparency, quality improvement and more efficiency in health care are important features of indicators. Besides that data validity is questioned. Due to the absence of data verification, the allogeneic blood transfusion indicator is also positively influenced by misuse of costs from other health care bodies. It is probable that hospitals provide socially-desirable answers because no data verification has been performed. The indicator sets are based on the guidelines of the scientific professional associations. Acceptable percentages are known and specified by the professional bodies. This is visible from the reports of all combined data from hospitals and independent treatment centres.[4] Of the 97 hospitals, 92 hospitals reported their allogeneic blood transfusion data. These percentages show that 28% of

the hospitals have no allogeneic blood transfusions in total hip- and knee arthroplasties. This can be concluded since they score 100% on the question 'percentage surgeries in which patients received no allogeneic blood transfusion in the perioperative setting in the case of total hip and knee arthroplasties'. The literature over the last decade regarding blood management in combination with the retrospective data from this research has shown that a percentage of 100% is unrealistic.

Additional information

Since each hospital tries to find solutions to reduce health care costs, the standardisation regarding implementation of erythropoietin in total joint arthroplasties remains a challenge. Research has concluded that erythropoietin is an effective way to prevent allogeneic blood transfusions, with less adverse events.[5] However, the costs related to its use are high. For this reason hospitals think differently about the usefulness of this product. There is no doubt about the indicator sets and the fact that erythropoietin could be helpful in blood management. The most important message of this research is that hospitals can improve their indicator set with funds from the extramural setting. It may be necessary to add additional questions to the indicator regarding allogeneic blood transfusion. In this case it may be helpful to provide information regarding the alternatives used in practice since it is possible to have higher ranking, while others pay for the alternative used. It is debateable whether erythropoietin alpha will still be prescribed in this magnitude if it became part of the DRG.

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Chapter 7

Autologous wound drains have no effect on allogeneic blood transfusions in primary total hip and knee replacement

A three-arm randomised trial

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ABSTRACT

We hypothesised there was no clinical value in using an autologous blood transfusion (ABT) drain in either primary total hip (THR) or total knee replacement (TKR) in terms of limiting allogeneic blood transfusions when a modern restrictive blood management regime was followed. A total of 575 patients (65.2% men), with a mean age of 68.9 years (range, 36 to 94 years) were randomised in this three-arm study to no drainage (group A), or to wound drainage with an ABT drain for either six hours (group B) or 24 hours (group C). The primary outcome was the number of patients receiving allogeneic blood transfusion. Secondary outcomes were post-operative haemoglobin (Hb) levels, length of hospital stay and adverse events.

This study identified only 41 (7.1%) transfused patients, with no significant difference in distribution between the three groups (p=0.857). The mean pre-operative Hb value in the transfused group was 12.8 g/dL (range, 9.8 to 15.5 g/dL) *versus* 14.3 g/dL (range, 10.6 to 18.0 g/dL) in the non-transfused group (p<0.001, 95% confidence interval: 1.08 to 1.86 g/dL). Post-operatively, the median of re-transfused shed blood in patients with a THR was 280 mL (Interquartile range (IQR) 150 to 400 mL) and in TKR patients 500 mL (IQR 350 to 650 mL) (p<0.001).

ABT drains had no effect on the proportion of transfused patients in primary THR and TKR. The secondary outcomes were also comparable between groups.

INTRODUCTION

The basis for modern patient blood management (PBM) is the application of a restrictive blood transfusion protocol combined with measures to reduce the need for peri-operative allogeneic blood transfusion.[1] Pre-operatively, erythropoietin injections combined with autologous blood donation can be used, although the use of the latter has declined in this millennium.[2] Intra-operatively tranexamic acid administration, cell saving of salvaged blood, and intra-operative blood volume dilution are other options in PBM.[3] Post-operatively, autologous blood transfusion (ABT) of shed blood along with clear transfusion thresholds are also used.[4-6] The optimal combination for particular patients and their cost effectiveness is still debated. Nevertheless, the largest benefit in modern PBM appears to be the introduction of a restrictive blood transfusion threshold in most hospitals.[5,7]

The use of wound drains in primary joint replacement is still controversial. Parker et al. reported in their meta-analysis that no conclusive evidence for the use of closed suction surgical drains in primary joint replacement but ABT drains were not included in their analysis.[8] With ABT drains the shed blood that accumulates in the suction bottles is re-infused into the patient within the first six hours. However, their usefulness in total hip (THR) or total knee (TKR) replacement is still uncertain. This is largely due to methodological difficulties in reporting, such as differences between studied groups, absence of randomisation, no formal power analysis, lack of controls, the use of varying end points, different transfusion thresholds and the use of different blood reinfusion devices.[9-12] The rate of drainage from a wound is important when determining the beneficial effect of ABT drains. An ABT drain removed at six hours post–operatively potentially achieves satisfactory early drainage while minimising overall blood loss, but any blood drained after six hours is discarded if these devices are still in situ.[13]

We initiated a multi-centre, prospective, randomised, single-blinded controlled trial on the effect of autologous blood transfusion at two postoperative time intervals (removal at six or 24 hours) compared to a control group (no wound drainage) in primary THR and TKR surgery, in the presence of a restrictive transfusion threshold. The primary outcome was the assessment of the requirement for allogeneic blood transfusions.

METHODS

The trial was undertaken in the Netherlands in two hospitals using the Bellovac ABT System (WellSpect Healthcare, Mölndal, Sweden), a wound blood reinfusion device. All consecutive patients planned for primary THR or TKR between November 2010 and November 2012 were eligible for the study. The study population consisted of 322 THRs and 253 TKRs, undertaken in 575 patients (Table 1, Figure 1). The primary goal was to compare the need for allogeneic blood transfusion in a) patients with no wound drainage (group A), b) in patients who received autologous blood reinfusion from their drain after six hours at which stage this drain was removed (group B) and c) in patients who received autologous blood reinfusion from their drain after six hours but drain removal after 24 hours (group C).
The medical ethics committee approved the study (NL27458.098.10), and all patients provided written informed consent before enrolment. The study was registered in the Dutch trial registry (NTR2501).

Table 1 Patient characteristics

		Group A	Group B	Group C
	N	190	191	194
Age (yrs)	Mean (range)*	68.9 (43-89)	69.5 (36-90)	68.2 (42-94)
BMI (kg/m^2)	Mean (range)†	28.2 (20.1-41.8)	28.2 (17.8-47)	28.1 (19.3-43.9)
Gender n (%)	Female	132 (69.5)	123 (64.4)	120 (61.9)
	Male	58 (30.5)	68 (35.6)	74 (38.1)
ASA n (%)	I	24 (12.6)	25 (13.1)	28 (14.4)
	II	149 (78.4)	141 (73.8)	146 (75.3)
	III	17 (8.9)	25 (13.1)	20 (10.3)
Surgery n (%)	THR	103 (54.2)	103 (53.9)	116 (59.8)
	TKR	87 (45.8)	88 (46.1)	78 (40.2)
Anaesthesia n (%)	Spinal	140 (73.7)	146 (76.4)	143 (73.7)
	General	50 (26.3)	45 (23.6)	51 (26.3)
Pre-operative Hb (g/dL)	Mean (range)‡	14.2 (9.8-17.9)	14.2 (10.6-17.1)	14.2 (10.6-18.0)
Erythropoietin n (%)	n=17	4 (2.1)	7 (3.7)	6 (3.1)
Surgical approach for THR (n = 332)	SL	50	51	50
	PL	48	45	62
	AS	5	7	4

ASA, classification according to the American Society of Anaesthesiologist[18]; BMI, Body Mass Index; Hb, haemoglobin; THR, total hip replacement; TKR, total knee replacement; SL, straight lateral; PL, posterolateral; AS, anterior supine.
*, *p*-value 0.411; one-way ANOVA test
† *p*-value 0.939; one-way ANOVA test
‡ *p*-value 0.790; one-way ANOVA test

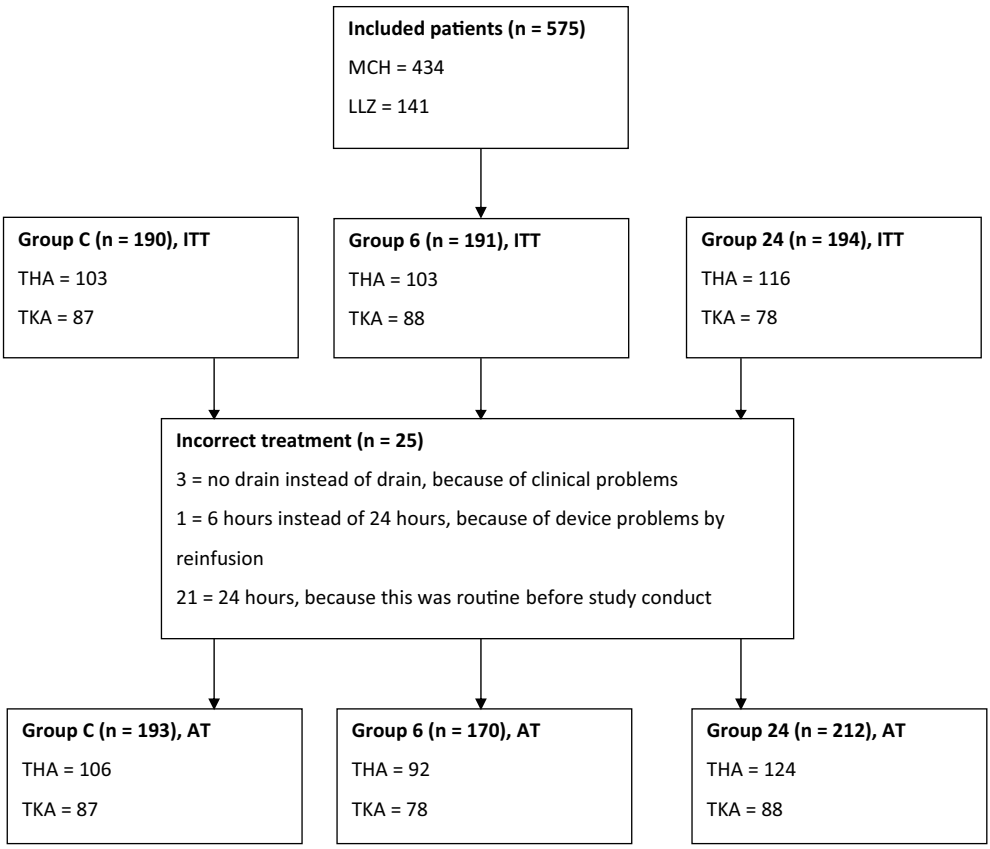

Figure 1 Flowchart

Group A, no wound drainage; group B, 6 hour drainage for six hours and removal of the drain; group C, wound drainage for six hours and removal of the drain 24 hours postoperatively. MCH, Medical Center Haaglanden; LLZ, Lange Land Hospital, AT, As Treated; ITT, Intention to Treat; THR, Total Hip Replacement; TKR, Total Knee Replacement.

Exclusion criteria were inability to give informed consent, patients with bleeding disorders, a religious objection to the concept of blood transfusion, and patients where bone grafting was expected during THR. Performance of a TKR without a tourniquet, previous major operations such as a tibial osteotomy or THR undertaken for post-traumatic secondary osteoarthritis, also resulted in exclusion. All surgical procedures were performed according to the surgeons' preference, using their customary approach. Each surgeon involved in the trial undertook a minimum of 50 joint replacements annually. There were three different approaches to THR: straight lateral (SL), posterolateral (PL) and anterior supine (AS). For TKRs a straight midline skin incision and medial parapatellar arthrotomy was used. The

tourniquet in TKR was released after skin closure and the application of compressive bandaging.

The re-infusion drains were used in groups B and C according to the manufacturer's instructions for post-operative autologous blood collection and re-infusion. The collected shed blood was returned to the patient in both re-infusion groups irrespective of their haemoglobin (Hb) level. In group B, the ABT drain was removed after six hours. In group C, the re-infusion drainage bottle was replaced with a low-vacuum Bellovac drain (WellSpect Healthcare, Mölndal, Sweden) after the first six hours, and then removed during the first post-operative morning (between 18 to 24 hours post-operatively).

Erythropoietin (Eprex, Janssen Pharmaceutical Companies of Johnson & Johnson, Tilburg, The Netherlands) was routinely used in one of the two hospitals in anaemic patients with a pre-operative Hb level below 13 g/dL (n=17). Three subcutaneous injections (40,000 IU of erythropoietin alpha in each injection) were given weekly, beginning three weeks before surgery with iron supplementation. Patients who used anticoagulation stopped these seven to ten days pre-operatively so that their INR was ≤1.8 before surgery.

All patients received thrombo-prophylaxis with low weight molecular heparin after surgery and continued until six weeks post-operatively. All patients received a single dose of cephalosporin prior to incision and two more doses within 24 hours postoperative, which was part of the routine protocol in use in both hospitals. Rehabilitation followed the standard procedure specific to each hospital. In general, patients' mobilisation started on the first post-operative day and planned discharge was between the second and fourth post-operative day.

The primary outcome was the proportion of post-operative patients receiving an allogeneic blood transfusion. The secondary outcomes were post-operative Hb values, measured peri-operative blood loss, transfusion volumes, length of hospital stay and adverse events, especially wound problems. All adverse events were coded according to Parvizi et al.[14] Intra-operative blood loss was only calculated for the THRs, as TKRs were undertaken with a tourniquet. Protocol violations regarding allogeneic transfusion were noted and recorded.

Eligible patients were consecutively randomised to receive either no drain (group A) or a Bellovac ABT System for re-infusion of shed blood (group B or C). Stratification of patients was carried out per clinic because each clinic has its own surgical technique and post-operative clinical procedures. Variable block sizes were used to ensure three balanced groups with an additional unknown randomisation factor. A computer generated randomisation plan was sealed in opaque envelopes by an independent person with randomisation performed in the operating theatre, but deferred until wound closure, to prevent changes in surgical

behaviour being introduced. Each patient' actual randomisation was checked against the randomisation list, inclusion date, surgery date and demographic data to ensure correct implementation and strict consecutive allocation.

The decision to transfuse allogeneic blood was taken according to the restrictive Dutch transfusion threshold regime (Table 2) known as the "4-5-6 (mmol/L) flexi norm".[15]

For all transfusions the indication was registered. Allogeneic blood transfusion was only given when the Hb level exceeded 8 g/dL if the patient was symptomatic from their anaemia, such as experiencing tachycardia and/or hypotension. Each allogeneic transfusion was evaluated (correct or probably incorrect) at the end of the study by certain authors (BT, PdH, HK and PP). The decision, if a transfusion was given correctly was based on pre-transfusion Hb, comorbidity, Hb increase after transfusion and day of transfusion. All outcome measures were collected prospectively and analysed as applicable by personnel unaware of the treatment allocation.

Table 2 The transfusion threshold[15]

Hb level, 6.4 g/dL
ASA 1 ASA 2 and 3, and uncomplicated surgery
Hb level, 8 g/dL
ASA 2 and 3, and significant blood loss during surgery (more than 500 mL)
Hb level, 9.6 g/dL
ASA 2 and 3, and minor complications during surgery (i.e. ST deviation on electrocardiogram) ASA 4

ASA, classification according to the American Society of Anesthesiologists[18]

Statistical analysis

Sample size calculation. The use of allogeneic blood in THR and TKR patients (i.e. percentage transfused patients) in the presence of a restrictive transfusion threshold (Table 2) was estimated to be 19%.[17] The expected transfusion rate in the re-infusion group was estimated to be 7%.[16,17] Therefore, the expected mean difference in transfusion rate was 12%. With a 5% significance level, two-sided hypothesis and 90% power, a total of 184 patients would be required in each group. Allowing for a drop-out rate of 3%, a total of 190 patients per group would be required.

Analyses were based on an intention-to-treat (ITT) principle, analysed in the assigned group. To assess the effect of the actual treatment (i.e. re-infusion of shed blood) an "As Treated" (AT) analysis was also performed.

For data which were not normally distributed median and interquartile range (IQR) were presented. Demographic and baseline data were based on the results from the PP procedure. Conclusions related to effectiveness and efficacy were explored by using the AT analysis set. Risk for variability due to the multi-centre study design, with for example differences in routines for hospital stay and discharge, was mitigated by use of stratification. Pearson's chi squared test was used to test frequencies of categorical response variables. The non-parametric Kruskal-Wallis test was used to analyse differences in continuous response variables between the treatment groups. A p-value < 0.05 was considered statistically significant. Tables with descriptive data were generated and hypotheses tested using statistical software PASW Statistics version 20.0 (IBM SPSS Statistics for Windows, Chicago, Illinois).

RESULTS

According to the ITT principle, 25 (4%) patients did not receive the treatment as randomised, and were analysed as AT. The three groups were comparable with regards to mean age, body mass index (BMI) and American Society of Anaesthesiologists (ASA) classification.[18] The three different surgical approaches used for THR (151 SL, 155 PL and 16 AS), were equally divided between the transfusion subgroups (Table 1). In 188 of 202 (93%) TKR patients who received spinal anaesthesia, it was a combination of spinal and epidural anaesthesia (CSE). In total 41 patients (7.1%) received an allogeneic blood transfusion of packed cells (mean 2.1 units, range 1 to 6). We did not identify any significant difference in the requirement of allogeneic transfusion (Table 3).

Table 3 Transfusion per analysis

	Group A	Group B	Group C	Total	*p-value*[$]
ITT	190	191	194	575	
Transfused patients (%)	12 (6.3)	14 (7.3)	15 (7.7)	41 (7.1)	0.857
THR[*]	8 (7.8)	5 (4.9)	12 (10.3)	25 (7.8)	0.317
TKR[*]	4 (4.6)	9 (10.2)	3 (3.8)	16 (6.3)	0.173
AT	193	170	212	575	
Transfused patients (%)	12 (6.2)	12 (7.1)	17 (8)	41 (7.1)	0.780
THR[#]	8 (7.5)	4 (4.3)	13 (10.5)	25 (7.8)	0.248
TKR[#]	4 (4.6)	8 (10.3)	4 (4.5)	16 (6.3)	0.230

ITT, intention-to-treat; THR, total hip replacement; TKR, total knee replacement; AT, as treated.
[$] Pearson Chi-square
[*] calculated from 322 THR (103, 103, 116 for respectively group A, B, C) and 253 TKR patients (87, 88, 78 for respectively group A, B, C).
[#] calculated from 322 THR (106, 92, 124 for respectively group A, B, C) and 253 TKR patients (87, 78, 88 for respectively group A, B, C).

Patients who required an allogeneic transfusion had significantly different pre-operative Hb levels compared with the non-transfused patients (p<0.001, independent samples t-test; 95% confidence interval (CI): 1.08 to 1.86 g/dL). The mean pre-operative Hb value in the transfused group was 12.8 g/dL (9.8 to 15.5 g/dL) *versus* 14.3 g/dL (9.8 to 15.5 g/dL) in the non-transfused group. The mean Hb level increased from 8.3 g/dL (6.3 to 9.8 g/dL) before transfusion to 10.3 g/dL (8.4 to 12.2 g/dL) after allogeneic transfusions. The evaluation whether those allogenic transfusions were justifiable, showed that in 15 of the 41 (37%) transfusions were probably incorrect based on the pre-study defined criteria. The distribution between group A, B and C was six, five and four patients, respectively.

The length of hospital stay was similar between all groups (p=0.15; Kruskal-Wallis test) with a median of four days (three nights) (IQR group A and B: 4 to 6 and IQR group C: 4 to 5). The median intra-operative blood loss in THR patients was 350 mL (IQR: 250 to 500 mL), with no differences between the groups (p=0.095; Kruskal-Wallis test).

A total of 385 patients were randomised for post-operative autologous re-infusion. Due to insufficient shed blood collection (<80 mL, n=38) or problems with the Bellovac ABT System (n=4), 42 patients (11%) did not receive autologous blood reinfusion. The median amount of re-infused autologous blood was 350 mL (IQR: 200 to 500 mL). The volume of autologous blood re-infused between procedures was: THR median 280 mL (IQR: 150 to 400 mL), TKR median 500 mL (IQR: 350 to 650 mL), which was significantly different (p<0.001; Mann-Whitney U test) between the two joint types.

Table 4 All adverse events

	Group A	Group B	Group C
N	190	191	194
Systemic complications - major	14*	14*	10
Acute renal failure	1	1	-
Hypotensive crisis	1	-	1
Deep (THR / TKR) infection†	4	5	2
Myocardial infarction	1	-	-
Pulmonary embolus	1	2	1
Tachyarrhythmia	6	5	6
Transient ischemic attack	-	1	-
Systemic complications - minor	14‡	24‡	25‡
Anaemia	7	11	8
Deep venous thrombosis	1	-	2
Mental status change	2	2	4
Pneumonia	-	2	2
Urinary problems	3	4	2
Others	1	5	7
Local complications - major	5	6	1
Dislocation§	4	4	-
Peripheral nerve injury	1	2	1
Local complications - minor	19	18**	22
Drain hole oozing	na	4	4
Haematoma	2	-	2
Persistent wound drainage	9	5	6
Skin blisters	6	3	6
Superficial wound infection	1	3	1
Others	1	3	3

NA, not applicable; THR, total hip replacement; TKR, total knee replacement.
* one patient in group A and two patients in group B with a double adverse event in this category.
†all patients underwent debridement for infection.
‡ There was one patient (group A) and two patients (group B and C) that had a double adverse event in this category. One patient in group B had three adverse events in this category.
§ two patients had two dislocations within six weeks, one patient underwent revision surgery for recurrent dislocation within these six weeks.
** one patient in group B had a double adverse event in this category.

Within the first six post-operative weeks of the study period, 147 (26%) patients (91 hips and 56 knees) presented with a total of 172 adverse events; three patients had three adverse events and 18 patients had two adverse events (Table 4). Of these, 13 patients had a re-operation on the THR or TKR surgical site. In 12 patients a debridement due to deep wound infection was carried out. One patient underwent revision surgery for recurrent

dislocations of her THR. Of the adverse events 22 patients were re-admitted to the hospital, which included the 13 re-operated patients. The other seven patients were re-admitted for observation of an adverse event.

DISCUSSION

Only 41 (7%) patients received an allogeneic transfusion with no differences between the re-infusion and control groups in either THRs or TKRs. Post-operative Hb values, length of hospital stay and adverse events were comparable between the three groups. It appeared that the Bellovac ABT System had no effect on these outcome variables.

Previous studies have only compared closed suction drainage with no drainage in THR.[19] Our allogeneic blood transfusion rates were between 6% and 8% in all groups and considerably lower than in most other studies.[9-11] The low allogeneic blood transfusion rate could possibly be explained by the fact that both centres have applied a strict modern transfusion regime for several years.[5] Although the current study was powered on the assumption of higher transfusion rates, the actual transfusion rate did not differ between the three groups. A larger sample size might detect a smaller difference in transfusion rate, but this would probably not be clinically relevant.

The need for ABT drains in total joint replacement has been repeatedly questioned. Our data are supported by other studies but neither had a control group where no drainage is used.[9,10] Only one study compared ABT drainage and re-infusion with closed suction drainage or with no drainage.[20] The strength of that study was the inclusion of only uncemented THRs operated through one approach (direct anterior). A major limitation, however, was that their primary endpoint of the difference between pre- and post-operative Hb values did not take into account the treatment differences such as allogeneic blood transfusion post-surgery and the drains in that study were in situ for 48 hours.

Other studies on ABT drains found an allogeneic transfusion reduction ranging from 40% in favour of no drainage to 86% in favour of the autologous drain groups.[10,12,15,21] These studies were relatively small with 20 to 80 patients in each group looking at either one or both of THRs and TKRs.

Most reports on blood management trials state the protocol used for allogeneic blood transfusion decisions. However, the issue of whether the patients were symptomatic or not make it difficult to interpret the significance of the allogeneic blood transfusion volumes given. Our secondary outcome measures, such as length of hospital stay and amount of re-infused autologous blood, showed no differences as with other studies.[4,11,12]

Our study has some limitations. Erythropoietin was used in only one of the participating hospitals and could have a possible impact. Pre-operative Hb levels are known to be of significance when dealing with transfusions in the post-operative phase.[22] In all, 17 patients (3%) of the study population received erythropoietin. This was 15% of eligible erythropoietin patients. It is noteworthy that five patients with pre-operative erythropoietin usage still had Hb level below 12.9 g/dL at surgery, but none of these patients received an allogeneic blood transfusion.

Our study was also limited in that the decision whether or not to use allogeneic transfusions was not blinded. After evaluating the decision to transfuse, on basis of pre-transfusion Hb, comorbidity, Hb increase after transfusion and the day of transfusion, in 15 of the 41 patients the allogeneic blood transfusion was of questionable value. However, this was only based on retrospective evaluation of the medical data, which could not identify any patient who justifiably received blood. If the strict transfusion rules were followed the 7.1% transfusion rate could theoretically be lowered to 4.5%.

Finally, 25 (4%) of the patients did not receive the treatment as randomised. This was mainly because the standard hospital protocol before the study started called for the drain to be left in situ for 24 hours. Twenty-one cases had the drain *in situ* for 24 hours. In the other four patients, three patients received no drain and one patient had a drain in situ for 6 hours instead of 24 hours.

This large study has demonstrated that ABT drains have no beneficial effect on the post-operative transfusion requirements in THR and TKR in hospitals with a restrictive transfusion protocol.

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Chapter 8

Limit Allogeneic Blood Use with Routine Re-use of Patient's Own Blood: A Prospective, Randomized, Controlled Trial in Total Hip Surgery

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ABSTRACT

There are risks related to blood incompatibility and blood-borne diseases when using allogeneic blood transfusion. Several alternatives exist today, one of which, used for autologous blood salvage perioperatively, is the Sangvia Blood Management System. This study was designed to investigate the efficacy of the system and to add data to previously reported safety results.

Two hundred sixteen patients undergoing primary or revision total hip arthroplasty (THA) were enrolled in this randomized, controlled, assessor-blinded multicenter study. Randomization was either autologous blood transfusion (Sangvia group) or no use of autologous blood (Control group), both in combination with a transfusion protocol for allogeneic transfusion. Patients were followed during hospital stay and at two months after discharge. The primary outcome was allogeneic blood transfusion frequency. Data on blood loss, postoperative hemoglobin/hematocrit, safety and quality of life were also collected. The effectiveness analysis including all patients showed an allogeneic blood transfusion rate of 14% in both groups. The efficacy analysis included 197 patients and showed a transfusion rate of 9% in the Sangvia group as compared to 13% in the Control group (95%CI -0.05-0.12, p=0.502). A mean of 522 mL autologous blood was returned in the Sangvia group and lower calculated blood loss was seen 1095 mL vs 1285 mL in the Control group (95%CI 31-346, p=0.018). No differences in postoperative hemoglobin was detected but a lower hematocrit reduction after surgery was seen among patients receiving autologous blood. No relevant differences were found for safety parameters or quality of life.

General low use of allogeneic blood in THA is seen in the current study of the Sangvia system used together with a transfusion protocol. The trial setting is underpowered due to premature termination and therefore not able to verify efficacy for the system itself but contributes with descriptive data on safety.

Trial registration

Clinicaltrials.gov NCT00822588

INTRODUCTION

In major orthopedic procedures, there is considerable blood loss during and after surgery which causes acute postoperative anemia and often leads to a rising need for allogeneic blood transfusions. Allogeneic blood transfusion is not a risk-free therapy, as it is associated with potential risks of matching errors, down-modulation of the immune system, increased infection rate, absence of clotting factors and transmission of infectious diseases, which may result in poorer postoperative outcomes and higher mortality.[1-8] In addition, some patients refuse to have an allogeneic blood transfusion for religious reasons and allogeneic blood is a limited and increasingly expensive resource.[9] To minimize these disadvantages, a variety of alternative interventions has been developed to reduce the need for allogeneic transfusions. These interventions are generally either agents to diminish blood loss (e.g. tranexamic acid), agents that promote red blood cell production (e.g. erythropoietin) or techniques for re-infusing the patient's own blood (e.g. cell salvage).[10-16] A systematic review of previously studied cell salvage systems suggested that their use is efficacious in reducing the need for allogeneic transfusion in cardiac and orthopaedic surgery even though it concluded that the methodology was poor.[17]

Both 'filtered' and 'washed' cell salvage systems are commonly used and known contraindications are mainly related to the quality of the collected blood. While it is known that salvaged blood is laden with complement split products, interleukins, various inflammatory mediators and fat particles the clinical implication of these factors is not clear.[18-21]

This study was designed to evaluate the clinical efficacy of a new device for cell salvage, i.e. the Sangvia™ Blood Management System (Astra Tech AB, Mölndal, Sweden), by using a scientifically sound research methodology. The study was also done to further investigate the safety aspect of 'filtered' cell salvage and to confirm previously reported safety findings for this new device for cell salvage.[20,21]

METHODS

This was an international multicenter, prospective, assessor-blinded, randomized, controlled trial with an adaptive statistical study design. Six European hospitals were involved, located in The Netherlands (three clinics), Spain, Norway and Austria. The protocol for this trial and supporting CONSORT checklist are available as supporting information; see CONSORT checklist S1 and Study protocol S2.

Participants

For inclusion in the study, patients had to be scheduled for primary or revision total hip arthroplasty and be classified as American Society of Anesthesiology (ASA) class I, II or III. The following criteria excluded the patients from participation in the study: Exclusion due to ethical concern included previous randomization in this study, involvement in the planning and/or conduct of this study, and participation in an interfering study. Exclusion due to safety concerns included current symptoms of hemophilia and contraindications for autologous blood use, i.e. hyperkalaemia, current systemic infection or local infection in the operation field or impaired renal function (elevated creatinine/clearance levels), known malignancy in the last five years and expected use of cytotoxic drugs. Exclusion due to expected impact on outcome included untreated anemia (hemoglobin (Hb) level <11 g/dL), revision total hip arthroplasties with expected serious bone grafting, and use of other alternatives for blood conservation such as recombinant erythropoietin, fibrin sealant, aprotinin and other autologous blood transfusion.

Use of tranexamic acid was allowed if routinely used in the individual clinic and thus equally distributed between the treatment groups. The decision for tranexamic acid use had to be made before randomization.

Ethics

Written informed consent was obtained from all participating patients. The study was approved by applicable local ethics committees before its initiation and was conducted in accordance with the Declaration of Helsinki, ICH/Good Clinical Practice, and regulatory requirements. The following ethics committees approved the study: Medisch-ethische commissie at Onze lieve vrouwe gasthuis (reference WO 09.033), METC Zuidwest Holland (reference 09-031), Medisch Centrum Haaglanden (reference RVB/RZ/1444), Reinier de Graaf Groep (reference CZ/CS/2009-086), CEIC-IMAS (reference YA-DRA-0001, version 2.0, date 12/01/2009), Det medisinske fakultet Regional komite for medisinsk og helsefaglig forskningsetikk Helseregion Midt-Norge (reference 4.2009.421), Ethik-kommission der Medizinischen Universität Wien und des Allgemeinen Krankenhauses Der stadt Wien AKH (reference 011/2009).

Interventions

Prior surgery patients scheduled for primary or revision total hip arthroplasty (THA) were randomized to receive either autologous blood transfusion (Sangvia group) or no use of autologous blood (Control group) in combination with using a transfusion protocol

limiting allogeneic blood transfusions to patients with hemoglobin (Hb) values below 8.5 g/dL or significant clinical symptoms of anemia. Surgery was performed by orthopedic surgeons following their routine procedures. The Sangvia group used the Sangvia™ Blood Management System (Astra Tech AB, Mölndal, Sweden) for surgery. The system was used according to the manufacturer's instructions for both intra-operative and postoperative autologous blood collection and transfusion. Details about the system are published in Kvarström et al. and Stachura et al.[20,21] Postoperative drains were used in both groups to standardize postoperative routines and minimize differences between the two treatment groups, i.e. the Sangvia drain for postoperative autologous blood collection and transfusion in the Sangvia group and a regular postoperative low-vacuum drain (Bellovac™, Astra Tech AB, Mölndal, Sweden) in the Control group. Both drainage systems were used until the first postoperative morning. Before patient recruitment started ten systems were used to train operating room staff at each of the study sites.

Rehabilitation followed the standard procedure at each specific hospital.

Outcomes

The primary outcome measure was allogeneic blood transfusion frequency, given as a relative percentage, and measured at the day of discharge. Allogeneic blood transfusions were also described by the number of transfusion decisions taken for a patient, the transfusion volume and the calculated transfusion index (total number of units per transfused patient).

Secondary outcome measures included blood loss, postoperative Hb and hematocrit (Hct), safety and quality of life. The intra-operative blood loss was estimated by the surgeon by evaluating intra-operative cell saving volumes, waste suction volumes and weighing gauzes. The research assistant estimated blood loss after surgery based on drain volumes. The sum of intra- and postoperative blood loss represents the total value of estimated blood loss. In addition to the estimated values, blood loss was calculated on the basis of blood volume and Hct values, i.e. calculated blood loss (mL) = [Total blood volume (mL) x ($Hct_{pre\text{-}op} - Hct_{post\text{-}op}$)] / [($Hct_{pre\text{-}op} + Hct_{post\text{-}op}$)/2]. Total blood volume was calculated in liters by the formula (0.3669 x height (m^3)) + (0.03219 x weight (kg)) + 0.6041 for men and (0.3561 x height (m^3)) + (0.03308 x weight (kg)) + 0.1833 for women.[22,23]

Safety data included vital signs (heart rate, blood pressure, temperature), laboratory variables (potassium, sodium, creatinine and Glomerular Filtration Rate) and adverse events classified by severity and causality. Quality of life was assessed by the EuroQol (EQ-5D) health status questionnaire.[24,25] All patients were followed during surgery and their

hospital stay with outcome measures collected pre-operatively, at three hours, on one, two and four days after surgery, and on the day of discharge. A final check-up to fill out the EQ-5D questionnaire was done two months after surgery.

Sample size

The study used an adaptive statistical design where a preplanned interim analysis on half of the population was done to confirm or reject sample size estimations. The null hypothesis tested for rejection was if the allogeneic transfusion frequency was equal in the Sangvia and in the Control group. The initial sample size calculation (power 90%, 5% two-sided level of significance) was based on the literature and normal use of allogeneic blood in the Control group was estimated to be 21%.[13,26-28] The expected value for transfusion frequency in the Sangvia group was estimated to be around 7% based on an expected added value to previous reported findings from postoperative autologous systems.[13] The sample size necessary for detection of the expected difference in transfusion frequency was calculated to be 260 patients.[29] A further 40 patients were planned to be included to adjust for non-evaluable patients or drop-outs.

Randomization

Eligible patients were consecutively randomized to receive either autologous blood transfusion, by the Sangvia™ Blood Management System (Sangvia group), or to no use of autologous blood (Control group).

Treatment allocation was stratified by hospital and type of surgery, i.e. primary or revision arthroplasty. For randomization a block size of 4 and allocation distribution 1:1 were used. For each hospital, a separate randomization list was generated by a computer and implemented in a web-based login system. The randomization plan and generated list were only known to study personnel not involved in clinical procedures.

The principal investigator/study coordinator randomized the patients as close as possible prior to surgery in the web-based login system. In the majority of cases this was an investigator not involved in surgery. Each patient's actual randomization was checked against the randomization list, inclusion date, surgery date and demographical data to ensure correct implementation and strict consecutive allocation.

Blinding

To mitigate the risk of bias, the decision for allogeneic blood transfusion was taken on the basis of a transfusion trigger, a Hb value $\leq$8.5 g/dL, by an assessor unaware of the

treatment group. The majority of the clinics used a representative from the blood bank for the decision. In acute situations, i.e. during surgery, the decision had to be taken by the surgeon/anesthesiologist who was aware of the treatment allocation. For all transfusions, indication was registered and for allogeneic blood transfusions with Hb values above 8.5 g/dL, the requirement was for the patient to have clinical symptoms, i.e. signs of anemia, such as tachycardia and/or hypotension. Secondary outcome measures were collected prospectively and analyzed as applicable by independent laboratory personnel unaware of the treatment allocation. Clinical variables such as vital signs, evaluated by personnel in contact with the patient, could not be blinded during the first postoperative day due to the differences in drains used in the Sangvia and Control groups.

Statistical methods

Analyses were made on both an Intention To Treat (ITT) and a Per Protocol (PP) principle. Demographic and baseline data were based on the results from the ITT procedure. Conclusions related to effectiveness were explored by using the ITT analysis set, and those related to efficacy were based on the results in the PP analysis set. Conclusions related to safety and quality of life were also based on the ITT analysis set. The risk for variability due to the multicenter study design, with for example differences in routines for hospital stay and discharge, was mitigated by use of stratification. Thus the results of the statistical analyses do not present data for each individual clinic.

The Fisher Exact test was used to test frequencies of dichotomous response variables. The non-parametric Wilcoxon Rank Sum rank test was used to analyze differences in continuous response variables between the treatment groups. *P*-values ≤ 0.05 were considered statistically significant. In addition, 95% confidence intervals (CI) were calculated based on independent sample *t*-test (equal variances assumed) and presented for comparative data. No correction for multiplicity was made since hypotheses were considered statistically independent.

Tables with descriptive data were generated and hypotheses tested using statistical software PASW Statistics version 18.0 (IBM® SPSS® Statistics).

RESULTS

Participant flow

The pre-planned interim analysis was performed in 135 patients, 66 in the Sangvia group and 69 in the Control group, and concluded that the transfusion rate in the Control group was 12% instead of the expected 21%. Accordingly, the study was at risk of being underpowered and inconclusive and was prematurely stopped. This resulted in 227 enrolled patients instead of the planned 300. Randomization was done before surgery, and thus all enrolled patients were randomized. Some of the exclusion criteria could only be completely verified after randomization just before, during or after surgery, e.g. local infection in the operation field. Only limited demographical and no follow up data were collected for patients for whom exclusion criteria were identified after randomization but before surgery. Of the 227 patients, this was applicable in 11 patients who were excluded due to withdrawn consent (five patients), exclusion criteria fulfilled (two patients with an ongoing local infection, one patient with a missing creatinine value) and three patients whose surgery was rescheduled after the study was prematurely discontinued. These patients were registered and are presented in Figure 1 but are not represented in any of the analyses due to lacking data. Thus, treatment was allocated and data were collected from a total of 216 patients (ITT analysis), 106 in the Sangvia group and 110 in the Control group. Major protocol deviations were detected in some patients after treatment, and for that reason two analysis sets were identified, i.e. ITT and PP (Figure 1). Although it is recognized that the ITT analysis set should include all patients intended for treatment the actual ITT analysis set in this study was limited to all treated patients due to missing follow-up data for patients excluded before treatment allocation. The PP analysis set excluded 19 patients for whom major protocol deviations were detected. Ten patients were excluded from the PP analysis in the Sangvia group; other autologous blood devices were used by mistake in four cases, erythropoietin was given by mistake in one case, a preoperatively creatinine level outside the normal range was detected late for one case and no treatment was given due to technical and management difficulties in four cases. Nine patients were excluded from the PP analysis in the Control group; other autologous blood was given by mistake in five cases, preoperatively creatinine level outside normal range was detected late for one case, a preoperatively Hb level below the exclusion criteria was detected late for one case, a history of malignancy was detected late for one case and incorrect treatment allocation was used by mistake in one case, i.e. Sangvia was used. The PP analysis consisted of 197 patients, 96 in the Sangvia group and 101 in the Control group.

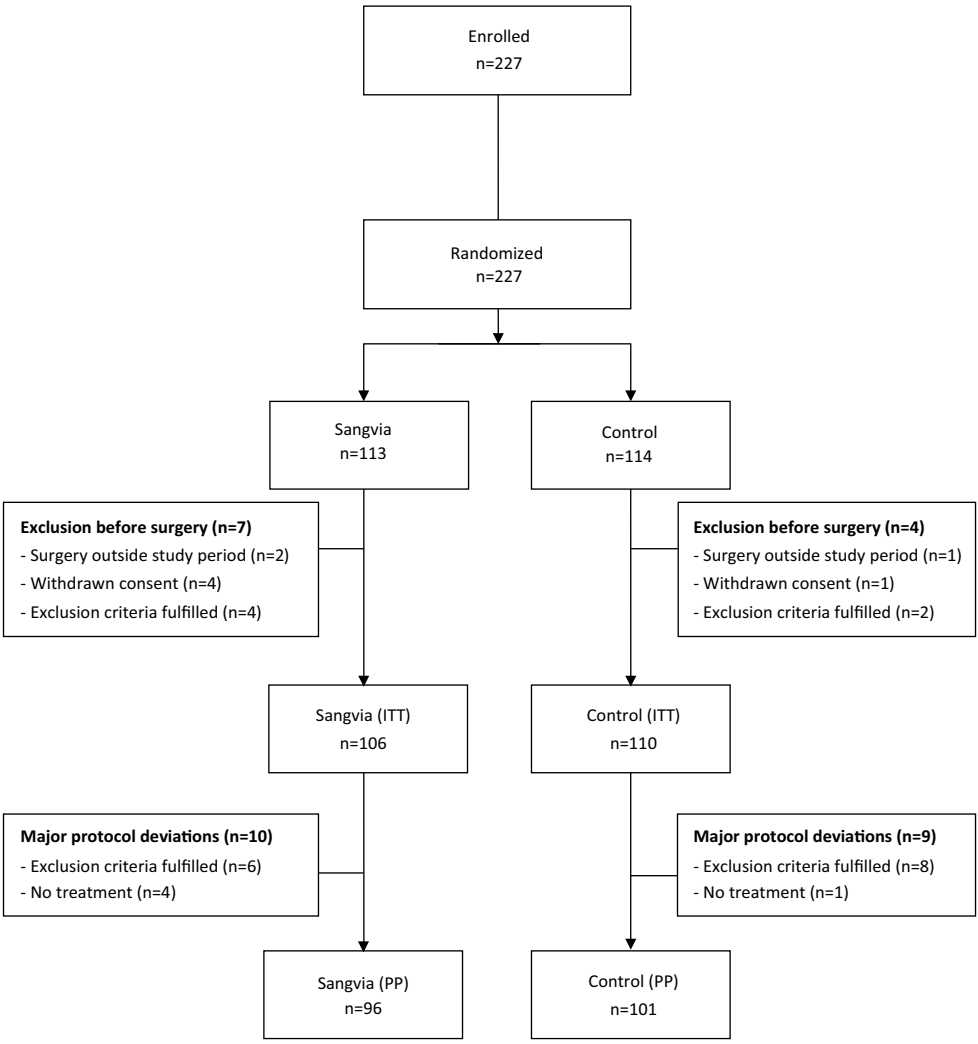

Figure 1 Study patient flow and definition of analysis sets

Recruitment

Patients were enrolled in the study between May 2009 and April 2010. The last patient completed the trial in May 2010.

Table 1 Patients characteristics

		Sangvia	Control	*p*-value[1]
	N	106	110	
Age (years)	Mean (SD)	67 (11)	65 (12)	0.163
BMI	Mean (SD)	27.3 (4.6)	27.5 (4.6)	0.509
Sex n (%)	Female	76 (72)	70 (64)	
	Male	30 (28)	40 (36)	0.245
ASA n (%)	I	28 (26)	31 (28)	
	II	59 (56)	66 (60)	
	III	19 (18)	13 (12)	0.402
Surgery n (%)	Primary	100 (94)	104 (95)	
	Revision	6 (6)	6 (6)	1.000
Anesthesia n (%)	Spinal	63 (60)	63 (57)	
	General	40 (38)	42 (38)	
	Combined	2 (2)	5(5)	0.826
Pre-op Hb (g/dL)	Mean (SD)	13.87 (1.16)	13.98 (1.16)	0.474
Pre-op Hct (%)	Mean (SD)	41 (4)	42 (3)	0.346

BMI = Body Mass Index

[1]Mann-Whitney U/Wilcoxon rank sum test: Exact Sig. (2-tailed) was used to give an indication of the size of chance imbalances between the treatment groups.

Baseline data

The study population was found to be homogeneous with a mean age of 66 years old, BMI of 27.4 and a majority (68%) of female patients of ASA class I (27%) or II (58%). Patient characteristics seemed to be similar in the Sangvia and Control groups (Table 1). One clinic routinely used tranexamic acid, five patients received it, two in the Control group and three in the Sangvia group. All except four patients in the Sangvia group received autologous blood transfusion, collected either intra-operatively and/or postoperatively, and a mean of 522 mL was transfused (PP analysis).

Outcomes and estimation

Primary outcome

The ITT analysis showed a generally low allogeneic blood transfusion frequency of 14% in both groups (95% CI -0.09-0.10, *p*=1.00) and efficacy was studied in the PP analysis where nine of 96 (9%) patients needed an allogeneic blood transfusion in the Sangvia group and 13 of 101 (13%) in the Control group. The 4% difference between the groups was not statistically significant (95% CI -0.05-0.12, *p*=0.502), the power for detecting it was 14%. A total of 15 transfusion decisions were taken for the nine patients transfused in the Sangvia group and 26 for the 13 patients transfused in the Control group (PP analysis). The transfusion volume among the patients receiving allogeneic blood was 756 mL (2.3 units), transfusion index =2.33 in the Sangvia group and 856 mL (2.5 units), transfusion index =2.54 in the Control group (PP analysis). Corresponding values from the ITT analysis were 24 transfusion decisions for 15 patients transfused, 735 mL (2.3 units) and transfusion index =2.33 in the Sangvia group and 29 transfusion decisions for 15 patients transfused, 834 mL (2.6 units), transfusion index =2.60 in the Control group. None of the differences measured were found to be statistically significant. Of the 30 patients that were transfused (53 transfusions), only 4 patients (5 transfusions) underwent revision surgery. Five transfusions were given during surgery without a known Hb value. For 28 transfusions the transfusion trigger of ≤8.5 g/dL was reached. The other 20 transfusions were given based on clinical symptoms. The transfusion percentage per center showed a large variance, ranging from 4% to 52% (4%, 9%, 11% twice, 20%, 52%).

Table 2 Estimated and calculated blood loss per treatment group

		Sangvia	Control	95% CI, *p*-value[1]
ITT analysis set				
Estimated blood loss (mL)				
Intra-operative	Mean (SD)	479 (329)	517 (305)	-124-48, 0.239
Postoperative 0-6h	Mean (SD)	305 (188)	*292 (182)*	-40-66, 0.696
Postoperative 6-24h	Mean (SD)	*220 (126)*	*212 (171)*	-36-52, 0.186
Total	Mean (SD)	*931 (486)*	*927 (431)*	-119-127, 0.947
PP analysis set				
Calculated blood loss (mL)				
3 hours after surgery	Mean (SD)	*923 (407)*	*952 (419)*	-147-89, 0.667
Postoperative day 1	Mean (SD)	1104 (418)	*1140 (449)*	-159-87, 0.385
Postoperative day 2	Mean (SD)	*1145 (436)*	*1296 (500)*	17-285, 0.063
Postoperative day 4	Mean (SD)	1095 (480)	*1285 (562)*	31-349, 0.0175

[1]Mann-Whitney U/Wilcoxon rank sum test: Exact Sig. (2-tailed), 95% CI based on independent sample t-test, equal variances assumed.

Secondary outcomes

The results of the estimated and calculated blood loss are presented in Table 2. The PP analysis showed that the total estimated blood loss was 914 mL in the Sangvia group and 921 mL in the Control group (95% CI -31-117, p=0.879). Corresponding values from the ITT analysis were 931 mL in the Sangvia group and 927 mL in the Control group (95% CI -119-127, p=0.947). A smaller calculated blood loss was seen in the Sangvia group at days 2 and 4 compared to the Control group (PP analysis); 1145 mL vs. 1296 mL on day 2 (95% CI 17-285, p=0.063) and 1095 mL vs. 1285 mL on day 4 (95% CI 31-349, p=0.018). No early differences were seen at three hours (923 mL vs. 952 mL, 95% CI -147-89, p=0.667) or at day 1 (1104 mL vs. 1140 mL, 95% CI -159-87, p=0.385) after surgery. Corresponding values from the ITT analysis were 935 mL vs. 970 mL three hours after surgery (95% CI -155-85, p=0.251), 1081 mL vs. 1160 mL on day 1 (95% CI -199-41, p=0.066), 1148 mL vs. 1311 mL on day 2 (95% CI 36-290, p=0.013) and 1104 mL vs. 1284 mL on day 4 (95% CI 26-334, p=0.009).

The Hb and Hct values are presented in Table 3 as relative change from screening (PP analysis). For the Hb values, lower reduction was seen in the Sangvia group but no statistically significant differences were detected in a comparison of the two treatment groups. Corresponding values from the ITT analysis set were 2.53 g/dL vs. 2.58 g/dL at three hours (95% CI -0.35-0.25, p=0.963), 3.03 g/dL vs. 3.14 g/dL at day 1 (95% CI -0.40-0.18,

p=0.322), 3.13 g/dL vs. 3.41 g/dL at day 2 (95% CI -0.57-0.01, *p*=0.074) and 3.05 g/dL vs. 3.30 g/dL at day 4 (95% CI -0.60-0.10, *p*=0.123).

Regarding the change in Hct percentages, the reduction in the Sangvia group was significantly lower than in the Control group on day 4 (95% CI -2-0, *p*=0.02). Corresponding values from the ITT analysis set were 8% vs. 8% at three hours (95% CI -1-1, *p*=0.996), 9% vs. 9% at day 1 (95% CI -1-1, *p*=0.337), 9% vs. 10% at day 2 (95% CI -2-0, *p*=0.068) and 9% vs. 10% at day 4 (95% CI -2-0, *p*=0.017).

Table 3 Hb and Hct change from screening per treatment group (PP analysis set)

		Sangvia	Control	95% CI, *p*-value[1]
Hb (g/dL)				
3 h after surgery	Mean (SD)	2.53 (0.98)	2.54 (1.12)	-0.31-029, 0.735
1 day after surgery	Mean (SD)	3.11 (1.04)	3.10 (1.11)	-0.29-0.31, 0.809
2 days after surgery	Mean (SD)	*3.14 (1.06)*	3.38 (1.06)	-0.54-0.06, 0.130
4 days after surgery	Mean (SD)	*3.06 (1.16)*	*3.31 (1.22)*	-0.61-0.11, 0.141
Hct (%)				
3 h after surgery	Mean (SD)	8 (3)	8 (3)	-1-1, 0.687
1 day after surgery	Mean (SD)	9 (3)	9 (4)	-1-1, 0.802
2 days after surgery	Mean (SD)	9 (3)	10 (4)	-2-0, 0.140
4 days after surgery	Mean (SD)	9 (4)	10 (4)	-2-0, 0.021

[1]Mann-Whitney U/Wilcoxon rank sum test: Exact Sig. (2-tailed), 95% CI based on independent sample *t*-test, equal variances assumed.

Laboratory parameters and vital signs showed no differences in overall heart rate and temperature between the two treatment groups at any time point (ITT analysis). The blood pressure measurements however indicated that there was a smaller reduction in blood pressure during surgery in patients in the Sangvia group, i.e. difference of 8 mmHg in systolic blood pressure (95% CI 4-12, *p*=0.005*)* and 6 mmHg in diastolic blood pressure (95% CI 3-9, *p*=0.001*)*, as compared to the Control group (ITT analysis). The difference in diastolic blood pressure also seemed to persist on day 1 (difference 3 mmHg: 95% CI 0-6, *p*=0.027), day 2 (difference 5 mmHg: 95% CI 1-9, *p*=0.009), day 3 (difference 6 mmHg: 95% CI 2-10, *p*=0.005) and day 4 (difference 8 mmHg, 95% CI 3-13, *p*=0.001) after surgery (ITT analysis). All mean/median values for sodium, potassium, creatinine and Glomerular Filtration Rate were within normal reference intervals of 135-145 mmol/L, 3.5-5.0 mmol/L, 62-95 µmol/L and 55-134 mL/min/1.73m^2, respectively, and no differences were detected between the groups at any time point (ITT/PP analysis).

The assessment with the EQ-5D questionnaire showed an expected general improvement in mobility, self-care, usual activity, pain and anxiety in both groups (ITT analysis). After two months, problems in mobility, self-care, usual activity, pain and anxiety were reported for 48%, 28%, 38% 46% and 10%, respectively, in the Sangvia group and for 52%, 27%, 54%, 47% and 10%, respectively, in the Control group. The median general improvement in health status was from 70 to 80 on the Visual Analogue Scale (VAS) in both groups.

Adverse events

Forty-three of 106 (41%) patients in the Sangvia group and 46 of 110 (42%) patients in the Control group had one or more adverse events (difference 1%: 95% CI -0.14-0.12, p=0.891), leading to a total of 141 adverse events. The numbers of patients with one, two or three reported adverse events were coded and are compared in Table 4. Twelve patients (11%) in the Sangvia group reported 14 adverse events that were classified as either possibly or probably/definitely device related. The following adverse events were classified as possibly related: 1x anaemia, 2x headache/vertigo/nausea, 2 x pain during transfusion, 2x seroma, 2x wound leakage, 1x wound swelling, 1x hematuria, 1x saturation depression and 1x high heart beat. In addition, one reported wound leakage was classified as probably/definitely device related.

Seven serious adverse events occurred in both groups (difference 1%, 95% CI -0.06-0.07, p=1.00). One patient in the Control group died 13 days after surgery. All other events were serious due to prolongation of hospitalization. Table 5 list all serious adverse events per treatment group collected in the study. To further explore the correlation between adverse events and autologous blood transfusion special attention was paid to reported adverse events among patients with the highest transfusion volumes in the Sangvia group (i.e. 75% percentile, representing transfusion volume >669 mL). These are listed in Table 6. One reported serious adverse event (i.e. vasovagal episode) was found in one patient with a total transfusion volume of 700 mL. No indications were otherwise seen of more severe adverse events with increasing transfusion volume.

Table 4 All (serious) adverse events coded according to WHO-ART

		Sangvia	Control
	N	106	110
Adverse events per system-organ class[1]	**N events**		
Skin and appendages disorders	1	1	1
Musculo-skeletal system disorders	1	3	1
Central & peripheral nervous system disorders[2]	1	7	1
	2	1	0
Psychiatric disorders	1	1	3
Gastro-intestinal system disorders	1	8	7
	2	4	3
Metabolic and nutritional disorders	1	3	0
Cardiovascular disorders, general	1	4	9
Heart rate and rhythm disorders	1	3	2
Respiratory system disorders	1	3	2
Red blood cell disorders	1	2	3
Platelet, bleeding and clotting disorders	1	0	1
Urinary system disorders	1	3	3
Body as a whole - general disorders[3, 4]	1	13	18
	2	4	1
	3	1	1
Resistance mechanism disorders	1	3	4

Number of patients with 1, 2 or 3 reported adverse events per system organ class.

[1]System organ class according to WHO Adverse Reaction Terminology (WHO-ART) was used for coding by means of Primary System according to the Adverse Event Dictionary Version 029 (equivalent to MedDRA).

[2]Reported AEs were dizziness, headache, nausea, myoclonus, vertigo, restless legs, and needling sensation during transfusion.

[3]Body as a whole – general disorders include for example postoperative complications (e.g. wound seroma and/or redness and hip joint dislocation), peripheral edema, pain and death.

[4]There was one reported death in the Control group, which occurred 13 days after discharge.

Table 5 Reported serious[1] adverse events

Adverse event	Sangvia	Control
Cardiac insufficiency	1	0
Dehydration	1	0
Hip dislocation/luxation	1	1
Lung embolism	0	1
Paralytic ileus	1	0
Periprosthetic fissure (intra-op)	0	1
Saturation depression	1	0
Death	0	1
Infection hip	0	1
Suspected infection (positive bacterial culture)	1	0
Wound infection	0	1
Wound leakage	1	1
Total	7	7

[1]Serious definition according to ICH/Good Clinical Practice as any untoward and unintended response that results in death, is immediately life-threatening, requires in-subject hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital abnormality or birth defect or is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Table 6 Reported adverse events for Sangvia group with autologous transfusion volume > 669 mL[1]

Transfusion volume (mL) pp	Number of patients	Number of AEs per patient	AE specification
675	1	0	
700	4	0	
700	2	1	Needling stings in skin during blood transfusion Delirium
700	1	2	Nausea Vomiting
700	1	4	Anterior cortical femur fracture Dizziness and light-headedness Hip dislocation Vasovagal episode
725	1	0	
750	1	0	
750	1	1	Leg pain 3 weeks after surgery
800	1	0	
825	1	0	
850	1	3	Oedema of scrotum and both legs Seroma Three small wounds (1x1 cm), circulatory disorder
900	2	0	
950	2	0	
1000	1	0	
1050	2	1	Pain in the leg Anaemia bleeding
1050	1	3	Headache and nausea Vertigo and nausea Vomiting
1300	1	0	
1400	1	2	Abscess perianal with purulent secretion Seroma
2720	1	3	Hematuria Muscle cramp in upper thigh Wound leakage

[1]The Sangvia transfusion volume was divided by percentile, i.e. 25% = 306 mL, 50% = 475 mL and 75% = 669 mL.

DISCUSSION

Interpretation

In our assessor–blinded, randomized, controlled, parallel-group trial that included 216 patients, a low use of allogeneic blood was seen when the Sangvia Blood Management System was used together with a transfusion protocol. The trial setting was not able to verify efficacy with regards to allogeneic transfusion frequency for the system itself, but a lower calculated blood loss and lower hematocrit reduction was seen four days after surgery among patients receiving autologous blood. The study contributes descriptive data on safety, and no safety issues were discovered with the use of the new device. Further large-scale, randomized, controlled trials are warranted to continue to investigate the safety and efficacy of the device.

Carless et al. conducted a systematic review to investigate the effectiveness of cell salvage in orthopedic, cardiac and vascular surgery.[17] Overall, the findings showed that cell salvage reduces the need for transfusions of donated blood in cardiac and orthopedic surgery. These conclusions were drawn with the remark that the methodological quality of the trials was poor and that the findings may be biased in favor of cell salvage.[17] This is why large trials of high methodological quality that assess the relative effectiveness, safety and cost-effectiveness of cell salvage are necessary. Although the quality of the current study design was strengthened by using an independent and blinded transfusion trigger assessor, we cannot rule out potential bias as allogeneic transfusions were also allowed for clinical symptoms and transfusion decisions were taken by clinicians aware of treatment allocation in acute situations during surgery. Blinding is a cornerstone of therapeutic assessment to mitigate the risk of bias and previous studies have shown larger treatment effects in cases of un-blinded endpoint assessment.[30] However, blinding patients, care providers and outcome assessors is difficult to achieve when surgery techniques are being studied, and unblinding may thus occur more often in such studies.[31] The results of the current study, based on blinded laboratory analyses, show some efficacy benefits with lower calculated blood loss and hemaocrit reduction, supporting the use of cell salvage. However, efficacy with regard to allogeneic blood transfusion needs to be further verified in a larger trial setting.

Our study seems to confirm previously reported safety results with the Sangvia Blood Management System and proposes that it might be safe to use in orthopedic surgery even though it is recognized that the study was not primarily powered for safety conclusions.[20,21] This speculation is based on the fact that laboratory variables collected for safety analysis

did not show any differences between the two groups and all stayed within the reference ranges, and that the majority of reported adverse events were non-severe. In addition, no general safety issues were raised when investigating reported adverse events and both treatment groups had very similar adverse event profiles, as shown in Table 4. Furthermore, no indications were seen of more severe adverse events with increasing transfusion volume when examining the adverse events reported from patients that received the highest transfusion volumes with Sangvia, as shown in Table 6.

Limitations and Generalizability

Our study is strengthened by using an independent and blinded transfusion trigger assessor. Blinding is a cornerstone of therapeutic assessment to mitigate the risk of bias. For instance, previous studies have shown larger treatment effects in cases of un-blinded endpoint assessment.[30] Blinding patients, care providers and outcome assessors when assessing a non-pharmacological trial is more difficult than in pharmacological trials, which is why blinding is not always appropriate and unblinding may occur more often.[31]

The primary limitation of the study relates to low power since an adaptive interim analysis concluded that the allogeneic transfusion rate in the Control group was much lower (12%) than the expected 21% and the study was prematurely discontinued. The results of the PP analysis showed a transfusion rate of 9% in the Sangvia group and 13% in the Control group, indicating a 4% difference between the groups (95% CI -0.05-0.12, p=0.502). This difference was not statistically verified, however, and the power for detecting it, if true, was only 14%. A new study, performed in the same trial setting and having the aim to detect a potential difference at the 4% level, with a power of 90% and a two-sided level of significance of 5%, would require at least 2572 patients. The ITT analysis did not indicate any differences in transfusion rate between the treatment groups (14% in both groups, 95% confidence interval -9-10, p=1.00). However, this analysis set should be used with care when drawing efficacy conclusions because it included patients with major protocol deviations (e.g. Sangvia was used in the Control group and epoetin alfa and other autologous blood transfusion were used with a potential impact on the need for allogeneic blood transfusion). As described in the participant flow in the results section it is worth to mention once again that the data presented in the ITT analysis was limited to all treated patients due to missing follow-up data for patients excluded before treatment allocation. It is recognized that this is not per definition a formal ITT analysis since it should include all patients intended for treatment, for our study that means also the ones that did not make it into the operating room. Thus, our study may have skewed results due to post-randomisation bias. This

illustrates the more complicated nature of surgical randomized trials and stresses the need for randomization as close as possible to the intervention or control treatment preventing this limitation in our study and subsequent difficulties in analysing the results using formal ITT analysis.

Accordingly, any potential differences in the efficacy of the intervention would be weakened and unlikely to be discovered in the ITT analysis set owing to the low power of the study. However, the ITT is interesting in exploring the effectiveness of the treatment, although it is difficult to relate to the reason why there are differences in the results of the ITT and PP analyses, i.e. they may either relate to poor treatment efficacy or poor treatment implementation.

The low allogeneic transfusion frequency found in the study affects the generalizability of the results. First, the literature refers to the use of transfusion trigger protocols in transfusion medicine but it is likely that this was used more strictly in the current clinical trial setting than in normal practice based on the facts that an assessor-blinded study design was used and allogeneic transfusion frequencies found in the literature were much higher than those observed in the study.[12,26] Second, the study population was homogeneous with regard to demographic and baseline variables but generally healthier than the expected target population of the study. For example, the patients were young (mean age of 66 years) and healthy (ASA class I in 27% of the cases) and very few revision hip arthroplasties were included (only 6%). The latter was prominent in one clinic that primarily included ASA class I patients with high pre-operative Hb levels since the epoetin alfa guideline at the hospital restricted the inclusion of patients with lower Hb levels. Third, there were some indications of selection bias toward uncomplicated surgery in the study. For example, no revision hip arthroplasties were included at one clinic. In summary, the present results were based on a population that was challenging in terms of studying efficacy improvements.

Further limitations of the study relate to the generalizability of the results. For instance, the inclusion and exclusion criteria regarding hemoglobin values were very strict, i.e. a Hb level above 11 g/dL and no use of epoetin alfa. The latter excluded patients with a pre-operative hemoglobin value between 11 g/dL and 13 g/dL in centers using a routine regimen of epoetin alfa. Salido et al. showed that pre-operative hemoglobin values have a predictive value for the need for allogeneic blood transfusions why it could be expected to be easier to detect efficacy differences in centers without implemented blood management programs.[32] Furthermore, some patients were excluded from the PP analysis as a result of poor protocol implementation, e.g. other autologous blood devices and erythropoietin were used by mistake. Although study personnel were trained before the study was

started, it can be concluded that this was not sufficient to avoid major protocol deviations in the study. This was especially true for clinics that had to change their normal practice to adapt to the standardized clinical study protocol. More emphasis should thus be placed on training before initiating future clinical studies in this area.

Overall evidence

Our study was not able to draw general conclusions on efficacy, but the safety data propose that the Sangvia Blood Management System may be safe to use in orthopedic surgery. Both these aspects need to be further investigated in large-scale clinical research. It could also be interesting to compare the cost-effectiveness with other therapy options. For instance, a comparison could be made with a preoperative alternative such as epoetin alfa in a non-inferiority design. Epoetin alfa is paid in most countries by other health care resources than the hospital budget, and thus cost effectiveness should focus on the whole health care community. It would also be interesting to conduct a clinical efficacy trial for the Sangvia Blood Management System in patients with a higher allogeneic transfusion rate risk, e.g. revision surgery, and/or in patients with low pre-operative Hb values, with a special focus on the methodological quality, and as utilized in the presented study.[17,33]

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Chapter 9

Should assessors be blinded to study results when judging risk of bias?

A randomised study of withholding study results of blood management interventions in orthopaedic surgery

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ABSTRACT

Blinding is one of the methodological safeguards and has impact on the effect sizes measured. We aimed to evaluate the impact of blinding assessors for study results when judging risk of bias.

Studies were randomly allocated in a blinded or non-blinded fashion for study results to four assessors. Four assessors all received blinded and non-blinded studies. We focused our search in standard databases to human, English-language, randomised controlled trials and studies published between January 2000 and September 2010. Presence of bias (i.e. randomisation, blinding and selection) with the Jadad and Chalmers instruments was evaluated in 132 articles. Agreement between the assessors of the same kind (blinded or non-blinded for study results) was measured with a Kappa (κ) coefficient. By measuring a sum score per instrument we estimated the blinding effect in this study design.

The assessors blinded for study results had higher κ values on all items (0.66, 0.51, 0.42, 0.54) compared to the non-blinded assessors (0.60, 0.50, 0.35, 0.21). Furthermore, the agreement between the assessors of the same kind on the Jadad items (κ range, 0.5-0.66) was higher than on the Chalmers items (κ range, 0.21-0.54). Articles received a higher sum score, 3.66 versus 3.38 points and 2.23 versus 2.13 points on respectively Jadad and Chalmers, from the assessors blinded for study results compared to the non-blinded assessors. Despite the statistically significant data, the differences found are marginal and therefore probably methodologically irrelevant.

Blinded assessors were more optimistic about the study quality, as measured by Jadad and Chalmers scales, compared to assessors with access to study results. However, it remains questionable if this difference is methodologically relevant when performing a systematic review. Further research has to be performed to evaluate its impact when conducting a systematic review, especially in studies regarding the screening of methodological quality.

BACKGROUND

Quality of studies is a multi-dimensional concept that is related to the validity of the study findings. These findings are a result of study design; conduct and analysis of a trial; its clinical relevance; and the quality of reporting.[1] Literature shows that poor study design frequently results in positive findings or larger effect sizes.[2-4] Moher et al. reported statistically significant differences in effect sizes in studies with a high or unclear risk of bias compared with those studies with a low risk of bias.[5] As a consequence, the quality of the primary studies can influence the magnitude of the effect in a SR or MA. Therefore, it is important to downgrade the quality of evidence if a study shows major limitations, if the results are inconsistent or when the evidence is indirect or imprecise.[6]

The three generally accepted and most relevant methodological safeguards for internal validity are randomisation, blinding persons for the intervention and selection (i.e. limitation of the occurrence of withdrawals, attrition bias).[7] Despite these three important methodological aspects, the diversity in instruments for scoring methodological quality is large. As concluded by Jüni et al. there is a considerable heterogeneity in available instruments, and the scoring on each tool has also influence.[8] Since assessors that score the quality of articles can be biased as well, agreement among assessors is frequently evaluated in SRs or Mas.[9-11] Hartling et al. studied the interrater reliability on the risk of bias tool introduced by the Cochrane Collaboration and concluded that a clear and detailed guidance is necessary. Due to the low agreement this could have implications for interpretation of a SR.[11] Scoring articles in a slightly different way/manner or with different instruments may even result in contrary conclusions in a systematic review. Morissette et al. did a methodological review comparing the difference in risk of bias assessment when the assessment is blinded or non-blinded for basic study characteristics (authors name, journal etc.) and concluded that there is discordance but that the effort to conceal is probably disproportionate.[12]

We considered that blinding for study results could be important as well. To evaluate the latter we conducted an experiment in which assessors were either blinded or non-blinded for study results when evaluating the risk of bias in studies. We hypothesized that blinded assessors show more agreement when evaluating the quality of papers. Furthermore, blinded and non-blinded assessors score differently when evaluating the quality of papers, because we think that the blinded assessors are less distracted by the study results than the non-blinded assessors.

METHODS

We performed a randomised trial on published blood management interventions in orthopaedic surgery. Each article was randomised in twice blinded and ones non-blinded for study results. Four assessors, aware of the study design, received the articles in blinded or non-blinded for study results when evaluating risk of bias in studies (Table 1).

Trial identification

We searched standard databases MEDLINE (Pubmed), EMBASE and The Cochrane Central Register of Controlled Trials on two distinct orthopaedic topics. The keywords used were: "Arthroplasty, Replacement, Hip" OR "Hip Prosthesis" OR "Arthroplasty, Replacement, Knee" OR "Knee Prosthesis". We focused our search to human, English-language, randomised controlled trials and studies published between January 2000 and September 2010 (additional file 1). We did not use any terms on blood conservation in the primary search strategy to prevent loss of articles.

Studies selection

Two independent assessors (BT, WV) selected articles based on title and abstract. Inclusion criteria were: primary outcome blood management, full-text in English, study performed on human subjects and randomised studies. Disagreement between the two assessors was resolved by discussion and consensus. When no consensus was found a third assessor (RP) decided to include or exclude articles. SRs and MAs discussing blood management were checked for relevant references. The full text articles of the potentially relevant titles were retrieved.

Randomisation and blinding

This section was completely performed by one author (BT) who also scored all articles in a non-blinded fashion to prevent bias. All selected articles were placed in a random order, based on their reference ID, generated by Reference Manager (version 12.03, Thomson Reuters, New York, USA). A computer program (www.randomization.com) randomised each article (for the randomisation program 'a random patient' in the units ('treatment labels'): blinded, blinded and non-blinded for study results, like a crossover design. The assessors (WV, CP and SW) had a fixed position in the crossover and were not aware of the randomisation plan. So each assessor received articles in a "blinded" or "non-blinded" fashion, depending on the randomisation (Table 1). Blinding for the study results was

performed by covering/hiding the abstract, results and discussion sections on a hard copy of the article, which was then recopied. If necessary, the title was also blinded for the assessors.

Table 1 Randomisation schedule

Article	Option	Assessor 1	Assessor 2	Assessor 3
1	1	Blind	Non-blind	Blind
2	2	Non-blind	Blind	Blind
3	3	Blind	Blind	Non-blind
4	2	Non-blind	Blind	Blind
5	1	Blind	Non-blind	Blind
And so on for 132 articles				

Each article was randomised in one of the three options in a random order. Assessor WV, CP and SdW had a fixed position respectively assessor 1, 2 and 3. Assessor BT scored each article non-blinded.

Outcomes

Each article was assessed by four independent assessors (BT, WV, CP and SW) in two different manners (blinded and non-blinded for study results). Out of all instruments available and validated we decided to choose two instruments, Jadad and Chalmers, to assess risk of bias. The choice of these two instruments was made because no full articles (no abstract, results and discussion section) were available for the blinded assessors so the quality assessment had to be measured from the materials and methods section.[13,14] Furthermore, we wanted instruments that had the same amount and equivalent items.

The *Jadad instrumen*t (Table 2) focuses on randomisation (2 points), blinding for treatment (2 points) and patients account (1 point). This scale gave a deduction of 1-point if the items randomisation or blinding were inappropriate.[13]

The *Chalmers instrument* (Table 3) also consists of three items (treatment assignment, selection bias and blinding for treatment) on which a maximum of 9 points was possible. Each item was divided in four options (0 to 3 points) with increasing points for better methodology.[14]

The items per instrument have different names but they are measuring the same subject. However, the criteria of the items between the instruments differ, detailed information is found in Table 2 and 3. We used the following terms during analysis, “randomisation”, “blinding” and “selection”.

Statistical analyses

The blinded assessors had the possibility to give the answer "unknown" if data regarding the item "selection" was not available in the methods section of the article. This led to only 30 articles that could be evaluated. For this reason the item "selection" was not taken into account when calculating the sum score of the instrument.

Our primary outcome was level of agreement between assessors of the same kind, blinded or non-blinded for study results. Kappa statistics (κ) was utilized to check level of agreement between the two assessors of the same kind. For this agreement Fleiss criteria were used: 0-0.20 as poor, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as good, and 0.81-1 as very good agreement.[15] Kappa confidence intervals were estimated using 1.000 bootstrap replications in the software STATA version 12.1. Secondary outcome was the so-called blinding effect, which was defined as the difference in scoring between the assessors blinded versus non-blinded for study results. A sum score per instrument per assessor was calculated, in which we excluded the item "selection". The sum scores of the same assessor were summed and divided by two (called "difference"). Then the groups (blind versus non-blind) were compared using the Wilcoxon rank test. Data were analysed using IBM SPSS Statistics 19.0 (IBM SPSS Statistics, Chicago: SPSS Inc.).

Table 2 Jadad instrument, classification per point[13]

Randomisation	**+1**	Randomisation is mentioned
	+1	The method of randomisation is appropriate (computer-generated random number list, coin toss or well-shuffled envelopes)
	-1	The method of randomisation is inappropriate (alternate assignment, by birthday, hospital number, or day of the week)
Blinding	**+1**	Blinding is mentioned (conducted in a double-blind fashion)
	+1	The method of blinding is appropriate (use of identical tablets or injectables)
	-1	The method of blinding is inappropriate (incomplete masking)
Patients account	**+1**	The fate of all patients in the trial is known. If there are no data the reason is stated.

Table 3 Chalmers instrument, classification per point[14]

Treatment Assignment	**3**	The treatment assignment process was deemed to have been truly randomised, as with a telephone or computer system, and the investigator was unlikely to have been able to predict (or identify) the assigned treatment prior to trial entry. When a study was stated to be randomised and double-blind/masked (but the method of assignment to the treatment group was not described), three points were given only if the summary report also presented adequate data to suggest that the treatments could not be distinguished from each other and that the treatment groups were similar with regard to prerandomisation risk factors.
	2	The study was stated to have involved randomisation, but the method of assignment was not described, or when assignment was made by envelope or by some other method that made it unlikely (but still possible) that the treatment to be assigned could be known or suspected by the investigators.
	1	The study was stated to have involved randomisation, but the method of assignment was not described and the investigator was not "blinded" at treatment assignment.
	0	Randomisation was not mentioned explicitly or when the investigators could easily have predicted or influenced the treatment assignment.
Control of Selection Bias	**3**	The report stated that all patients entered in the trial and assigned treatment were included in the analysis, or if any withdrawals from the trial had been listed and the results analysed both by original treatment assignment and by treatment received.
	2	Withdrawals had actually been listed in the report and the results had been analysed by original treatment assignment only.
	1	Reports did not mention withdrawals or the results had been analysed only by treatment received.
	0	Withdrawals had occurred but were not described in the report and the results were analysed only by treatment received, or if withdrawals accounted for more than 15% of the sample of randomised patients.
Blinding of Participants and Investigators	**3**	The study was reported to have been double-blinded, such that (1) patients, (2) care givers, and (3) investigators assessing outcome were all kept unaware of the treatment assignment.
	2	The investigator assessing outcomes had been blinded to the treatment assignment or if two of the three categories listed above had been blinded.
	1	Blinding was impossible or when it was impossible to judge whether it had been attempted.
	0	When a study could have been conducted as double-blinded, but had not been.

RESULTS

Our search yielded 3016 articles in the three databases after duplicates were removed. Based on title/abstract the two assessors had an agreement of 99.3% when in- or excluding an article, 206 (6.8%) articles passed to the next stage of inclusion. Twenty-two studies (0.7%) had to be viewed by the third assessor (RP) for in- or exclusion, of which 14 were included. In the eleven systematic reviews and meta-analyses about blood management 16 relevant references were checked. Based on the full text, over 100 articles were excluded for several reasons; i.e. the study was not randomised, full-text was non-English. A total of 132 articles were selected (Figure 1). Characteristics of the selected articles are presented in Table 4.

Table 4 Descriptive statistics of the included articles

	n	%
Publication year		
2000	12	9.1
2001	16	12.1
2002	8	6.1
2003	8	6.1
2004	9	6.8
2005	21	15.9
2006	11	8.3
2007	13	9.8
2008	9	6.8
2009	9	6.8
2010	13	9.8
2011	3	2.3
Body region		
Hip	51	38.6
Knee	67	50.8
Both	14	10.6
Type of journal	**n**	
Orthopaedics	87	65.9
Anaesthesiology	20	15.2
Haematology	11	8.3
Surgery	7	5.3
Biology	5	3.8
General	2	1.5

	n	%
Continent		
America	22	16.7
Asia	23	17.4
Australia	5	3.8
UK	24	18.2
West-Europe	47	35.6
East-Europe	11	8.3
Number of centres		
Single	114	86.4
2 or more	18	13.6

The blinded assessors had good agreement on the Jadad item "randomisation" compared to a moderate agreement of the non-blinded assessors (Table 5). The Jadad item "blinding" showed a moderate agreement for both types of assessors (blinded and non-blinded). The Chalmers items showed lower agreement of all assessors per item compared with the Jadad items. The Chalmers items "randomisation" and "blinding" both scored moderate agreement for the blinded assessors and fair agreement for the non-blinded assessors. As mentioned earlier, the item "selection" was not interpretable for the blinded assessors. For the non-blinded assessors, a poor agreement was found for the "selection" item on the Jadad and Chalmers instrument.

Table 5 Kappa agreement between the two assessors of the same kind

	Jadad		Chalmers	
	Blinded	**Non-blinded**	**Blinded**	**Non-blinded**
Randomisation	0.663 (0.551-0.778)	0.600 (0.479-0.722)	0.415 (0.305-0.545)	0.346 (0.219-0.468)
Blinding	0.510 (0.397-0.624)	0.501 (0.378-0.622)	0.543 (0.427-0.663)	0.212 (0.115-0.324)
Selection	-	-0.040 (-0.156-0.076)$^{\$}$	-	0.122 (0.032-0.236)$^{\wedge}$

Data are presented as κ value (95%CI).
All κ values have a significant difference of *P-value* <0.001; $^{\$}$*P-value* = 0.718, $^{\wedge}$*P-value* = 0.004

Thus, blinded assessors had better agreement on each single item of the two instruments than the non-blinded assessors. Furthermore, the agreement on the Jadad items was higher in comparison with the agreement on the Chalmers items.

A mean overall score per instrument is presented in Table 6. The blinded assessors had a significantly higher mean score 2.23 and 3.66 points on respectively the Jadad and Chalmers instrument, compared to 2.13 and 3.38 points for the non-blinded assessors. However, sum score for the Jadad instrument ranged between 53-56% of the total possible points (4) and on the Chalmers instrument the values ranged between 56-61% of the total possible points (6).

Table 6 Sum score per instrument according to assessor type

	Jadad	Chalmers
Blinded	2.23 (2.04-2.42)	3.66 (3.42-3.90)
Non-blinded	2.13 (1.95-2.31)	3.38 (3.15-3.61)
Difference	0.10 (0.01-0.19)	0.28 (0.14-0.42)
P-value (Wilcoxon Ranks Test)*	0.047	0.000

Data are presented as mean (95%CI). Jadad and Chalmers could contain a maximum of respectively 4 and 6 points. * Theoretical median tested: difference equal zero.

DISCUSSION

Assessors blinded for study results are more optimistic in their judgement on bias of primary articles than non-blinded assessors, suggesting that when the risk of bias is evaluated, blinding assessors for study results could be valid. Furthermore, the overall risk of bias judgement with the Jadad instrument showed more agreement than with the Chalmers instrument.

To our knowledge no similar research design has been published on the topic of blinding assessors for study results when judging the risk of bias. The studies that focus on blinding integrate this aspect in their study design (blinded for treatment or during analyses) or focus on its effect in the review process (blinded reviewers) for a journal. The latter is widely studied with contrary results. As concluded from studies in the editorial face there is no evidence for an open, transparent, review process. Especially because unblinding the information about the reviewers and authors has influence on the amount of possible reviewers and the acceptance of a study.[16-18]

Misclassifications of the quality of studies, related to observer bias can be characterized by “optimism error” and “intervention preoccupation”. These are unpredictable; since they are subjective and vary between studies.[4] Within our data we detected superior agreement if the assessors were blinded for results, compared to non-blinded assessors. This underscores the conclusions from clinical studies that found that the odds ratio point

estimate of the effect size was higher (i.e. more in favour or optimistic on the treatment), when outcome assessors were non-blinded.[2,4] In our study this is seen as the blinding effect, the result that blinded assessors had higher mean scores on the instruments than the non-blinded assessors. However, the question remains which of the assessors (blinded or non-blinded) are correct and if this difference yields systematically different results. Despite statistical significant results the sum score between the blinded and non-blinded assessors remains small which makes blinding for study results methodologically irrelevant.

Morissette et al. performed a systematic review about blinding for basic study characteristics. This review also concluded that there was discordance between blinded or non-blinded risk of bias assessments. However, the best approach could not be defined in which the time consuming aspect of blinded assessments could be crucial in making a choice.[12]

Strengths of our study include the fact that we randomised each paper like a crossover design, for both blinded and non-blinded assessors, which makes the interpretation of our results more valid. By randomising, the risk of bias by a specific assessor is minimised. To further minimise the bias during assessment of the quality of the papers, the review process was validated with specific instructions (both written and oral). Furthermore, the outcome of the first five reviewed papers were evaluated with the first assessor (BT). As studied by others, training has only a slight impact on the quality of peer reviewing.[19-21] However, we think that this contributes to a better usage of the instruments, but we are aware of the fact that each tool and its instruction is an interpretation of a specific person. Various instruments for assessing risk of bias are available, which makes the generalizability of our results for other instruments less valid. The Cochrane risk of bias tool is mostly used in the review process. Unfortunately, this tool was not possible to use in this study because some of the domains are only presented in the results section. The domains "sequence generation", "allocation concealment" and "blinding of participants, personnel and outcome assessors" are partly covered by the Jadad and Chalmers items. This is one of our study limitations, assessing other instruments would perhaps lead to other conclusions. Jüni et al. illustrated this in their study where 25 scale-based instruments were compared and concluded that the overall quality scores of these instruments could not be extrapolated because of the heterogeneous nature of the instruments.[1,8] For this reason we only looked at the individual items of each instrument. This, however, creates controversies as well, if different quality assessment scores are compared. For example, in the Jadad item "selection bias", one point is earned if a statement is made regarding withdrawals and dropouts, whereas the Chalmers-item "selection bias" has more subcategories. The latter also scores the method of data analyses (as treated or per protocol). Especially these items on "selection bias" showed poor agreement between assessors in our study. Furthermore

data were missing to a considerable extent in the blinded group. The latter can be explained by the fact that this item is mostly covered in the results section of a paper and was thus not available for the blinded assessors in the current study design. In addition, the superior agreement on the Jadad instrument could possibly be explained by the subgroups of the items. The Jadad instrument has a more simple interpretation of the different items that makes the assessment easier in comparison with the Chalmers instrument. Our study had some more limitations. First, the agreement on quality score in this research was only based on two assessors. As mentioned earlier observer bias can despite the blinding of assessors still be present, more assessors would give a better interpretation of results, but is in reality not possible, due to its time consuming aspect. Secondly, one person (BT) was not randomised for blinded or non-blinded because someone had to blind the study sections. In addition, the assessors could accidentally be non-blinded for a specific study when they already knew the published paper. This has not been checked, but may be limited because none of the assessors (WV, CP, SW) was working in this specific field. Thirdly, one specific field (patient blood management in orthopaedic surgery) was explored in this study. It is unknown if these results can be extrapolated to other fields. Apart from this the field investigated is known to have blinding difficulties in study design, however this would have minor or no influence of this study because the focus is on another type of blinding. Fourthly, the relationship between the score and the study results is not examined; because another subjective outcome is than introduced with the expert based opinion if the study results found were to be expected.

With increasing numbers of published articles, assessment of study quality is important, thus numerous quality assessment scales and checklists have been published.[22] The Cochrane Collaboration is still debating on the best way, how to incorporate the quality assessment in the interpretation of the study results (unpublished abstract Cochrane). The GRADE working group made an effort to develop clear guidelines to assess trial quality with special focus on the specific context in which the evidence is used.[6]

In conclusion, the assessment of methodological quality may be biased when assessors are aware (i.e. non-blinded) of study results. This study showed that the blinded assessors were more optimistic about the study quality measured with the Jadad and Chalmers scale than the non-blinded assessors. However, if this could influence a systematic review remains unclear and the optimal approach could not be defined. In studies regarding risk of bias assessment there should be more focus on how articles are presented to the assessors. Especially if a new research instrument for quality assessment is being tested. Further research has to be performed to evaluate its impact when conducting a systematic review.

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Chapter 10

Transfusion trigger heterogeneity biases results on blood transfusion

An illustrative meta-analysis on transfusion triggers in hip and knee arthroplasty

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Submitted

ABSTRACT

We hypothesized that heterogeneity is a major problem in patient blood management (PBM) studies, more specific with respect to outcome in drainage studies in orthopaedic surgery. The aim was to identify heterogeneity for the blood transfusion trigger in hip and knee arthroplasty. The latter is directly associated with the outcome transfusion percentage as well as number of units of blood.

A search strategy on drainage strategies in elective total joint surgery (no drainage, closed suction (CS) drainage and autologous blood transfusion (ABT) drainage) was done. MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials were used for data extraction. Studies were scored with respect to transfusion policy, methodological quality and quality of reporting.

Fourteen studies (64%) reported presence of both a transfusion trigger value as well as transfusion policy. In 57% of the included studies an allogeneic blood transfusion was given based on non-defined "clinical" symptoms. Furthermore, none of the studies gave additional information neither on the transfusion trigger decisions nor on the "clinical" symptoms.

Transfusion percentages ranged from 0 to 64%. Nine studies (45%) had a transfusion rate of $\leq$20%, five of these studies reported a transfusion threshold of <8 g/dL, while four studies (44%) did not report a transfusion trigger. Presence of no transfusion trigger resulted in a risk difference (RD) of 0.05 (95%CI: -0.05, 0.14) in allogeneic transfusion events compared to a RD -0.09 (95%CI: -0.16, -0.02) when a transfusion trigger was reported. Methodology scores showed good (r=0.61, p<0.05) and moderate (r=0.44, p<0.05*)* correlation for respectively the CONSORT NPT and Chalmers scale with the year of publication.

Larger heterogeneity exists on the transfusion trigger and policy; the latter has impact on interpretation of outcomes in patient blood management studies of total joint (hip and knee) surgery. Studies should include transfusion trigger decision rules in order to make valid comparisons possible. An intention-to-treat (ITT) and as treated (AT) principle flow chart for transfusion trigger decisions will improve interpretation of outcome results between studies.

INTRODUCTION

Patient blood management (PBM) in orthopaedic surgery is important for quality in patient care. In PBM the use of closed suction drains and autologous blood transfusion (ABT) drains have been studied extensively in many randomized clinical trials (RCTs) and with several systematic reviews or meta-analyses in the last decade.[1-5] However, data from these studies are still not conclusive for neither clinical nor economic benefits. Furthermore, large differences in both allogeneic transfusion needs and study groups are reported. Although the study designs appear comparable, these large differences in outcome are hard to explain by known risk of bias aspects. Heterogeneity between the studies could be the driving factor for this variety in conclusions.

Heterogeneity can be subdivided in clinical, methodological and statistical heterogeneity. Variability in participants, interventions and outcomes studied can be described as clinical heterogeneity, and variability in study design and risk of bias may be described as methodological heterogeneity. Statistical heterogeneity manifests itself in the observed intervention effects that are greater than would be expected solely on random errors, which is a consequence of clinical or methodological diversity, or both.[6] These different types of heterogeneity are closely intertwined, however this relationship is not straightforward, but depends on the differences or covariates present in a study.[7]

For example in orthopaedic surgery, the possible differences in drainage could arise from drain duration, number and position of drains. These factors seem obvious, but another major flaw in PBM studies may be inference with the reason for allogeneic blood transfusion, such as the different definitions on outcome, the use of a transfusion trigger value, the number of units of blood that have to be transfused, and the percentage of cases that are actually treated by these predefined trigger values. Although, an allogeneic blood transfusion seems a “hard” endpoint the reason for transfusion can be less objective, because an allogeneic blood transfusion is often tailored to the patient’s needs.[8] This tailoring can be regarded as a weak link in clinical studies on PBM since the interpretation of clinical symptoms remains subjective and no clear objective parameters are available besides the haemoglobin level.[9]

We hypothesized that results from pooled data from randomised controlled trials in a meta-analysis are negatively biased, mainly due to clinical heterogeneity for blood transfusion indications (e.g. trigger value, transfusion indication) between studies, which makes the generalizability impossible. For this reason a systematic review and illustrative meta-analysis was performed to give insight in the difference in transfusion trigger strategies

and subsequent impact on pooled outcomes. Thus, the aim was to identify presence of heterogeneity for the blood transfusion trigger in hip and knee arthroplasty. The latter is directly associated with the outcome transfusion percentage as well as number of units of blood.

METHODS

Study Design

We conducted a systematic review and illustrative meta-analysis to describe the heterogeneity of randomized controlled trials on blood drainage in hip and knee arthroplasty. We followed the PRISMA statement for reporting of systematic reviews. An electronic search of MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials was conducted. The key words used were: “Arthroplasty, Replacement, Hip” OR “Hip Prosthesis” OR “Arthroplasty, Replacement, Knee” OR “Knee Prosthesis”. We limited our search to human, English-language, randomized controlled trials and published between January 2000 and January 2013. We did not use any term on blood conservation in the primary search strategy to prevent loss of articles. English-language inclusion was pragmatic chosen because we needed additional information from the full text article, which could not be found in the abstract of these studies.

Eligibility criteria

Two reviewers (BT, WV) independently scanned the titles and abstracts of the identified articles for potential relevance and eligibility. Eligible studies included those reported as randomized, performed on human subjects with focus on blood drainage, full text article available in English and published between 2000 and 2013. Also the systematic reviews and meta-analyses of this topic were checked for relevant articles.[1-3,5] If there was any disagreement, consensus was reached through discussion with a third person (RWP). A log of all excluded articles and the reasons for exclusion was kept. Blood drainage was defined as studies with focus on closed suction (CS) drains and/or autologous blood transfusion (ABT) drains, the eligible studies could make an in-between comparison or a comparison with no drainage.

Heterogeneity assessment

Two independent reviewers (BT, WV) extracted data. Relevant descriptive data included (1) year of publication, (2) type of journal, (3) body region (hip, knee or both), (4) number

of centres (single or more) (Table 1). Specific data regarding PBM policy were collected and registered (Table 2). All these factors were compared to give an overview of the heterogeneity between studies.

Methodological Quality Assessment

The CONSORT NPT checklist was used to assess the quality of reporting in studies.[10,11] This checklist, which comprises 25 items, is developed as a reporting guideline and endorsed by many journals. Each item received 1 point when information was available; if no information was available no points were given. Thus, the total possible score was 25 points. Further two scale-based instruments, Jadad et al. and Chalmers et al., were used to evaluate utilization of methodological safeguards (risk of bias).[12,13] Jadad focuses on randomization (2 points), blinding (2 points) and patients account (1 point). A deduction of 1-point was given if the items randomization or blinding were inappropriate.[12] Chalmers also consists of three items (treatment assignment, selection bias and blinding) on which a maximum of 9 points can be scored. Each item was divided in four options with increasing points for better methodology (0 to 3 points).[13]

Statistics

Descriptive data were used as background information. Binominal and categorical data were expressed as proportions.

Data pooling was only performed to show that the interpretation and pooling of drain studies has limited or no additional value when these features are not taken into account despite the random effects model. The data were pooled using Review Manager (RevMan), version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Studies with three or more treatment arms were excluded when data were pooled based on the transfusion trigger. For each study, we calculated a risk difference (RD) for allogeneic transfusion need with 95% confidence intervals (CIs) with a random effects model to forestall the empty cell problem and heterogeneity. Furthermore, 2005 was used as a cut-off point for the evaluation of methodological quality and quality of reporting. This arbitrary cut-off was taken since this was the year of implementation of a new PBM policy in the Netherlands.

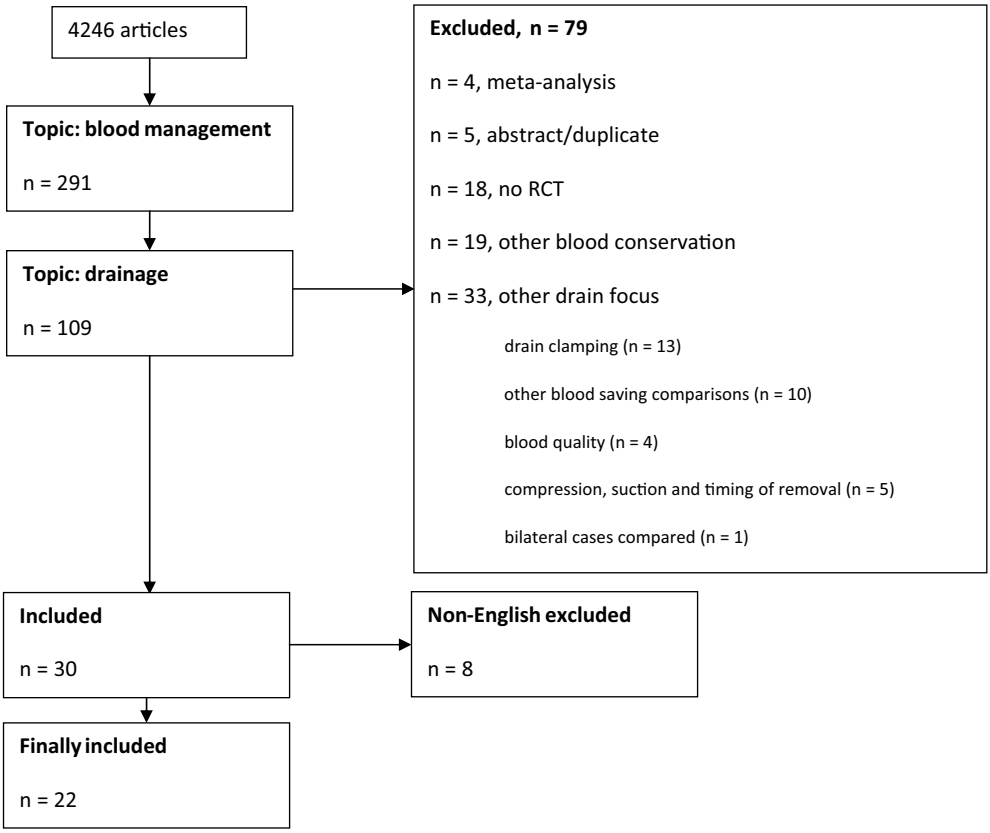

Figure 1 Flowchart of included and excluded articles

RESULTS

The literature search yielded 4.246 potentially relevant articles after removing the duplicate articles. Title and abstract screening eliminated 3.955 articles that did not have blood conservation as the primary outcome. The 291 remaining articles were screened for eligibility based on drainage comparison. A total number of 22 articles were included in the analysis (Figure 1, Table 1). Five meta-analyses were screened for missing references, but they included no new references that fulfilled our inclusion criteria.[1-5]

Table 1 Key characteristics of included studies

	n
Year of publication	
< 2005	7
> 2005	15
Type of Journal	
Orthopaedic	21
Haematology	1
Number of Centers	
Single	21
Multiple	1
Body region	
Hip	10
Knee	9
Both	3
Direction of results	
Positive	7
Negative	15

Drainage comparisons

Different drain comparisons were made in the included studies; no drainage vs. closed suction drainage (CS drainage) (n=10), no drainage vs. autologous blood retransfusion drainage (ABT drainage) (n=3) and CS drainage vs. ABT drainage (n=7). Two studies compared three different treatments (no drainage vs. CS drainage vs. ABT drainage).

The forest plots (Figure 2, 3 and 4) represent the several drain comparisons in the studies with exclusion of two studies because they only reported transfusion units as outcome measure.[14,15] The no drainage group has a 12% lower risk (RD -0.12, 95%CI -0.21, -0.03) (Figure 2) for an allogeneic blood transfusion compared to the CS drainage group. The comparison between no drainage and ABT drainage showed no difference in allogeneic blood transfusions, the risk difference was 0.04 (95% CI -0.02, 0.09 (Figure 3). Fewer allogeneic blood transfusions, with a risk difference of 0.12 (95% CI, 0.06-0.18), were also found when the ABT drainage group was compared with the CS drainage group (Figure 4).

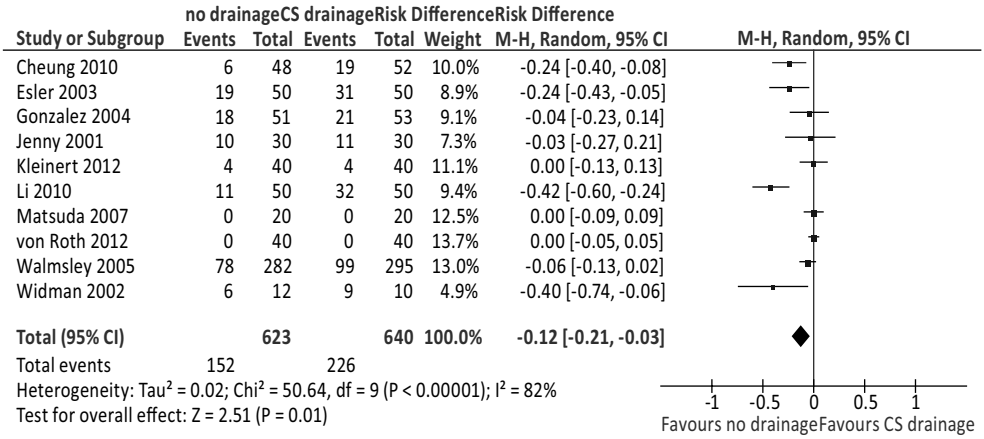

Figure 2 The risk difference of allogeneic blood transfusions between no drainage and CS drainage

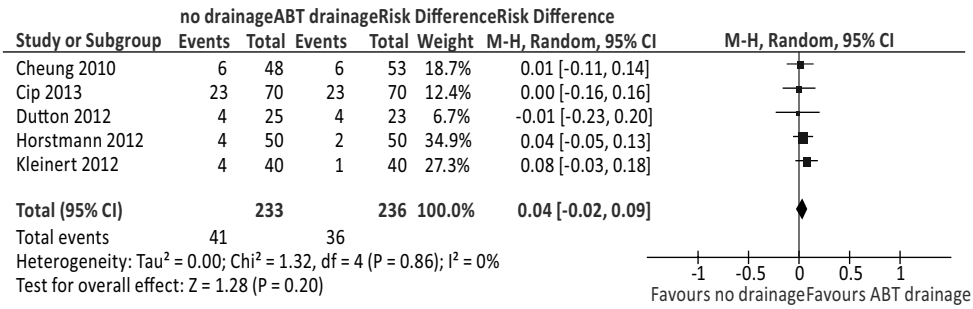

Figure 3 The risk difference of allogeneic blood transfusions between no drainage and ABT drainage

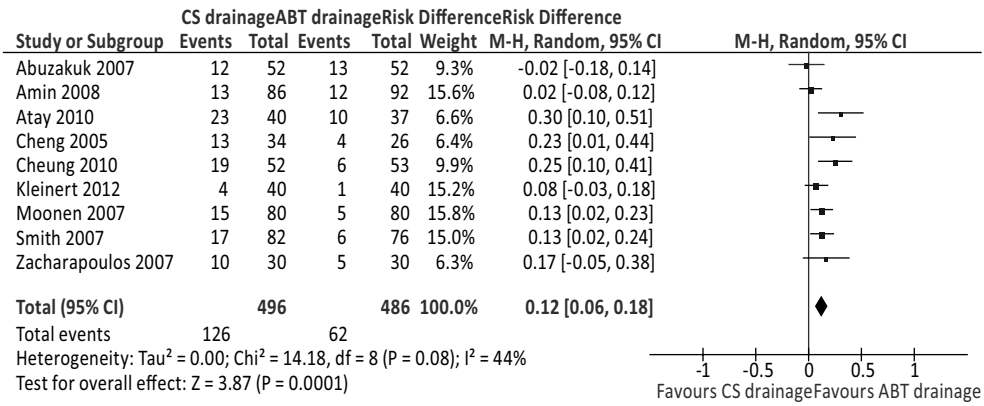

Figure 4 The risk difference of allogeneic blood transfusions between CS drainage and ABT drainage

Clinical heterogeneity

The literature search included primary THA and TKA surgeries, though some studies used more specific in- and/or exclusion criteria. One study reported only uncemented hip arthroplasties by the postero-lateral approach, one study only included cemented hip arthroplasties, and others reported a mix of cemented and uncemented arthroplasties.[15,16] With respect to the drainage devices eleven different drain-systems were used and in five studies (23%) no information was reported on the kind of drainage system.[15,17-20] Furthermore, several drainage techniques were used, studies reported on drainage for 48 hours, while some reported only six hours postoperative drain use.[16,21-24] While others depended the drainage time on the volume drained or even no specific information was presented.[25,26] Two studies (9%) included other blood saving alternatives (Table 2) as well.[27,28] Ten studies excluded patients using anticoagulation therapy for cardiovascular problems. Only ten (45%) studies reported a formal sample size calculation. However, six different endpoints were used in the included studies to calculate this sample size: blood loss, adverse events, length of hospital stay, haemoglobin level at different time points, reduction in the number of allogeneic transfusions and wound problems.

Table 2 Characteristics of included studies

Study	Joint	SS	QR	Primary outcome	Preop Hb (g/dL)	Trigger level	Policy	Clinical symp
No drainage vs. CS drainage								
Dora, 2007[14]	THA	100	18 / 2 / 5	Complications	-	-	-	-
Esler, 2003[21]	TKA	100	9 / 1 / 3	Other	-	Hb<10 g/dL	-	-
Gonzalez, 2004[20]	THA	104	12 / 0 / 4	-	-	-	-	-
Jenny, 2001[19]	TKA	60	6 / 1 / 3	LOHS	-	Ht<30%		Yes
Li, 2010[18]	TKA	100	11 / 1 / 2	Blood loss	13.2 / 12.9	Hb<10 g/dL	-	-
Matsuda, 2007[27]	THA	40	19 / 3 / 4	Hb	13.6 / 13.4	Depending on Hb, blood loss and collected blood		Yes
Niskanen, 2000[15]	Both	96	8 / 1 / 3	-	-	-	-	-
von Roth, 2012[17]	THA	80	14 / 2 / 4	Blood loss	-	-	-	-
Walmsley, 2005[28]	THA	577	17 / 4 / 5	Complications	13.6 / 13.4	Hb<8 g/dL	2 units	Yes
Widman, 2002[36]	THA	22	12 / 1 / 1	Wound	-	Hb<8 g/dL	-	Yes
No drainage vs. ABT drainage								
Cip, 2012[37]	TKA	140	22 / 4 / 5	Transfusion	-	Hb<8 g/dL	-	Yes
Dutton, 2012[23]	TKA	48	18 / 2 / 5	Transfusion	13.3 / 13.7	-	-	-
Horstmann, 2012[24]	THA	100	19 / 3 / 5	Hb	13.9 / 13.9	Hb<8 g/dL	1 unit	-
CS drainage vs. ABT drainage								
Abuzakuk, 2007[26]	TKA	104	18 / 3 / 7	Transfusion	13.5 / 13.6	Hb<9 g/dL	-	-
Amin, 2008[38]	TKA	178	19 / 2 / 4	Transfusion	13.4 / 13.2	Hb<8 g/dL	-	Yes
Atay, 2010[16]	Both	77	14 / 1 / 3	Transfusion	13.1 / 13	Hb<8 g/dL	-	Yes
Cheng, 2005[39]	TKA	60	20 / 4 / 4	Transfusion	12.8 / 12.4	Hb<9 g/dL	Variable units depending on Hb	-

	Reduction	Transfusion checked	Blind	Type of system	No. of drains	Drain position	Alternatives used	Other findings	Conc
	-0.1 U	-	-	Redon	1	-	-	Mean age 66 years	CS +
	24	-	-	Medinorm	1	IA	-	Drain in situ >48hr	CS -
	4.6	-	-	-	2	FL	-	Pilot study	CS -
	4	-	-	-	-	-	-	Drain in situ >24hr, anticoagulation excluded	CS -
	42	-	-	-	-	-	-	No mobilisation during drain in situ	CS -
	0	-	-	SBVac	2	FL	Yes	Conclusion not based on primary outcome, excessive blood loss intraop excluded	CS +
	0.9 U	-	-	-	-	-	-	Anticoagulation excluded	CS -
	0	-	-	-	-	FL	-	Ratio men:women not standard	CS -
	6.6	-	-	Redivac	1	-	Yes	4 deaths in drainage group	CS -
	3	-	-	Bellovac	-	-	-	Hematoma on scintigraphy	CS -
	0	-	-	OrthoPAT	-	-	-	No info of the 11 exclusions	ABT -
	1.4	-	-	Bellovac ABT	-	-	-	>6hr drain removed	ABT -
	-4	-	-	Bellovac ABT	-	-	-	Ward doctors blind?, >6hr standard drainage	ABT -
	1.9	-	-	Bellovac ABT	1	IA	-	After 150mL collected retransfusion, average of 2.3 PC transfused	ABT -
	-2.1	-	-	Bellovac ABT	1	IA	-	Expected reduction of 50%	ABT -
	-30.5	-	-	Transolog	-	-	-	Exclusion Hb <12 g/dL, drain in situ 48hr	ABT +
	-22.6	-	-	Donor	-	-	-	Drain in situ >24hr	ABT +

Table 2 Continued

Study	Joint	SS	QR	Primary outcome	Preop Hb (g/dL)	Trigger level	Policy	Clin symp
Moonen, 2007[40]	Both	160	20 / 3 / 6	Transfusion	14 / 14	Hb<8 g/dL	1 unit	-
Smith, 2007[29]	THA	158	20 / 3 / 4	Hb	13.6 / 13.6	Hb<8 g/dL	2 units	Yes
Zacharapoulos, 2007[41]	TKA	60	12 / 1 / 3	Transfusion	13.8 / 14	Hb<9 g/dL	-	Yes
No drainage vs. CS drainage vs. ABT drainage								
Cheung, 2010[25]	THA	153*	19 / 2 / 5	Transfusion	14 / 13.7 / 13.6	-	-	Yes
Kleinert, 2012[22]	THA	120*	19 / 4 / 6	Hb	13.6 / 14 / 14.2	Hb<8 g/dL	-	Yes

Data collection of the reviewed articles, cells with a dash were not recorded or presented as 'no' in the article. Sample size is overall study size (* in three groups), quality report presented as CONSORT NPT / Jadad / Chalmers. Trigger level shows the value when a transfusion was justified for the specific study. Policy describes the action taken when the trigger level was reached. Clinical symptoms represents the studies in which this was an escape. Reduction is percentage allogeneic blood transfusions. Reduction is calculated as intervention – control. In the three arm comparisons the first value is none vs. CS, second is none vs. ABT, third is CS vs. ABT.
Transfusion checked, blind and alternatives used were binominal (yes/no) answered. Conclusion is answered as positive results or not for a specific drain type.
ABT = autologous blood transfusion; Conc = conclusion; CS = closed suction; FL = fascia lata; Hb = haemoglobin; Ht = haematocrit; IA =intra articular; LOHS = length of hospital stay; QR = quality and methodology report; SC = subcutaneous; SS = sample size; THA = total hip arthroplasty; TKA = total knee arthroplasty; U = unit

	Reduction	Transfusion checked	Blind	Type of system	No. of drains	Drain position	Alternatives used	Other findings	Conc
	-13	-	-	Abdovac and Bellovac ABT	2	IA and SC	-	Inclusion Hb 13-14.6 g/dL, >6hr standard drainage	ABT +
	-12.8	Yes	-	Medinorm and ABTrans	2	FL	-	Retransfusion given at 4hr interval	ABT +
	-17	-	-	Gish Orthofuser	-	-	-	1 PC was standard given after surgery	ABT +
	24, 4.5 and -19.5	-	-	Medinorm and Bellovac ABT	1	FL	-	ABT transfusion when necessary, anticoagulation excluded	Both -
	0, -6 and -6	-	-	Redon and Bellovac ABT	2	FL	-	Drain in situ 48hr, mean age 66 years	Both -

Transfusion percentages and trigger values

Fourteen studies (64%) reported a transfusion trigger policy as well as the threshold value for the transfusion trigger. Administrating only a single unit of allogeneic blood when the set trigger value was reached was not common practice; three studies gave routinely two units when the trigger reached the value of 8 g/dL. Two-thirds of these fourteen studies were performed before 2005 (defined as cut-off point regarding implementation of a restrictive transfusion policy in the Netherlands). Eight of the fourteen (57%) studies that reported a transfusion trigger had an additional 'clinical symptom' escape for justifying allogeneic blood transfusion. In none of the studies the transfusion decision was blinded. Furthermore, only one study (4%) checked post hoc whether the transfusion decisions were made correctly, by looking both at the transfusion trigger as well as the recorded clinical symptoms of the patient.[29]

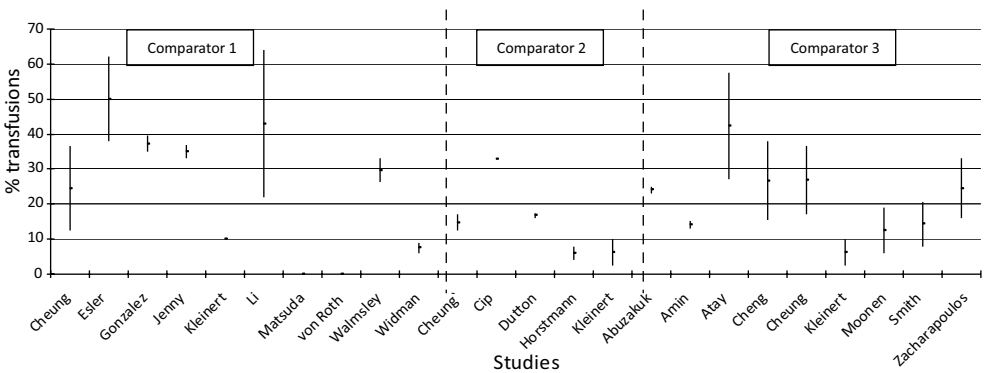

Figure 5 Transfusion percentages per study comparison

Comparator 1 is no drainage vs. CS drainage, comparator 2 is no drainage vs. ABT drainage and comparator 3 is CS drainage vs. ABT drainage. The line represents the control (lowest end) and the intervention group (highest end) with the point as average allogeneic blood transfusion percentage per study. Niskanen and Dora excluded.[14,15]

Figure 5 demonstrates the large range of transfusion percentages between studies. Especially in the no drainage vs. CS drainage and the CS drainage vs. ABT drainage studies, the transfusion percentages differ largely between groups. Seventy percent (n=14) of the studies had a low variability (difference between groups <20%). Comparing studies evaluating "no-drainage vs. CS-drainage" had lowest transfusion variability. Nine of the twenty studies (45%) with a low transfusion rate (≤20%) had the transfusion trigger set at

<8 g/dL, although 44% (n=4) of these studies did not report the actual transfusion trigger value (Figure 6).

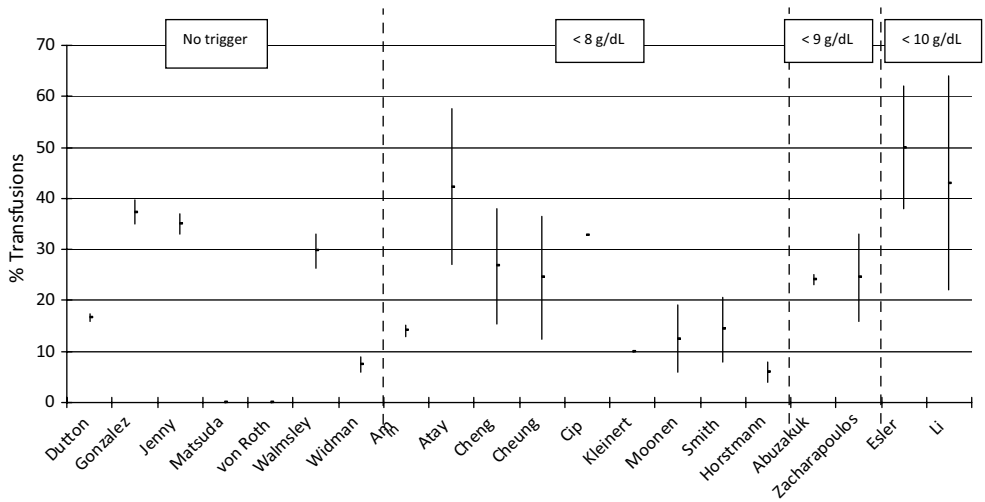

Figure 6 Transfusion percentages per type of transfusion trigger

The line represents the control (lowest end) and the intervention group (highest end) with the point as average allogeneic blood transfusion percentage per study. Niskanen and Dora excluded.[14,15]

Reporting of a transfusion trigger value showed that the treatment effect of the experimental group (CS drainage and ABT drainage) estimate became smaller, with a risk difference of -0.09 (95% CI: -0,16, -0.02) to no significant difference when no trigger is reported, risk difference of 0.05 (95% CI: -0.05, 0.14, Figure 7). The pooled risk difference was -0.05 (95% CI: -0.10, 0.01) indicating that there is no beneficial effect for using a drain system.

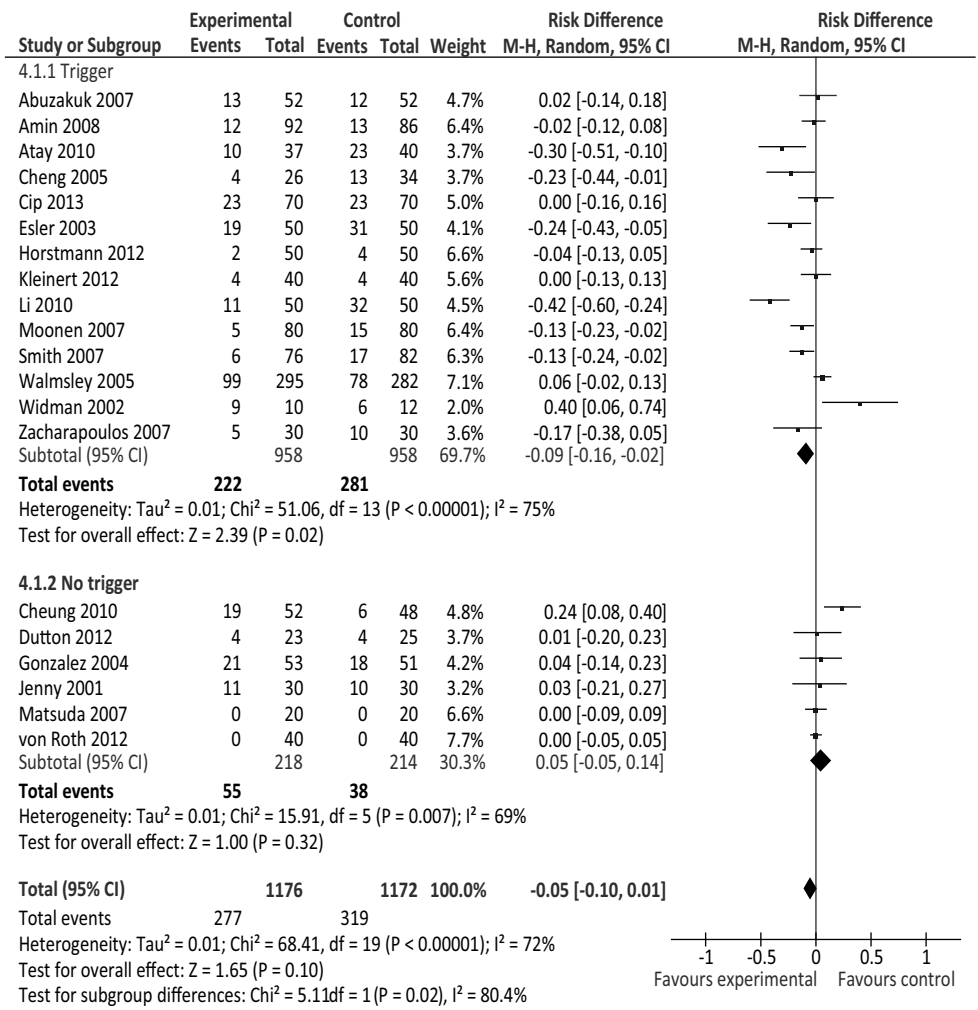

Figure 7 The effect of using a transfusion trigger on the magnitude of the treatment effect

For the three arm studies the comparison no drainage vs. CS drainage was used. Niskanen and Dora excluded.[14,15] The experimental group includes the CS drainage and ABT drainage groups

Methodological quality and report quality

The quality of reporting (measured with the CONSORT NPT) had a median overall score of 17.5 points (70% of the total). The year of publication had a good correlation (r=0.61, p<0.05) with the CONSORT score, 12 points vs. 18 points in respectively years before 2005 and after 2005 (Table 3).

The risk of bias assessment (methodological quality) showed lower percentages on the mean overall score, respectively 40% (2 points) and 44% (4 points) on the Jadad and Chalmers

instrument (Table 3). The CONSORT NPT and Chalmers showed a significant improvement between studies published before and after 2005, respectively *P-value* of 0.005 and 0.047. The correlation of Chalmers with the year of publication was moderate (r=0.44, p<0.05).

Table 3 Quality of the included studies

	CONSORT NPT	JADAD	CHALMERS
All studies	17.5 (12-19)	2 (1-3)	4 (3-5)
Drainage comparison			
None vs. CS drainage	12 (9.5-16.3)	1 (1-2)	3.5 (3-4)
None vs. ABT drainage	19 (18.5-20.5)	3 (2.5-3.5)	5 (5-5)
CS drainage vs. ABT drainage	19 (16-20)	3 (2-3)	4 (3.5-5)
Year of publication			
≤ 2005*	12 (8.5-14.5)	1 (1-2.5)	3 (3-4)
> 2005[$]	18 (14-19)	2 (2-3)	4 (4-5)

Three arm studies are excluded. Median and IQR (interquartile range) are presented. The instrument had a maximum of respectively 25, 5 and 9 points on CONSORT NPT, Jadad and Chalmers.
* based on 7 studies
[$] based on 13 studies

DISCUSSION

Key findings

We found that despite the significant improvement of methodological quality (risk of bias) and reporting of studies on wound drainage (no-drainage, CS or ABT drainage) in orthopaedic surgery over the last decade, great variation in transfusion percentages remain. An important confounder for the latter is high variability in the actual reason to give an allogenic blood transfusion: either different trigger values are used or only non-defined clinical reasons for transfusion are used. Since this has a direct impact on the outcome variable transfusion (i.e. number and percentage) only studies with comparable transfusion triggers can be compared irrespective of the devices used. This is also true for any study on patient blood management irrespective of the PBM modality or patient group studied. We found several potential confounders in the studied articles: (1) different levels for transfusion trigger (or even, no defined triggers) (2) non-specific clinical symptoms as pre-defined possible escape for a transfusion (3) absence of post hoc check on the transfusion decisions for validity (4) heterogeneity on study demographics (population, devices, surgical procedures and transfusion practice) (5) non-blinded transfusion decisions. Most studies

lack information on these factors, causing problems in the interpretation of outcome of these studies on allogeneic blood transfusions.

Strengths and limitations

The strength of our systematic review is that we performed a comprehensive search in duplicate without specific PBM limitations. Further the specific focus on the transfusion policy is another aspect that has not been studied yet. Since this extensive clinical heterogeneity focus could be combined with the methodological and statistical heterogeneity of these trials.

Limitations were that we excluded non-English papers that could have influenced the data. This exclusion was pragmatic chosen because we needed additional information from papers. Only drainage studies in orthopaedic surgery are evaluated, if these data could be generalized to other medical specialities is unknown and if these findings are also present in other PBM studies in orthopaedic surgery is questionable. Further we evaluated and screened each paper thoroughly but did not contact authors for additional information ignoring potential publication bias, because only published information has given us feedback on the study. We are aware that the CONSORT NPT is not a tool to measure quality, but it evaluates and improves the reporting of a study. Over the years more journals have endorsed the CONSORT statement, which is also seen by our study results with a positive correlation between the year of publication and the CONSORT score.

Previous literature

A critical review of the conducted meta-analysis makes the generalizability of these studies difficult. Markar et al. and Haien et al. compared CS drainage vs. ABT drainage. However, Markar et al. only reported on TKA while Haien et al. reported on both TKA and THA. Zhang et al. and Kelly et al. had another scoop; they compared CS drainage with no drainage. But Zhang et al. in TKA patients whereas Kelly et al. in THA.[3,5] An important finding was that Markar et al. excluded studies with focus on both joints (THA and TKA).[1] Haien et al. stated that RCTs were included without consideration of primary or revision replacements.[2] It is known that revision arthroplasty have other bleeding kinetics than primary arthroplasty. Only Zhang et al. and Kelly et al. made a statement regarding clinical heterogeneity and thereof stated that the results should be used with caution because not all variables are favouring the same procedure.[3,5]

Sharma et al. also checked the methodological quality by the Detsky scale and concluded that the reporting in blood conservation trials between 2000 and 2007 was poor. However, other items for evaluation were used but findings in our study support this information.[30]

Implications for future research

Our data showed that the reporting of a transfusion trigger influenced the overall effect estimate of the studies. However, our results also showed that a transfusion trigger might be seen as a real confounder, because adjustment of the outcomes for the used trigger value was not possible since large variation in outcomes exists throughout the different trigger groups. Despite, these findings we think that information of the transfusion trigger in a study report has additional value for the reader when statements regarding allogeneic transfusion are made.

Implications for clinical practice

The transfusion trigger threshold and adherence to this trigger in allogeneic blood transfusions varies considerably in PBM studies. This can have an impact on the interpretation of PBM strategies. All PBM modalities like erythropoietin, cell saving and drains are influenced by the decision to transfuse, since this is the endpoint in most studies. The transfusion trigger is part of the causal relation between symptoms and allogeneic blood transfusion decisions and by this responsible for the decision when to transfuse and how much to transfuse. We found that 57% of the studies had clinical symptoms added as possibility for transfusions. This is on the one side the tailoring of PBM but on the other side probably the weakness of PBM studies since clinical symptoms are subjective. The question remains whether blinding, a proven method to improve quality of the trial is the solution to solve this problem in PBM studies.[31] The decision maker still has to navigate on the information given by the caregiver and can only judge if the symptoms are part of the anaemia present. This remains a rather subjective part of the treatment indicating a need for more objective measurement tools.

Surprisingly, the transfusion rates in the studies varied largely regardless of the trigger value set. Thirty percent of the studies had a large bandwidth, >20% difference in transfusion rate, between the two compared groups. This makes the studies difficult to compare, the trigger level influences the amount of transfusions because the higher the trigger the more transfusions are given in both the experimental and control group. This is also seen in the preoperative haemoglobin values of patients, a lower preoperative Hb level is prone for more allogeneic transfusions.[32]

Based on our study, only adding the transfusion trigger seems not enough. More detailed reporting on the followed transfusion practise, i.e. at what trigger and with which symptoms transfusions were performed is needed. The aspect 'clinical symptoms' should suggest information on (patho) physiological parameters like blood pressure and heart rate to validate a transfusion.[8,9] None of the included studies in this systematic review gave detailed (patho) physiological information of the actual patient' situation when a transfusion was given. An idea on the potential bias of the latter could be analysed by dividing the transfusions given based on the predefined trigger by the total amount of actual transfusions in a study. In this respect the concept of intention-to-treat (ITT) versus as treated (AT) could be used for making an assessment of the validity of the transfusion decisions. This could probably discriminate between what was to be expected based on the haemoglobin level and the true level of transfusion and gives more insight information about the adherence to the study protocol and how clinical symptoms are associated.
Results of the Focus trial and a posthoc analysis of an RCT support a more restrictive transfusion policy (<8 g/dL) in orthopaedic surgery.[33-35] However, the question remains of this restrictive transfusion policy is actually implemented in the evaluated studies. A transfusion trigger between 8 and 10 g/dL for a single unit allogeneic blood in non-complicated elective total hip and knee arthroplasty could nowadays be seen as liberal and thus giving a larger difference between groups.

Conclusion

Heterogeneity exists on the transfusion trigger, the latter has impact on interpretation of outcomes in patient blood management studies in drainage studies of total joint (hip and knee) surgery. Studies should include transfusion trigger decision rules in order to make valid comparisons possible. An intention-to-treat (ITT) and as treated (AT) principle flow chart for transfusion trigger decisions will improve interpretation of outcome results between studies. As for the methodological quality of the reported studies, this improved over time.

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Chapter 11

Discussion

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In total hip and total knee arthroplasty patients both patient pain management (PPM) and patient blood management (PBM) significantly improved throughout the last decades. Since the end of the previous century more awareness on potential hazards of the existing liberal blood transfusion policy arose, resulting in the introduction of more rational blood transfusion guidelines (single unit; 4-5-6 mmol/L rule) and several blood saving alternatives, like the use of erythropoietin, tranexamic acid, cell saver and postoperative blood reinfusion devices. Besides the restrictive transfusion policy, pain management in patients care had a special focus because it is seen as one of the key performance indicators for health care quality. More specific, prevention of the side effects of an analgesia regimen was the focus, to enhance postoperative recovery and reduce morbidity to the patient.

Patient Pain Management

In the 19th century cocaine, ether and chloroform were the first real agents used to sedate patients.[1] Since then, local anesthetics have been widely used for many indications, most commonly for local and regional anesthesia. Despite optimising both surgical and anaesthesia techniques functional changes in the human body still occurs after an intervention, which are believed to be mediated by trauma-induced endocrine metabolic changes and activation of several biological cascade systems.[2] The reduction of this *surgical stress response* is now seen as the most important part of the postoperative outcome and thus of a successful surgical procedure. The introduction of this term by Kehlet in the seventies has shifted "regular" anaesthesia to a multimodal approach for the patient, which is used to control undesired sequelae after surgery impeding recovery.[3] Thus addressing this *surgical stress response* patient recovery after a surgical procedure will be enhanced.

The use of peripheral nerve blockade offers several advantages when compared to general anaesthesia or local anaesthesia. However, muscle weakness, i.e. quadriceps muscle weakness after a femoral nerve block, is often mentioned as a potential disadvantage for early ambulation of the patient.[4-7] To counteract, this problem of the motor block, an optimal dose for good pain relief was necessary (**chapter 2**). A further improvement of anaesthesia techniques was the introduction of local infiltration techniques with local anaesthetics, local infiltration analgesia (LIA) was developed specifically to avoid motor nerve blocks and facilitate rapid physiological recovery after lower limb arthroplasty in order to enable early mobilization and hospital discharge. Several LIA variations have been described in the last decades, with different routes of administration, types of anaesthetics,

and the combination of intraoperative infiltrations with postoperative catheters. Presently no uniformity exists with regard to the most optimal LIA technique. A pharmacokinetic analysis of LIA should be a research field to optimise the use of this technique.
Combining LIA and retransfusion drains could be a potential danger to the patient, since the shed blood from the retransfusion device is collected in the same area where high concentrations local anaesthetics are injected. Although we showed (**chapter 3, 4**) that the combination was safe, formal analysis of the anaesthetic concentration is mandatory. Eektimmerman et al. found a so-called 'flip-flop model' implying that the absorption of ropivacaine from the tissues around the knee into the systemic circulation is a rate-limiting step in drug elimination.(submitted data)

Patient Blood Management

Patient blood management encompasses a lot of different alternatives of which usage of a trigger rational is probably the most important.[8] In this thesis we focussed on the following alternatives: erythropoietin, per-operative cell saving and postoperative retransfusion devices.
Erythropoietin is widely studied with effective results on transfusion avoidance.[9-11] In **chapter 5** we showed in a RCT that erythropoietin was superior in mildly anaemic patients compared with a postoperative retransfusion system at that time. Although the efficacy of erythropoietin is superior to retransfusion drains the costs related to this treatment are enormous and should be questioned. It significantly exceeds (5-10 fold) the direct cost of allogeneic blood transfusions.[12] In **chapter 6** we calculated the costs associate with routine administration. We found that introducing erythropoietin alpha (EPO) as a standard treatment in our hospital setting would increase the costs by a factor 6. The generalizability of the results on erythropoietin in the Dutch setting should be questioned, looking at the low general transfusion percentages reported by Dutch hospitals over the last few years the efficacy of EPO is questionable.[13,14]
In a recent review from Voorn et al. was shown that 69% of the Dutch clinics were using retransfusion drains on at least regular basis.[15] Although there is lack of evidence to support the use of drains, retransfusion drains are still used in many hospitals. It seems traditions keep them in place.[15] Our results in **chapter 7 and 8** could be added to this evidence.
In **chapter 8** we studied the efficacy of a new disposable perioperative cell saving device in total hip arthroplasty surgeries. In this study we found a 12% allogeneic blood transfusion rate in the control group were a percentage of 21% was expected. Therefore the study turned out to be underpowered and was prematurely terminated. In a review on cell

salvage, Carless et al. reported that cell salvage reduces the need for allogeneic blood transfusions of donated blood in cardiac and orthopaedic surgery. However, this can be questioned for the Dutch situation since low transfusion percentages are reported in the Netherlands.[12] In 2011 80% of the Dutch hospitals reported to have less than 10% blood transfusions in TKA and less than 20% in THA, which was also found in a Dutch multicentre study on over 2200 patients (11%).[12-14]

In **chapter 10** we tried to find an explanation for the large heterogeneity of published data in drainage studies. This variation in transfusion numbers can be explained by several factors, but the most crucial one is the lack of an uniform transfusion policy. Probably the most important blood saving strategy is the use of a restrictive blood transfusion policy and continuous education.[12,16] In the Netherlands, PBM is an important part of patients care in hospitals. Sanquin, the Dutch blood bank, invests a lot in basic research and on knowledge about PBM not only by transfusion specialists but also anaesthesiologists and other medical specialties (e.g. gynaecology, orthopaedic surgeons). The transfusion figures in the Netherlands declined over the last decade but the used transfusion alternatives are still very divers. This is caused by the physician's behaviour and traditions present in hospitals as well as the "success" of introducing transfusion alternatives.[15] The introduction of a transfusion trigger came in many cases along with the implementation of transfusion alternatives, which makes it difficult to relate the reduction in allogeneic transfusions to one specific item. As mentioned before, transfusion percentages between hospitals are very divers and for that reason a critical appraisal of these studies is necessary to considerate an extrapolation of the results to a specific hospital.

Currently a Dutch study is under its way, with the aims to change the blood management behaviour of orthopaedic surgeons and anaesthesiologists in primary elective total hip and knee arthroplasties, using a tailored intervention strategy for de-implementation of erythropoietin and postoperative blood salvage.[17] This study will lead to generalized knowledge regarding relevant factors for the de-implementation of non-cost-effective interventions and insight in the differences between implementation and de-implementation strategies.[17]

Conclusion and future perspectives

Today there is still place for the use of PBM alternatives, however the number of valid alternatives is declining because surgical techniques have improved and a trigger rational (single unit; 4-5-6 mmol/L rule) is used in a vast majority of the hospitals.

Erythropoietin is one of the most conflicting alternatives. Studies in the past have shown that erythropoietin was effective to prevent preoperative anaemia and by this reducing the chance on an allogeneic blood transfusions. But the costs for routine administration largely exceed the reduction in allogeneic blood transfusions and average transfusion rates have gone down questioning whether the previously published results are still valid.

Another alternative is tranexamic acid (TXA), most meta-analysis show reduced blood loss and blood transfusion requirements in patients undergoing orthopaedic surgery, with no increase in the risk of DVT.[18,19] However, this alternative is still little used in daily practice, despite its low costs.

The evidence on the efficacy of drains is clearly in favour of not using drains in primary elective total hip and knee arthroplasty. The evidence for retransfusion drains is more conflicting.[12] However, the large study presented in **chapter 7** and other studies in hospitals with a restrictive blood transfusion policy lack the evidence to support its use.

The limited adherence to trigger values of physicians and the clinicians' interpretation of "clinical symptoms of anaemia" might be important explanations for the heterogeneity found in PBM studies. Critical review of the literature in combination with analysis of the hospital's transfusion numbers is therefore mandatory.

Paradigms on PBM must be modified and, more specifically the quest for a universal transfusion trigger, the holy grail of transfusion medicine, must be abandoned as is proposed by others.[20-22] All allogeneic transfusions must be tailored to the patient's needs. To a certain extend this has been done by the identification of high and low risk groups in the transfusion guideline. But more objective tools are necessary for tailoring the patient's needs, as rational for allogeneic transfusions.[23]

The introduction of a transfusion trigger had an enormous impact on transfusion numbers in the Netherlands in elective orthopaedic surgery and further adaptation of this transfusion rational throughout the world would probably reduce blood transfusions worldwide. Nevertheless, stricter adherence to this transfusion trigger is still necessary, without jeopardising individual patient care. This could probably be obtained by educating clinicians on general (patho) physiology of the cardiovascular system and to give more inside in transfusion medicine.

The clinical heterogeneity in blood transfusion studies ("what is the transfusion trigger") presented in **chapter 10** seems to be an obvious finding, but is still present in the majority of articles and since it has a great effect on outcome of these studies showed by all authors. Patient blood management studies should clarify the 'need' for an allogeneic transfusion in their articles, especially when the set transfusion trigger is waved. Parameters like blood

tension and heart rate should be reported. Finally, reporting the reason for transfusion and the percentage of adherence to a transfusion trigger value (according to an intention-to-treat principle) will help interpreting the results in PBM studies and improvement of the evidence. A study that looks at the intra- and interobserver variations of transfusion decisions could be helpful to find an explanation for differences in transfusion percentages within and between randomised trials.

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Chapter 12

Summary

Chapter 1 gives a general introduction on postoperative local analgesia and patient blood management. This chapter divides the thesis in two sections, patient pain management (PPM) and patient blood management (PBM). The PPM section starts with a study (**chapter 2**) performed to find the optimal dose for good pain relief and lowest side effects that would hamper early mobilisation when using a femoral nerve block for postoperative analgesia. The three dose regimes tested in this study (0.1%, 0.05% and 0.025%) indicated no apparent advantage in decreasing the concentration of ropivacaine administered as bolus injections via the femoral nerve catheter below 0.1% on the patient's ability to actively participate in the rehabilitation programme after total knee arthroplasty (TKA). In fact, the lowest studied concentration (i.e. 0.025%) resulted in a lower patient's satisfaction with the pain treatment, while not improving recovery after TKA.

In **chapter 3** the safety of LIA (local infiltration analgesia) combined with retransfusion of shed blood was evaluated. TKA patients received two peri-articular injections during surgery followed by continuous infusion, both with ropivacaine (567 mg). Ropivacaine plasma concentrations were determined in blood samples taken at 0, 3, 6 and 24 hours postoperatively. The collected shed blood was not retransfused instead retransfusion was modelled by estimating the cumulative plasma concentrations at 6 hours postoperative. Total and unbound ropivacaine plasma concentrations ranged respectively from 0.08 to 1.9 mg/L and 0.003 to 0.11 mg/L. An average of 13.1 ± 3.7 mg unbound ropivacaine would have been returned to the patient. The estimated cumulative ropivacaine plasma levels showed that instant retransfusion would have led to plasma levels below 0.26 mg/L, which is the minimum safety level for systemic toxicity. Thus, it appears to be safe to transfuse autologous blood in combination with LIA if an actual plasma concentration of infused anaesthetics is performed. In **chapter 4** the plasma concentrations of ropivacaine in twenty-two TKA patients that received three peri-articular injections with ropivacaine (300 mg) during surgery were analysed. Plasma and shed blood samples were taken at 0, 1, 3, 6, 7 and 24 hours postoperatively. The calculated (modelled) estimation regarding the maximum unbound ropivacaine plasma concentration showed a median value of 0.114 mg/L (IQR: 0.09, 0.12 mg/L). All concentrations were well below reported toxicity thresholds. The combination of LIA and shed blood retransfusion is considered safe. However, differences in pain protocol (i.e. amount, kind and concentration of anaesthetic) lead to changes in the presented safety evaluation. Compared with previous studies, the technique of administration is of greater importance for the effect on unbound ropivacaine. The latter pharmacokinetic mechanism is unclear.

The RCT in **chapter 5** showed that erythropoietin alpha (EPO) was superior in mildly anaemic patients compared with a postoperative retransfusion system. In mildly anaemic patients, preoperative haemoglobin levels between 10 g/dL and 13 g/dL at screening, the preoperative haemoglobin level increased to a higher level by EPO and reduced the likelihood of receiving an allogeneic blood transfusion. Although the efficacy of erythropoietin is superior to retransfusion drains the costs related to this treatment are large. Furthermore, currently the number of patients in need for blood transfusion in elective orthopaedic surgery is much lower than at the time of this study.

In **chapter 6** the costs associated with routine administration of erythropoietin alpha were calculated. We found that introducing EPO as a standard treatment in our hospital setting would increase the costs by a factor 6. It was showed that health care indicators on PBM could be positively influenced by money from the extramural setting. Even more important, the generalizability of the results on EPO in the Dutch setting should be questioned, looking at the low general transfusion percentages reported ('zichtbare zorg') by Dutch hospitals over the past few years.

In **chapter 7** the percentage of allogeneic blood transfusion requirement was evaluated in a randomised controlled trial (RCT), in 575 patients, comparing three arms: no drain, autologous blood transfusion (ABT) drain with removal after 6 hours (effective ABT time) and ABT with removal the postoperative morning. Secondary outcomes were postoperative haemoglobin (Hb) values, length of hospital stay and adverse events. This study showed a low percentage (6-8%) of transfused patients, with no differences between the three groups (*P=0.857*). The mean preoperative Hb value in the transfused group was 12.8 g/dL versus 14.3 g/dL in the non-transfused group (*P*<0.001, 95% CI: 1.08-1.86 g/dL). Postoperative the median of retransfused shed blood in patients with a THA was 280 mL (IQR 150, 400 mL) and in TKA patients 500 mL (IQR 350, 650 mL) (*P*<0.001). ABT drains had no effect on the percentage of transfused patients in primary THA and TKA. Also the secondary outcomes were comparable between groups.

In **Chapter 8** we studied the efficacy of a new disposable perioperative cell saving device (Sangvia™) in total hip arthroplasty (THA) surgeries. The blinded interim analysis included in the protocol concluded that the original power analysis (outcome percentage of allogenic blood transfusions) was based on a too high percentage of patients in need for blood transfusion from literature data. The setting turned out to be underpowered. The latter resulted in a premature termination of the trial. For that reason the study was not able to draw general conclusions on efficacy. A 12% allogeneic blood transfusion rate was found in the control group, compared to an expected percentage of 21% from literature data.

Blinding is one of the methodological safeguards to improve the internal validity of a study. Furthermore, it has impact on the effect sizes measured. In **chapter 9** we evaluated the impact of blinding assessors for study results when interpreting risk of bias. This type of blinding could have influence on the evaluation of studies for a systematic review or meta-analysis. A randomised, crossover trial was performed between four assessors judging articles in either a blinded or a non-blinded way. A total of 132 articles were selected. The differences in agreement and sum scores on the scales between the assessors suggest that risk of bias judgement may be biased by awareness of study results. However, it remains questionable if this bias is methodologically relevant when performing a systematic review. Further research has to be performed to evaluate its impact when conducting a systematic review, especially in studies regarding the screening of methodological quality.

Heterogeneity is a major problem in PBM studies, especially in drainage studies in orthopaedic surgery. In **chapter 10** a systematic review was performed with focus on the effect of confounders in PBM on the interpretation of outcome results. To this end clinical and methodological quality was checked in all included studies, with special focus on the presented information on the transfusion policy in the studies. In 57% of the included studies an allogeneic blood transfusion was given based only on “clinical symptoms” without a properly defined trigger level. Furthermore, none of the studies gave additional information on the decision when to transfuse blood. The latter was neither based on a specific haemoglobin value nor on specific clinical symptoms. For that matter, this heterogeneity on the reason for blood transfusion in PBM studies severely obscures the possibility to draw conclusions from studies on whether to use either regular or autologous blood transfusion (ABT) drains. A first step in further improvement on PBM policies lies in clear-cut reporting of transfusion trigger information, possibly the use of quantitative physiological transfusion parameters (e.g. adequately monitor tissue oxygenation and haemodynamic stability) in order to compare PBM strategies.

Chapter 13

Samenvatting (summary in Dutch)

Hoofdstuk 1 begint met een algemene inleiding over postoperatieve lokale analgesie en bloedmanagement. Dit hoofdstuk verdeelt dit proefschrift in twee secties, Patiënt Pijn Management (PPM) en Patiënt Bloed Management (PBM). Het onderdeel PPM begint met een zogenaamde dose-finding studie (**hoofdstuk 2**). Hierin zijn we op zoek naar de optimale dosis van een femorale zenuwblokkade voor postoperatieve analgesie die een goede verlichting van de pijn geeft en de minste bijwerkingen heeft die vroege mobilisatie kan belemmeren. De drie geteste dosisregimes (0,1%, 0,05% en 0,025%) geven geen duidelijk voordeel in het verlagen van de concentratie van ropivacaine, toegediend als bolusinjecties via de femorale zenuwkatheter, onder de 0,1%. In feite, de laagst onderzochte concentratie (0,025%) resulteerde in een lagere patiënttevredenheid over de pijnbehandeling, zonder een verbetering in het herstel na een totale knieprothese (TKP).

In **hoofdstuk 3** wordt geëvalueerd of LIA (lokale infiltratie analgesie) veilig gecombineerd kan worden met retransfusie van opgevangen wondbloed. De patiënten ontvingen twee peri-articulaire injecties in de knie tijdens de operatie, gevolgd door continue infusie aldaar, beide met ropivacaine. In totaliteit werd 567 mg ropivacaine gegeven. De plasmaconcentraties van ropivacaine werden bepaald in bloedmonsters van de patiënt, afgenomen op 0, 3, 6 en 24 uur postoperatief. De patiënt kreeg zijn opgevangen wondbloed niet intraveneus terug, daarentegen werd retransfusie gemodelleerd door een schatting te geven van de cumulatieve plasmaconcentraties 6 uur na de operatie. De totaal en ongebonden ropivacaine plasmaconcentraties varieerden respectievelijk tussen de 0,08 en 1,9 mg/L en 0,003 en 0,11 mg/L. Als het opgevangen wondbloed teruggegeven zou worden aan de patiënt zou hier gemiddeld 13,1 ± 3,7 mg ongebonden ropivacaine in zitten. De geschatte cumulatieve ropivacaine plasmaspiegels na retransfusie zou geleid hebben tot plasmaspiegels onder de 0,26 mg/L, het minimale veiligheidsniveau voor systemische toxiciteit. Hiermee is aangetoond dat deze LIA-concentraties veilig zijn om te gebruiken in combinatie met een autoloog bloedretransfusiesysteem bij TKP patiënten.

In **hoofdstuk 4** werden de plasmaconcentraties van ropivacaine in tweeëntwintig TKP patiënten geanalyseerd, die drie peri-articulaire injecties met ropivacaine (300 mg) tijdens de operatie kregen. Plasma van de patiënt en wondbloedmonsters werden afgenomen op de volgende 6 tijdsmomenten; 0, 1, 3, 6, 7 en 24 uur postoperatief. De berekende (gemodelleerde) maximale ongebonden ropivacaine plasmaconcentratie toonde een mediane waarde van 0,114 mg/L (IQR: 0,09, 0,12 mg/L). Alle individuele concentraties waren duidelijk lager dan de gerapporteerde toxiciteitsdrempels. De combinatie van LIA en wondbloed retransfusie wordt als veilig beschouwd. De verschillen in

pijnprotocol (zoals hoeveelheid, soort en concentratie van anesthesie) kunnen leiden tot veranderingen in de gepresenteerde veiligheidsevaluatie. Dit gecombineerd met eerdere studies blijkt dat de methode van toediening van groter belang is dan de concentratie, dit vanwege het effect op de ongebonden ropivacaine hoeveelheid. Het farmacokinetische mechanisme hierachter is nog onduidelijk.

Uit de RCT in **hoofdstuk 5** bleek dat erytropoëtine alpha (EPO) superieur was in mild anemische patiënten in vergelijking met een postoperatief retransfusiesysteem. Bij mild anemische patiënten, preoperatieve hemoglobine niveaus tussen 10 g/dL en 13 g/dL bij screening, werd het preoperatieve hemoglobinegehalte hoger door EPO, wat de kans op het ontvangen van een allogene bloedtransfusie verminderd. Hoewel de werkzaamheid van erytropoëtine alpha superieur is aan een retransfusie zijn de kosten van een dergelijke behandeling hoog. Bovendien is het aantal patiënten dat een bloedtransfusie nodig heeft na electieve orthopedische chirurgie nu veel lager dan op het moment dat dit onderzoek werd uitgevoerd.

In **hoofdstuk 6** worden de kosten in verband met routineus toepassen van erytropoëtine alpha in de praktijk berekend. Wij vonden dat indien EPO als standaardbehandeling zou worden ingevoerd in ons ziekenhuis, de kosten toe zouden nemen met een factor 6. Daarnaast is het mogelijk om gezondheidszorgindicatoren over PBM positief te beïnvloeden door geld uit te geven dat komt uit de extramurale setting. Maar nog belangrijker, momenteel kan men vraagtekens zetten over de generaliseerbaarheid van de EPO resultaten in de Nederlandse setting., dit kijkend naar de lage algemene transfusiepercentages gerapporteerd (‘Zichtbare Zorg’) door Nederlandse ziekenhuizen in de afgelopen jaren.

In **hoofdstuk 7** is het percentage allogene bloedtransfusies geëvalueerd in een gerandomiseerd gecontroleerd onderzoek (RCT) bij 575 patiënten. Deze studie had drie behandelarmen: geen drain, autologe bloedtransfusie (ABT) met verwijdering van de drain na 6 uur (effectieve ABT tijd) en ABT met het verwijderen van de drain de eerste postoperatieve ochtend. Secundaire uitkomsten waren postoperatief hemoglobine (Hb) niveau, de duur van verblijf in het ziekenhuis en bijwerkingen tot 6 weken na operatie. Deze studie had een laag transfusiepercentage (6-8%) met geen verschil tussen de drie groepen (p=0.857). De gemiddelde preoperatieve Hb-waarde in de transfusiegroep was 12,8 g/dL versus 14,3 g/dL in de niet-transfusiegroep (p <0,001, 95% CI: 1,08-1,86 g/dL). De mediaan van geretransfundeerd bloed bij patiënten met een THA was 280 mL (IQR: 150, 400 mL) en in TKA patiënten 500 mL (IQR: 350, 650 mL) (p <0,001). Ook de secundaire uitkomsten waren vergelijkbaar tussen de groepen. ABT-drains hebben geen effect op het transfusie percentage van patiënten in primaire THA en TKA.

In **hoofdstuk 8** hebben we de werkzaamheid van een nieuw disposable perioperatief bloedsysteem (Sangvia™ Bloed Management System, AstraTech AB, Mölndal, Zweden) bij totale heupprothese (THA) chirurgie onderzocht. De tussentijdse analyse, die uitgevoerd werd volgens protocol, toonde aan dat de oorspronkelijke berekening van groepsgrootte gebaseerd was op een te hoog percentage patiënten die een bloedtransfusie nodig hadden. De studie bleek underpowered om de verwachte uitkomst aan te tonen, dit resulteerde in het voortijdig stoppen van de inclusie van nieuwe patiënten in het onderzoek. Om die reden was de studie niet in staat om algemene conclusies te trekken over de werkzaamheid maar alleen te kijken naar kwaliteit van opgevangen bloed. Het percentage allogene bloedtransfusies was 12% in de controlegroep vergeleken met een verwacht percentage van 21% vanuit de literatuur. De complicaties na het gebruik van dit systeem waren vergelijkbaar tussen de twee groepen en de lab waarden toonden geen onveilige bloedwaarden aan waardoor de veiligheid van het systeem verder is aangetoond.

Blindering is een van de methodologische kernpunten om de interne validiteit van een studie te waarborgen c.q. verbeteren. Bovendien heeft blindering invloed op de effectmaten die worden gemeten.

In **hoofdstuk 9** evalueerden we de impact van beoordelaars, die blind waren voor de studieresultaten, op hun interpretatie van het risico op bias in een studie. Deze vorm van blindering kan invloed hebben op de evaluatie van studies voor een systematisch review of meta-analyse. Een gerandomiseerde, cross-over studie werd uitgevoerd tussen vier beoordelaars die 132 artikelen beoordeelden op ofwel een geblindeerde of een niet-geblindeerde wijze. De verschillen in de overeenkomst en somscores op de schalen tussen de beoordelaars suggereren dat het risico op bias beïnvloed kan worden door het bewustzijn van de studieresultaten. Het blijft echter de vraag of dit methodologisch relevant is bij het uitvoeren van een systematisch review. Verder onderzoek moet gedaan worden om de impact hiervan bij het uitvoeren van een systematische review te beoordelen, vooral in studies die de focus leggen op screening van methodologische kwaliteit.

Heterogeniteit is een groot probleem in PBM-studies. In **hoofdstuk 10** werd een systematisch review uitgevoerd met focus op het effect van verstorende factoren in PBM op de interpretatie van de uitkomstmaten. Daarnaast werden klinische en methodologische kwaliteit gecontroleerd in de geïncludeerde studies, met speciale aandacht voor de gepresenteerde informatie over het gevoerde transfusiebeleid. In 57% van de geïncludeerde studies bestond de mogelijkheid een allogene bloedtransfusie te geven gebaseerd op “klinische symptomen”. Bovendien presenteerden geen van de studies aanvullende informatie over de beslissing wanneer allogeen bloed getransfundeerd werd. Om die

reden is het lastig om in PBM-studies conclusies te trekken wat betreft de waarde van een gewone of autologe bloedretransfusiedrain op het percentage allogene bloedtransfusies. Een eerste stap in de verdere verbetering van het PBM-beleid ligt in duidelijkere rapportage van transfusie trigger-informatie, mogelijk het gebruik van kwantitatieve fysiologische transfusieparameters (bijvoorbeeld een adequate zuurstofvoorziening van de weefsels en de hemodynamische stabiliteit te bewaken) om PBM-strategieën te vergelijken.

Appendix

Elevator pitch

ELEVATOR PITCH

What is already known on this topic

Local infiltration analgesia in combination with a multimodal pain approach helps for adequate postoperative pain control.

Blood saving alternatives should be implemented in the process of primary total hip and knee arthroplasties.

The endpoint in patient blood management studies is usually Transfusion.

What this thesis adds

Local infiltration as defined in this study can be used safely in combination with an autologous blood transfusion drainage system.

Key clinical components of a randomised trial are frequently inadequately taken into account when performing a systematic review.

The endpoint transfusion in patient blood management studies needs additional information to make it a strong endpoint.

What is necessary in the future

More evidence based practice, use the correct available evidence in the light of your own hospital figures, in patient blood management.

More adequate reporting of and explanations for the transfusion decisions made in patient blood management trials.

Appendix

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Appendix

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DANKWOORD

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Lieve Peter, waar moet ik beginnen, waar het is begonnen? Wat een drive heb jij, super dat je die met regelmaat op mij overbrengt. Onwijs bedankt voor alle input die jij hebt geleverd. "Hoe bevalt deze plek in de zaal?" Een samenwerking die niet alleen op wetenschappelijk vlak succesvol is gebleken. Het mooiste resultaat van onze samenwerking zien we iedere dag. Op naar meer mooie en bijzondere momenten met onze 'mennekes' Siem en Vigo. Ik hou van jullie!

Appendix

List of publications

LIST OF PUBLICATIONS

- Bregje JW Thomassen, Peter HC den Hollander, Herman H Kaptijn, Rob GHH Nelissen, Peter Pilot. Autologous wound drains have no effect on allogeneic blood transfusions in primary total hip and knee replacement. A three arm randomised trial. *Bone Joint J 2014 Jun;96-B:765-71*
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Appendix

Curriculum Vitae

CURRICULUM VITAE

Bregje Josephina Wilhelmina Thomassen was born on 17th of February 1982 in Roermond, the Netherlands. She completed secondary school at the Bisschoppelijk College Schöndeln in Roermond in 1999. In that same year she started to study Food and Dietetics at the Hogeschool van Arnhem and Nijmegen (HAN). This study was followed with a Masters degree (2005) in Health Sciences (Movement Science) at Maastricht University. She started working as research coordinator at the Orthopaedic Department of the Maaslandziekenhuis in Sittard (now: Orbis Medical Center). She changed her working position to the Medical Center Haaglanden in the Hague in 2008 and completed in 2012 her Master in Epidemiology at the VU in Amsterdam. Now she works at the orthopaedic department and is staff member research at the Landsteiner Instituut (MCH graduate school).