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The safety of peri-articular local anaesthetic injection for patients undergoing total knee replacement with autologous blood transfusion

A RANDOMISED TRIAL

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Intra-operative, peri-articular injection of local anaesthesia is an increasingly popular way of controlling pain following total knee replacement. At the same time, the problems associated with allogenic blood transfusion have led to interest in alternative methods for managing blood loss after total knee replacement, including the use of auto-transfusion of fluid from the patient's surgical drain. It is safe to combine peri-articular infiltration with auto-transfusion from the drain. We performed a randomised clinical trial to compare the concentration of local anaesthetic in the blood and in the fluid collected in the knee drain in patients having either a peri-articular injection or a femoral nerve block. Clinically relevant concentrations of local anaesthetic were found in the fluid from the drains of patients having peri-articular injections (4.92 µg/ml (SD 3.151)). However, none of the patients having femoral nerve blockade had detectable levels. None of the patients in either group had clinically relevant concentrations of local anaesthetic in their blood after re-transfusion.

The evidence from this study suggests that it is safe to use peri-articular injection in combination with auto-transfusion of blood from peri-articular drains during knee replacement surgery.

Effective analgesia facilitates early mobilisation and rapid recovery of knee movement and is said to have an effect on the overall outcome of total knee replacement (TKR).^{1,2} Subsequent delay in rehabilitation can lead to prolonged hospitalisation, suboptimal outcome and post-operative complications.³ Epidural analgesia, patient-controlled opioid administration and femoral nerve block have been used either in isolation or combination to achieve effective analgesia.⁴⁻⁶ However such methods are associated with both local and systemic side-effects and complications (Table I).⁷⁻⁹

Recently, the use of intra-operative, peri-articular administration of analgesics has gained popularity.¹⁰ This has the advantage of delivering drugs directly to the source of pain, particularly the posterior capsule of the knee joint that is innervated by branches of the sciatic nerve and thus unaffected in femoral nerve blockade. The reported advantages of peri-articular injection for TKR include early mobilisation, reduced analgesic requirements and early discharge from hospital.¹⁰⁻¹⁵

At the same time, the problems associated with allogenic blood transfusion^{16,17} have led

to increasing interest in alternative methods for managing blood loss after TKR; these include the use of auto-transfusion drains.¹⁸ However, since local anaesthetic from peri-articular injections may enter the drain, there is a potential risk of intravenous infusion of potentially harmful levels of local anaesthetic.

This study explores the safety of peri-articular injection, in association with the use of autologous transfusion of drain contents after TKR. We compare the concentration of local anaesthetic in the blood of patients who have received a transfusion of the drainage from their knee drains when randomised to receive either a peri-articular injection or a femoral nerve block.

Patients and Methods

This study was approved by the West Midlands Research Ethics Committee and took place in a single University Hospital. A total of 46 patients undergoing TKR were randomised to have either peri-articular injections or femoral nerve blocks (as part of an on-going pilot randomised trial: ISRCTN29107680). The treatment of the patients was allocated on the

Table I. Recognised side effects and complications of analgesic methods used in knee replacement post-operatively⁷⁻⁹

Epidural analgesia	Patient-controlled opioid analgesia	Femoral nerve block
Pruritus	Nausea and vomiting	Vascular puncture
Urinary retention	Respiratory depression	Nerve damage
Motor block	Drowsiness	Infection
Spinal cord ischaemia	Pruritus	Inhibition of quadriceps
Vertebral canal haematoma	Reduced gut motility	
Vertebral canal abscess	Urinary retention	
Infective meningitis		
Nerve and spinal cord injury		
Wrong route administration		
Cardiovascular collapse		

basis of a computer generated randomisation sequence. On advice of the trial statistician (HP) and anaesthetist (SB) the analysis was based upon 20 to 25 patients per experimental group and data from 23 participants in each group is reported. All patients undergoing a primary unilateral TKR under general anaesthesia were potentially eligible for the study. Patients who lacked capacity to give consent and those who had a specific contraindication to the analgesic agents, including those with renal failure, were excluded.

The femoral nerve block was performed by the attending anaesthetist who used nerve stimulation to identify the femoral nerve before injecting 30 ml of levobupivacaine 0.25%.

The peri-articular infiltration of local anaesthetic consisted of 150 mg of levobupivacaine, 10 mg morphine and 30 mg ketorolac, with 0.5 ml 1:1000 adrenaline diluted in 0.9% saline to make up a volume of 100 ml. Half of the mixture was injected into the posterior, medial and lateral soft tissues just before implantation of the knee replacement components. The other 50 ml was injected into the anterior soft tissues including the extensor mechanism, before the knee wound was closed.¹²

Both groups of patients had an auto-transfusion drain (Bellovac ABT retransfusion system; Astra Tech Ltd, Gloucester, United Kingdom) inserted and then the tourniquet was released and the time noted. Previous studies have indicated that following administration of levobupivacaine or bupivacaine epidurally,¹⁹ locally^{20,21} or intra-articularly,²² the time to maximum serum concentration (T_{max}) is between 28 and 43 minutes.

A 5 ml blood sample was taken 40 minutes after the tourniquet was released in order to measure the pre-retransfusion serum levobupivacaine levels (pre-transfusion sample). A further six hours later the contents of the re-transfusion drain was routinely transfused to the patient intravenously with a 5 ml sample of the blood from the drain (the drain sample) collected before the remainder being transfused. Another 40 minutes after the end of auto-transfusion, a further blood sample was collected from the participant to ascertain the post-transfusion serum concentration of levobupivacaine (post-transfusion sample).

The samples were collected in yellow (BD; SST gel/clot activator) blood bottles and each was centrifuged and the serum was stored in a -80°C freezer. All samples were treated in accordance with terms set out in the study protocol and the Human Tissue Act Codes of Practice.

Samples were analysed by an independent laboratory (Cemas, Berkshire, United Kingdom). Biochemical and levobupivacaine quantification was performed by High Performance Liquid Chromatography analysis using a Waters C8 4.6 × 100 mm, 3.5 µm column with ultraviolet detection at 220 nm (Waters Corporation, Milford, Pennsylvania). The mobile phase (A) was 0.005 M ammonium formate adjusted to pH 4 with formic acid with an organic mobile phase (B) of acetonitrile. All samples were run in isocratic separation: 78:22 of A:B. Sample analysis was performed blind to the allocated treatment.

Statistical analysis. Two sided *t*-tests were used to test for differences between patients in the intervention groups at each of the three sampling points on an intention-to-treat basis. Significance was set at the 5% level for all analyses. Samples that were found to have levels of local anaesthetic below the limit of detection (< 0.4 µg/ml) were said to have 0 µg/ml and missing values were excluded from the analysis. A Bonferroni correction was applied to the three *t*-tests to reduce the rate of false positives. Statistical analysis and graphical summaries of the data were conducted using the R statistical package (version 2.12.1).²³

Results

The baseline demographics of the trial population demonstrate that the two groups of 23 patients are broadly similar (Table II).

Biochemical HPLC analysis of levobupivacaine revealed limits of detection from 0.4 µg/ml to 12 µg/ml. The levels of local anaesthesia at each of the three collection points are shown in Table III. The distributions of these values are shown in Figure 1. There was a statistically significant difference between the two treatment groups for the drain sample only ($p < 0.001$).

During the course of the study one patient in the peri-articular infiltration group had an unexpected episode of

Table II. Baseline characteristics of patients (n = 46) (IQR, interquartile range)

	Femoral nerve block (n = 23)	Peri-articular injection (n = 23)
Female:male	10:13	13:10
Median age (yrs) (IQR)	63.5 (61 to 74)	63.5 (55.5 to 65)
Side of knee replacement (left:right)	11:12	12:11

Table III. Levels of local anaesthetic at the three time points. Means and ranges are shown with standard deviation (SD) in brackets. Quantification of the anaesthetic levobupivacaine occurs between 0.4 to 12 µg/ml

	Femoral nerve block (n = 23)	Peri-articular injection (n = 23)
Pre-transfusion sample		
Mean (SD) anaesthetic level (µg/ml)	0.018 (0.0855)	0 (0)
Number within quantification limit	1	0
Number below quantification limit	22	23
Number of missing values	0	0
Drain sample		
Mean (SD) anaesthetic level (µg/ml)	0 (0)	4.92 (3.151)*
Number within quantification limit	0	23
Number below quantification limit	22	0
Number of missing values	1	0
Post-transfusion sample		
Mean (SD) anaesthetic level (µg/ml)	0 (0)	0.077 (0.196)
Number within quantification limit	0	3
Number below quantification limit	20	18
Number of missing values	3	2

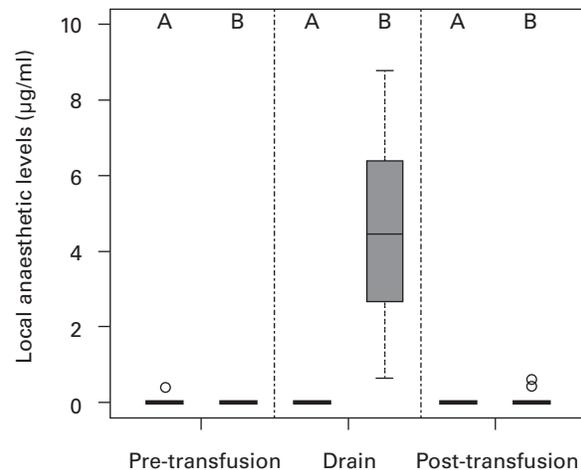
* one sample was initially above the quantification threshold and re-analysed

paroxysmal atrial fibrillation in the immediate post-operative period. The episode occurred before the patient had re-transfusion of blood from their drain and resolved following the administration of beta-blockers.

Discussion

This trial has demonstrated that clinically relevant concentrations of local anaesthesia are found in the drain fluid of patients having intra-operative peri-articular infiltration after TKR. However, none of the patients having autologous re-transfusion of the fluid from the drain had clinically important levels of local anaesthetic in their blood, and in the majority of patients the concentration of local anaesthetic was below the detectable level.

Most of the evidence related to the systemic effects of local anaesthesia comes from work on the use of intravenous regional anaesthesia.^{24,25} The preferred anaesthetic for intravenous regional use is either prilocaine or lidocaine due to their short duration of action and low systemic toxicity.^{22,25} Longer-acting agents such as levobupivacaine are preferable for peri-operative pain relief in knee replacement surgery.²⁵ The use of levobupivacaine is associated with less serious side-effects than bupivacaine, which can cause adverse central nervous system and cardiovascular effects²; the former drug has been advocated by some as a primary agent.²⁵ However, there have been a number of case reports involving the accidental intravascular administration of levobupivacaine that have produced differing degrees of

**Fig. 1**

Boxplot showing distribution of the levels of local anaesthesia (µg/ml) in the pre-transfusion, drain and post-transfusion samples for groups treated by femoral nerve block (A) and peri-articular injection (B).

central nervous system toxicity but no cardiac dysrhythmias. Although the risk of systemic side-effects is at face value greatly reduced in peri-articular infiltration compared with intravenous regional anaesthesia, there may be systemic effects when intra-articular drain contents are used for autologous transfusion. A study of 12 healthy

adult volunteers receiving intravenous levobupivacaine showed that plasma concentrations of 2.38 µg/ml can be associated with central nervous system side effects.² In our patients receiving autologous drain transfusion, the maximum drug concentrations were all substantially below the level that may cause side effects. Indeed, 18 of the 23 patients were below the detectable limit of 0.04 µg/ml. This suggests that it is safe to use autologous blood transfusion from a drain in TKR in combination with peri-articular injection of local anaesthetic as part of a multi-modal infiltration of analgesia.

In the pre-transfusion sample none of the patients having peri-articular injections had quantifiable levels of levobupivacaine in their blood serum. One patient in the group undergoing femoral nerve block did have a measurable serum level that might be explained by an inadvertent intravascular injection of the drug.

None of the patients in the femoral nerve block arm of the study had quantifiable levels of levobupivacaine in their drain sample and all 23 of the samples from the peri-articular injection group did. This confirms that some of the local anaesthesia from the peri-articular injection does leak into the knee joint. The mean drain concentration of levobupivacaine was 4.92 µg/ml (SD 3.2), which is above the total serum levobupivacaine concentration at which patients might demonstrate central nervous system symptoms. If these drain concentrations were given as a rapid bolus infusion there is a theoretical risk of levobupivacaine associated symptoms. However it is standard practice with autologous transfusion to re-transfusion slowly over one to two hours. Of the measured drug levels 40 minutes after transfusion only three of the 20 patients for whom a post-transfusion sample was available had quantifiable levels of local anaesthesia in their serum; the rest were below the limits of detection. This trial refers to patients having a single peri-articular injection during unilateral knee replacement and the results should not be extrapolated to include patients having continuous post-operative infiltration of local anaesthetic agents or bilateral knee replacements.

Surgeons are already aware of the need to reduce the use of allogenic blood products in knee replacement surgery, although there is still inconsistency in the indications for and incidence of transfusion.²⁶ Although quantifiable levels of local anaesthesia are found in the drain fluid of patients having peri-articular knee injections the auto-transfusion of fluid from these drains subsequently results in non-toxic levels of local anaesthetic in the blood serum. This supports the contention that it is safe to use peri-articular injection in combination with auto-transfusion of fluid from peri-articular drains used during TKR.

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