The technique of delivery of peri-operative analgesia does not affect the rehabilitation or outcomes following total knee arthroplasty

McDonald, D. A.; Deakin, A.H.; Ellis, B.M.; Robb, Y.; Howe, T.E.; Kinninmonth, A.W.G.; Scott, N.B.

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Peri-operative analgesic method does not affect rehabilitation outcomes following total knee arthroplasty.

D A McDonald (Prof D, BSc) - Clinical Researcher, Department of Rehabilitation, Golden Jubilee National Hospital, Agamemnon St, Clydebank, Scotland, G81 4DY.

A H Deakin (PhD) – Orthopaedic Audit & Research Manager, Department of Orthopaedics, Golden Jubilee National Hospital, Agamemnon St, Clydebank, Scotland, G81 4DY

B M Ellis (PhD) - Deputy Director, Graduate School, Glasgow Caledonian University, Cowcaddens Road, Glasgow, Scotland, G4 0BA

Y Robb (PhD) - Lecturer, School of Health & Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, Scotland, G4 0BA

T E Howe (PhD) - Professor of Rehabilitation, School of Health & Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, Scotland, G4 0BA

A W G Kinninmonth (FRCS) - Consultant Orthopaedic Surgeon Department of Orthopaedics, Golden Jubilee National Hospital, Agamemnon St, Clydebank, Scotland, G81 4DY

N B Scott (FRCA, FRCS) - Consultant Anaesthetist, Department of Anaesthesia, Golden Jubilee National Hospital, Agamemnon St, Clydebank, Scotland, G81 4DY

ABSTRACT

This non-blinded randomised controlled trial compared the effect of patient controlled epidural analgesia (PCEA) versus local infiltration analgesia (LIA) within an established Enhanced Recovery Programme on attainment of discharge criteria and recovery at one year following surgery. The hypothesis was that LIA would increase the proportion of patients discharged from rehabilitation by post-operative day four but not affect outcomes at one year. 242 patients were randomized with 109 patients receiving PCEA (mean age 66 SD (11)) and 113 receiving LIA (mean age 68 SD (10)). Patients were followed up at six weeks and one year. No difference was noted in the proportion of patients discharged from rehabilitation by post-operative day 4, PCEA =77% vs. LIA =82% (p=0.33) or mean length of stay (both 4 days, p=0.540). No difference was observed in day of first mobilisation (p= 0.013) or pain scores (P=0.278). At one year follow up there were no differences in Oxford Knee Scores (both 41, p=0.915) or complication rates (two vs. six, p=0.281). Both techniques provided adequate pain relief, enabled early ambulation and accelerated rehabilitation and continued improvement in functional and patient reported outcomes up to one year following surgery. PCEA and LIA enable equitable clinical outcomes following TKA.

INTRODUCTION

Enhanced Recovery Programmes (ERP) following total knee arthroplasty (TKA) have demonstrated reductions in both morbidity and mortality[1-3]. Their implementation has included several major alterations in clinical practice simultaneously and therefore it is difficult to ascertain which component(s) of the programme may be most significant in the improvements reported[4]. Emerging evidence supports both pre-operative education[5,6] and accelerated rehabilitation[7], however the optimum method(s) of multimodal analgesia throughout the peri-operative period remains unclear[8]. Regional analgesic techniques have demonstrated improvements in pain control and outcomes following TKA compared to opioid analgesia alone[9,10]. However, they are associated with rare major risk factors such as spinal haematoma for epidurals[11] and prolonged motor blockade and falls in femoral nerve blocks[12,13] which may hinder early ambulation and delay rehabilitation[13,14]. The effect of these regional analgesic techniques on rehabilitation outcomes and long term follow up is poorly understood[9,15].

Local Infiltration Analgesia (LIA) has been reported as an alternative analgesic regime with a number of studies demonstrating equitable or improved outcomes compared to opioid analgesia[16] and other regional anaesthetic techniques[14,17-21]. However due to the varying cocktail of infiltration medicines, the volume of infiltrate and limited number of high quality evidence studies comparing two regional techniques which allow early ambulation, it is difficult to draw comparisons and extrapolate the findings[22]. Furthermore, there is a lack of data from randomised

trials looking at long-term follow up.

The aim of this study was to compare the effect of two regional analgesic techniques, patient controlled epidural analgesia (PCEA) versus local infiltration analgesia (LIA) within an established Enhanced Recovery Programme to ascertain their impact on attainment of rehabilitation discharge criteria and outcomes at six weeks and one-year post-surgery.

The primary outcome measure was the proportion of patients discharged from rehabilitation on post-operative day 4 (POD 4). Secondary outcome measures included in-patient data: verbal rated pain scores (VRS); use of additional rescue analgesia; post-operative urinary catheterisation rates; ambulation rates on the day of theatre; length of hospital stay; and rehabilitation outcomes: Oxford Knee Scores and complication rates at six weeks and one-year post-surgery.

PATIENTS AND METHODS

The study was a randomised controlled parallel group trial with an equal allocation ratio. Ethical approval was obtained from the West of Scotland Research Ethics Committee (NRES:09/S10014/56). The study was conducted in accordance with the Declaration of Helsinki and conformed to the CONSORT Guidelines[23] and has been registered at clinicaltrial.gov (NCT02478372). From April 2010-August 2011 patients aged over 18 years undergoing primary unilateral TKA for osteoarthritis were considered eligible for inclusion into the study. Exclusion criteria included: patients listed for uni-compartmental/bilateral or revision knee surgery, a diagnosis of rheumatoid arthritis, coagulation or anatomical defects preventing the use of spinal anaesthesia or known allergies to any medications within the trial, inability to give written

consent, requiring pre- operative catheterisation for urinary outflow dysfunction and a known neurological incident that would limit or make impossible early mobilisation following surgery. Written and informed consent for the trial was obtained on the day prior to surgery. Participation within the trial ended following the routine one-year follow-up appointment.

A simple unrestricted (non-block) randomisation method was used to generate the random allocation sequence. Patients were randomised to either patient controlled epidural analgesia (PCEA) or local infiltration analgesia (LIA). Randomisation was carried out using sequentially numbered opaque sealed envelopes[24]. Once written informed consent was obtained by the surgeon, the anaesthetist in charge of the patient's care collected the next numbered envelope on the morning of surgery.

All patients received standardised peri-operative care. This included pre-operative education in the form of written information, an education class and exercise DVD. All patients received the pre- operative and post-operative analgesic regime in Table 1. Surgery was performed under spinal via the L2/3 or L3/4 interspaces using 2.5ml hyperbaric bupivacaine 5 mg.ml-1 supplemented by a target-controlled infusion of propofol to maintain sedation. In the event of a general anaesthesia being required because of failed spinal anaesthesia, the patient was excluded from the trial. Tranexamic acid (2.5 g) was administered intravenously to minimise post-operative blood loss. A medial parapatellar or lateral parapatellar arthrotomy under tourniquet was used as per surgeon preference. Cemented implants were as per surgeon preference (Triathlon™, Stryker, Michigan, USA or Columbus™, BBraun Medical Ltd. Melsungen, Germany).

The PCEA group had a catheter sited between L1 and L3 pre-operatively. They received 4ml of

2.5 mg.ml-1 levobupivacaine at the end of surgery prior to leaving the operating room. Thereafter they self-medicated with 2ml of 1.25 mg.ml-1 bupivacaine via a Patient Controlled Epidural Analgesia (PCEA) system (BodyGuard Colourvision 545™ Epidural Infusion Pump (CME Medical UK Limited, Blackpool, UK)) with a lockout of 15 minutes until 8 a.m. the following morning (post-operative day one) when it was stopped. Nurse-administered rescue top-ups of 4ml of 2.5 mg.ml-1 levobupivacaine were available for inadequate analgesia.

The LIA group received standardised intra-articular and subcutaneous infiltration during surgery using a total of 200 ml of 2mg.ml-1 ropivacaine (Naropin®, AstraZeneca, Sweden) without adrenaline or additives[3]. 50ml was injected following bone preparation parallel to the posterior femur through the posterior joint capsule in even 10ml aliquots. 30ml was inserted through the skin proximal to the suprapatellar pouch down to the level of the femur. 100ml was spread around the subcutaneous tissues including the collateral ligaments and cruciate ligaments (when preserved) and fatty and connective tissue on the anterior aspect of the incision. A 16-gauge epidural catheter (BBraun Medical Ltd. Melsungen, Germany) was inserted via a medial portal several centimetres from the wound and passed into the posterior region of the knee. Finally, 20ml was injected via the catheter following closure of the surgical wound. The catheter was then capped off and a bacterial epidural filter applied.

On return to the ward, patients received nurse-administered boluses of 40ml 2mg.ml-1 ropivacaine via a BodyGuard 595™ Regional Analgesia Infusion Pump (CME Medical UK Limited, Blackpool, UK) four hours after leaving theatre, at 22:00 and then at 08:00 on the morning of post-operative day one, after which the catheter was removed. In the event of uncontrolled pain two additional top ups of 40ml 2mg.ml-1 ropivacaine were prescribed if

required within this time frame. All wounds were closed with sutures or clips and standard dressings applied[25] Prior to 6pm on the day of theatre, all patients were reviewed by a physiotherapist to begin ambulation. Pain scores in the form of summary 24-hour verbal rating scores (VRS)[26] were collected for the first three post-operative days as were daily nausea and vomiting scores as per the standard care in our institution at the time. The usage of PRN analgesia, post-operative urinary catheterisation rates and the reason for catheterisation were also recorded. From post-operative day (POD) one patients were reviewed daily by rehabilitation staff and were discharged from rehabilitation once they had achieved established standardised discharge criteria (Table 2)[3]. Maximum flexion angle achieved at discharge from rehabilitation was measured using a hand held goniometer[27]. Patients who were unable to achieve the required flexion or demonstrate a return of sufficient quadriceps muscle strength after day five post-surgery were referred on to outpatient physiotherapy. All patients were discharged directly home.

Patients attended routine independent arthroplasty follow up clinic appointments at six weeks and one year after surgery. Oxford Knee Scores (OKS, 0 to 48 scale)[28] and maximum flexion were recorded. Any adverse events whilst patients were in hospital following surgery were recorded. Transfusion policy was a haemoglobin of <= 8g/dL or if significant symptoms of anaemia developed. Information Services Division (ISD) NHS Scotland, provided complication data based on readmission to any hospital in Scotland. up to one-year post surgery. They also provided mortality data.

Statistics

Preliminary data demonstrated that 49% patients (22/45) receiving PCEA could be discharged

from rehabilitation by POD 4 compared to 75% (40/53) who had LIA. Therefore, to achieve a 90% power at a 1% significance level with 50% discharged in PCEA group and 75% in the LIA group it was calculated that the study would require 110 patients in each arm. Allowing for a 10% fall out rate, it was intended to recruit 121 patients into each arm of the study. Due to the large number of secondary outcome measures statistical significance was set at $p<0.01$.

Statistical analysis was performed using SSPS version 19 (SPSS Inc., Chicago, IL, USA). Data were analysed on a per protocol basis. The primary outcome for the study was assessed using a Chi- squared test. The secondary outcomes of length of stay, post-operative mobilisation and post- operative catheterisation were assessed using a Chi-squared test. Pain scores, use of PRN analgesia, maximal flexion at discharge and follow up along with OKS were not normally distributed so were assessed with a Mann-Whitney test. Due to the small numbers of complication data, a Fishers Exact Test was used.

RESULTS

308 patients attending the outpatient appointment were assessed for eligibility to the trial (Figure 1). A total of 242 patients were recruited and randomised to the two groups (121 patients per group). Demographic data for all randomised patients were similar between groups (Table 3). Twenty patients were excluded from the analysis, 12 in the PCEA group and eight in the LIA group, all due to failed spinal anaesthesia.

For the PCEA (n=109) and LIA (n=113) groups no difference was observed between the proportions of patients discharged from rehabilitation by POD 4 p=0.332 (Table 4, Figure 2). No differences in the time (days) to achieve the discharge criteria, length of hospital stay, pain VRS, the PRN analgesia usage or incidence of nausea and vomiting, maximum knee flexion on

discharge or proportion of patients sent for further outpatient physiotherapy were seen (Table 4). One patient within each group required a PCA morphine pump to be started due to poor pain control on post-operative day one.

A higher proportion of patients within the LIA group were able to ambulate for the first time on the afternoon of theatre however this was not statistically significant based on our a-priori criterion of $p<0.01$ (Table 4). All patients within the LIA group had ambulated within 24 hours of surgery but four patients within the PCEA group did not achieve this until the morning of post-operative day two. The main reason for failed ambulation on theatre day was an unresolved spinal anaesthesia block resulting in motor weakness preventing safe ambulation.

At six weeks and one year follow up no statistically significant difference were observed in outcomes (Table 5). Up to one-year post-operation the PCEA group had two complications (one wash-out for suspected infection and one acute myocardial infarction) and the LIA group had six (one gastro-intestinal bleed, two suspected infections, one renal failure, two deaths (causes unknown) ($p= 0.281$).

DISCUSSION

This study demonstrated no differences between the proportion of patients obtaining set discharge criteria by POD 4 following a primary TKA within an established Enhanced Recovery Programme whether PCEA (77.1%) or LIA (82.3%) analgesia was used. Similarly, the median time to attain discharge criteria (3 days) and total post-operative stay (4 days) showed no difference between groups. These findings are contrary to two previous randomised trials of continuous epidural and LIA following TKA[14, 29]. Although the time to attain discharge criteria for the LIA groups was similar to our trial, the times within the epidural groups was much greater (5.5 and 4 days respectfully vs. 3 in our study). In both previous studies the epidural regimes were in-situ for 48 hours and had a continuous background infusion of between 4- 10 ml/hr running delaying early ambulation and commencement of rehabilitation post-surgery. Within the present trial the PCEA regime had no background rate infusion and was stopped on the morning of post-operative day one at 8a.m. To our knowledge this is the first trial to utilise a PCEA regime with no background infusion that enabled early safe ambulation and commencement of rehabilitation and provided a greater comparator technique to the LIA than previous trial designs. Two recent trials compared PCEA +FNB versus LIA[19,20] and report a similar timeframe to attainment of discharge criteria for both groups within their trial and the current trial (3.2 days each). However, due to limited detail of the specific method including volume and timing of the PCEA +FNB under investigation, it is difficult to compare these results to the PCEA method and findings within the current trial.

Both PCEA and LIA techniques provided good analgesia comparable to that achieved following femoral nerve block for the first 24 and 48-hour period following surgery[17,19,21]. We have

demonstrated equitable pain control and outcomes using only local anaesthetic with no additives compared to other randomised trials comparing LIA and continuous epidural regimes with additives included (i.e. +/- morphine, NSAIDS, steroids and epinephrine)[14,29,30]. The extrapolation from this is that these additives may be unnecessary for either infiltration or epidural administration and raises further questions around the benefits of the numerous cocktails used[31]. However, to confirm this other trials directly comparing regimes are required.

The use of LIA boluses following the large volume infiltration in theatre was facilitated via an indwelling catheter until the morning (8a.m.) of post-operative day one. Several literature reviews suggest that there is insufficient evidence for catheters following large volume injection in theatre[22,32]. However recent studies support our findings that there does appear to be further benefit in enabling better pain control within the first 24 hours and possibly beyond this period[33,34].

Early ambulation demonstrates both physiological benefits in reducing complications[35] and improving satisfaction with pain control[36] whilst shortening length of hospital stay following TKA[3]. No statistical difference was noted between the two groups in the proportion of patients ambulated on theatre day or within 24 hour following surgery. The main reasons for delays in ambulation on theatre day were a dense bilateral residual motor blockade from the spinal anaesthetic or that the patient had not returned from theatre. No incidence of transient peroneal nerve palsy was observed within the LIA group compared to other studies which report an incidence of 12%[30].

The changes in OKS over the 12-month period (PCEA=24(-20-38) vs. LIA=22(-3-40), p=0.640) suggests an above average predicted improvement compared to published literature (predicted improvement in score= 18.4 (9.5))[28]. The improvement in score is also better than previous published data from our hospital[3]. The reason for this is difficult to ascertain as no fundamental changes were made to the Enhanced Recovery Programme.

Of major concern with the use of the LIA technique and specifically an indwelling catheter is the risk of infection[37]. Although two patients were recorded as having a wound infection with one patient returning to theatre for a lavage, no difference was observed between groups (p=1.000). The reported incidence (1.7%) of wound infection with the use of a wound catheter is the same (1.7%) as a large cohort series (n=1081) from the same hospital[3] and considerably lower than rates (11%) reported by a recent trial from Scandinavia[38]. No deaths within 30 days of surgery were recorded within either group. Two deaths were recorded at one-year post-surgery within the LIA group, the cause of death was unknown. It is unlikely these were related directly to the surgical intervention or methods of analgesia under investigation within this trial. These findings support the efficacy and safety of both techniques however as this study was not powered specifically to look at complications, further large-scale cohort studies specifically powered to look at each adverse incident in more detail with the use of these techniques are required.

As with all randomised controlled trials this study has some limitations. It was not blinded which may have introduced some reporting bias. A large number of surgeons (n=11) were involved in the recruitment and consenting of patients and as a result, a large cohort of eligible patients were not approached during the pre-operative assessment clinics. To conform to the ethical

submission and trial protocol, only patients who had been identified by the Consultant surgeon, were eligible for inclusion within the current study. This could have introduced performance bias into the patients included within the study cohort. However, trial demographics for each group are very similar to a large consecutive cohort from within the same institution[3] and appears representative of the standard population attending for TKA surgery within Scotland[39]. In addition, the exclusion criteria mean that this trial did not include the whole TKA population. There are a minority of patients who cannot have a spinal anaesthetic for clinical reasons and the results of this study cannot be applied to this group. Similarly, we excluded those requiring pre-operative catheterisation as we wished to accurately identify the need for post-operative catheterisation in each group and with particular reference to the epidural group. Therefore, it is not known whether these results would be seen in these patients. However this study was more inclusive than previously reported trials[14,29]. A further limitation is that the time for which patients received analgesia would vary dependent on where they were on the theatre list. This was true for both groups. However, both groups had similar distributions of positions on the list so we do not feel this affected the results in terms of differences between the groups. Further work is required to ascertain how much difference the position on the list makes to analgesia efficacy. The fact that the study data did not conform to the preliminary data used for the power calculation means that the small differences seen in the primary outcome were not significant. This current study demonstrates why conclusions on small sample sizes should not be drawn. The preliminary data was collected during the introduction of the PCEA as compared to a traditional continuous epidural with a background rate limiting ambulation which had been standard care within our institution. The potential learning curve of staff in mobilising patients early with epidurals may have contributed to the preliminary data and resultant power

calculation.

This randomised control trial demonstrates that the methods of patient controlled peri-operative regional analgesia, PCEA and LIA, used within the current trial do not affect the time taken to reach standardised discharge criteria within an established Enhanced Recovery Programme. Both techniques provided adequate pain relief and enabled early ambulation and accelerated rehabilitation and continued improvement in functional and patient reported outcomes up to one year following surgery.

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Table 1 Peri-operative Analgesia Regimen

Time	**Multimodal Analgesic Regime**
Oral pre-medication (2 h before surgery)	10–20 mg Temazepam 150mg Ranatidine 10 mg Dexamethasone 300 mg Gabapentin 1 g Paracetamol
Post-operative	300 mg Gabapentin twice daily for 5 days 1 g Paracetamol 4 times daily 400 mg Ibuprofen 3 times daily 10 mg Oxycontin® 12 hourly for 3 doses 5–10 mg Oxynorm® 2–4 hourly as required

Table 2. Standardised Rehabilitation Discharge Criteria

Standardised Discharge Criteria
Independent (able to dress and personal care)
Ability to transfer independently on/off bed/chair/toilet/stairs
80° flexion of the operated knee joint
Ability to straight leg raise operated limb with minimal lag in extension

Table 3: Demographic data of all randomised patients and patients excluded following randomisation. Data presented as median (inter quartile range).

	Randomised Patients		Patients excluded following randomisation	
	PCEA	LIA	Excluded Pts PCEA	Excluded Pts LIA
N	121	121	12	8
Age	66 (11)	68 (10)	67 (13)	70 (10)
BMI	31 (8)	31 (8)	35 (9)	30 (5)
Gender – Males	46%	41%	36%	33%
Operative side – Left	50%	58%	63%	66%
Pre-Operative OKS	17	17		
ASA 1	11%	18%	0	12.5%
ASA 2	67%	66%	75%	75%
ASA 3	22%	15%	25%	12.5%
ASA 4	0%	1%	0	0

ASA=American Society of Anaesthesia Score

Table 4: In-patient data for all included patients. Data presented as median (IQR) [range].

	PCEA n=109	LIA n=113	P value
D/C from rehabilitation by POD 4 [§]	77%	82%	0.332
Days to D/C from rehabilitation [‡]	3 [1-20]	3 [1-8]	0.755
Length of stay (days) [‡]	4 [2-20]	4 [2-12]	0.554
Post-Op Urinary Catheterisation (%)[§]	9.2%	4.4%	0.159
Verbal Rating pain Score (VRS)			
VRS POD 0[‡]	3 (4)	3 (4)	0.278
VRS POD 1[‡]	3 (3)	4 (3)	0.041
VRS POD 2[‡]	3 (2)	4 (3)	0.319
Oxynorm usage (10mg Dose)			
POD 1 [‡]	1 [0-6]	1 [0-5]	0.896
POD 2 [‡]	2 [0-7]	2 [0-9]	0.336
POD 3 [‡]	1 [0-6]	0 [0-5]	0.773
Total usage [‡]	4 [0-15]	4 [0-15]	0.554
Post-Op Nausea and Vomiting	16%	14%	
Proportion of patients ambulating (Cumulative %)			
Theatre Day [§]	35%	51%	0.013
POD 1[§]	96%	100%	0.040
> 24 hours post-surgery	100%	100%	
Position on Theatre List [§]			0.300
1st	31%	30%	
2nd	32%	36%	
3rd	26%	24%	
4th	10%	9%	
5th	5%	0%	
Post-operative blood transfusion (n)	0	0	
D/C Maximum Flexion Angle [‡]	80° [60-100]	80° [65-105]	0.795
Outpatient Physiotherapy referrals on D/C	18%	19%	

D/C=discharge, POD=Post-operative day, [‡]Mann Whitney test [§] Chi-squared test

Table 5: Six week and one year follow up. Data presented as median [range]

Appointment	Variable	PCEA	LIA	P Value
Six weeks post-op	Maximum flexion	n=108 95° [50 to 120°]	n=113 100° [20 to 120°]	0.316
	OKS	n=109 32 [7 to 47]	n=112 34 [12 to 47]	0.204
One year post-op	Maximum flexion	n=103 103° [65 to 130°]	n=105 105° [80 to 130°]	0.720
	OKS	n=98 41 [14 to 48]	n=104 41 [6 to 48]	0.915
	Change in OKS from pre-op	n=92 24 [-20 to 38]	n=98 22 [-3 to 40]	0.640

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Figure 1. CONSORT Flow Diagram

Figure 2. Proportion of patients discharged from Rehabilitation per post-operative day