Peri-articular steroid injection improves the outcome after unicondylar knee replacement

A PROSPECTIVE, RANDOMISED CONTROLLED TRIAL WITH A TWO-YEAR FOLLOW-UP

H.-N. Pang,
N.-N. Lo,
K.-Y. Yang,
H.-C. Chong,
S.-J. Yeo

From Singapore
General Hospital,
Singapore, Singapore

We have performed a prospective double-blind, randomised controlled trial over two years to evaluate the efficacy and safety of an intra-operative peri-articular injection of triamcinolone acetonide in patients undergoing medial unicondylar knee replacement. We randomised 90 patients into two equal groups. The study group received an injection of triamcinolone acetonide, bupivacaine, and epinephrine into the peri-articular tissues at the end of the operation. The control group received the same injection mixture but without the addition of triamcinolone. The peri-operative analgesic regimen was standardised.

The study group reported a significant reduction in pain ($p = 0.014$ at 12 hours, $p = 0.031$ at 18 hours and $p = 0.031$ at 24 hours) and had a better range of movement ($p = 0.023$ at three months). There was no significant difference in the rate of infection and no incidence of tendon rupture in either group.

The addition of corticosteroid to the peri-articular injection after unicondylar knee replacement had both immediate and short-term benefits in terms of relief from pain, and rehabilitation with no increased risk of infection.

The multifactorial aetiology of post-operative pain includes that arising from both neuro-genic and inflammatory pathways.¹ Parenteral opioid is associated with dose-related side-effects such as nausea, vomiting, constipation, urinary retention, respiratory depression and drowsiness.²⁻⁴ A multimodal analgesic regime is required to cover the different pain pathways, to reduce the systemic opioid requirements and to improve the relief from pain.^{5,6} Intra-articular injection of morphine has been shown to provide good relief from pain after knee surgery⁷ although a few reports have disputed its efficacy.^{4,8} Various authors have described the use of peri-articular injections of various anaesthetics in combination which have given improved post-operative pain control⁹⁻¹¹ and a few^{11,12-14} have included the use of a non-steroidal anti-inflammatory agent in the mixture used for wound infiltration. There has been concern regarding an increased risk of post-operative infection^{15,16} and tendon rupture^{17,18} after intra-articular injection of steroid.

Our aim in this prospective, randomised, controlled study was to assess, over two years the efficacy and safety of a peri-articular injection of steroid for control of pain after unicondylar knee replacement (UKR) for medial compartment arthritis.

Patients and Methods

The study had ethical approval and written consent was obtained from each patient. Indications for UKR included minimal pain at rest, a minimum range of movement of 90° with flexion contracture of not more than 5° and an angular deformity of < 10° of varus with minimal or no involvement of the adjacent tibio-femoral and patellofemoral compartments.¹⁹

Exclusion criteria included patients with contraindications for UKR, those undergoing bilateral UKR and those with diabetes, previous surgery to the knee, immunodeficiency, hypothyroidism, renal failure, allergies or intolerance to any component of the injection or to oral non-steroidal anti-inflammatory medication. Ten patients were excluded based on these criteria.

A power calculation was conducted using Power and Precision statistical software version 3.0 (Biostat Inc., Englewood, New Jersey). It was determined that 36 patients were required in each group for the study to detect a difference of 25 mg in the use of morphine in 24 hours and to achieve a power of 0.80.^{10,20,21} This was based on an SD of 25 mg in consumption of morphine per 24 hours for each patient. With this number of patients, the study would be able to detect a difference of 5° (SD 20) in the post-operative range of movement and to achieve a power of 0.90.

■ H.-N. Pang, MRCS Ed, MMed(Orth), Registrar
■ N.-N. Lo, MMed(Surg), FRCS(Ed), FAMS, Senior Consultant Orthopaedic Surgeon
■ K.-Y. Yang, FRCS(G), FAMS, Consultant Orthopaedic Surgeon
■ H.-C. Chong, BSc(Physio), Principal Physiotherapist
■ S.-J. Yeo, FRCS(Ed), FAMS, Senior Consultant Orthopaedic Surgeon
Department of Orthopaedic Surgery
Singapore General Hospital, 1 Outram Road, Singapore 169608, Singapore.

Correspondence should be sent to Dr H.-N. Pang; e-mail: pangheene@hotmail.com

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A total of 90 patients who underwent medial compartment UKR by the three senior authors (N-NL, S-JY, K-YY) in 2004 and 2005 were recruited. Each surgeon contributed 30 patients and these were randomised equally into the two arms of the study by the use of randomisation tables. In the study group, 45 patients received intra-operative infiltration with a mixture which included the local anaesthetic bupivacaine 0.5% with epinephrine 1:200 000 (Astra Zeneca, Sodertalje, Sweden) and the corticosteroid triamcinolone acetonide (Kenocort; Bristol-Myers, New York, New York). In the control group, 45 patients received the local anaesthetic and epinephrine mixture but without the corticosteroid. The patients and the post-operative team who assessed them, were blinded as to which arm of the study they had been entered into.

Operative technique. Operative anaesthesia was either general or spinal. However, there was no difference between the two groups, with 23 patients receiving general and 22 spinal anaesthesia in each group. No long-acting analgesia or nerve blockade was used and spinal anaesthesia was accomplished with 10 ml of 0.5% bupivacaine. A tourniquet was used and inflated after draping. A minimally-invasive approach was followed by a short incision from the medial pole of the patella to the tibial tuberosity.

Caution was taken to ensure minimal disruption of the extensor mechanism. The patella was not dislocated, and the synovium of the suprapatellar pouch was not disturbed. The Zimmer MG II prosthesis (Zimmer, Warsaw, Indiana) was used in all patients with cemented femoral and metal-backed tibial components and was implanted using extramedullary femoral and tibial guides. After cementing the components, the injection was delivered into the peri-articular tissues. The study group received an infiltrative mixture of 0.5 ml/kg²¹ of 1:200 000 epinephrine and 0.5% bupivacaine diluted in 30 ml of normal saline with 40 mg of triamcinolone acetonide²² added to half of this mixture. The anaesthetic solution containing the corticosteroid was injected into the deep tissues including quadriceps muscle, the medial collateral ligament, the posterior capsule and the synovium, with care taken to avoid injecting the solution into either the quadriceps or the patellar tendons. The remaining half of the anaesthetic mixture, without the corticosteroid, was injected along the skin incision before closure. This was to avoid potential subcutaneous atrophy at the injection site from the triamcinolone.²³⁻²⁵

The control group was treated in an identical manner with diluted bupivacaine and epinephrine but without corticosteroid. No drains were used in either group and the tourniquet time was documented at the end of the operation. All the patients received 500 mg BD (twice daily) post-operative oral naproxen for two weeks and patient-controlled analgesia with a 1 mg bolus of morphine, a lock-out time of five minutes and a maximum dose of 8 mg/hour for 48 hours. The use of patient-controlled analgesia was an important aspect of the measurement of pain since it allowed timely and accurate measurements of the consumption of morphine.

Outcome measures. The main outcome measure was the control of post-operative pain, which was estimated by the patient using a visual analogue scale (VAS) in which zero represented no pain and ten maximum pain. The level of pain control was assessed for the first five post-operative days initially every six hours. The amount of morphine consumption was measured using the patient-controlled analgesia pump at six-hourly intervals for 48 hours.

The range of movement of each knee was documented daily by a physiotherapist (H-CC) using a goniometer. Other parameters measured included the length of time required to perform a straight-leg raise as a measure of the recovery of muscular strength and to walk independently, and the decrease in haemoglobin level on the first post-operative day. The patients were further evaluated using the Short-form (SF)-36 questionnaire²⁶ and the Oxford knee score as modified by Dawson et al²⁷ at intervals of three and six months and at two years. Complications such as post-operative infection and tendon rupture were documented. All the data were collected by a physiotherapist (H-CC) who was blinded to the study.

Statistical analysis. This was performed using SPSS statistical software version 11.0 (SPSS Inc., Chicago, Illinois). Univariate analysis was performed by the chi-squared or Fisher's exact tests for comparison of proportions between categorical data. The Mann-Whitney U test was used to compare the non-parametric data between two independent samples. A p-value ≤ 0.05 was considered to be statistically significant.

Results

The pre-operative clinical details were similar in both the study and control groups (Table I). The trend in the post-operative VAS score for pain showed slightly lower mean values for the patients who received steroid injection and this became statistically significant from the fourth post-operative day (Fig. 1). The patients who received the steroid injection had a significantly lower mean requirement for parenteral morphine using the patient-controlled analgesia device at 12 hours, 18 hours and 24 hours after the operation (2.7 mg/hour (SD 1.2) $p = 0.014$, 1.0 mg/hour (SD 1.1) $p = 0.0031$ and 1.7 mg/hour (SD 1.2) $p = 0.031$, respectively (all, Mann-Whitney U test)) (Fig. 2).

Patients who received a steroid injection had a greater range of movement post-operatively (Fig. 3) and this was statistically significant on the second, third, fourth and fifth post-operative days (all Mann-Whitney U test, $p = 0.015$, $p = 0.001$, $p = 0.004$ and $p = 0.003$, respectively). This trend was continued for up to two years post-operatively with statistical significance still being demonstrated at three months post-operatively (Fig. 4).

Patients who received a steroid injection were able to perform a straight-leg raise significantly earlier at a mean of 2.2 days (1 to 3) after the operation compared with the control group who performed the same task at a mean of 2.7 days (1 to 5) post-operatively (Mann-Whitney U test, $p = 0.019$).

Table I. Clinical details of the study (n = 45) and control (n = 45) groups

	Study group (with steroid)	Control group (without steroid)	p-value*
Mean age in yrs (range)	68 (54 to 80)	67 (54 to 80)	0.277
Gender (%)			
Male	8 (17.8)	8 (17.8)	0.321
Female	37 (82.2)	37 (82.2)	0.465
Side (%)			
Left	20 (44.4)	23 (51.1)	0.156
Right	25 (55.6)	22 (48.9)	0.501
Mean (SD) body mass index in kg/m ²	27.3 (6.1)	27.5 (5.6)	0.595
Mean (SD) pre-operative haemoglobin in g/dl	13.1 (0.5)	13.2 (0.6)	0.560
Type of anaesthesia (%)			
General	23 (51.1)	23 (51.1)	0.734
Regional	22 (48.9)	22 (48.9)	0.812
Mean (SD) pre-operative SF-36 questionnaire score			
Physical functioning	30.5 (5.1)	37.1 (4.5)	0.315
Role physical	23.1 (5.9)	45.5 (6.1)	0.491
Role emotional	64.6 (7.2)	76.3 (4.9)	0.138
Social functioning	54.4 (8.1)	61.9 (5.3)	0.214
Mental health	71.5 (9.3)	73.1 (4.3)	0.111
Energy/vitality	57.2 (7.2)	64.3 (7.2)	0.109
Bodily pain	37.3 (7.1)	47.7 (7.8)	0.413
General health perception	70.4 (6.2)	70.8 (3.9)	0.213
Changes in health	45.5 (4.9)	48.4 (3.6)	0.209
Mean (SD) pre-operative Oxford knee score	20.2 (4.3)	20.6 (5.8)	0.279

* chi-squared or Fisher's exact test used to compare the proportions between categorical data. Mann-Whitney U test used to compare non-parametric data between two independent samples

The control group was able to walk at a mean of 1.9 days (1 to 4) post-operatively and the study group earlier at a mean of 1.8 days (1 to 2) after the operation but this difference did not reach statistical significance (Mann-Whitney U test, $p = 0.466$).

There was no significant difference in the mean tourniquet time between the two groups (Mann-Whitney U test, $p = 0.429$). The study group had a significantly lower mean decrease in haemoglobin level (Mann-Whitney U test, $p = 0.028$) (Table II). Neither the SF-36 nor the Oxford knee score showed any statistically significant difference between the groups at the three-month, six-month and two-year follow-up (Table II). There was no significant difference in the rate of infection (Fisher's exact test, $p = 0.382$) between the groups. In each case the infection was superficial and responded to oral antibiotics. None of the patients experienced disruption of the extensor mechanism.

Discussion

Good management of post-operative pain is required to obtain effective rehabilitation after knee replacement.^{9,28} Traditionally, this has been provided by epidural analgesia or peripheral nerve blockades.^{29,30} However, these methods

are technically demanding, costly and associated with potential side-effects.^{3,4} Some studies have shown improved pain scores and a decreased use of opiate analgesia with soft-tissue injection of local anaesthetic agents^{10,11} while others have been unable to replicate these findings.^{8,31-33} Recently, a multimodal wound infiltration technique has been reported^{9,10,12} which has been found to be safe and simple to perform. Toftdahl et al¹⁴ compared local peri- and intra-articular infiltration with a continuous femoral nerve block, and demonstrated better post-operative relief from pain and faster rehabilitation with no increased risk in patients who received the local infiltration. We have added triamcinolone to our infiltration and found it to be effective and safe in post-operative pain control and rehabilitation in UKR.

Although this was a small study with only 90 patients, the number was sufficient to demonstrate a statistically significant difference in the short-term functional outcome between the two groups.

The post-operative pain after knee replacement may result from trauma to the soft tissue or bone.³⁴ Several authors had proposed the presence of opioid receptors in the synovial membrane.^{7,31} Vendittoli et al¹⁰ reported that

Fig. 1

Graph showing the mean visual analogue scale (VAS) scores for both groups after surgery.

Fig. 2

Graph showing the mean (SD) morphine usage in patient-controlled analgesia in both groups up to 42 hours after surgery (p-values derived using the Mann-Whitney U test).

Fig. 3

Graph showing the mean range of movement immediately post-operatively for both groups. Error bars are given (p-values derived using the Mann-Whitney U test).

Fig. 4

Graph showing the mean range of movement up to two years after discharge from hospital for both groups. Error bars are given (p-values derived using the Mann-Whitney U test).

the intra-operative peri-articular injection of analgesia allowed direct visualisation and accurate placement of the injection into the injured tissues and nerve endings. In addition, the entrapment of the medication within the soft tissue enhanced and prolonged the analgesic blockade, and decreased the leakage from the wound.¹⁰

In addition to the direct effect, the use of local anaesthesia may enhance relief from pain by inhibiting the neuro-endocrine stress response to surgery.³⁵ The use of 0.5% bupivacaine has been shown to be effective in patients after arthroscopy.^{36,37} Badner et al³⁸ reported that the mean serum concentration remained well below the toxic levels in

patients who received up to 30 ml of 0.5% bupivacaine intra-articularly. Lombardi et al¹¹ found no intra-operative or peri-operative complications directly related to the injection. The addition of epinephrine to the injection helps to reduce the toxicity of the local anaesthetic by keeping it localised to the area of injection.³⁹ Lombardi et al¹¹ and Karaoglu et al⁴⁰ were able to demonstrate diminished blood loss after the release of the tourniquet when epinephrine was present in the injection.

The anti-inflammatory action of the corticosteroid involves disrupting the prostaglandin and cyclo-oxygenase pathways at several levels.⁴¹ In summary, glucocorticoids

Table II. Comparison of the results in the two groups

	Study group (with steroid)	Control group (without steroid)	p-value*
Mean (SD) tourniquet time in minutes	55 (2.5)	54 (3.1)	0.429
Mean (SD) decrease in haemoglobin in g/dl	2.1 (0.5)	2.5 (0.3)	0.028
At six months post-operatively			
Mean (SD) SF-36 questionnaire score			
Physical functioning	60.1 (6.7)	55.6 (7.6)	0.241
Role physical	72.3 (5.9)	69.1 (8.1)	0.491
Role emotional	89.4 (4.6)	87.3 (9.1)	0.513
Social functioning	83.2 (7.6)	79.4 (6.7)	0.467
Mental health	79.2 (7.1)	75.5 (6.3)	0.159
Energy/vitality	71.8 (9.1)	69.6 (8.2)	0.281
Bodily pain	69.5 (5.9)	66.4 (7.1)	0.109
General health perception	75.4 (7.1)	73.7 (5.1)	0.195
Changes in health	72.3 (5.6)	70.1 (4.7)	0.385
Mean (SD) Oxford knee score	37.8 (5.9)	35.4 (7.1)	0.485
At two years post-operatively			
Mean (SD) SF-36 questionnaire score			
Physical functioning	61.2 (7.4)	57.1 (5.6)	0.376
Role physical	73.4 (7.9)	71.2 (4.1)	0.456
Role emotional	88.1 (6.7)	86.7 (6.7)	0.629
Social functioning	84.5 (8.1)	82.4 (9.3)	0.319
Mental health	81.9 (8.3)	76.2 (6.9)	0.295
Energy/vitality	73.1 (6.9)	71.9 (9.2)	0.362
Bodily pain	73.0 (7.1)	68.9 (7.3)	0.524
General health perception	78.2 (5.3)	74.3 (8.3)	0.296
Changes in health	76.9 (7.2)	74.7 (8.3)	0.726
Mean (SD) Oxford knee score	38.4 (6.1)	37.3 (7.8)	0.319
Infection (%)	2 (4.4)	2 (4.4)	0.382
Tendon rupture (%)	0 (0.0)	0 (0.0)	0.215

* chi-squared or Fisher's exact test used to compare the proportions between categorical data. Mann-Whitney U test used to compare non-parametric data between two independent samples

act directly on nuclear steroid receptors to control the rate of synthesis of mRNA and proteins. This has a number of consequences, including changes in T- and B-cell function, changes in white blood cell activity, alterations in the level of cytokines and enzymes and inhibition of phospholipase A2 resulting in a reduction in pro-inflammatory derivatives of arachidonic acid.⁴² Injection of steroids into the surrounding soft tissues can therefore provide good relief from pain by reducing the inflammation at the sites of surgical trauma^{43,44} and can decrease blood loss through the reduction of these prostaglandins, in particularly the vasodilating agents⁴⁵ prostacyclin and prostaglandin D₂ and E₂. The enhanced pain relief with the use of steroids in the infiltration was in line with the results of the study by Parvataneni et al,⁴⁶ who used methylprednisolone acetate in their injections.

Triamcinolone acetonide injectable suspension is an insoluble synthetic glucocorticoid with anti-inflammatory action and is suitable for intra-articular use.⁴⁷ It has an extended duration of effect which exceeds that of methylprednisolone and may be sustained over a period of several weeks. Studies indicate that after a single intramuscular

dose of 60 mg to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days.^{47,48} Our study demonstrated an improved mean range of movement in patients who received peri-articular injections of steroid which was statistically significant at three months but still demonstrated a difference beyond this period. We postulate that the insoluble particles of triamcinolone acetonide persist in the tissues and continue to exert anti-inflammatory effects over time, thereby reducing post-operative fibrosis and scarring. Consequently, patients enjoy a better range of movement and a more rapid rehabilitation.

Local injection of corticosteroids has been used extensively in musculoskeletal tissues and joints without impairment of wound healing or other complications.^{46,47,49,50} The reported complications of intra-articular steroids are rare and include septic arthritis, tissue atrophy and osteonecrosis.⁵¹ By observing strict asepsis and stringent exclusion criteria, we found no increase in infection at follow-up at two years. Caution was taken to avoid injecting steroid into the patellar tendon and there was no incidence of tendon rupture in our patients.

We have demonstrated the efficacy and safety of an intra-operative peri-articular injection of bupivacaine, epinephrine and triamcinolone after UKR. The patients who received the steroid injection had better relief from pain, faster rehabilitation and less blood loss, with no increased risk of infection or tendon rupture at follow-up at two years.

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