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Title:

Effect of Methylprednisolone in Peri-articular Infiltration for Primary Total Knee Arthroplasty on Pain and Rehabilitation

A PROSPECTIVE COMPARATIVE STUDY

M Kulkarni¹, M Mallesh¹, H Wakankar¹, R Prajapati¹, H Pandit².

*1: Department of Joint Replacement, Deenanath Mangeshkar Hospital,
Pune, India.*

2: University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, UK

Details of authors:

Institute (1-4):

Joint Replacement department

Deenanath Mangeshkar Hospital and Research Center

Erandwane, Pune, India. PIN-411004

1. **Dr Mahesh Kulkarni.**, M S.Ortho.,F.R.C.S. Ed.,M.Ch.Orth., F.R.C.S..Ortho

Consultant Joint Replacement Surgeon.

2. **Dr. Mallesh M.**, MS Ortho.

Fellow in Joint replacement.

3. **Dr Hemant Wakankar .**, M S.Ortho ., D.N.B, F.R.C.S. Ed.,M.Ch.Orth., F.R.C.S..Ortho

Consultant Joint Replacement Surgeon.

4. **Dr Ravikumar Prajapati.**, D.Ortho.

Fellow in Joint replacement.

5. **Professor Hemant G Pandit** FRCS (Orth), D Phil (Oxon)

Professor of Orthopaedic Surgery and Honorary Consultant Orthopaedic Surgeon,

Institute: University of Leeds and Leeds Teaching Hospitals NHS Trust, UK.

Corresponding Author:

Dr Mallesh M.

Phone: +919886293972; Email: drmalleh4@gmail.com

Postal Address: Flat No 106, Arya Lotus apartment, No 2/2, Abhayadhama Road, Whitefield,
Bengaluru, India. PIN-560066

Effect of Methylprednisolone in Peri-articular Infiltration for Primary Total Knee Arthroplasty on Pain and Rehabilitation

A PROSPECTIVE COMPARATIVE STUDY

Abstract:

Background: Optimal pain management post-total knee arthroplasty is important to ensure timely rehabilitation and patient satisfaction. This study examines the efficacy of adding corticosteroid in peri-articular infiltration cocktail with relation to post-operative pain management and rehabilitation in patients undergoing simultaneous bilateral total knee arthroplasty.

Methods: 50 patients with symptomatic end-stage bilateral knee osteoarthritis undergoing bilateral TKA under the same anaesthetic were recruited. More painful knee was operated first and the study solution containing ropivacaine, clonidine, epinephrine, and ketorolac with methylprednisolone was infiltrated in one knee and an identical mixture but without methylprednisolone was infiltrated in the second knee. Outcome measures included comparison of VAS on movement of each knee and range of motion achieved during the first three days post-surgery.

Results: Difference of VAS score and ROM at day one and three between the two groups of knees were significant ($p < 0.05$). Post-operative inflammation as well as ability to straight leg raise showed better trends in the knees receiving prednisolone although this did not reach statistical significance.

23 **Conclusion:** Addition of Methylprednisolone to periarticular infiltration cocktail
24 for patients undergoing TKA has significant influence on reduction of pain in early
25 post-operative period and patients are able to regain knee flexion more quickly.

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27 **Key Words:** Periarticular infiltration, Methylprednisolone, Post-operative Pain,
28 Range of motion, Total Knee Arthroplasty.

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47 **Introduction:**

48 Total knee arthroplasty (TKA) is established as treatment of choice for end-stage
49 symptomatic knee osteoarthritis (OA). It provides reliable function and implant
50 survival is reported at around 95% at 10 years^{1,2}. One key unresolved issue is post-
51 operative pain in the peri-operative period. Effective post-operative pain relief
52 helps early rehabilitation, prevention of deconditioning, and timely discharge to
53 ensure optimal outcomes and make resources more available. Pain has been
54 shown to be one of the main clinical reasons for hospital stay after knee
55 arthroplasty and finding the best post-operative pain control regimen is at the top
56 of priority setting partnerships³.

57 Intra-operative peri-articular infiltration is routinely used to reduce the intensity
58 and severity of post-operative pain^{4,5,6,7}. This infiltration typically contains a
59 mixture of various agents including a local anaesthetic, an anti-inflammatory
60 agent and epinephrine. In addition, use of intermediate acting corticosteroid such
61 as Methylprednisolone is recommended by some experts due to its anti-
62 inflammatory properties^{8, 9, 10}. However, use of corticosteroids can increase the
63 risk of infection and therefore not routinely used in the peri-articular filtration.

64 At present, there is no consensus about the use of corticosteroids in the peri-
65 operative period following knee arthroplasty. In addition, the intensity of post-
66 operative pain after surgery varies among different patients. It not only depends
67 upon patient factors but also upon surgeon factors. It is difficult to control for
68 various confounders to establish whether indeed addition of a corticosteroid to
69 local infiltration is safe and effective. One way to overcome this is to assess the
70 impact in a cohort of patients who undergo bilateral TKA performed by the same

71 surgeon using the same surgical technique under the same anaesthetic. This study
72 aims to compare the safety and efficacy of adding a corticosteroid to the peri-
73 articular infiltration in patients undergoing single-stage bilateral TKA.

74 **Materials and Methods:**

75 This prospective non-randomized study was conducted over a nine month period
76 (September 2017 to June 2018). Institutional scientific advisory committee and
77 ethical committee approval was duly obtained and all patients consented to
78 taking part in the study. 50 patients with bilateral symptomatic end-stage knee
79 OA listed for single staged bilateral TKA were approached. Eligible patients were
80 aged between 50 and 80 years. Patients with any of the following were excluded
81 from the study: poorly controlled Diabetes (HbA1C > 7.0), history of inflammatory
82 arthritis, renal insufficiency (eGFR<90 mL/min per 1.73m²), hypersensitivity to the
83 study drug, prolonged QT interval in ECG and/or patients with history of knee
84 infection were excluded from the study.

85 Pre-operative knee range of motion was documented. Patients were asked about
86 the more painful knee pre-operatively. All patients received similar pre-operative
87 medications which included 650 mg of oral Paracetamol and 100 mg of oral
88 Gabapentin on the previous night of surgery and at 2 hours before surgery. All the
89 patients received spinal anaesthesia with plain 0.5% Bupivacaine and 500 mg of
90 systemic Tranexamic acid was given pre-operatively, and in addition three hours
91 and six hours from the time of first dose.

92 Ropivacaine was the long acting local anaesthetic used in the cocktail along with
93 Epinephrine to prolong its action. Clonidine being an alpha-2 receptor agonist acts

94 on C and A δ fibers, and decreases the conduction to prolong the action of local
95 anesthetic and also through vasoconstrictor effect which reduces the drug wash-
96 out from perineural tissues. Ketorolac is the adjuvant NSAID in the cocktail.

97 All patients underwent single stage bilateral TKA. More painful knee was operated
98 first and received methylprednisolone which was added to the peri-articular
99 infiltration (study group: Group S). The second knee received peri-articular
100 infiltration identical to the first except the methylprednisolone (Group C). The
101 surgeries were performed by either of the two senior surgeons (MK or HW). All
102 surgeries were performed under tourniquet control with a standard midline
103 incision and a medial parapatellar arthrotomy. Posterior stabilized prosthesis was
104 used in all patients and in none of the cases patella was resurfaced. Patellar
105 osteophyte excision with circumferential denervation was done with diathermy.
106 After preparation of the bony surfaces and just prior to cementation of the
107 definitive TKA components the solution containing ropivacaine, clonidine ,
108 epinephrine, and ketorolac (details of dosage provided in table 1) with one ml of
109 methylprednisolone(40 mg) was infiltrated in the peri-articular tissues using a
110 standardized protocol in the first knee and similar procedure was repeated for the
111 second knee with the infiltration used being identical to the first solution except
112 methylprednisolone. Infiltrated sites in order being posterior capsule, medial and
113 lateral meniscal bed, synovium, iliotibial band, collateral ligaments before
114 cementing and quadriceps, retinaculum, patellar tendon after implanting the
115 components. Tourniquet was released and haemostasis achieved before closing
116 the joint. No drain was used.

117

118 DVT chemoprophylaxis included 40mcg of sub cutaneous low molecular weight
119 heparin for five days post operatively followed by oral Rivaroxaban 10mg for
120 fourteen days. Patients were also provided with below knee anti-embolism
121 compression stockings to be used in the post-operative period for six weeks.

122
123 Patients were encouraged to stand with support on the same day of surgery and
124 used ice packs to both the knees four times a day during their hospital stay.
125 Patients received six hourly intravenous (IV) Paracetamol 1g along with twelve
126 hourly IV Tramadol 50 mg and Diclofenac 75 mg post-operatively for the first 48
127 hours post-surgery. Later, PRN oral analgesics were prescribed (Paracetamol and
128 tramadol). All patients received standard DVT chemoprophylaxis for first two
129 week post-surgery.

130
131 Pain on movement was recorded separately for each knee as VAS (Score 0 -10; 0 -
132 No pain; 10 - worst pain) at 24 hours and 72 hours post-surgery. Active range of
133 motion (ROM) was measured with a goniometer on post-operative day one and
134 day three. Time for straight leg raise in both lower limbs and appearance of any
135 ecchymosis/inflammation were documented. Patients were assessed for any local
136 (hypersensitivity reaction, infection, bleeding or tendon rupture) or systemic
137 (cardiovascular issues, renal impairment, stroke) adverse events. All assessments
138 were conducted by an independent blinded observer who was not a part of
139 operating team. The assessor did not know the order in which surgeries were
140 performed (or which knee received which peri-articular injection). The assessor
141 asked questions about either knee in a random sequence. All patients were
142 assessed at 2 weeks post-surgery, at one month and contacted a 6 months post-

143 surgery to check if they needed any further intervention or treatment for their
144 bilateral TKAs. Methylprednisolone knee was identified with data in operative
145 records showing the first operated knee.

146

147 *Statistical analysis:*

148 Baseline data, range of motion and VAS scores at first day and third day post-
149 surgery were compared using paired T test. Categorical data was compared using
150 chi-squared test. All analysis was performed using SPSS (IBM SPSS statistics
151 version 20) with $p < 0.05$ deemed statistically significant.

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155

156 **Results:**

157 Mean age of patients was 67 years (range: 53 - 82, SD 7.5) of which 13 were males
158 and 37 were females. The two groups were well matched for pre-operative
159 flexion deformity, further flexion and surgical time (table 2).

160

161 No patient died in the first six months post-surgery. No patient was lost to follow
162 up and none of the patients needed any further intervention related to their
163 replaced knees. At six months follow up none of the patients included in study
164 had suffered from superficial or deep infection in either of the knees.

165

166 The mean VAS at 24 hours post-surgery was 2.9 (range: 1 - 6, SD 1.2) and 4.6
167 (range: 2 - 6, SD 1.0) for group S and group C respectively. The difference
168 between the two groups was statistically significant ($p < 0.05$). The mean VAS at
169 72 hours post-surgery was 2.0 (range: 1 - 4, SD 0.9) and 3.5 (range: 1 - 6, SD 1.0)
170 for group S and group C respectively. The difference between the two groups was
171 statistically significant ($p < 0.05$).

172
173 The mean ROM at 24 hours post-surgery was 67° (range: 30° - 90° , SD 13.7) and
174 55° (range: 30° - 80° , SD 12.1) for group S and group C respectively. The
175 difference between the two groups was statistically significant ($p < 0.05$). The
176 mean ROM at 72 hours was 80° (range 50° - 100° , SD 12.0) and 72° (range: 50° -
177 90° , SD 12.0) for group S and group C respectively. The difference between the
178 two groups was statistically significant ($p < 0.05$). Inflammatory signs (redness,
179 edema and tenderness) were present in 9 knees with steroid infiltration
180 compared with 17 knees without steroid. The difference was non-significant ($p >$
181 0.05). The mean time to achieve straight leg raise was 3.3 days (range: 1 - 4, SD
182 0.8) for group S as compared to 3.6 days (range: 2 - 4, SD 0.6) for group C. The
183 difference between the two was non-significant ($p > 0.05$).

184

185 **Discussion:**

186

187 This study has shown that addition of 40 mg of methylprednisolone in the peri-
188 articular infiltration for patients undergoing TKA is effective in terms of reducing
189 pain at least for the first 72 hours post-surgery and also helps to regain knee
190 flexion more quickly. It is the first study in patients undergoing simultaneous

191 bilateral TKA under the same anaesthetic using same surgical technique by the
192 same surgeon comparing the use of steroid in the local infiltration.

193
194 Corticosteroid is an established post-operative pain control drug via systemic
195 routes¹¹. Intra articular use of corticosteroids in knee osteoarthritis management
196 has been studied extensively both for benefits and complications^{12, 13}. Studies
197 related to periarticular use of the drug are limited. The aim of our study was to
198 compare the effect of using a corticosteroid in periarticular infiltration solution
199 with reference to its effect in post-operative pain control. This study compared
200 the effect with periarticular infiltrations between the knees of same patient. This
201 greatly reduced bias of the subjective difference in pain perception as it occurs of
202 different patients. Many previous studies have shown the beneficial effects^{14, 15, 16}
203 of corticosteroid in the infiltration cocktail with some reporting complications¹⁷
204 related to its use. Our study showed statistically significant improvement in VAS
205 score and knee flexion on day one and three between two groups. The use of
206 steroid in the infiltration helped patients achieve straight leg raise more quickly
207 and the incidence of post-operative inflammation was less although the
208 differences were not statistically significant.

209
210 The study¹⁷ conducted by Christian P. Christensen et al. with two different groups
211 for steroid and without steroid infiltration (steroid: 37 patients, no steroid: 39
212 patients) suggested that the addition of a corticosteroid to intraoperative
213 periarticular injections does not provide benefit when compared with injections
214 that do not contain a corticosteroid. They also reported complications like deep
215 knee joint sepsis and requirement of manipulation under anaesthesia at nine

216 weeks post knee replacement surgery in steroid patients group. However our
217 study did not encounter any such complications during the study period.

218
219 Sae Kwang et al. conducted a study¹⁸ with 76 patients who underwent sequential
220 bilateral TKA with an interval of three months between the two surgeries. In this
221 study, one knee was randomly assigned to the steroid (40 mg triamcinolone
222 acetate) or non-steroid peri-articular infiltration group. After 3 months, the
223 contralateral knee was assigned to the opposite group. Patients were assessed for
224 nighttime pain, functional recovery [straight leg raising (SLR) ability and maximal
225 flexion], patient satisfaction, and complications during the post-operative period.
226 Authors reported significantly lower pain level in the steroid than the non-steroid
227 group on the night of the operation (VAS, 1.2 vs. 2.3; $p=0.021$). No significant
228 differences were reported in maximum flexion between the two groups although
229 the authors did notice earlier ability to achieve straight leg raise in the steroid
230 group. S. Tsukada et al. conducted a double blind randomized control study¹⁰ with
231 total of 77 patients. They noticed that the corticosteroid group had a significantly
232 lower cumulative pain score than the no corticosteroid group during the first 24
233 hours after surgery ($p = 0.024$). The rate of complications, including surgical site
234 infection, was not significantly different between the two groups up to one year
235 postoperatively. In a study¹⁹ conducted by Chia et al. they concluded that
236 injecting steroid to the extensor mechanism has the risk of delayed tendon
237 rupture. In our study also infiltration of steroid into extensor mechanism was
238 avoided. Probably owing to that, post operatively no difference was noticed in
239 number of days required by the patient to perform straight leg raising.

240

241 This study has certain limitations. Period of post-operative follow up is short and
242 range of motion and pain scores beyond third day were not compared between
243 two groups. As the effect of methylprednisolone is unlikely to last after 72 hours,
244 we do not expect any difference in pain scores or ROM in the long-term although
245 this needs to be proven. Although there were no complications in this specified
246 period, long term follow up will be helpful for monitoring complications. In our
247 practice, patients travel from far and wide and find it difficult to attend routine
248 face to face follow up appointment. We did manage to communicate with all the
249 patients to establish that none of them needed further intervention (either
250 surgical or medical including use of oral antibiotics) for suspected infection in
251 either of the replaced knees.

252

253 One key strength of this study is patients undergoing simultaneous bilateral TKAs
254 for end-stage OA under the same anaesthetic by the same surgical team using
255 identical technique and implants in both the knees. This has minimized the effect
256 of potential confounders and allowed us to conduct a meaningful comparison.

257

258

259 **Conclusion:**

260

261 Addition of Methylprednisolone to periarticular infiltration cocktail in patients
262 undergoing total knee arthroplasty has significant influence on reduction of pain
263 in early postoperative period. It also helps patients to regain knee range of
264 motion quickly and thus may help in reducing length of stay. Longer follow up is

265 required to assess if these advantages are maintained in the long-term and also if
266 indeed any of the patients develop any possible complications.

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Tables:

Table 1: Periarticular infiltration cocktail

Details	Solution in ml used in each knee in patients with weight < 70 KGs	Solution in ml used in each knee in patients with weight ≥ 70 KGs
Ropivacaine (0.75%)	40	54
Clonidine(150mg/ml)	0.6	0.8
Adrenaline	0.3	0.3
Ketorolac(30 mg)	2	2
Normal Saline (0.9%)	57	63
TOTAL (Both Knees)	100 (50ml for each knee)*	120 (60 ml for each knee)*

* After preparation of the solution for peri-articular infiltration for each patient, the solution was divided into two equal parts. 40 mg of methylprednisolone was added to the first half of the solution which was used for the peri-articular infiltration in the first knee (Group S) and the second half of the solution was used for the peri-articular infiltration in the second knee (Group C).

Table 2: Preoperative FFD, flexion and operative tourniquet time comparison

Group	Mean FFD in degrees (range, SD)	P value	Mean Flexion in degrees (range, SD)	P	Mean tourniquet time (Minutes)	P value
Group S	7.8 (range: -5 to 30, SD 7.18)	0.44	107.2 (range:60 to 140, SD 16.66)	0.47	51.54 (range: 36 to 80, SD 10.24)	0.97
Group C	7.2 (range: -10 to 20, SD 5.72)		108 (range:70 to 140, SD 16.28)		51.48 (range: 38 to 70, SD 7.75)	

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