

Review Article

Periarticular use of Steroid for Knee Replacement Surgery

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Abstract

Knee replacement surgery has been associated with short-term morbidity that may impair postoperative recovery. Local anaesthetic delivered to the knee joint at the time of surgery has been touted as a way of attenuating post surgical pain, facilitating earlier engagement in rehabilitation and attainment of functional milestones. Arthroplasty surgeons use corticosteroids as part of their analgesic cocktail to enhance these properties. However, concern has been raised regarding the increased risk for infection and possible tendon rupture. Infection can be a devastating complication and many authors have questioned the safety profile of steroids when used in this manner. We aim to systematically review articles investigating the safety and efficacy of periarticular corticosteroids in knee replacement surgery.

ABBREVIATIONS

TKA: Total Knee Arthroplasty

INTRODUCTION

Knee replacement surgery has been associated with short-term morbidity that may delay patient engagement with their immediate postoperative rehabilitation [1,2]. Despite the most sophisticated intraoperative surgical and anaesthetic techniques, and enhanced recovery programs, pain and swelling around the surgical site appears to be significant contributors to this short-term morbidity. Infiltration of local anaesthesia in and around the surgical site has been used to reduce pain and subsequently reduce opioid consumption allowing for earlier range of motion and function [3]. Arthroplasty surgeons have realized the benefits of local analgesia and have experimented with augmenting the properties of local anaesthetic with non-steroidal anti-inflammatories, adrenaline, and more recently corticosteroids.

The periarticular use of steroid in knee arthroplasty was first published by Parvataneni et al in an attempt to take advantage of its anti-inflammatory properties in the hope of reducing postoperative swelling and pain [4]. Glucocorticosteroids are used for their anti-inflammatory effects with many mechanisms at the cellular and gene regulation levels proposed. Glucocorticoids reduce inflammation through its inhibitory effects on prostaglandins E2 and F2 produced by fibroblasts and have also been shown to reduce the pro-inflammatory enzyme nitric oxide synthase, which is present in high levels in the setting of trauma [5].

Special Issue on

Modern Anesthesia Techniques for Total Joint Arthroplasty: from Blood Preservation to Modern Pain Control

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- Enhanced recovery

Recent evidence indicates preoperative intraarticular steroid use does not confer additional risk for the development of deep joint infection following total joint arthroplasty [6]. Extrapolating this to periarticular administration of steroid at the time of surgery would be bold. There is currently no consensus around the use of periarticular corticosteroids and for most surgeons a point of contention in perioperative analgesia [7]. Concern has been raised regarding a higher risk for wound infection and tendon rupture with the use of periarticular steroid [7,8] and some have even questioned their usefulness [8,9].

Our aim for the review was to evaluate the safety and efficacy of corticosteroids around the knee joint prosthesis and whether its use translates into any significant improvements in clinical outcomes. We sought to establish whether corticosteroid provided safe analgesia with the view of determining what type and administration technique was most effective.

PATIENTS AND METHODS

A comprehensive review of the literature was performed in accordance with methods outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10] (PRISMA) statement by two authors (MDJS and RG) (Figure 1). MEDLINE, PubMed and Embase were last searched on 30 March 2014. Two independent reviewers (MDJS and RG) performed separate searches and combined articles found. Once duplicates had been

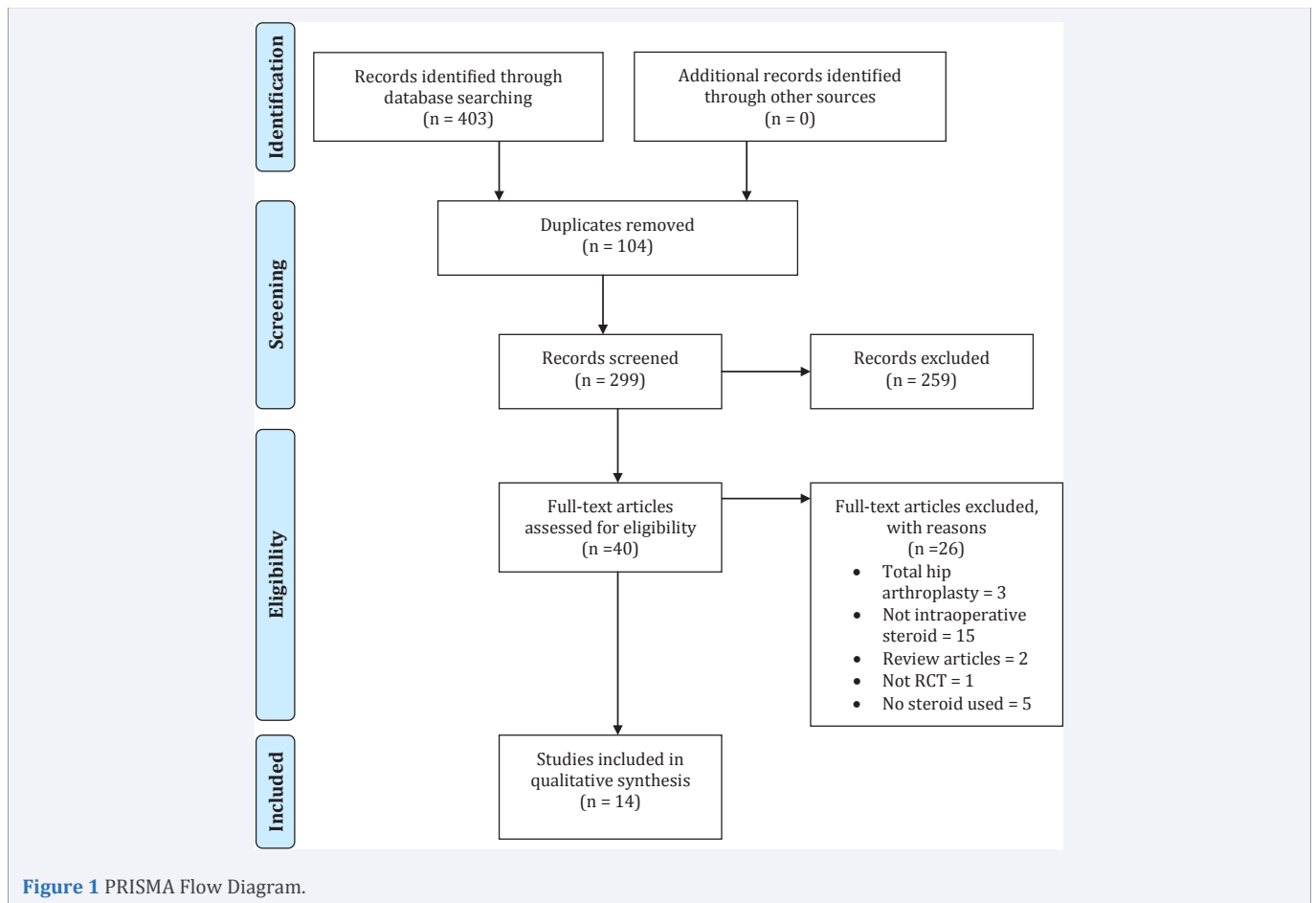


Figure 1 PRISMA Flow Diagram.

excluded, the remaining studies were then screened by title and abstract in order to determine relevance to the systematic review. Once articles had been screened, a hand search of all remaining articles' references was performed by three authors (MDJS, RG and RP). We used a combination of key terms to allow for a thorough review (Table 1).

Non-randomized controlled trials, non-English articles and those articles including surgery other than knee joint replacement were excluded from the study. Jadad Score was used to assess the quality of randomized control trials included for review (0=poor, 5=good) [11].

Outcome measures

Primary endpoints used in the studies included pain scores (rest and dynamic) typically measured using the Visual Analogue Scale (VAS), opiate consumption and Range of Movement (ROM). Secondary endpoints included in studies were varied but included Length of Hospital Stay (LOS), time to Straight Leg Raise (SLR), adverse outcomes including blood loss, infection and tendon rupture. A large proportion of studies also reported on validated functional outcomes (Oxford Score, American Knee Society Score, SF-36, WOMAC Index).

RESULTS

14 studies met criteria to be included in our study for review [4,7-9,12-21]. A total of 1,271 patients underwent 1,500 total

knee joint replacements and 173 unicompartamental replacement surgeries. Choice of steroid used in studies varied: 5 studies used triamcinolone acetonide [12,15,16,18,21], 3 studies used betamethasone [7,13,20], 4 studies used methylprednisolone acetate [8,9,14], 1 used dexamethasone [19] and 1 used an unspecified corticosteroid of 40mg [17](Table 2). In 2 studies, randomization occurred in a single patient undergoing bilateral total knee joint replacements either simultaneously or in a staged manner [9,21]. For the 14 studies, the Jadad Score ranged from 1-5 with eleven studies achieving a score of 3 or more [7-9,12-16,18,19,21].

Studies including a control group and administration of analgesics with steroid to the knee

Of the 14 studies, eleven demonstrated that the addition of steroid in their respective analgesic cocktail was beneficial in reducing pain, achieving functional milestones earlier and reducing narcotic consumption [4,7,9,12,13,15-17,19-21], whereas three concluded no benefit [8,14,18]. One study showing no benefit demonstrated a trend for high dose steroid to reduce rest pain from 2 through to 12 weeks by up to 17%, however, this failed to reach statistical significance [18]. Three studies reported a significant reduction in LOS in the steroid group, on average saving 1 day in hospital [8,15,16].

Table 1: Search terms used and combined with 'AND'.

Key search terms		
Steroid\$ OR dexamethasone\$ OR corticosteroid\$	Periarticular\$ OR articular\$ OR intraarticular\$	Arthroplasty\$ OR knee arthroplasty\$ OR joint replacement\$

Table 2: Summary of studies.

Author	Year	Patient number (EG/CG)	Surgery Type	Steroid Type (dose)	Key findings [§]	Adverse outcomes [‡]	Study Quality
Kwon et al. [21]	2014	76/76	Bilateral staged TKA	Triamcinolone acetonide (40mg)	Reduced immediate pain relief but not sustained after POD1 SLR achieved earlier	Infection: 0 Tendon rupture: 0	5
Chia et al. [18]	2013	42/42/43	Unilateral TKA	Triamcinolone acetonide (40mg/80mg)	Trend towards a reduction in VAS at 2 through to 12 weeks, however, failed to reach statistical significance	Infection: 1 deep infection in high dose group Tendon rupture: 0	4
Nakai et al. [20]	2013	19/21/20	Unilateral TKA	Betamethasone (4mg)	Lower VAS and NSAID consumption immediately postop indicating better pain control in intervention groups	Infection: 0 Tendon rupture: 0	2
Ikeuchi et al. [19]	2013	20/20	Unilateral TKA	Dexamethasone (6.6mg)	Reduced pain at POD1 and POD3 Decreased time to SLR and less drain output Reduced CRP	Infection: 0 Tendon rupture: 0	3
Yue et al. [7]	2013	36/36	Unilateral TKA	Betamethasone (4mg)	Knee scores significantly better at 1 and 3 months, use of celecoxib shorter than control group	Infection: 0 Tendon rupture: 0	3
Meftah et al. [17]	2012	45/45	Unilateral TKA	Unspecified corticosteroid (40mg)	Reduced pain POD1 with ambulation	Infection: 0 Tendon rupture: 0	1
Joo et al. [14]	2011	286/286	Bilateral TKA	Methylprednisolone acetate (40mg)	No difference in pain, satisfaction, ROM and blood loss	Infection: 0 Tendon rupture: 0	5
Sean et al. [16]	2011	50/50	Unilateral TKA	Triamcinolone acetonide (40mg)	Lower pain scores, reduced morphine consumption and earlier discharge Reduced LOS 5.2 vs 6.8 days	Infection: 1 deep infection in each group Tendon rupture: 0	5
Ng et al. [15]	2011	41/42	UKA	Triamcinolone acetonide (40mg)	Lower ESR and CRP until POD3 Improved ROM until POD2 Reduced LOS 3.7 vs 4.7 days	Infection: 0 Tendon rupture: 0	3
Mullaji et al. [9]	2010	40/40	Bilateral TKA	Methylprednisolone acetate (40mg)	Reduced pain scores at all time points in 37 of 40 patients Improved knee ROM at discharge	Infection: 1 deep infection in steroid group* Tendon rupture: 0	3
Fu et al. [13]	2009	40/40	Unilateral TKA	Betamethasone (4mg)	Reduced morphine consumption in first 36 hours Lower VAS (rest and activity) in first 36 hours	Infection: 0 Tendon rupture: 0	4
Christensen et al. [8]	2009	39/37	Unilateral TKA	Methylprednisolone acetate (40mg)	Reduced LOS 2.6 vs 3.5 days	Infection: 1 deep joint sepsis in steroid group# Tendon rupture: 0	5

Pang et al. [12]	2008	45/45	UKA	Triamcinolone acetonide (40mg)	Reduced VAS in steroid group from POD4 Lower morphine consumption up to 24 hours Greater ROM up to 3 months Less blood loss on average	Infection: 0 Tendon rupture: 0	3
Parvataneni et al. [4]	2007	31/29	Unilateral TKA	Methylprednisolone acetate (40mg)	Greater proportion of patients achieving SLR POD 1	Infection: 0 Tendon rupture: 0	2

Abbreviations: EG: Exposure Group; CG: Control Group; TKA: Total Knee Arthroplasty; VAS: Visual Analogue Scale; UKA: Unicompartmental Knee Arthroplasty; POD: Postoperative day; SLR: Straight Leg Raise; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; LOS: Length of Stay

[§]reported findings are significant and favour steroid group, unless stated otherwise

[¶]pertains to deep infection only

*required 2 stage revision

#causing death

Studies including local analgesic and steroid, with or without antibiotics

Four of the 14 studies included antibiotic into their cocktail, with all but one study using 750mg cefuroxime [4,8,9,17]. Deep infection occurred in 4 cases in 3 studies. Three cases of infection occurred in knee replacements that had steroid injected into their deep tissue and of these knees, 2 received concomitant antibiotics as part of their cocktail [8, 9]. Chia et al compared 40mg and 80mg of triamcinolone acetonide against a control. Their single deep infection occurred in the high dose group in a reportedly non-compliant patient [18]. Kwon et al demonstrated no wound or deep infections but did report wound ooze in both steroid and control groups, 8.3% and 6.5% (p=0.294), respectively [21].

Timing and sites of injection

Eleven studies adopted a staged injection protocol involving two time points for injection separated by implantation of the prosthesis (Table 3). In six studies, steroid was only injected into the deep tissue and the remaining steroid free aliquot was injected into the superficial tissues (subcutaneous and skin) [7,12,15-18]. Two studies administered the injections at a single time point [8,9] and one study utilized the use of a drain as a conduit for administration of local analgesia boluses in the first 48 hours [19].

Apart from Nakai et al, all other studies clearly documented the specific sites of injection around the knee joint. Eleven studies clearly documented injecting into the extensor mechanism. However, Chia et al only used local anaesthetic with adrenaline into the extensor tendons and omitted the steroid. Their sole deep joint infection occurred in the high dose (80mg triamcinolone) group. Conversely, Pang et al only administered injections into the quadriceps muscle and not the extensor tendons [12]. Extensor tendon rupture did not occur in any of the studies reviewed.

DISCUSSION

There is evidence that local analgesia using corticosteroids, as part of a local anaesthetic cocktail, is safe and can reduce immediate postoperative pain, aid early knee ROM recovery and reduce narcotic consumption.

Corticosteroids have been used to attenuate the stress response induced by surgery. Whilst the exact mechanism of action is not fully elucidated, a number of theories have been

proposed for the beneficial effects of corticosteroids. Inhibition of phospholipase A2 is often touted as a common pathway reducing the pro-inflammatory derivatives of arachidonic acid [15,16]. At a cellular level, corticosteroids are lipophilic and as a consequence are able to bind to nuclei of cells. Evidence suggests that steroids are responsible for gene regulation by altering DNA transcription [22]. Genes activated include annexin-1 and SLP1 which have an anti-inflammatory role. Inflammation is also a result of cytokines released by immune cells, most importantly T-lymphocytes and monocyte-macrophages. Levels of pro-inflammatory prostaglandins E2 and F2 produced by fibroblast cells are also inhibited by corticosteroids. The proposed mechanisms combine to reduce inflammation and pain allowing for earlier engagement in rehabilitation through soft tissue compliance. One study contained in our review confirmed their anti-inflammatory effects, reporting a significantly lower postoperative ESR and CRP that correlated positively with increased knee ROM [15]. Two other studies measured postoperative drain output as a marker of potential oedema and postoperative swelling with similar findings. One reported less drain output in the non-steroid group but this failed to reach statistical significance; and the other demonstrated significantly more (p=0.015) drain output in the steroid group [14,16]. Joo et al explains this difference as a 'rebound' phenomenon where the addition of adrenaline to the cocktail induces a reactive hyperemia with resultant increased perfusion once the drug has worn off. The contralateral knee acting as a control, received only sterile normal saline. Kwon et al reported on an indirect measure of output in each group and noted comparable rates of wound ooze [21]. These findings may question the anti-vasodilatory effects of steroid in total knee arthroplasty.

Inflammatory response following surgery is also subject to the interaction between cell surface molecules of lymphocytes and primary antigen presenting cells. Corticosteroids have been shown to reduce expression of ELAM-1, L-selectin, E-selectin and VCAM-1[23]. This down regulation leads to reduced leukocyte adhesion to target tissue and the subsequent inflammatory response usually triggered by those leukocytes. Although this may reduce inflammation, the trade off for such benefits equates to a predisposition of the patient to potential infection. The addition of antibiotic to the cocktail does not appear to safe guard patients from deep infection [8,9].

Table 3: Local anaesthetic composition and injection technique.

Author	Staged injection?	Extensor mechanism injected?	Cocktail Composition	Antibiotic included	Timing and sites of injection
Kwon et al[21]	Yes	Yes	Drugs 1. 10mg morphine sulfate 2. 300mg ropivacaine 3. 30mg ketorolac 4. 300mcg 1:1000 adrenaline Steroid, 40mg triamcinolone acetamide Volume 100mls	No	Pre-implantation: posterior capsule, MCL, LCL, soft tissues above femoral epicondyles Post-implantation: capsule, quadriceps, pesanserinus, subcutaneous tissue, peripatellar aponeurosis
Chia et al[18]	Yes*	Yes [#]	Drugs 1. 0.2% ropivacaine 2. 1:1000 adrenaline Steroid 40mg and 80mg triamcinolone acetamide Volume 100mls	No	Pre-implantation: posterior capsule, MCL, meniscal rims, synovium. Post-implantation: quadriceps, patellar tendon, subcutaneous.
Nakai et al[20]	Yes	Unknown	Drugs 1. 30mls 0.75% ropivacaine 2. 10mg morphine 3. 0.25mg adrenaline Steroid 4mg betamethasone Volume 50mls	No	Pre and Post-implantation: injection sites not specified.
Ikeuchi et al[19]	N/A	No	Drugs 1. 20mls 0.75% ropivacaine 2. 400mg isepamicin Steroid 6.6mg dexamethasone Volume postoperative boluses	No	Postoperative pain delivery via drain at 12 hour intervals for the first 48 hours, and clamped for an hour.
Yue et al[20]	Yes*	Yes	Drugs 1. 30mls 0.75% ropivacaine 2. 0.5mls 1:1000 adrenaline Steroid 4mg betamethasone Volume 100mls	No	Pre-implantation: quadriceps, patellar tendon, posterior capsule, MCL, LCL, subcutaneous Post implantation: skin
Meftah et al[17]	Yes*	Yes	Drugs 1. 200-400mg 0.5% bupivacaine 2. 0.8cc morphine sulfate 3. 0.3cc 1:1000 adrenaline 4. 750mg antibiotic Steroid 40mg unspecified corticosteroid Volume not specified	Yes	Pre-implantation: posterior capsule, posteromedial soft tissue, synovium Post implantation: extensor mechanism, pesanserinus, anteromedial capsule, periosteum, ITB, subcutaneous
Joo et al[14]	Yes	Yes	Drugs 1. 200mg 0.5% bupivacaine 2. 10mg morphine 3. 300mcg adrenaline Steroid 40mg methylprednisolone acetate Volume 50mls	No	Pre-implantation: posterior capsule, MCL, LCL Post implantation: quadriceps, retinaculum
Sean et al[16]	Yes*	Yes	Drugs 1. 0.5% bupivacaine 2. 1:200,000 adrenaline 0.5ml/kg diluted in 30mls of normal saline Steroid 40mg triamcinolone acetamide Volume at least 30mls	No	Post implantation: quadriceps, posterior capsule, MCL, synovium
Ng et al[15]	Yes*	Yes	Drugs 1. 0.5% bupivacaine 2. 1:200,000 adrenaline 0.5ml/kg diluted in 30mls of normal saline Steroid 40mg triamcinolone acetamide Volume not specified	No	Pre-implantation: quadriceps, posterior capsule, MCL Post implantation: subcutaneous

Mullaji et al[9]	No	Yes	Drugs 1. 2mg/kg bupivacaine 2. 100mcg fentanyl 3. 750mg cefuroxime Steroid 40mg methylprednisolone acetate Volume at least 25mls	Yes	Post implantation: quadriceps, MCL, retropatellar fat pad, posteromedial soft tissue
Fu et al[13]	Yes	Yes	Drugs 1. 30mg bupivacaine 2. 5mg morphine sulfate Steroid 4mg betamethasone Volume 60mls	No	Pre-implantation: quadriceps, posterior capsule, MCL, LCL Post implantation: quadriceps, patellar tendon, fat pad, synovium, retinaculum, periosteum and subcutaneous
Christensen et al[8]	No	No	Drugs 1. 80mg bupivacaine 2. 4mg morphine sulfate 3. 300mcg adrenaline 4. 100mcg clonidine 5. 750mg cefuroxime Steroid 40mg methylprednisolone acetate Volume not specified	Yes	Timing not specified. Sites: Posterior capsule, MCL, LCL, synovium
Pang et al[12]	Yes*	Yes [†]	Drugs 1. 0.5% bupivacaine 2. 1:200,000 adrenaline 0.5ml/kg diluted in 30mls of normal saline Steroid 40mg triamcinolone acetonide Volume not specified	No	Post implantation: quadriceps, capsule, MCL, synovium Before closure: skin
Parvataneni et al[4]	Yes	Yes	Drugs 1. 200-400mg 0.5% bupivacaine 2. 4-10mg morphine sulfate 3. 300mcg adrenaline 4. 750mg cefuroxime Steroid 40mg methylprednisolone acetate Volume at least 22mls	Yes	Before reduction: posterior capsule After reduction: capsule, MCL, LCL, extensor mechanism, synovium, pesanserinus, periosteum, ITB

Abbreviations: ITB: Iliotibial Band; MCL: Medial Collateral Ligament; LCL: Lateral Collateral Ligament

*injection was staged but superficial injection did not contain steroid

#quadriceps muscle injected, not tendon

[†]Extensor tendons injected only with local anaesthetics and adrenaline.

Corticosteroids most used across studies were triamcinolone, methylprednisolone and betamethasone. In 2009, Hepper et al reviewed the literature attempting to answer which intraarticular corticosteroid was most effective at reducing arthritic pain [24]. Based on 4 studies comparing the aforementioned steroids, authors found that triamcinolone was more effective at reducing pain at both 1 and 3 weeks when compared to betamethasone and methylprednisolone. Based on 2 of these studies they concluded triamcinolone to be the more efficacious drug [24]. None of the studies identified in our review compared different corticosteroids. Studies investigating 40mg of triamcinolone consistently reduced pain scores in the immediate postoperative period [12,16,21]. Chia et al investigated 2 different doses of triamcinolone when compared to a control group which failed to show any benefit [18] Triamcinolone acetonide has a longer duration of action along (low solubility) with higher incidence of cutaneous side effects [25]. This is likely to have influenced investigators decision to only infiltrate the deeper structures of the knee when triamcinolone was used [12,15,16,18,21]. The National Health Service recommends triamcinolone and

methylprednisolone as preferred agents for large joint arthritis [25].

A recent review article of 29 randomized controlled trials concluded a single intraoperative cocktail be administered in a systematic fashion to all exposed tissue, including the posterior capsule [3]. Their recommendations come largely from Andersen et al who investigated small variations in cocktail administration in 5 randomized controlled trials that showed minimal therapeutic benefit[3]. Nine studies included for review specified routine systematic administration of their cocktail in relation to implantation and reduction [4,7,12-15,17,18,21]. All but 3 studies indicated that the posterior capsule be infiltrated with local anaesthetic including the steroid [4,7,8,12-18,21]. No reports of tendon rupture occurred across all studies despite three studies injecting corticosteroid directly into the patella tendon. It is well known that infiltration of peritendinous steroid may play a role in subsequent rupture [26]. However, in a low demand patient population this finding may not be unexpected.

CONCLUSION

In conclusion, corticosteroids in isolation or as an adjunct to the cocktail of local anaesthetic in knee joint replacement has been shown to be safe and demonstrates a comparable risk of infection and tendon rupture as placebo or control. There is, however, a lack of evidence in this setting determining steroid of choice, timing and necessary structures required to be infiltrated around the knee joint in order to achieve optimal analgesic effect.

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