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Research article

Effect of intra-articular alpha-agonists on post-operative outcomes following arthroscopic knee surgery: A systematic review and meta-analysis

Elizabeth Perritt [a], Hilary Wallace [b], S. Singh [c], A. Banerjee [c,*]

[a] 51 Mill Lane, Upton, Chester CH2 1BS, United Kingdom
[b] 3 Cheyne Gardens, Aigburth, Liverpool L19 3PH, United Kingdom
[c] Department of Anaesthesia, Royal Liverpool and Broadgreen University Hospital NHS Trust, Prescot Street, Liverpool L7 8XP, United Kingdom

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ABSTRACT

Context and aim: The addition of alpha-2 agonists clonidine and dexmedetomidine to intra-articular (IA) infiltration of local anaesthetics (LA) may prolong the duration of action of analgesia following arthroscopic knee surgery. The objective of this systematic review and meta-analysis was to evaluate the analgesic effect of addition of alpha-2 agonists to LA when used for day case arthroscopic knee surgery.
Methods: PubMed, EMBASE, Cochrane Library, Google Scholar, conference abstracts and bibliographic references were searched for RCTs comparing IA LA to IA LA+ adjuvant. The primary outcome was the duration of analgesia (determined by the time to first request for additional analgesia post-operatively). Secondary outcomes were Visual Analogue Scale (VAS) scores at various time intervals, opiate consumption over 24 h and incidence of hypotension and bradycardia. The data were analysed using RevMan software.
Results: Eight trials (390 patients) were included with patients receiving dexmedetomidine and clonidine in addition to LA. Alpha-2 agonists significantly prolonged the duration of action of LA [SMD 3.00 [95% CI2.39, 3.62] ($p < 0.00001$)] (Mean Difference 282 min). VAS scores were statistically significantly lower at one [SMD −1.06 [95% CI −1.98, −0.13] ($p = 0.02$)], two [SMD −1.29 [95% CI −2.11, −0.47] ($p < 0.002$)] and eight hours [SMD −0.86 [95% CI −1.25, −0.47] ($p < 0.0001$)], when alpha-2 agonists were used. Total opiate consumption was reduced in the experimental group (SMD −3.19 [95% CI, −4.74, −1.64] ($p < 0.0001$)] (Mean Difference 15.45 mg). There were no significant differences in adverse effects.
Conclusions: Addition of alpha-2 agonists to IALA significantly prolongs duration of analgesia and reduces VAS scores in the immediate postoperative period following day case arthroscopic knee surgery.

1. Introduction

Arthroscopic knee surgery is commonly performed as a day case procedure, where a key goal is that of early ambulation and discharge. A barrier to this goal is moderate to severe postoperative pain, which can be problematic [1]. Not only does pain have a negative impact on the patients' experience and satisfaction, it is associated with significant impact on provision of day case services [2].

Given that pain following knee arthroscopy is thought to result from irritation of free nerve endings within the joint [3], intra-articular (IA) analgesic techniques have generated significant interest. A number of studies provide evidence of improved analgesia using intra-articular local anaesthetics (IALA), although improvements seen were often of short duration [4]. In view of the limited benefit of LA alone, there has been considerable interest into the addition of adjuvants to IALA. The analgesic efficacy of IALA with morphine, for example, has been demonstrated, but side effects are a concern [5,6]. There is now growing evidence to support the use of the alpha-2 agonists, clonidine and dexmedetomidine, as useful adjuncts to LA in orthopaedics and neurosurgery [7–11].

Clonidine has been shown to prolong the duration of action of LA in the laboratory settings [12] and several studies have examined the effects of IA clonidine on post-operative pain following arthroscopic knee surgery [7,10,11,13,14]. Dexmedetomidine has also been evaluated as an adjuvant. Al-Metwalli and colleagues demonstrated an increased time to first analgesic request and a

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* Corresponding author.
E-mail address: abanerjeeuk@googlemail.com (A. Banerjee).

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decreased need for postoperative analgesia when IA dexmedetomidine was used alone [15]. The addition of dexmedetomidine to LA for IA use has also been shown to improve the quality and duration of post-operative analgesia [8,15–17]. Therefore it appears that addition of alpha-2 agonists as adjuvants might be beneficial for postoperative pain relief after arthroscopic surgery.

Sun and colleagues in their analysis of IA clonidine versus saline placebo [18] concluded that a single dose of IA clonidine has a definite analgesic effect, albeit mild and short-lived. We sought to analyse the use of IA clonidine or dexmedetomidine with LA (experimental group), compared to the use of LA infiltration alone (control group), as to our knowledge, no meta-analysis has examined addition of IA LA + IA clonidine/dexmedetomidine. The aim of our meta-analysis was to quantify the duration of analgesia following arthroscopic knee surgery when clonidine or dexmedetomidine (alpha-2 agonists) are used as an adjunct to LA.

2. Methods

2.1. Search strategy

RCTs were identified by searching the following electronic databases: (i) MEDLINE (1946-Feb 2016), (ii) EMBASE (1980-Feb 2016), (iii) Cochrane Central Register of Controlled Trials (2005-March 2016) and (iv) Google Scholar. The search keywords and text words were 'Intra-articular, local anaesthetics/anaesthetics, alpha-agonists, clonidine, dexmedetomidine'. Bibliographic searches of all identified articles were also conducted to identify any additional article not identified in the initial search. The abstract databases from major international meetings were also reviewed (ASRA, ESRA, ASA) as well as published protocols on www.clinicaltrials.gov. The last literature search was conducted on 29th February 2016.

2.2. Eligibility criteria

We sought to identify all randomized controlled trials that made a comparison of IA LA with IA LA plus alpha-2 agonist, following arthroscopic knee surgery. Studies were excluded if they examined the alpha-2 agonist alone or if the control did not use local anaesthetic. Animal studies were excluded. There were no language restrictions.

2.3. Data collection and presentation

All the authors independently evaluated the methodological quality of the included trials using the Jadad score [19], and performed data extraction. Data extracted were: patient numbers, alpha-2 agonist, blinding of allocation information, type of surgery, anaesthetic details, control and experimental group characteristics (numbers, dose of local anaesthetic, volume used, dose of alpha-2 agonists). The primary outcome was the duration of analgesia (as determined by the time to first request for additional analgesia post-operatively as per authors definition). Secondary outcomes were pain intensity – Visual Analogue Scores (VAS) at various time intervals in the postoperative period, total opiate consumption over 24 h and incidence of cardiovascular disturbance (hypotension or bradycardia). Pain intensity was determined by use of the pain VAS at rest as per authors' definition. Some studies [8,17,20–22] used mean VAS scores and for the purpose of analysis, these were assumed to be at rest scores. Overall VAS scores were rounded to whole numbers for better interpretation of data. Attempts were made to contact study authors to obtain raw data where it was missing.

2.4. Analysis

The study characteristics are presented in Table 1. Data entry was performed by the authors into RevMan 5.1 software. Meta-analytic techniques were used where possible to combine the results. For dichotomous variables, the odds ratio (OR) and 95% confidence interval (CI) were calculated and combined using a random effects model. A statistically significant difference occurred when the 95% CI did not include 1.0. For continuous variables, the standardized mean difference (SMD) and 95% CI were calculated using random effects modeling. A statistically significant difference occurred when the 95% CI did not include 0. If continuous data were only reported as median or range, the mean was estimated as equivalent to the median and the standard deviation was computed to be approximately one-quarter of the typical ranges of data values. Sensitivity analysis was undertaken for the primary outcome. When there was more than one intervention group [21] the control group was split to avoid unit of analysis error.

Heterogeneity was assessed using the I^2 statistic. The I^2 statistic describes the percentage of total variation in study findings that is due to between study differences rather than due to chance. If significant heterogeneity was detected, it was assumed that there was no single 'true' effect underlying the data, which was constant across different populations and a random effects model was used. The mean, SD and confidence intervals were reported for each outcome. Heterogeneity of the pooled results was assessed using the Tau^2 statistic. A funnel plot was used for assessing publication bias [23].

To allow comparisons between studies to be made, where possible drugs were converted into equivalent oral opiate (morphine) doses using a dose conversion tool (http://www.global-rph.com/narcoticonv.html).

3. Results

The study flow chart is presented in Fig. 1. The search yielded 22 RCTs after removal of duplicates identified between databases. Studies were excluded if they did not use LA as a control, or if the data was inadequate to make statistical comparisons. A number of studies had more than two treatment groups [7,17,21,22] but only those groups that used LA alone and LA + alpha-2 agonist groups were included in the final analysis. Six of the studies examined IA dexmedetomidine (1 μg/kg, 2 μg/kg or 100 mcg) [8,17,20–22,24] and two studied IA clonidine (1 μg/kg) in the experimental arm [7,25]. LA used was bupivacaine (72.5 mg and 75 mg), Levobupivacaine (75 mg) or Ropivacaine (40 mg, 47.5 mg and 50 mg). The IA solution was administered by the surgeon at the end of procedure in all studies bar one, in which the solution was administered before insertion of arthroscope [25]. A funnel plot did not demonstrate asymmetry.

On accessing www.clinicaltrials.gov, there were no on-going trials, but one completed study titled 'Adding Intra-articular Dexmedetomidine to Levobupivacaine for Postoperative Analgesia in Arthroscopic Knee Surgery', with identifier NCT01918917. For this study, no study results were posted and therefore no text was available.

4. Primary outcome

4.1. Duration of analgesia

Addition of an alpha-2 agonist to LA was associated with a significant increase in the time to request first analgesic dose [SMD 3.00 [95% CI 2.39, 3.62] ($p < 0.00001$)] with heterogeneity