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Review article

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

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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.

Contents

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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 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.

Table 1
Characteristics of included studies.

Study details			No of Patients		Perioperative details				Control Group		Experimental Group		
Name of Author	Alpha Agonist & Dose	Blinding of Allocation	Control	Experimental	Procedures	GA/LA	Type of LA used	Voulme of IA Solution (mls)	Patient weight (mean ± SD, kg)	Dose of LA	Patient weight (mean ± SD, kg)	Dose of alpha agonist (μg)	Dose of LA
Reuben et al. [7]	Clonidine 1 μg/kg	No mention	10	10	Meniscal surgery	GA	Bupivacaine 0.25%	30	74 ± 8	75 mg	72 ± 12	72 ± 12	75 mg
Paul et al. [8]	Dexmedetomidine 100 μg	Random table assignment	30	30	Meniscectomy, ligament repair	GA	Ropivacaine 0.25%	20	54.35 ± 8.86	47.5 mg	56.32 ± 11.48	100	47.5 mg
El-Hamasy et al. [17]	Dexmedetomidine 1 μg/kg	Sealed envelope	30	30	Arthroscopy, meniscectomy, debridement	GA	Bupivacaine 0.25%	30	83 ± 12	75 mg	85 ± 17	85 ± 17	75 mg
Tarlika et al. [20]	Dexmedetomidine 1 μg/kg	Not described	25	25	Arthroscopic knee surgery (unspecified)	Spinal	Ropivacaine 0.25%	20	No details	50 mg	No details	Not known	50 mg
Panigrahi et al. [21]	Dexmedetomidine 1 μg/kg, 2 μg/kg	Block randomisation	20	20 20	Ligament reconstruction, meniscectomy, combined	Spinal	Ropivacaine 0.2%	20	63.6 ± 5.4	40 mg	63.9 ± 11.6 66.3 ± 6.9	63.9 ± 11.6 132.6 ± 13.8	36 mg 36 mg
Elbadawy et al. [22]	Dexmedetomidine 1 μg/kg	Computer generated, sealed envelopes	25	25	Arthroscopic knee surgery (unspecified)	GA	Bupivacaine 0.25%	25	74.2 ± 10.3	72.5 mg	76 ± 7.8	76 ± 7.8	72.5 mg
Joshi et al. [25]	Clonidine 1 μg/kg	Not described	15	15	Meniscectomy	Sedation	Bupivacaine 0.25%	30	71 ± 12	75 mg	69 ± 11	69 ± 11	75 mg
Wang et al. [24]	Dexmedetomidine 1 μg/kg	Random number table	30	30	Arthroscopic knee surgery (unspecified)	GA	Ropivacaine 0.25%	20	54 ± 7	47.5 mg	56 ± 8	56 ± 8	47.5 mg

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 ($I^2 = 75\%$) (Fig. 2). There is a Mean Difference of 282 min compared to the control group [95% CI 219.98, 343.99] ($P < 0.00001$).

4.2. Secondary outcomes

4.2.1. Vas scores at rest

Visual analogue scores (VAS) scores at rest following surgery were reported by all included studies, although VAS scores could not be reliably extracted from graphical data in one study [17] and another did not provide standard deviation values and data was therefore not used [21]. The addition of alpha agonist to IA LA resulted in lower mean VAS scores at rest (Table 2). VAS scores at rest 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] ($p < 0.0001$)] postoperatively. VAS scores were not statistically significant at 24 h [SMD, (95%CI) = 0.42, (−0.91, 0.08), $P = 0.1$] postoperatively.

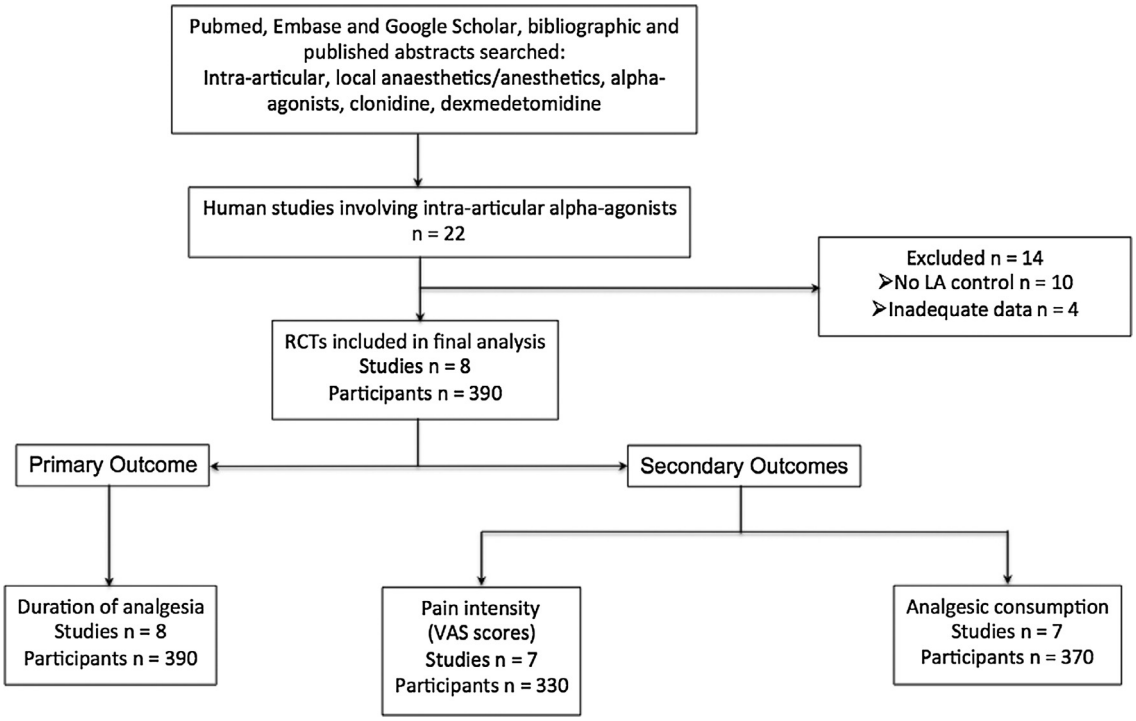

Fig. 1. Study flow diagram.

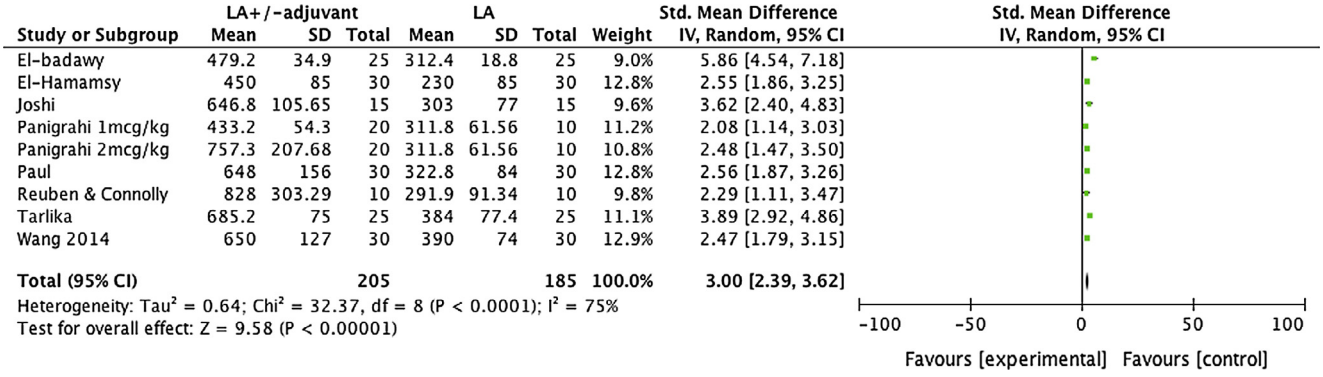

Fig. 2. Time to request of first analgesia.

4.2.2. Postoperative analgesic consumption

All studies examined 24-h analgesic consumption. The drugs administered were Paracetamol, Codeine, Fentanyl, Meperidine, Oxycodone and Diclofenac (Table 3). Fentanyl, Codeine, Meperidine and oxycodone were converted to equi-analgesic oral morphine (http://www.globalrph.com/narcoticonv.htm). Total opiate consumption was significantly lower in the experimental group (SMD −3.19 [95% CI, −4.74, −1.64] ($p < 0.0001$)] (Fig. 3). This equates to a mean difference of 15.45 mg.

4.2.3. Physiological parameters

Of the eight included studies [7,8,17,20–22,24,25], there were only four studies that reported on hypotension [7,8,21,22], with 3/80 (3.75%) patients receiving intraarticular alpha agonist who experienced hypotension compared to 1/80 (1.25%) receiving IA LA. Meta-analysis was not possible due to the small number of studies. Three studies reported on incidence of bradycardia [7,8,25]. There was only 1/55 (1.82%) patient who had experienced bradycardia having received IA alpha agonist compared to 0/55 in the control group [8].

5. Discussion

The antinociceptive effects of α-2 adrenoceptor agonists have been demonstrated in both animals [26] and human studies. Postulated mechanisms of action include inhibition of C and A delta fibres, release of endogenous encephalin-like substances and inhibition of noradrenaline release at nerve endings [27]. This meta-analysis demonstrates that the addition of alpha-2 agonists to LA for arthroscopic knee surgery significantly improves duration of analgesia, and reduces pain intensity, with no adverse effects. Other meta-analysis has compared alpha-2 agonists to saline [18]. Not only do we consider the use of LA to be clinically more relevant, it is also ethically sound, given the ethical considerations for any study using an invasive placebo [28].

Table 2
Mean VAS scores at rest.

Study (name of author)	Control group						Experimental group					
	VAS 1 h	VAS 2 h	VAS 6 h	VAS 8 h	VAS 18 h	Vas 24 h	VAS 1 h	VAS 2 h	VAS 8 h	VAS 12 h	VAS 18 h	VAS 24 h
Reuben et al. [7]	2.5 ± 0.7	3 + /-0.7				3.2 + /-0.6	2.3 ± 0.8	2.8 + /-0.6				3.2 + /-0.6
Paul et al. [8]	2.8 ± 0.64	3.01 + /-0.76	4.01 ± 1.13		3.5 ± 1.01		1.9 ± 0.62	2.3 + /-0.61			3.32 ± 1.04	
Tarlika et al. [20]		1.64 + /-0.86	3.24 ± 0.93	2.84 + /-0.94	2.68 ± 1.03	2.72 + /-0.84		0.92 + /-0.28	2.08 + /-0.28	3.37 ± 0.88	2.71 ± 0.55	2.25 + /-0.53
Elbadawy et al. [22]	2.7 ± 0.7	3.2 + /-0.4	4.6 ± 0.5				1.3 ± 0.5	1.7 + /-0.5		4.3 ± 0.5		
Joshi et al. [25]	2.3 ± 0.8	3.2 + /-0.6				3.9 + /-0.6	2.1 ± 0.9	2.7 + /-0.6				3.3 + /-0.5
Wang et al. [24]				3.9 + /-1.0		3.4 + /-0.6			3.2 + /-1.0	3.6 ± 0.9		3.4 + /-0.7

We found that adding alpha agonists to LA increases the duration of analgesia SMD 3.00 (95%CI) [2.39, 3.62], P < 0.0001 (MD = 282 min). Furthermore, pain intensity was measured as VAS scores up to 24 h after surgery. The VAS analysis has shown statistically significant improvement in scores up to eight hours postoperatively. We therefore assert that LA can be used in addition to alpha-2 agonist to provide adequate analgesia of clinical relevance.

Opiates are associated with a number of adverse effects, such as sedation, postoperative nausea and vomiting, urinary retention, ileus, and respiratory depression [29]. Certainly, such complications may occur following the use of intravenous morphine after arthroscopic and major knee surgery, which can result in an increased length of hospital stay [30,31]. Avoidance of opioids, with focus on multimodal analgesia, is a key component of Enhanced Recovery After Surgery (ERAS) [32]. In our meta-analysis, opiate requirement was reduced in the experimental group by 15 mgs. NSAID usage (albeit in only two studies) also shows a trend towards decreasing use in the postoperative period [20,21]. These findings perhaps lend further support to the use of IA alpha-2 agonists within a multi-modal analgesic regimen for arthroscopic knee surgery.

Local anaesthetics are not without possible side-effects. There have been reports of post-operative chondrolysis after arthroscopic shoulder and ankle surgery [33,34]. Chondrolysis is a condition in which extensive loss of articular cartilage occurs over a relatively short period of time. The pathogenesis is unclear, and the condition is rare, but a number of experimental studies have suggested that LA may damage articular cartilage [35,33,36,37]. Addition of an alpha-2 agonist appears to improve post-operative analgesia and thus allows a reduction in concentration of LA to be used. This may reduce the (albeit small) risk of chondrotoxicity, which can be debilitating in young athletes, but warrants further investigation by way of large randomized controlled trials.

Hypotension and bradycardia are the most problematic side effects associated with the use of alpha-2 agonists, given either systemically or peripherally [18,38,39]. Hypotension is a particular problem in the day-case setting, where it may delay mobilisation and discharge. An increase in post-operative hypotension with IA clonidine has been shown in previous studies [11,17,40]. In our analysis, four studies reported details on hypotension [7,8,21,22], with 3/80 (3.75%) patients in the experimental group experiencing hypotension and 1/80 (1.25%) in the control group. Similarly, we did not demonstrate any significant link between use of IA alpha-2 agonists with LA and bradycardia, with only one reported incidence of bradycardia in an experimental group (1/55, 1.82%) [8]. Dexmedetomidine may be less likely to cause hypotension as has been found when used in other clinical settings [41,42]. In our analysis, hypotension was only noted in the experimental groups using dexmedetomidine (3/55, 5.45%) compared to the experimental clonidine groups (0/25). However, it is worth noting that given the limited number of studies in our analysis these results should be treated with caution and more robustly conducted trials are needed. Certainly, dexmedetomidine has increased affinity towards the alpha-2 receptor, binding up to eight times more avidly than clonidine [43] and may explain the above findings.

Indeed, Panigrahi et al. examined the effect of an increased dose of dexmedetomidine (2 μg/kg) and found superior analgesic efficacy with better post-operative pain relief when compared to a lower dose of 1 μg/kg [21]. Furthermore, a recent clinical observation study has compared IA ropivacaine + clonidine to IA ropivacaine + dexmedetomidine, and concluded that dexmedetomidine had better efficacy than clonidine in the day case setting [44]. It appears that a minimum dose of 40 μg of dexmedetomidine pro-

Table 3
24 h analgesic consumption.

Study (Name of Author)	Drug	Dose (Control Group)	Dose (Experimental Group)	p value
Reuben et al. [7]	Paracetamol (mg) Codeine (mg)	1059+/−357 105.9+/−35.7	381+/−264 38.1+/−26.4	<0.0001
Paul et al. [8]	Fentanyl (μg)	282.8+/−40.12	204.65+/−36.48	<0.001
El Hamasy et al. [17]	Meperidine (mg)	75.7+/−14	35+/−11	<0.05
Tarlika et al. [20]	Diclofenac (mg)	201+/−36	141+/−25.5	<0.0001
Panigrahi et al. [21]	Diclofenac (mg)	221+/−56.93	153.8+/−51.5 82.5+/−48.1	<0.01
Elbadawy et al. [22]	Paracetamol (mg)	1368.0+/−227.2	758+/−153	<0.05
Joshi et al. [25]	Paracetamol (mg) Oxycodone (mg)	1860.63+/−471.25 28.63+/−7.25	1064.38+/−471.25 16.38+/−7.25	<0.001
Wang et al. [24]	Fentanyl (μg)	146+/−21	22+/−6	p < 0.01

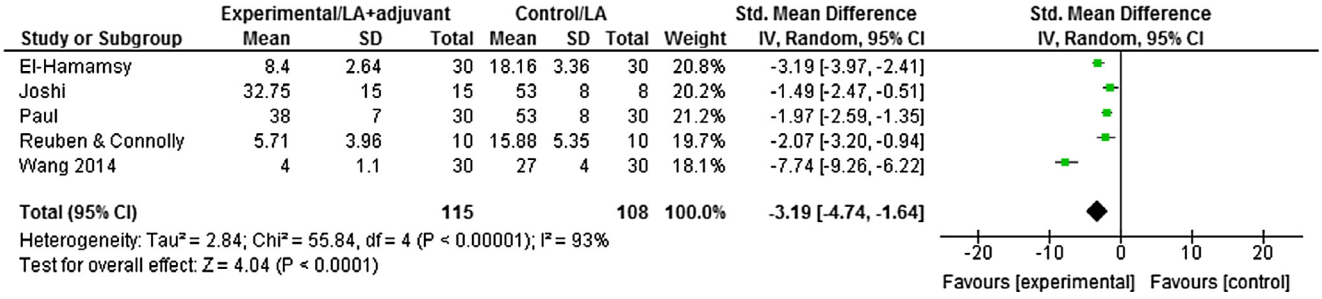

Fig. 3. Total morphine consumption.

vides adequate pain relief, however more robustly conducted trials are needed to ascertain this.

6. Limitations

This meta-analysis does have limitations. It is possible that differences in outcomes seen could be linked to the type of LA used, rather than solely the use of an adjunct. Das et al. found 0.5% levobupivacaine to provide superior analgesia compared to 0.75% ropivacaine, with respect to duration and quality of analgesia [45]. Further work to inform on choice of LA with/without adjunct is needed. Sensitivity analysis excluding ropivacaine or different doses of LA used did not alter the significance or the direction of the overall outcome with regards to duration of analgesia. Moreover, the dose of alpha agonists varied between studies as well, but due to small number of studies we could not perform a subgroup analysis to assess the impact of different doses of alpha agonists. However, further sensitivity analysis excluding the 2 μg/kg dose of alpha agonist did not alter the significance nor direction of the overall result.

There are also some differences in anaesthetic technique that must be acknowledged. In two studies [20,21], a spinal anaesthetic was given prior to arthroscopy. The duration of analgesia from spinal LA can be variable, and residual spinal anaesthesia could have contributed towards reduced pain in these patients. Performing a sensitivity analysis based on GA only, did not alter the direction of the overall outcome, or the p value, but heterogeneity increased to 80%. Furthermore, we performed sensitivity analysis excluding studies that used intraoperative nitrous oxide [7,8,17]. This did not change the direction of the overall outcome, but increased heterogeneity to 73% without any alteration to the p value.

The timing of tourniquet application and removal may also affect the duration of local action of a drug and its rate of absorption from a joint [21,46]. In three studies, no details were provided about timing of tourniquet release [7,8,25]. However, performing a sensitivity analysis excluding them did not alter the P value or the direction of the overall result. Three studies did not describe the blinding of allocation [7,20,25]. We were unable to perform a meta-regression due to small number of studies to account for heterogeneity. The small number of studies with limited number of participants made some outcomes imprecise, hence a systematic approach was adopted reporting the results. With regard to reporting of VAS scores, the constraints were that there were few studies measuring VAS at consistent time intervals and although there were little clinical differences in the VAS scores, there was significant statistical differences observed up to 8 h postoperatively – a limiting factor when considering the duration of analgesia as determined by VAS scores.

7. Conclusion

This is the only meta-analysis to our knowledge comparing LA with alpha-2 agonist to LA alone. It demonstrates that the addition of alpha-2 agonists to local anaesthetics may prolong the duration of analgesia following arthroscopic knee surgery, with reduced pain intensity in the early post-operative period up to eight hours, and without significant adverse effects. The choice of LA, and dose of alpha-2 agonists warrants further investigation.

Key Messages: This meta-analysis suggests that the addition of alpha-2 agonists to IA LA prolongs the duration of analgesia, with reduced pain intensity up to eight hours following arthroscopic knee surgery, and without significant adverse effects. It is possible that dexmedetomidine is superior to clonidine in this aspect.

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