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Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults (Review)

Prabhakar H, Singh GP, Ali Z, Kalaivani M, Smith MA

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[Intervention Review]

Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

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ABSTRACT

Background

Rocuronium bromide is a routinely used muscle relaxant in anaesthetic practice. Its use, however, is associated with intense pain on injection. While it is well established that rocuronium bromide injection causes pain in awake patients, anaesthetized patients also tend to show withdrawal movements of the limbs when this muscle relaxant is administered. Various strategies, both pharmacological and non-pharmacological, have been studied to reduce the incidence and severity of pain on rocuronium bromide injection. We wanted to find out which of the existing modalities was best to reduce pain on rocuronium injection.

Objectives

The objectives of this review were to assess the ability of both pharmacological and non-pharmacological interventions to reduce or eliminate the pain that accompanies rocuronium bromide administration.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 7), MEDLINE via Ovid SP (1966 to July 2013) and EMBASE via Ovid SP (1980 to July 2013). We also searched specific websites. We reran the searches in February 2015 and will deal with the 11 studies of interest found through this search when we update the review.

Selection criteria

We included all randomized controlled trials (RCTs) that compared the use of any drug or a non-pharmacological method with control patients, or those receiving no treatment to reduce the severity of pain with rocuronium injection. Our primary outcome was pain on rocuronium bromide injection measured by a pain score assessment. Our secondary outcomes were rise in heart rate and blood pressure following administration of rocuronium and adverse events related to the interventions.

Data collection and analysis

We used the standardized methods for conducting a systematic review as described in the *Cochrane Handbook for Systematic Reviews of Interventions*. Two authors independently extracted details of trial methodology and outcome data from reports of all trials considered eligible for inclusion. We made all analyses on an intention-to-treat basis. We used a fixed-effect model where there was no evidence of significant heterogeneity between studies and a random-effects model if heterogeneity was likely.

Main results

We included 66 studies with 7840 participants in the review, though most analyses were based on data from fewer participants. In total there are 17 studies awaiting classification. No studies were at a low risk of bias. We noted substantial statistical and clinical heterogeneity between trials. Most of the studies reported the primary outcome pain as assessed by verbal response from participants in an awake state but some trials reported withdrawal of the injected limb as a proxy for pain after induction of anaesthesia in response to rocuronium administration. Few studies reported adverse events and no study reported heart rate and blood pressure changes after administration of rocuronium. Lidocaine was the most commonly studied intervention drug, used in 29 trials with 2256 participants. The risk ratio (RR) of pain on injection if given lidocaine compared to placebo was 0.23 (95% confidence interval (CI) 0.17 to 0.31; I^2 = 65%, low quality of evidence). The RR of pain on injection if fentanyl and remifentanil were given compared to placebo was 0.42 (95% CI 0.26 to 0.70; I^2 = 79%, low quality of evidence) and (RR 0.10, 95% CI 0.04 to 0.26; I^2 = 74%, low quality of evidence), respectively. Pain on injection of intervention drugs was reported with the use of lidocaine and acetaminophen in one study. Cough was reported with the use of fentanyl (one study), remifentanil (five studies, low quality evidence) and alfentanil (one study). Breath holding and chest tightness were reported with the use of remifentanil in two studies (very low quality evidence) and one study (very low quality evidence), respectively. The overall rate of complications was low.

Authors' conclusions

The evidence to suggest that the most commonly investigated pharmacological interventions reduce pain on injection of rocuronium is of low quality due to risk of bias and inconsistency. There is low or very low quality evidence for adverse events, due to risk of bias, inconsistency and imprecision of effect. We did not compare the various interventions with one another and so cannot comment on the superiority of one intervention over another. Complications were reported more often with use of opioids.

PLAIN LANGUAGE SUMMARY

Use of drug and non-drug interventions to reduce pain associated with rocuronium bromide injection in patients undergoing general anaesthesia

Review question

What is the effect of using drug or non-drug treatments (such as diluting the rocuronium or warming the site of injection) for reducing the pain associated with injecting the muscle relaxant rocuronium bromide in children and adults?

Background

Rocuronium bromide is a muscle relaxant used as part of general anaesthesia for surgery. Muscle relaxants are used to relax the muscles of the airway to enable endotracheal intubation (placing a breathing tube in the windpipe to support the airway while the person is unconscious) and to facilitate the surgery. However, rocuronium bromide can cause intense pain as it is injected in some people. We wanted to find out whether giving another drug, such as a painkiller or another anaesthetic, or a non-drug intervention, such as diluting the rocuronium, would be useful in reducing the pain experienced by some people on injection of rocuronium.

Study characteristics

We included trials up to July 2013 in our review. We re-ran the searches in February 2015. In total there are 17 studies awaiting classification. We included 66 studies with 7840 participants, both male and female, and including children and adults. Most of these participants were undergoing various planned surgical procedures in hospitals in several countries including Korea, Turkey and India. The trials compared an intervention aiming to reduce pain on injection with a placebo to ascertain whether any intervention was effective at reducing pain. The outcome was assessed by recording the level of pain reported by patients when injected with rocuronium bromide.

Key results

The most studied treatments were injection of the local anaesthetic lidocaine, or the painkillers fentanyl or remifentanil, into the vein before injecting rocuronium. These treatments may reduce the pain associated with injecting rocuronium, but the evidence is of low quality. Some interventions, for example using painkillers such as fentanyl, may increase cough, chest tightness and breath holding. These are recognized side effects of these drugs.

Quality of the evidence

The low quality of the evidence for the assessment of changes in the level of pain was due to inadequate reporting of study design and variation in the study results. In addition to these limitations, for some adverse event outcomes we did not have enough information to be certain about the average effect. Further research is needed with high quality, well designed studies to determine whether pain on injection of rocuronium bromide can be reduced by using an appropriate intervention.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Lidocaine compared with placebo for rocuronium bromide induced pain on injection in adults and children

Patient or population: adults and children undergoing general anaesthesia including the muscle relaxant rocuronium bromide
Settings: hospital operating theatres in high-income countries
Intervention: lidocaine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lidocaine				
Pain - lidocaine	Study population		RR 0.23 (0.17 to 0.31)	2256 (29 studies)	⊕⊕◯◯ **low** [1,2]	-
	551 per 1000	127 per 1000 (94 to 171)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of bias. Most of the studies did not mention the method of randomization and are of poor methodological quality and so we downgraded the evidence by one level.
[2]Significant heterogeneity noted across the included studies and so we downgraded the evidence by one level for inconsistency.

BACKGROUND

The muscle relaxant succinylcholine is known to produce the most suitable conditions for tracheal intubation but has distinct disadvantages such as producing myalgia (muscle pain), a rise in blood potassium levels and a rise in intraocular and intracranial pressures (Abbas 2009; Orebaugh 1999). Rocuronium is free of all of these side effects and produces intubating conditions similar to succinylcholine. Rocuronium bromide is, therefore, an important addition to anaesthetic practice because of its rapid onset of action, thereby allowing rapid tracheal intubation. However, pain on injection of rocuronium is common and is reported in 50% to 80% of patients (Borgeat 1997; Lockey 1995). Although the pain lasts for only a few seconds at the injection site, its intensity is severe and distressing (Cheong 2000). While it is well established that rocuronium bromide injection causes pain in awake patients, anaesthetized patients also tend to show withdrawal movements of the limbs when this muscle relaxant is administered (Kim 2007; Shevchenko 1999).

Description of the condition

The administration of rocuronium produces intense and severe pain with a burning sensation. This has been noted when rocuronium is used in priming doses just prior to induction of anaesthesia (Borgeat 1997; Lockey 1995). Rocuronium is usually administered after induction of general anaesthesia in order to facilitate tracheal intubation. The exact mechanism for the production of pain on rocuronium injection is unknown. Of the various muscle relaxants in clinical use, rocuronium is the only one associated with pain. Attenuation of pain caused by injection of rocuronium could relieve distress and avoid any consequences of the stress response. So far, there are no approved drugs for prevention of pain on injection of rocuronium bromide.

Description of the intervention

Various strategies have been studied to reduce the incidence and severity of pain on rocuronium bromide injection. These measures are either pharmacological, with usage of drugs, or non-pharmacological, where saline dilution methods or warming at the site of injection have been tried (Mahajan 2010) (Appendix 1). Pretreatment with various drugs, such as lidocaine (Cheong 2000; Shevchenko 1999), opioids including fentanyl, alfentanil, sufentanil and remifentanil (Choi 2008; Kim 2008a; Oh 2007; Singh 2007), ondansetron (Reddy 2001), metoclopramide (Ertugrul 2006), tramadol (Memis 2002), magnesium sulphate (Turan 2003), thiopental sodium (Park 2005), dexmedetomidine (Memis 2005), and esmolol (Yavascaoglu 2007), have shown varying results. In addition, dilution of rocuronium or the addition of sodium bicarbonate to alter the pH have also been tried (Kim 2008b; Tuncali 2004; Turan 2003). Many studies have been published suggesting various interventions (Ertugrul 2006; Memis 2002; Turan 2003). Lidocaine has shown favourable results in most studies (Memis 2002; Reddy 2001; Singh 2007; Turan 2003).

How the intervention might work

Pretreatment with various drugs has been shown to reduce pain on rocuronium injection and lidocaine is a popularly used drug for this purpose, probably due to its local anaesthetic properties. Drugs such as ondansetron and tramadol have also been shown to possess local anaesthetic action and this may be responsible for their role in preventing rocuronium induced pain. Opioids are another group of drugs that have been widely used for prevention of rocuronium induced pain, possibly through their action on opioid receptors in the peripheral sensory nerve fibres (Kim 2008a). Rocuronium is an isotonic solution with a pH of 4.0 and pain on injection has been associated with a pH of 4 or less. Pretreatment with sodium bicarbonate may neutralize the acidic pH of rocuronium thus reducing pain on injection (Turan 2003). The mechanism of the analgesic effect of magnesium is unclear but interference with calcium channels and N-methyl-D-aspartate (NMDA) receptors seems to play a role (Turan 2003).

Why it is important to do this review

We know that secondary to pain patients show a response characterized by hypertension and tachycardia. The disturbed haemodynamics can have adverse effects, especially in neurosurgical patients where large fluctuations in blood pressure can affect intracranial pressure. The level of pain after injection of rocuronium bromide is severe and can lead to hypertension and tachycardia in anaesthetized patients (Kim 2007; Shevchenko 1999). To date, there has been no systematic review on this subject although many studies have been published suggesting various strategies to reduce rocuronium induced pain on injection.

OBJECTIVES

The objectives of this review were to assess the ability of both pharmacological and non-pharmacological interventions to reduce or eliminate the pain that accompanies rocuronium bromide administration.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that compared the use of any drug or a non-pharmacological method with a control or no treatment to reduce the severity of pain with rocuronium injection. We planned to include studies where two or more interventions had been used in the same patient population to prevent pain on injection of rocuronium.

Types of participants

We included participants of all age groups, both paediatric and adult, who received rocuronium bromide, whether in an awake or unconscious state.

Types of interventions

We included any intervention designed to prevent pain on rocuronium injection. We included non-pharmacological techniques, admixtures of various drugs with the rocuronium and the local and systemic administration of agents prior to rocuronium administration. Some agents may have been administered by more than one method and they are therefore included in separate analyses grouped by technique (e.g. lidocaine has been used both by intravenous injection prior to rocuronium and as an admixture) (Appendix 1). The methods included (but were not limited to) the following:

1. Non-pharmacological interventions, e.g. temperature, saline admixture or dilution, massaging or rubbing at the site of injection, or speed of injection.
2. Pharmacological agents including:
   i) local anaesthetic agents such as lidocaine;
   ii) opioids such as fentanyl, alfentanil, sufentanil and remifentanil;
   iii) general anaesthetic agents, both volatile and intravenous, administered in sub-anaesthetic doses;
   iv) antihistamines;
   v) antiemetics: metoclopramide, ondansetron;
   vi) antihistamines: pheniramine;
   vii) miscellaneous drugs: magnesium sulphate, esmolol, dexmedetomidine, 8.4% sodium bicarbonate.

We accepted trials where the control group was no treatment or placebo.

Types of outcome measures

Primary outcomes

1. Pain on rocuronium bromide injection measured by a pain score assessment.

We analysed pain as a dichotomous variable. For a three-point scale, we defined 'pain' as a score of 2 where 0 = no pain, 1 = mild pain and 2 = severe pain. For studies using a four-point scale, we defined 'pain' as a score of 2 or 3. The four-point scales were typically 0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain for awake patients, or for anaesthetized patients 0 = no movement, 1 = movement of wrist only, 2 = movement of the arm and 3 = generalized movement. For five-point scales, we defined 'pain' as a score of 2, 3 or 4. We graded five-point scales in awake patients as 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain and 4 = very severe pain, and in anaesthetized patients 0 = no movement, 1 = movement to wrist, 2 = movement to elbow, 3 = movement to shoulder, 4 = whole body movement.
We measured the outcome in children ($\leq$ 14 years) and adults separately (Appendix 2).

Secondary outcomes

1. Rise in blood pressure.
2. Increase in heart rate.
3. Any adverse effect of interventional agent.

We planned to measure the continuous outcomes of rise in blood pressure and increase in heart rate from their baseline values after administration of rocuronium. We noted the values as mean and standard deviation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 7), MEDLINE via Ovid SP (1966 to July 2013) and EMBASE via Ovid SP (1980 to July 2013) (Lefebvre 2011). We developed a specific search strategy for each database. Please see Appendix 3.
We did not apply any language restriction. We reran the searches in February 2015 and will deal with the 11 studies of interest, found through this search, when we update the review.

Searching other resources

We searched for relevant ongoing trials on specific websites such as:

1. www.indmed.nic.in;
2. www.cochrane-sadcct.org;
3. www.ClinicalTrials.gov.

Data collection and analysis

Selection of studies

Using the results of the above searches, we screened all titles and abstracts for eligibility. Two authors (ZA and GPS) independently performed this screening. We obtained and assessed the full articles of all potentially eligible RCTs for relevance based on the preplanned checklist. Each author documented the reason for each trial that was excluded (Appendix 4). We resolved any disagreement between the two authors by discussion with the third author (HP), who decided on the inclusion or exclusion of the study. We compiled a list of all eligible trials (Appendix 4 ; Appendix 5).

Data extraction and management

Two authors (ZA and GPS) independently extracted the data and assessed the trial quality using a standardized form (Appendix 6; Appendix 7). We resolved any disagreement through consultation with the third author (HP). In case of additional information being required, HP contacted the corresponding author of the relevant trial.

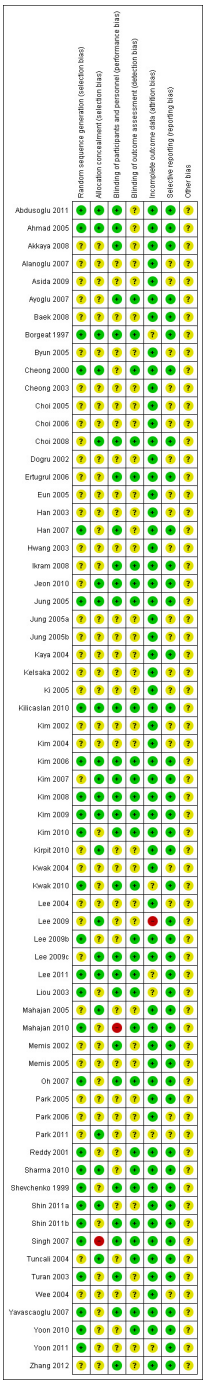
Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias of the eligible trials (ZA and GPS). We resolved any disagreement by discussion with the third author (HP). We performed the assessment as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged the quality of the studies on the basis of the risk of bias domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel, and outcome assessment;
4. incomplete outcome data;
5. selective reporting; and
6. other bias.

We considered a trial as having a low risk of bias if we assessed all domains as low risk. We considered a trial as having a high risk of bias if we assessed one or more domain as high risk or unclear. We included a 'Risk of bias' table as part of the Characteristics of included studies table and a 'Risk of bias summary' (Figure 1), which details all of the judgements made for all included studies in the review.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We undertook the analysis using RevMan 5.3 software. We used the risk ratio (RR) to measure treatment effect for proportions (dichotomous outcomes) among adverse effects and non-numerical pain assessments. For the secondary outcomes of rise in blood pressure and increase in heart rate, we planned to convert continuous data to the mean difference (MD) using the inverse variance method and calculating an overall MD. We planned to use a fixed-effect model where there was no evidence of significant heterogeneity between studies and a random-effects model if heterogeneity was likely (DerSimonian 1986).

As an estimate of the statistical significance of a difference between the experimental and control interventions, we planned to calculate the RR and MD between groups and the 95% confidence interval (CI). We assumed a statistically significant difference between the intervention and control groups if the 95% CI did not include the value of no differential effect.

Unit of analysis issues

We included only RCTs with a parallel-group design in our review. The nature of the intervention suggested that unit of analysis issues such as those associated with cluster-randomization were unlikely to arise. However, if we do include any cluster-randomized studies in any future update, we plan to assess the risk of bias following the suggestions in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.3.2) (Higgins 2011), and the approach to analysis as suggested in the subsequent sections. We plan to take a similar approach to any cross-over trials that are included in any future updated versions of the review.

Dealing with missing data

We performed quantitative analysis on an intention-to-treat (ITT) basis and contacted the authors in order to obtain any missing data. We analysed missing data, if any, by imputation using a best-case and worst-case scenario method. However, drop-outs or withdrawals were unlikely since data were collected during the operative period. Still, if we had found insufficient data, we would have considered the potential impact of the missing data in the interpretation of the results.

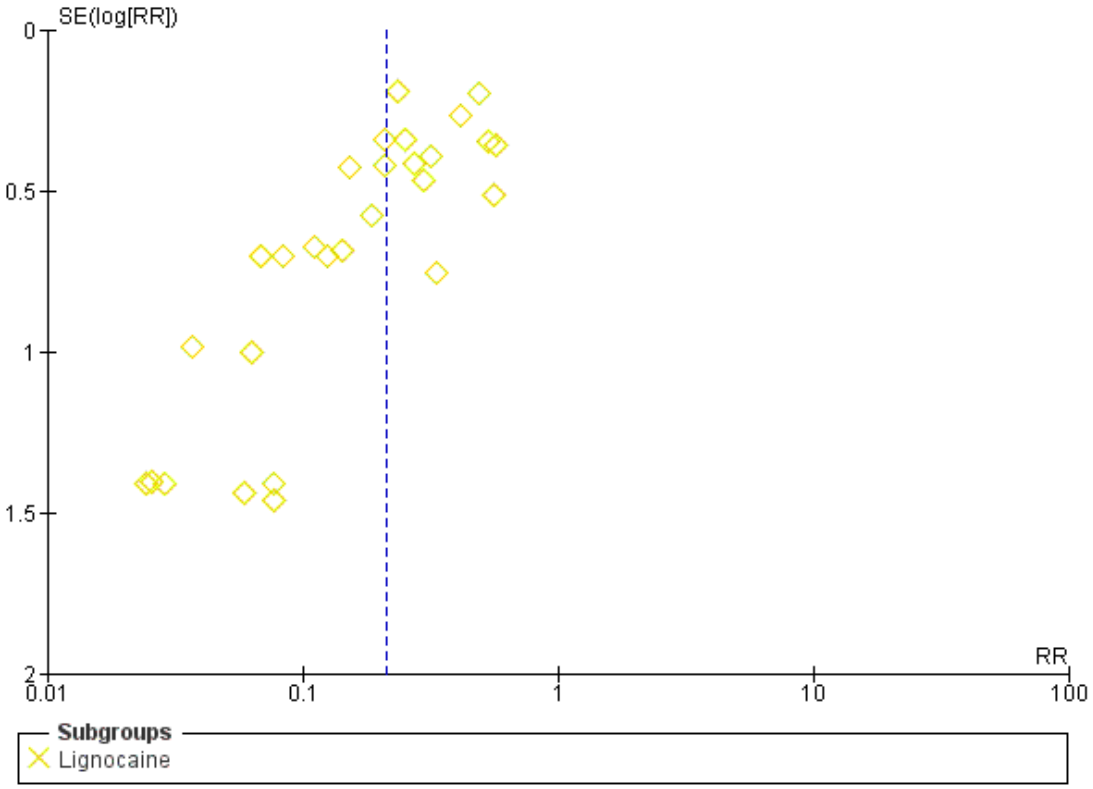
Assessment of heterogeneity

We planned not to perform meta-analysis if we suspected important clinical heterogeneity on examination of the included trials. We used the Q statistic to test the statistical heterogeneity between trials and considered a P value ≤ 0.05 as indicating significant heterogeneity. We used the I^2 statistic to assess the magnitude of heterogeneity (Higgins 2002). We considered an I^2 statistic above 50% to indicate that a meta-analysis was not appropriate, and we used a random-effects model analysis if the I^2 statistic was between 30% and 50%.

Assessment of reporting biases

We assessed publication bias and small study effects in a qualitative manner, using a funnel plot. We tested for funnel plot asymmetry if more than 10 studies were included in the meta-analysis. We created a funnel plot for trials assessing lidocaine as the intervention drug for prevention of pain on injection of rocuronium (Figure 2)

Figure 2. Funnel plot of comparison: lidocaine versus saline, outcome: pain



Data synthesis

We quantitatively reviewed the included data and combined data by intervention, outcome and population using Cochrane's statistical software (RevMan 5.3). We only synthesized the data in the absence of important clinical or statistical heterogeneity and we planned to express pooled estimates of the mean difference (MD) for continuous variables and risk ratio (RR) for proportions, as described above.

Subgroup analysis and investigation of heterogeneity

Where appropriate, based on obvious clinical heterogeneity (for example, participants awake versus anaesthetized) or statistical heterogeneity (I^2 statistic above 40%), we considered subgroup analysis based on gender, technique followed for rocuronium administration (conscious or unconscious state), and intervention alleviating pain by systemic (central) or local effects (application of tourniquet). We considered age and doses of rocuronium in subgroup analyses when the data indicated heterogeneity on that basis.

Sensitivity analysis

We performed sensitivity analyses to explore the consistency of effect size measures in trials with low risk of bias versus high risk of bias and to investigate the impact of any missing data using the imputation method described above.

'Summary of findings' tables

We used the principles of the GRADE approach, Guyatt 2008, to assess the quality of the body of evidence associated with specific outcomes (incidence and intensity of pain) in our review and constructed a 'Summary of findings' table using the GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The assessment of the quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

However, the studies included in this review were very different and the results heterogenous. We therefore could not group the

studies together to come to any robust conclusion and produce any evidence. Since lidocaine was the most popular intervention used in many studies and remifentanil and fentanyl are popular opioids, we created 'Summary of findings' tables for the use of these drugs only. For assessments of the overall quality of evidence for the outcome that included pooled data from RCTs only, we downgraded the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect or potential publication bias.

RESULTS

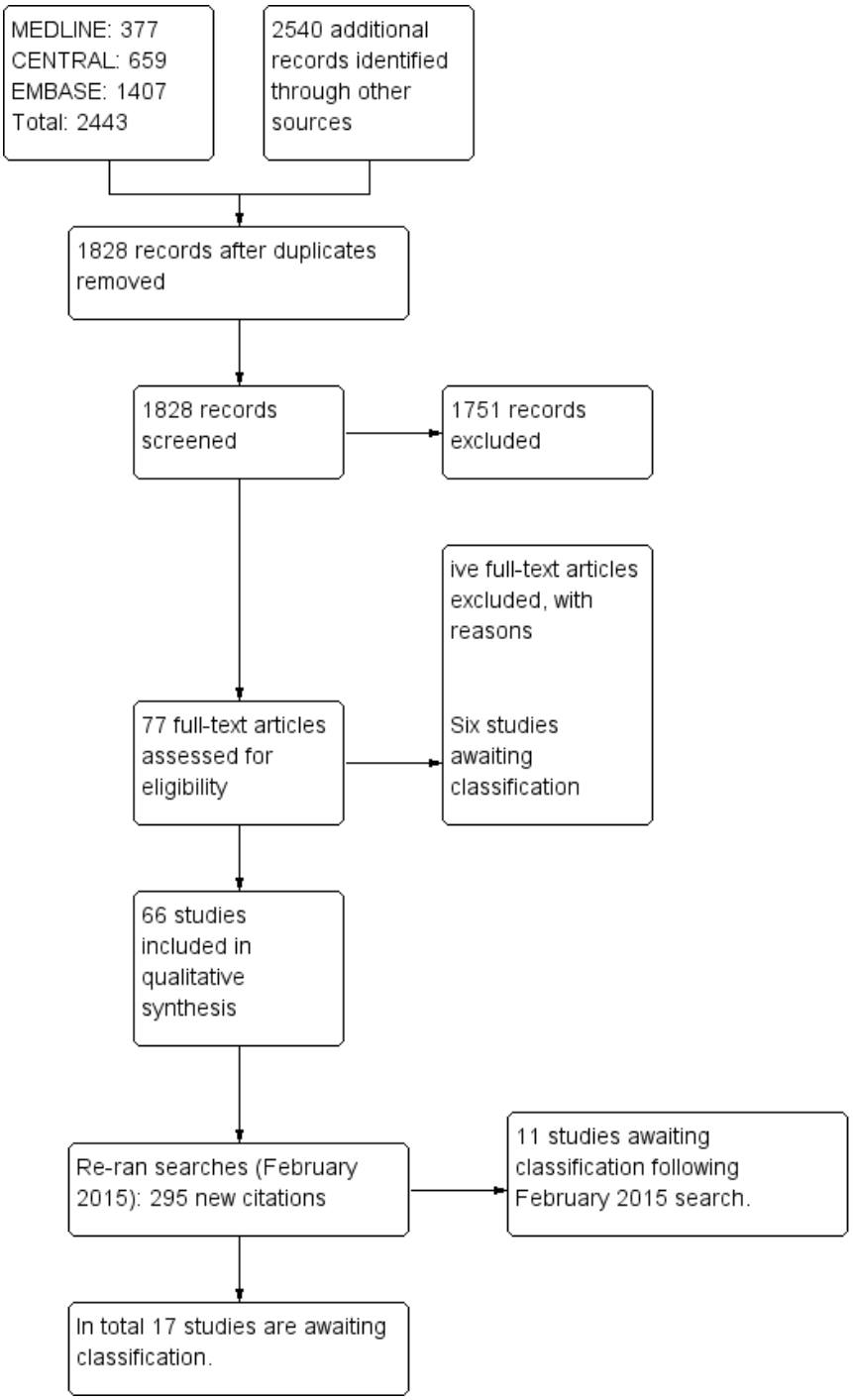
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification

Results of the search

We identified 1828 citations from the database searches and specific websites. After screening by titles and abstracts, we obtained full paper copies of 77 citations that were potentially eligible for inclusion in the review; six of those studies are awaiting classification. We excluded five of these articles for the reasons described in the Characteristics of excluded studies. We included 66 studies (7408 participants) in our review (Figure 3). We reran the searches in February 2015. Of the total of 295 new citations, we found a further 11 studies of interest. In total there are 17 studies awaiting classification. We will deal with them when we update the review.

Figure 3. Study flow diagram



Included studies

We included 66 studies (7840 participants) in our review. In general these trials enrolled adult participants (52 trials) and only 14 trials specifically enrolled a paediatric population. There were few that enrolled only women (four out of 71 trials: Choi 2005; Choi 2008; Han 2003; Han 2007). One trial did not report the age of the enrolled population (Asida 2009). The 66 included studies compared a large number of potential strategies to eliminate or modify pain on injection of rocuronium including drug admixtures, drug pre-administration, pH adjustment, adjusting the temperature of the injectate, changing the speed of injection and drug dilution. Appendix 1 tabulates the various interventions included in this review.

Nine studies compared admixtures of different drugs to reduce pain on rocuronium injection (Ayoglu 2007; Choi 2006; Han 2003; Han 2007; Jung 2005; Jung 2005b; Kwak 2004; Lee 2009c; Park 2006). One study compared dexmedetomidine plus lidocaine admixture (Ayoglu 2007); five studies compared admixtures of rocuronium with sodium bicarbonate (Choi 2006; Han 2003; Han 2007; Jung 2005; Jung 2005b); two studies compared rocuronium and lidocaine admixture (Jung 2005; Jung 2005b); two studies compared an admixture of rocuronium, lidocaine and sodium bicarbonate with placebo (Jung 2005; Jung 2005b); four studies compared the mixture of rocuronium with saline (Han 2003; Han 2007; Lee 2009c; Park 2006; Tuncali 2004); and one study compared the admixture of rocuronium, saline and lidocaine (Kwak 2004).

Six drugs belonging to the opioids class were used in 16 studies. Fentanyl was used in seven trials (504 participants) (Ahmad 2005; Asida 2009; Lee 2004; Lee 2011; Memis 2002; Oh 2007; Singh 2007); remifentanil was used in seven trials (494 participants) (Choi 2008; Ertugrul 2006; Kim 2007; Kim 2008; Kim 2009; Oh 2007; Yoon 2010); sufentanil was used in one study (Singh 2007); alfentanil was used in four studies (316 participants) (Kim 2008; Kim 2009; Oh 2007; Turan 2003); hydromorphone was used in one study (126 participants) (Lee 2011); and tramadol was used in three studies (Alanoglu 2007; Eun 2005; Memis 2002).

There were 38 studies (3122 participants) that compared various anaesthetic agents. Of those 38, 29 (2256 participants) compared lidocaine (Ahmad 2005; Akkaya 2008; Alanoglu 2007; Asida 2009; Ayoglu 2007; Byun 2005; Cheong 2000; Dogru 2002; Ertugrul 2006; Eun 2005; Hwang 2003; Ikram 2008; Jeon 2010; Kaya 2004; Kelsaka 2002; Kim 2002; Kirpit 2010; Kwak 2004; Lee 2004; Lee 2009b; Lee 2009c; Memis 2002; Reddy 2001; Shevchenko 1999; Singh 2007; Turan 2003; Wee 2004; Yavascaoglu 2007; Zhang 2012). Thiopentone sodium was compared in a single study with 90 participants (Park 2005). Seven studies (561 participants) compared ketamine with placebo (Abdusoglu 2011; Akkaya 2008; Cheong 2003; Choi 2005; Kirpit 2010; Liou 2003; Mahajan 2005). Inhalational anaesthetic agents such as sevoflurane and nitrous oxide were compared in one study with 72 participants (Park 2011), and two studies with 143 participants (Kwak 2010; Sharma 2010), respectively.

Eight studies (462 participants) compared two antiemetics for prevention of rocuronium induced pain on injection (Byun 2005; Ertugrul 2006; Eun 2005; Kelsaka 2002; Ki 2005; Lee 2004; Memis 2002; Reddy 2001). Ondansetron was compared in six studies with 380 participants (Eun 2005; Kelsaka 2002; Ki 2005; Lee 2004; Memis 2002; Reddy 2001). Metoclopramide was compared in two studies with 82 participants (Byun 2005; Ertugrul 2006).

Various analgesics, such as ketorolac, acetaminophen, parecoxib and gabapentin, were used in four studies with 335 participants. Ketorolac, acetaminophen, parecoxib and gabapentin were compared in one study each with 54, 79, 120 and 82 participants, respectively (Asida 2009; Jeon 2010; Yoon 2011; Zhang 2012).

Antihistaminic drugs, such as pheniramine and diphenhydramine, were compared in one study each with 120 and 60 participants, respectively (Lee 2009; Kilicaslan 2010).

Magnesium sulphate was compared in two studies with 300 participants (Shin 2011a; Turan 2003); esmolol was compared in a single study with 80 participants (Yavascaoglu 2007); dexmedetomidine in three studies with 210 participants (Ayoglu 2007; Kaya 2004; Memis 2005); sodium bicarbonate in one study with 100 participants (Turan 2003); and nafamostat and ephedrine were compared in single study each with 90 and 60 participants, respectively (Kim 2010; Kirpit 2010).

Seven studies compared various non-pharmacological intervention methods such as warming of the injection site (Mahajan 2010); slow versus rapid injection of rocuronium (Baek 2008; Lee 2009b; Shin 2011b); and compression of veins before injecting rocuronium versus no compression (Jung 2005a; Yoon 2010).

Adverse events were not reported in all studies. Pain on injection of intervention drugs was reported with use of lidocaine and acetaminophen in one study (Jeon 2010). Cough was reported with the use of fentanyl (Oh 2007), remifentanil (Choi 2008; Kim 2007; Kim 2008; Kim 2009; Oh 2007), and alfentanil (Kim 2009). Breath holding and chest tightness were reported with use of remifentanil in two studies (Kim 2009; Oh 2007), and one study (Choi 2008), respectively.

None of the studies measured changes in heart rate and blood pressure following administration of rocuronium bromide.

Excluded studies

We excluded five studies for the reasons detailed in the Characteristics of excluded studies table. None of these studies

were RCTs (Kim 2008; Min 2011; Shabana 2011; Yoon 2010a; Zeidan 2006).

Ongoing studies

There are no ongoing studies.

Studies awaiting classification

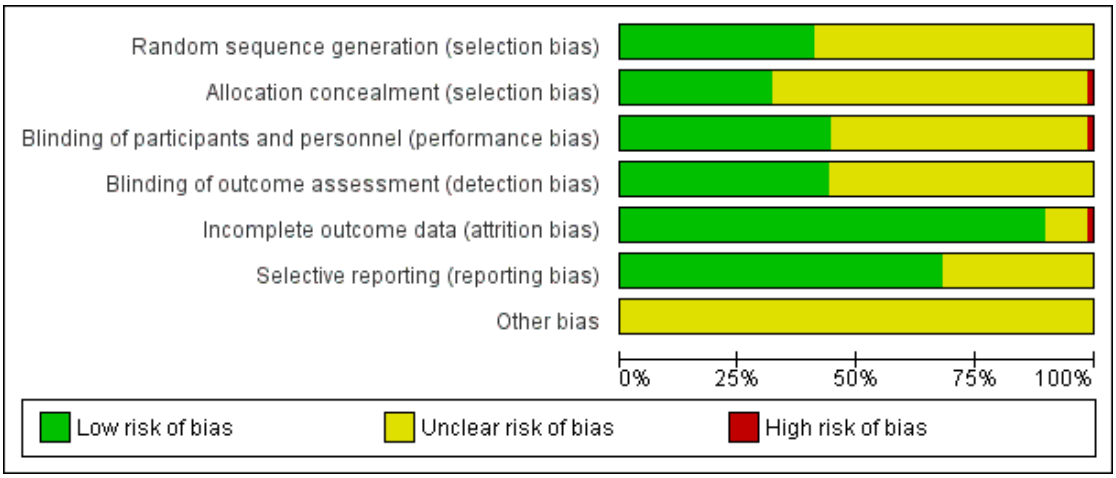
Seventeen studies, in total, are awaiting classification for the reasons described in the table Characteristics of studies awaiting classification. Five, of the 17 studies awaiting classification, did not provide appropriate data in the study reports and the study authors did not provide additional information; therefore, data from these studies are not included in this review (Chiarella 2003; Lee 2009a; Lim 2006; Prasanna 2005; Sari 2008). One study was published as an abstract and data could not be obtained from the authors as there was no address available for communication (Hwang 2004).

We found 11 of these trials when we reran the searches in February 2015 (Abu-Halaweh 2013; Abu-Halaweh 2014; Akcaboy 2012; Ates 2014; Aydin 2014; Choi 2012; Cho 2014; Honca 2013; Jeon 2013; Jung 2014; Kim 2013).

Risk of bias in included studies

We assessed the risk of bias of the included studies using the 'Risk of bias' tool developed by Cochrane (Higgins 2011). The 'Risk of bias' tool invites judgements on six items for each trial (selection bias, performance bias, detection bias, attrition bias, reporting bias, other potential sources of bias). All authors independently assessed the risk of bias for each study. We resolved disagreements by discussion. Our assessments of the risk of bias in the included studies are shown in Figure 1 and Figure 4. There were only five studies of high methodological quality (Jung 2005; Kilicaslan 2010; Kim 2006; Kim 2008; Kim 2009).

Figure 4. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Of the 66 included studies, only 27 reported adequate sequence generation (Abdusoglu 2011; Ahmad 2005; Borgeat 1997; Cheong 2000; Han 2007; Jung 2005; Kilicaslan 2010; Kim 2006; Kim 2008; Kim 2009; Kim 2010; Kwak 2010; Lee 2009b; Lee 2009c; Liou 2003; Mahajan 2010; Oh 2007; Reddy 2001; Sharma 2010; Shevchenko 1999; Shin 2011a; Shin 2011b; Singh 2007; Turan 2003; Yavascaoglu 2007; Yoon 2010; Yoon 2011). The remaining studies did not describe their sequence generation methods.

Allocation

Of the 66 included studies, 21 had adequate allocation concealment (Abdusoglu 2011; Ahmad 2005; Borgeat 1997; Cheong 2000; Choi 2008; Jeon 2010; Jung 2005; Kilicaslan 2010; Kim 2006; Kim 2007; Kim 2008; Kim 2009; Kirpit 2010; Lee 2009; Lee 2009c; Lee 2011; Mahajan 2005; Park 2011; Sharma 2010; Shin 2011a; Tuncali 2004). The remaining studies did not describe their allocation concealment.

Blinding

Of the 66 included studies, 22 had adequate blinding (Ayoglu 2007; Borgeat 1997; Choi 2008; Ertugrul 2006; Ikram 2008; Jeon 2010; Jung 2005; Kilicaslan 2010; Kim 2006; Kim 2007; Kim 2008; Kim 2009; Kim 2010; Kwak 2010; Lee 2009c; Lee 2011; Liou 2003; Oh 2007; Shevchenko 1999; Shin 2011b; Singh 2007; Yavascaoglu 2007). The remaining studies did not describe their blinding.

Incomplete outcome data

Eight studies reported drop-outs. Five participants complained of pain after propofol injection and one participant had spontaneous movement after propofol injection (Borgeat 1997); one participant became excited and started crying and two participants were unwilling to co-operate (Kwak 2010); 20 participants were excluded because they received succinylcholine instead of rocuronium, owing to poor mask ventilation or complained of pain after injection of thiopentone (Lee 2009); four participants met study exclusion criteria (Lee 2011); three participants were excluded as they moved their hands during injection of the study drug (Liou 2003); three participants were not compliant with the inhalational induction (Park 2011); and four participants dropped out but the reasons are unknown (Yoon 2011; Zhang 2012).

Selective reporting

We found that all planned outcomes were reported in the studies: authors reported all of the outcomes listed in their methods.

Other potential sources of bias

We could not find any other potential source of bias in the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Lidocaine versus placebo for reducing rocuronium bromide induced pain on injection; **Summary of findings 2** Fentanyl versus placebo for reducing rocuronium bromide induced pain on injection; **Summary of findings 3** Remifentanil versus placebo for reducing rocuronium bromide induced pain on injection; **Summary of findings 4** Adverse effects of pharmacological intervention versus control for reducing rocuronium induced pain on injection

In the included studies, assessments after rocuronium injection were made in patients under general anaesthetic or in the awake state, as reported. In the awake state, the participants themselves responded (on a five- or four-point scale). If asleep, pain was assessed by movement on injection, mostly using a four-point scale, but a five-point scale was used in one study (Kim 2002), and a three-point scale was used in another study (Choi 2005). Pain was assessed in 38 out of 66 trials whereas withdrawal of limb was assessed in 34 trials.

Primary outcome

Pain on rocuronium bromide injection

Studies used a three-, four- or five-point scale. Most studies used a four-point scale; seven studies used a five-point scale (Akkaya 2008; Jung 2005b; Kim 2002; Kim 2004; Mahajan 2010; Singh 2007; Tuncali 2004), and one study used a three-point scale (Choi 2005).

1. Non-pharmacological intervention

(See Analysis 1.1).

Seven trials enrolling 935 participants (10.1% of the total participants in this review) tested a variety of non-pharmacological interventions:

- warming the site of injection at 40 degrees centigrade for one minute: one trial, enrolling 90 participants (assessed awake, five-point scale) (Mahajan 2010);
- slowing the speed of injection by administering rocuronium as an infusion: three trials, enrolling 391 participants (assessed under general anaesthetic, four-point scale) (Baek 2008; Lee 2009b; Shin 2011a);
- compression of the arm or forearm by tourniquet prior to administering rocuronium: two trials, enrolling 214 participants (assessed under general anaesthetic, four-point scale) (Jung 2005a; Yoon 2010); and
- administering cold rocuronium at 4 to 5 degrees centigrade: one trial, enrolling 240 participants (assessed awake, five-point scale) (Kim 2004).

The single trial investigating warming of the site of injection suggested that this strategy reduces the incidence of severe pain from 27/45 (60%) to 11/45 (24%) (risk ratio (RR) 0.41, 95% confidence interval (CI) 0.23 to 0.72, P = 0.002).

Analysis of the three trials investigating the effect of speed of injection indicated extreme heterogeneity (I^2 = 96%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. Of the three trials, two reported some benefit from slow infusion of rocuronium (Baek 2008 reported a reduction in the incidence of severe pain by 98.4% and Shin 2011b reported a reduction in the incidence of pain by 44.85%). One trial reported an increase in the incidence of pain by 26% when rocuronium was administered slowly (Lee 2009b).

Analysis of the two trials investigating the effect of tourniquet compression on reducing pain on rocuronium injection indicated extreme heterogeneity (I^2 statistic = 94%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. Of the two trials, one trial reported reduction

in the incidence of pain on rocuronium injection by 21.3% when arm compression was applied (Jung 2005a), whereas Yoon 2010 found that the incidence of severe pain increased by 40.6% when compression was applied.

The single trial investigating cold rocuronium injection showed that the strategy reduced the incidence of pain from 22/120 to 17/120 (RR 0.77, 95% CI 0.43 to 1.38, P = 0.38). The difference was not statistically significant.

The high degree of heterogeneity for speed of injection and compression could not be explained using our pre-planned subgroup analyses relevant to these studies (gender, age or asleep/awake state of the participants was not reported in any study). We analysed all results using a random-effects model because heterogeneity was high.

2. Admixtures to rocuronium

(See Analysis 2.1).

The admixtures used were:

- dexmedetomidine plus lidocaine: one trial, enrolling 90 participants (assessed under general anaesthetic, four-point scale) (Ayoglu 2007);
- rocuronium plus sodium bicarbonate: five trials, enrolling 433 participants (assessed awake, four-point scale) (Choi 2006; Han 2003; Han 2007); (assessed under general anaesthetic, four-point scale) (Jung 2005); (assessed awake, five-point scale) (Jung 2005b);
- rocuronium plus lidocaine: two trials, enrolling 103 participants (assessed under general anaesthetic, four-point scale) (Jung 2005); (assessed awake, five-point scale) (Jung 2005b);
- rocuronium plus lidocaine plus sodium bicarbonate: two trials, enrolling 101 participants (assessed under general anaesthetic, four-point scale) (Jung 2005); (assessed awake, five-point scale) (Jung 2005b);
- rocuronium plus saline: four trials, enrolling 270 participants (assessed awake, four-point scale) (Han 2003; Han 2007); (assessed under general anaesthetic, four-point scale) (Lee 2009c; Park 2006); and
- rocuronium plus lidocaine plus saline: one trial, enrolling 50 participants (assessed awake, four-point scale) (Kwak 2004).

The comparator in all of the trials was undiluted rocuronium.

The single trial investigating a dexmedetomidine plus lidocaine admixture suggested that this strategy reduces the incidence of severe pain from 19/30 to 13/30 (RR 0.34, 95% CI 0.20 to 0.59, P = 0.0001).

Five trials investigating an admixture of rocuronium with sodium bicarbonate suggested that the incidence of severe pain reduces from 76/141 to 27/292 (RR 0.19, 95% CI 0.11 to 0.32; I^2 = 12%, P < 0.00001).

The admixture of rocuronium and lidocaine was investigated in two trials, which showed that the incidence of severe pain reduces from 28/51 to 24/52 (RR 0.85, 95% CI 0.58 to 1.25; I^2 = 0%, P = 0.4). The difference was not statistically significant.

Two trials investigating an admixture of rocuronium plus lidocaine plus sodium bicarbonate suggested that the incidence of severe pain reduces from 28/51 to 5/50 (RR 0.20, 95% CI 0.08 to 0.48; I^2 = 0%, P = 0.0003).

Analysis of four trials investigating rocuronium diluted with normal saline indicated extreme heterogeneity (I^2 statistic = 86%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. However, all of the trials did show a reduction in the incidence of severe pain with the intervention, which ranged from 10% in one study (Han 2003) to 75% in another (Park 2006).

A single study investigating an admixture of rocuronium with lidocaine plus saline suggested a reduction in the incidence of severe pain from 17/25 to 8/25 (RR 0.47, 95% CI 0.25 to 0.88; I^2 = 0%, P = 0.02).

3. Co-administration of opioids

(See Analysis 3.1).

Sixteen trials enrolling 1710 participants (18.5% of the total participants in this review) tested various drugs belonging to the group of opioids:

- fentanyl: seven trials, enrolling 504 participants (assessed under general anaesthetic, four-point scale) (Ahmad 2005; Asida 2009; Lee 2011; Oh 2007); (assessed awake, five-point scale) (Singh 2007); (assessed awake, four-point scale) (Lee 2004; Memis 2002);
- remifentanil: seven trials, enrolling 494 participants (assessed under general anaesthetic, four-point scale) (Choi 2008; Kim 2007; Kim 2008; Kim 2009; Oh 2007; Yoon 2010); (assessed awake, four-point scale) (Ertugrul 2006);
- sufentanil: one trial, enrolling 40 participants (assessed awake, five-point scale) (Singh 2007);
- alfentanil: four trials, enrolling 316 participants (assessed under general anaesthetic, four-point scale) (Kim 2008; Kim 2009; Oh 2007); (assessed awake, four-point scale) (Turan 2003);
- hydromorphone: one trial, enrolling 126 participants (assessed under general anaesthetic, four-point scale) (Lee 2011); and
- tramadol: three trials, enrolling 220 participants (assessed awake, four-point scale) (Alanoglu 2007; Eun 2005; Memis 2002).

The seven trials investigating fentanyl indicated extreme heterogeneity (I^2 = 79%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. However, all of the trials did show a reduction in the incidence of severe pain with the intervention, which ranged from 20% (Lee 2004) to 76% (Asida 2009).

The seven trials using remifentanil indicated high heterogeneity (I^2 = 74%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. However, all of the trials did show a reduction in the incidence of severe pain with the intervention, which ranged from 45% (Ertugrul 2006) to 85% (Oh 2007).
The single trial testing sufentanil suggested a reduction from 19/20 (95%) to 6/20 (30%) (RR 0.32, 95% CI 0.16 to 0.62, P = 0.0008).
The two trials using alfentanil suggested a reduction from 105/156 (67%) to 21/160 (13%) (RR 0.21, 95% CI 0.14 to 0.31; I^2 = 0%, P < 0.00001).
Hydromorphone reduced the incidence of severe pain from 31/61 to 1/65 (RR 0.03, 95% CI 0.00 to 0.22, P = 0.0005).
Three trials investigating tramadol indicated extreme heterogeneity (I^2 = 90%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. Of the three trials two showed a reduction in the incidence of severe pain by 43% (Alanoglu 2007) and 42% (Memis 2002); one trial showed a 7% increase in the incidence of severe pain (Eun 2005).
The comparator in all of the trials was normal saline.
We analysed all results using a random-effects model because heterogeneity was high and we downgraded the outcome from high to very low quality because of the risk of bias, imprecision and inconsistency.

4. Co-administration of anaesthetics

(See Analysis 4.1).
A total of 38 trials examined the effect of various anaesthetic agents:

- thiopentone: one trial, enrolling 90 participants (assessed under general anaesthetic, four-point scale) (Park 2005);
- ketamine: seven trials, enrolling 561 participants (assessed under general anaesthetic, four-point scale) (Abdusoglu 2011; Cheong 2003; Kirpit 2010; Liou 2003); (assessed under general anaesthetic, three-point scale) (Choi 2005); (Akkaya 2008; Mahajan 2005);
- sevoflurane: one trial, enrolling 72 participants (assessed under general anaesthetic, four-point scale) (Park 2011);
- nitrous oxide: two trials, enrolling 143 participants (assessed awake, four-point scale) (Kwak 2010;Sharma 2010); and
- lidocaine: 29 trials, enrolling 2256 participants (assessed under general anaesthetic, four-point scale) (Ahmad 2005; Asida 2009; Ayoglu 2007; Byun 2005; Ikram 2008; Jeon 2010; Kelsaka 2002; Kirpit 2010; Kwak 2004; Lee 2009b; Lee 2009c; Shevchenko 1999); (assessed under general anaesthetic, five-point scale) (Kim 2002); (assessed awake, four-point scale) (Akkaya 2008; Alanoglu 2007; Cheong 2000; Dogru 2002; Ertugrul 2006; Eun 2005; Hwang 2003; Kaya 2004; Lee 2004; Memis 2002; Singh 2007; Turan 2003; Wee 2004; Yavascaoglu 2007; Zhang 2012); (assessed awake, five-point scale) (Reddy 2001). Two trials assessed participants both awake and under general anaesthetic using a four-point scale (Kirpit 2010; Yavascaoglu 2007).

A single trial suggested that thiopentone reduces the incidence of severe pain from 16/45 to 2/45 (RR 0.12, 95% CI 0.03 to 0.51; I^2 = 0%, P = 0.004).
Analysis of seven trials investigating ketamine indicated extreme heterogeneity (I^2 statistic = 85%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. However, all of the trials did show a reduction in the incidence of severe pain with the intervention, which ranged from 4% (Abdusoglu 2011) to 72.5% (Cheong 2003).
Sevoflurane reduced the incidence of severe pain from 11/15 to 11/57 (RR 0.26, 95% CI 0.14 to 0.49; I^2 = 0%, P < 0.0001).
Nitrous oxide reduced the incidence of severe pain from 22/71 to 3/72 (RR 0.16, 95% CI 0.06 to 0.48; I^2 = 0%, P = 0.0009).
Analysis of 29 trials investigating lidocaine indicated severe heterogeneity (I^2 = 60%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. However, the funnel plot showed asymmetry of studies (Egger's test showed statistical significance, P < 0.001) where lidocaine was used as the intervention drug for prevention of pain. We conducted a subgroup analysis for the use of lidocaine in children, which showed a near identical risk ratio to adults but with wider confidence intervals (Analysis 4.1).
We analysed all results using a random-effects model because heterogeneity was high. For the effect of lidocaine on the outcome, we downgraded the evidence from high to very low quality because of the risk of bias, imprecision, inconsistency and suspected publication bias.

5. Co-administration of antiemetics

(See Analysis 5.1).
The antiemetics used were:

- ondansetron: six trials, enrolling 380 participants (assessed awake, four-point scale) (Eun 2005; Ki 2005; Lee 2004; Memis 2002); (assessed awake, five-point scale) (Reddy 2001); (assessed under general anaesthetic, four-point scale) (Kelsaka 2002); and
- metoclopramide: two trials, enrolling 82 participants (assessed under general anaesthetic, four-point scale) (Byun 2005); (assessed awake, four-point scale) (Ertugrul 2006).

Eight trials investigating antiemetics suggested that ondansetron reduces the incidence of severe pain from 112/170 to 58/210 (RR 0.41, 95% CI 0.33 to 0.52; I^2 = 0%, P < 0.00001) and metoclopramide reduces the incidence of severe pain from 33/41 to 8/41 (RR 0.28, 95% CI 0.15 to 0.50; I^2 = 0%, P < 0.0001).

6. Co-administration of analgesics

(See Analysis 6.1).
The analgesics used were:

- ketorolac: one trial, enrolling 54 participants (assessed under general anaesthetic, four-point scale) (Asida 2009);
- acetaminophen: one trial, enrolling 79 participants (assessed under general anaesthetic, four-point scale) (Jeon 2010);
- parecoxib: one trial, enrolling 120 participants (assessed awake, four-point scale) (Zhang 2012); and
- gabapentin: one trial, enrolling 82 participants (assessed under general anaesthetic, four-point scale) (Yoon 2011).

Ketorolac reduced the incidence of pain from 7/29 to 2/25 (RR 0.33, 95% CI 0.08 to 1.45, P = 0.14).
Acetaminophen reduced the incidence of pain from 17/39 to 10/40 (RR 0.57, 95% CI 0.30 to 1.09, P = 0.09).
Parecoxib reduced the incidence of severe pain from 24/40 to 13/80 (RR 0.27, 95% CI 0.15 to 0.47, P < 0.00001).
Gabapentin reduced the incidence of severe pain from 19/40 to 12/42 (RR 0.60, 95% CI 0.34 to 1.07, P = 0.09).
The difference was not statistically significant for any of the analgesics except parecoxib.

7. Co-administration of antihistamines

(See Analysis 7.1).
The antihistamines used were:
- pheniramine: one trial, enrolling 120 participants (assessed under general anaesthetic, four-point scale) (Lee 2009); and
- diphenhydramine: one trial, enrolling 60 participants (assessed awake, four-point scale) (Kilicaslan 2010).

Two trials investigating antihistamines suggested that pheniramine reduces the incidence of severe pain from 46/58 to 35/62 (RR 0.71, 95% CI 0.55 to 0.92, P = 0.009) and diphenhydramine reduces the incidence of severe pain from 20/30 to 2/30 (RR 0.10, 95% CI 0.03 to 0.39, P = 0.0009).

8. Co-administration of miscellaneous drugs

(See Analysis 8.1).
The miscellaneous drugs used were:
- magnesium sulphate: two trials, enrolling 300 participants (assessed under general anaesthetic, four-point scale) (Shin 2011a); (assessed awake, four-point scale) (Turan 2003);
- esmolol: one trial, enrolling 80 participants (assessed awake and under general anaesthetic, four-point scale) (Yavascaoglu 2007);
- dexmedetomidine: three trials, enrolling 210 participants (assessed under general anaesthetic, four-point scale) (Ayoglu 2007); (assessed awake, four-point scale) (Kaya 2004; Memis 2005);
- sodium bicarbonate: one trial, enrolling 100 participants (assessed awake, four-point scale) (Turan 2003);
- nafamostat: one trial, enrolling 90 participants (assessed under general anaesthetic, four-point scale) (Kim 2010); and
- ephedrine: one trial, enrolling 60 participants (assessed awake and under general anaesthetic, four-point scale) (Kirpit 2010).

Among the miscellaneous group of drugs, analysis of two trials investigating the effect of magnesium sulphate on the incidence of severe pain indicated extreme heterogeneity (I^2 statistic = 90%) that could not be explained by our planned subgroup analyses and this analysis is not formally reported. Of the two trials, one suggested a reduction in the incidence of severe pain by 23% (Shin 2011a), and the other suggested a reduction of 52% (Turan 2003).
A single trial investigating esmolol suggested that severe pain is reduced from 9/40 to 0/40 (RR 0.05, 95% CI 0.00 to 0.87, P = 0.04).
Three trials investigating dexmedetomidine suggested that the incidence of severe pain is reduced from 57/90 to 40/120 (RR 0.55, 95% CI 0.39 to 0.77; I^2 = 18%, P = 0.0005).
A single trial investigating sodium bicarbonate suggested that the incidence of severe pain is reduced from 29/50 to 3/50 (RR 0.10, 95% CI 0.03 to 0.32, P < 0.0001).
A single trial investigating nafamostat suggested that the incidence of severe pain is reduced from 28/45 to 4/45 (RR 0.14, 95% CI 0.05 to 0.37, P < 0.0001).
Another trial investigating ephedrine suggested that the incidence of severe pain is reduced from 16/30 to 8/30 (RR 0.50, 95% CI 0.25 to 0.99, P = 0.05).

Heterogeneity

The high degree of heterogeneity for strategies such as the admixture of rocuronium plus saline (Analysis 2.1), use of fentanyl and remifentanil (Analysis 3.1), ketamine and lidocaine (Analysis 4.1), tramadol (Analysis 6.1), and magnesium sulphate (Analysis 8.1) could not be explained using our pre-planned subgroup analyses.

Secondary outcomes

Rise in blood pressure

No study reported change in blood pressure after administration of rocuronium.

Increase in heart rate

No study reported change in heart rate after administration of rocuronium.

Any adverse effects of interventional agent

Seven studies reported adverse effects. Pain due to the injection of the intervention drugs lidocaine and acetaminophen was reported by one study (Jeon 2010). Opioids were the only group

of pharmacological agents that produced complications, such as cough, breath holding and chest tightness (fentanyl (Oh 2007), remifentanil (Choi 2008; Kim 2007; Kim 2008; Kim 2009; Oh 2007), and alfentanil (Kim 2009)).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Fentanyl compared with placebo for reducing rocuronium bromide induced pain on injection in adults and children

Patient or population: adults and children undergoing general anaesthesia including the muscle relaxant rocuronium bromide
Settings: hospital operating theatres in high-income countries
Intervention: fentanyl versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Fentanyl				
Pain - fentanyl	Study population		RR 0.42 (0.26 to 0.70)	514 (7 studies)	⊕⊕◯◯ **low** [1,2]	-
	589 per 1000	247 per 1000 (153 to 412)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of bias. Most of the studies did not mention the method of randomization and are at high risk of bias.
[2]Downgraded one level due to serious inconsistency. Significant heterogeneity noted across the included studies.

Remifentanil compared with placebo for rocuronium bromide induced pain on injection in adults and children

Patient or population: adults and children undergoing general anaesthesia including the muscle relaxant rocuronium bromide
Settings: hospital operating theatres in high-income countries
Intervention: remifentanil versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Remifentanil				
Pain - remifentanil	Study population		RR 0.1 (0.04 to 0.26)	494 (7 studies)	⊕⊕◯◯ **low** [1,2]	-
	710 per 1000	71 per 1000 (28 to 185)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of bias. Most of the studies did not mention the method of randomization and are of at high risk of bias.
[2]Downgraded one level due to serious inconsistency. Significant heterogeneity noted across the included studies.

Pharmacological interventions compared with control for rocuronium bromide induced pain on injection

Patient or population: adults and children undergoing general anaesthesia including the muscle relaxant rocuronium bromide
Settings: hospital operating rooms in high-income countries
Intervention: pharmacological intervention
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pharmacological Intervention				
Breath holding	Study population		RR 1.19 (0.12 to 11.65)	279 (2 studies)	⊕◯◯◯ very low [1,2,3]	-
	0 per 1000	10 per 1000 (1 to 98)				
Chest tightness	Study population		RR 2.61 (0.12 to 56.03)	90 (1 study)	⊕◯◯◯ very low [1,4]	-
	0 per 1000	33 per 1000 (2 to 708)				
Cough	Study population		RR 9.00 (2.77 to 29.29)	529 (5 studies)	⊕⊕◯◯ low [1,2]	-
	6 per 1000	52 per 1000 (17 to 176)				
Pain on injection	Study population		RR 0.47 (0.09 to 2.46)	118 (1 study)	⊕⊕◯◯ low [1,3]	-
	77 per 1000	40 per 1000 (7 to 189)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of bias. Most of the studies did not mention the method of randomization and are at high risk of bias.
[2]Downgraded one level due to serious inconsistency. Significant heterogeneity noted across the included studies.
[3]Downgraded one level due to serious imprecision. The confidence interval around the estimated effect is wide enough to include meaningful increases and reductions in risk with the intervention.
[4]Downgraded two levels due to very serious imprecision. The confidence interval is very wide.

DISCUSSION

The studies included in this review were conducted with numerous intervention drugs and the outcome was assessed as pain in an awake state or withdrawal of limb when the participants were in an asleep state. 'Asleep' was commonly used terminology for participants under general anaesthesia in many of the trials. While the need to alleviate pain on injection of rocuronium cannot be overemphasized, it is important that withdrawal movement of a participant in an asleep state should also be avoided. Sudden movement of limbs due to rocuronium injection can easily result in dislodgement of the intravenous cannula.

Summary of main results

The results of our review suggest that many pharmacological and some non-pharmacological strategies may reduce pain due to the injection of rocuronium, but there is uncertainty over the average reduction in pain due to the low quality of evidence for the most commonly investigated interventions. Among the pharmacological interventions, an admixture of rocuronium with sodium bicarbonate alone or along with lidocaine; opioids such as remifentanil, alfentanil and hydromorphone; ketamine; and pheniramine showed large effect sizes.

Our secondary outcomes of increase in heart rate and blood pressure after injection of rocuronium were not reported in any of the studies.

The overall incidence of adverse effects due to various pharmacological strategies was low but we rated the quality of the evidence for adverse effects as very low. We know opioids are potent analgesics and should be able to reduce pain on rocuronium injection. Opioids were the only group of drugs that resulted in minor adverse effects such as cough, chest tightness and breath holding.

Overall completeness and applicability of evidence

The studies included in this review were conducted very differently with numerous drug doses, intervention drugs, subgroups and strategies. As a result, it is difficult to reach reliable conclusions because relatively few of these trials could be included in the pooled analyses. The primary outcome of pain was reported in all of the 66 included studies but none of them reported our secondary outcomes, change in heart rate and blood pressure. Few studies reported adverse effects. Those that did so were mainly those investigating opioid drugs.

Quality of the evidence

We rated the evidence for the outcome of pain as low quality due to serious risk of bias and inconsistency of results (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3) and for adverse effects as very low quality (Summary of findings 4) due to serious risk of bias, inconsistency and imprecision. None of the studies were of good methodological quality. The studies were generally poorly reported such that a thorough assessment of methodological quality was not possible. Some of the most problematic biases were those related to random sequence generation, allocation concealment and blinding. Although the direction of the effect estimates for the outcome of pain were concordant for a number of the analyses, the combination of the variation in the size of effect and the variation between studies in terms of the trial characteristics noted above prompted us to downgrade for inconsistency.

Potential biases in the review process

We searched for ongoing trials in an attempt to reduce publication bias, however we did not search the grey literature or handsearch journals. The contact author of this review (Hemanshu Prabhakar) was also a co-author of two of the included studies (Mahajan 2010; Singh 2007), which were assessed independently by two other authors of this review (ZA and GPS).

Thresholds for the interpretation of the I^2 statistic can be misleading, as the inconsistency suggested by high values can arise from a number of sources. Although I^2 statistical values were higher than our pre-specified threshold of 50% for the analyses for many of the comparisons, we felt that this was likely to be due to clinical variables within the studies. We therefore chose to highlight the findings for three drugs for which there were a larger number of trials, namely lidocaine, fentanyl and remifentanil. For this reason, we included 'Summary of findings' tables for these three drugs, but acknowledge the low quality of evidence in these tables. We accept that this introduces a potential bias into the review and would bring this to readers' attention.

For a number of included studies, we extracted data principally from the abstract, tables and figures, as the text was not translated fully. Whilst numerical outcome data could easily be derived from these sources, it was not possible to assess the risk of bias and so we rated the risk of bias as 'unclear' for these studies. We conducted a random check of a sample of these studies using Google Translate. This showed that, because of incomplete reporting, the risk of bias was still unclear in the sampled studies. In addition, where such studies had been included in the analyses for lidocaine, fentanyl and remifentanil, we conducted a sensitivity analysis to assess the effect of excluding such studies on the overall estimate of effect. This did not change.

Agreements and disagreements with other studies or reviews

We are unaware of any published systematic reviews that have assessed methods for the prevention of pain on rocuronium injection. However, from our review it is evident that lidocaine is one of the most commonly studied pharmacological agents used in the various trials looking at prevention of pain.

AUTHORS' CONCLUSIONS

Implications for practice

We found many interventions that reduced pain following the injection of rocuronium in awake participants, but the quality of the evidence for the most commonly studied interventions is low due to risk of bias and inconsistency. The evidence for adverse effects was of low or very low quality due to risk of bias and imprecision or inconsistency. This finding has implications for practice where it is clinically desirable to inject rocuronium into non-anaesthetized patients (e.g. as a priming dose prior to rapid sequence induction). We also found many agents that reduced the degree of withdrawal of the limb into which rocuronium is injected when given to patients already anaesthetized. Our review does not suggest that any one agent or class of agents is more effective for either purpose as we did not make comparisons between the various interventions.

Implications for research

The methodology and patient populations in the studies included in this review varied. The intervention drugs belonged to different pharmacological classes, ranging from antiemetics to opioids to anaesthetics. The majority of the studies used rocuronium at a dose of 0.6 mg/kg but the analysis showed heterogeneity even on that basis, suggesting some other unknown factors as the cause of unexplained heterogeneity. The methodology of the studies was such that some assessed the effect of the intervention after application of a tourniquet (peripheral effect), while others assessed the central action. Certain drugs such as the opioids and anaesthetics could have both central and peripheral actions, which could create bias. There is a need to conduct further appropriately powered randomized controlled trials of high methodological rigour, which test the most promising agents identified in this review. In particular, a reliable method of randomization and blinding should be planned, as should the use of a fixed dose of rocuronium administered at a fixed time after induction of anaesthesia. An international, multi-centric trial would probably be useful. Lack of precision in the findings for non-pharmacological methods warrants further research activity. Dilution and admixture of rocuronium appears to be useful and should be investigated further.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdusoglu 2011

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 54 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: allergy to ketamine, propofol or rocuronium, previous history of neurologic disorder, trauma in hand, high ICP, uncontrolled HT, heart failure, IHD, DM, NMD, use of analgesics with last 24 hours and pregnancy
Interventions	IV ketamine: 0.5 mg/kg diluted to 5 ml with 0.9% NS Control: 5 ml of 0.9% NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 1 minute after pretreatment drug Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated randomly into one of the two groups which received either 5 ml of isotonic saline 0.9% (Group S) or ketamine 0.5 mg/kg diluted with isotonic saline 0.9% to a volume of 5 ml (Group K)" Comment: exact method of randomization not mentioned Authors contacted Author's response: "The randomization was done with envelope method. Every time we prepared two identical envelopes containing the information "ketamine" or "other" and let the patient choose one. The patient and the anaesthetist performing the choosing procedure were unaware about the content of the envelopes"

Abdusoglu 2011 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "The patients were allocated randomly into one of the two groups which received either 5 ml of isotonic saline 0.9% (Group S) or ketamine 0.5 mg/kg diluted with isotonic saline 0.9% to a volume of 5 ml (Group K)" Comment: based on author's response, allocation concealment was probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The anaesthesiologist who performed induction of anaesthesia was unaware of the contents of the study syringe. " Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It has not been stated by the authors whether the blinded anaesthesiologist was also the assessor of the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Ahmad 2005

Methods	RCT, parallel design, multi-centre, Malaysia
Participants	Total patients: 90 Age: 18 to 65 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: patients with chronic pain syndromes, neurological deficits, thrombophlebitis, difficult venous access, clinical conditions that contraindicated the administration of any of the drugs used in the study, patients who had received an analgesic within the previous 24 hours
Interventions	Fentanyl 100 µg (2 ml); 2% lidocaine 40 mg (2 ml) Control: 2 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg

Ahmad 2005 (*Continued*)

	No tourniquet application Duration of treatment (intervention drug): 120 seconds Central action of intervention drug assessed Pain assessed in asleep patients	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The appropriate syringe was selected by another anaesthesiologist according to the patient group allocation by using a computer-generated randomized number in a sealed envelope."
Allocation concealment (selection bias)	Low risk	Quote: The investigator prepared all study drugs in identical syringes and labelled them with removable stickers. The appropriate syringe was selected by another anaesthesiologist according to the patient group allocation by using a computer-generated randomized number in a sealed envelope and the syringe label was removed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Test drug given by a blinded investigator
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patient response was probably graded by the same investigator who administered the study drug and was blinded. Not clearly mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Akkaya 2008

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 120 Age: 20 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective orthopaedic and general surgery

	Exclusion criteria: patients with diabetes mellitus, operation longer than 3 hours or shorter than 1 hour, known allergy, neurological or psychiatric disorders, long-term analgesic treatment, thrombophlebitis or with poor dorsal hand veins
Interventions	1. Lidocaine (2%) 30 mg diluted to 2 ml with normal saline 2. Ketamine 0.5 mg/kg^{-1} diluted to 2 ml with normal saline Control: 2 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 5-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated randomly to one of the three groups" Comment: the exact method of randomization has not been mentioned Authors contacted
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were allocated randomly to one of the three groups" Comment: the exact method of allocation concealment has not been mentioned Authors contacted
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All the solutions were at ambient temperature (20-24 ºC) and the calculated drug doses were adjusted to a volume of 2 ml with saline solution. Syringes were prepared by an investigator who did not participate in the evaluation of injection pain. " Comment: equal volume of drugs was used (by diluting the drugs to make the volume 2 ml)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing has been mentioned. Authors contacted.

Akkaya 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Alanoglu 2007

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 90 Age: mean (SD) 44 (13); 41 (16) AND 40 (17) years Gender: both male and female Inclusion criteria: authors contacted Exclusion criteria: authors contacted
Interventions	Lidocaine 40 mg; tramadol 40 mg Control: 0.9% NS
Outcomes	Pain
Notes	Original paper in Turkish, data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 30 seconds Duration of treatment (intervention drug): 30 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted. No response.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted. No response.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted. No response.

Alanoglu 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Unclear risk	Authors contacted. No response.
Other bias	Unclear risk	Nothing suggestive

Asida 2009

Methods	RCT, parallel design
Participants	Total patients: 100 Age: not mentioned Gender: not mentioned Inclusion criteria: not mentioned Exclusion criteria: not mentioned
Interventions	1. Fentanyl 2 ml (100 μg) 2. Ketorolac 2 ml (30 mg) 3. Lidocaine (2%) 2 ml (40 mg) Control: 2 ml NS
Outcomes	Pain
Notes	Abstract; full text could not be retrieved. Authors could not be contacted Pain assessment: 4-point scale Rocuronium dose: intubating dose (?) No tourniquet application Duration of treatment (intervention drug): 120 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Abstract Full text could not be retrieved Authors could not be contacted
Allocation concealment (selection bias)	Unclear risk	Abstract Full text could not be retrieved Authors could not be contacted
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Abstract Full text could not be retrieved Authors could not be contacted

Asida 2009 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract Full text could not be retrieved Authors could not be contacted
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Unclear risk	Abstract Full text could not be retrieved Authors could not be contacted
Other bias	Unclear risk	Nothing suggestive

Ayoglu 2007

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 150 Age: 18 to 65 years Gender: both male and female Inclusion criteria: ASA I and II, minor elective surgeries Exclusion criteria: presence of neurological or psychiatric diseases, difficulty with communication, history of renal or hepatic insufficiency and hypersensitivity to the study drugs
Interventions	1. Dexmedetomidine 0.25 μg/kg (3 ml) 2. Lidocaine 0.5 mg/kg (3 ml) 3. Dexmedetomidine 0.25 μg/kg plus lidocaine 0.25 mg/kg (3 ml) 4. Dexmedetomidine 0.25 μg/kg plus lidocaine 0.5 mg/kg (3 ml) Control: 3 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 60 seconds Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned into five groups" Comment: the exact method of random-

Ayoglu 2007 (*Continued*)

		ization has not been mentioned. Authors contacted
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned into five groups" Comment: the exact method of allocation has not been mentioned. Authors contacted
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All pretreatment drugs were prepared in 3 ml saline in a 5 ml syringe that was covered by red tape. An independent anaesthesiologist prepared the pretreatment solutions, and the investigator did not know the contents of the solutions. " Comment: equal volume (3 ml) of drugs was prepared in 5 ml syringes that were covered with red tape by an independent anaesthesiologist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Another anaesthesiologist, who was unaware of the study groups assessed the intensity of pain after propofol and rocuronium injections" Comment: blinded assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Baek 2008

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 120 Age: 3 to 15 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgeries Exclusion criteria: muscular, cardiovascular, hepatic or kidney disorder, history of medication that would affect muscle relaxants
Interventions	0.6 mg/kg and 0.9 mg/kg rocuronium infusion lasting 1 minute Control: bolus injections of same dose
Outcomes	Pain

Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 and 0.9 mg/kg No tourniquet application Duration of treatment (intervention drug): 60 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "One hundred and twenty patients aged 3-15 years who were scheduled for elective operations were randomly enrolled into four groups for the study." Comment: the exact method of randomization has not been mentioned. Authors contacted
Allocation concealment (selection bias)	Unclear risk	Quote: "This study was designed in accordance with the double-blinded method; one nurse (IS Kim) prepared two differently labelled drugs (A: normal saline syringe and rocuronium infusion pump, B: rocuronium syringe and normal saline infusion pump). " Comment: Concealment of allocation is not clear by the above statement. Authors contacted
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for details. No response.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details.No response.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the outcome
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Borgeat 1997

Methods	RCT, parallel design, single centre, Switzerland
Participants	Total patients: 122 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, orthopaedic surgery Exclusion criteria: known allergy to trial drugs, having spontaneous movements or complaining of pain during propofol injection
Interventions	Fentanyl 2 µg/kg Control: NS
Outcomes	Pain Adverse events
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.8 mg/kg No tourniquet application Duration of treatment (intervention drug): 45 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized via computer-generated random number table to either group A (to receive fentanyl) or Group B (saline)." Comment: adequate
Allocation concealment (selection bias)	Low risk	Quote: "The syringes of fentanyl or placebo were prepared by a nurse who was not a part of the study." Comment: probably adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The syringes of fentanyl or placebo were prepared by a nurse who was not a part of the study." Comment: probably adequate.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An investigator who was unaware of patient group assignment was responsible for scoring the observed movement during rocuronium administration" Comment: adequate

Borgeat 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5% patients excluded from the study
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Byun 2005

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 90 Age: mean 29.9; 34.9 and 31.4 years in the 3 study groups Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	2% lidocaine 2 ml 0.5% metoclopramide 2 ml Control: NS 2 ml
Outcomes	Pain
Notes	Article in Korean language, data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 1 minute after pretreatment drug Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response

Byun 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Cheong 2000

Methods	RCT, parallel design, single centre, Singapore
Participants	Total patients: 90 Age: mean 34.9, 36.9, 37.3 years Gender: both male and female Inclusion criteria: ASA I and II, orthopaedic and general surgery Exclusion criteria: difficult venous access, requiring rapid sequence induction
Interventions	Lidocaine 10 mg and 30 mg Control: isotonic saline
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 10 seconds Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated randomly using sealed envelopes to receive isotonic saline (control group), lidocaine 10 mg or lidocaine 30 mg at ambient temperature (20-24^{o}C)" Comment: adequate

Cheong 2000 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Patients were allocated randomly using sealed envelopes to receive isotonic saline (control group), lidocaine 10 mg or lidocaine 30 mg at ambient temperature (20-24^{o}C)" Comment: adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comments on this by the authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All syringes were prepared by another investigator and covered so that the investigator who assessed the patient's response was unaware of the nature of the solution." Comment: seems adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Cheong 2003

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 60 Age: mean 8.4, 6.4 and 6.1 years Gender: both male and female Inclusion criteria: ASA I, elective surgery Exclusion criteria: translation required
Interventions	Ketamine: 0.5 mg/kg and 1.0 mg/kg Control: saline
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.9 mg/kg No tourniquet application Duration of treatment (intervention drug):translation required Central action of intervention drug assessed Pain assessed in asleep patients

Cheong 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Choi 2005

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 60 Age: mean 40.3, 41.2 and 39 years Gender: females Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	Ketamine 0.2 and 0.5 mg/kg Control: NS 2 ml
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 3-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 30 seconds

Choi 2005 (*Continued*)

	Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Choi 2006

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 250 Age: 20 to 80 years Gender: both male and female Inclusion criteria: ASA I to II Exclusion criteria: translation required
Interventions	1. Rocuronium 50 mg (5 ml) with 8.4% sodium bicarbonate (1 ml) 2. Rocuronium 50 mg (5 ml) with 8.4% sodium bicarbonate (2.5 ml) 3. Rocuronium 50 mg (5 ml) with 8.4% sodium bicarbonate (5 ml) 4. Rocuronium 50 mg (5 ml) with 8.4% sodium bicarbonate (7 ml) Control: rocuronium 5 ml
Outcomes	Pain

Choi 2006 (*Continued*)

Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 50 mg No tourniquet application Duration of treatment (intervention drug): translation required Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Choi 2008

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 90 Age: 19 to 65 years Gender: females Inclusion criteria: ASA I and II, undergoing elective thyroidectomy Exclusion criteria: hypertension, ischemic heart disease, severe bradycardia (heart rate < 45 beats/minute), chronic pain syndrome and neuromuscular disorders, patients who received analgesics or sedatives within 24 hours

Interventions	0.5 μg/kg and 1.0 μg/kg remifentanil Control: 4 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated into three groups using sealed envelope method to receive one of the three solutions of equal volume (4ml) intravenously" Comment: method of randomization not mentioned. Authors contacted and no response
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated into three groups using sealed envelope method to receive one of the three solutions of equal volume (4ml) intravenously" Comment: adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The administered volume of the remifentanil solution was adjusted to 4 ml by mixing normal saline. The syringes containing the study drug was prepared by an independent researcher." Comment: probably identical syringes were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, anesthesia providers and investigators who evaluated the withdrawal movements were blinded to the treatment group." Comment: adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed

Choi 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Dogru 2002

Methods	RCT, parallel design, 2 centres, Turkey
Participants	Total patients: 60 Age: mean 41.6 and 39.7 years Gender: both male and female Inclusion criteria: ASA I and II Exclusion criteria: translation required
Interventions	2% lidocaine 30 mg Control: saline 1.5 ml
Outcomes	Pain
Notes	Article in Turkish, data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response

Dogru 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Ertugrul 2006

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 44 Age: mean 41, 42.8, 65.6, 42.5 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: history of neurological deficits, drug allergy, asthma, patients who received analgesics or sedatives within 24 hours
Interventions	1. Metoclopramide 10 mg 2. Lidocaine 50 mg 3. Remifentanil 1 µg/kg Control: 3 ml 0.9% NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.06 mg/kg Tourniquet application for 10 seconds Duration of treatment (intervention drug): 10 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study patients were randomly allocated to receive one of four treatments by intravenous injection" Comment: exact method not mentioned
Allocation concealment (selection bias)	Unclear risk	Nothing mentioned. Authors contacted. No response.

Ertugrul 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patient and the anaesthetist were unaware of the treatment group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...Pain and burning sensation were determined by an anaesthetist, who was blinded to the treatment group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Eun 2005

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 120 Age: mean 34.8, 33.1, 38.1, 38.1 years Gender: both male and female Inclusion criteria: translations required Exclusion criteria: translations required
Interventions	1. Ondansetron 8 mg (4 ml) 2. Lidocaine 60 mg (4 ml) 3. Tramadol 50 mg (4 ml) Control: 4 ml NS
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.

Eun 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Han 2003

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 60 Age: mean 38.1, 36.9, 43 years Gender: female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	1. Rocuronium 50 mg/5 ml mixed with 0.9% NaCl 3 ml 2. Rocuronium 50 mg/5 ml mixed with $NaHCO_3$ 3 ml Control: rocuronium 5 ml
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg over 10 seconds No tourniquet application Duration of treatment (intervention drug): not given Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Han 2003 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Han 2007

Methods	RCT, parallel design, multi-centre, Korea and USA
Participants	Total patients: 60 Age: 20 to 50 years Gender: female Inclusion criteria: ASA I and II, elective gynaecologic surgery Exclusion criteria: not mentioned
Interventions	1. 50 mg rocuronium + 3 ml normal saline (0.9%) 3. 50 mg rocuronium + 3 ml 8.4% $NaHCO_3$ Control: rocuronium 3 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.4 mg/kg No tourniquet application Duration of treatment (intervention drug): not mentioned Central action of intervention drug assessed Pain assessed in awake patients
Risk of bias	

Han 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to 3 groups via table of random numbers, to receive one of the three mixtures (n=20 of each) of rocuronium for priming." Comment: table of random numbers was used to generate randomization and allocation of the patients into 3 groups. It was adequately done
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Syringes of mixture were prepared by an investigator who did not participate in the evaluation of injection pain. The mixture for injection were prepared in 2 ml syringes immediately before administration and then wrapped in aluminium foil and labelled." Comment: adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study conducted in a double-blinded manner. Not clearly specified, who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Hwang 2003

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 250 Age: 18 to 70 years Gender: both male and female Inclusion criteria: ASA I and II Exclusion criteria: translation required
Interventions	1. Lidocaine 10 mg (2 ml) 2. Lidocaine 20 mg (2 ml) 3. Lidocaine 30 mg (2 ml) 4. Lidocaine 40 mg (2 ml) Control: 2 ml NS

Hwang 2003 (*Continued*)

Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Ikram 2008

Methods	RCT, parallel design, single centre, Pakistan
Participants	Total patients: 120 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: patients with known neuromuscular disease, anticipated difficult airway, pregnant patients and those with chronic pain

Ikram 2008 (*Continued*)

Interventions	lidocaine 1% solution (plain) 3 ml Control: 3 ml NS
Outcomes	Pain
Notes	No email ID available and so authors could not be contacted Adult patients Pain assessment: 4-point scale Rocuronium dose: 1 mg/kg over 5 seconds Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. Authors could not be contacted.
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors could not be contacted.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The injection was prepared by one anaesthetist and was injected by another anaesthetist. The third anaesthetist who was unaware of the drug being given to the patient made all the observations."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The injection was prepared by one anaesthetist and was injected by another anaesthetist. The third anaesthetist who was unaware of the drug being given to the patient made all the observations."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Jeon 2010

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 120 Age: 19 to 69 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: patients with chronic pain syndrome, neurological deficits, thrombophlebitis, difficult venous access, contraindication to any of the drug used in the study
Interventions	1. Lidocaine 40 mg over 10 seconds 2. Acetaminophen 50 mg over 10 seconds Control: 0.9% NS 5 ml
Outcomes	Pain Adverse event: pain on injection of study drug
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 120 seconds Duration of treatment (intervention drug): 120 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned. No response from author.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Jung 2005

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 85 Age: 5 to 15 years Gender: both male and female Inclusion criteria: ASA physical status I or II, undergoing elective surgery requiring general anaesthesia Exclusion criteria: children with chronic pain syndromes, psycho-neurological disease, thrombophlebitis, difficult venous access, obesity more than BMI 25 and hypersensitivity to any of the drugs used in the study. Patients who had received an analgesic or sedative 24 hours before surgery were also excluded
Interventions	1. 2% lidocaine 5 ml mixed with rocuronium (50 mg) 5 ml 2. 8.4% $NaHCO_3$ 5 ml mixed with rocuronium (50 mg) 5 ml 3. 4% lidocaine 2.5 ml and 8.4% $NaHCO_3$ 2.5 ml mixed with rocuronium (50 mg) 5 ml Control: 0.9% normal saline 5 ml mixed with rocuronium (50 mg) 5 ml
Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg of premixed rocuronium over 5 seconds No tourniquet application Duration of treatment (intervention drug): not applicable Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**On communication**: Quote: "...computer-generated randomized number in a sealed envelope."
Allocation concealment (selection bias)	Low risk	**On communication**: Quote: "...computer-generated randomized number in a sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**On communication**: Quote: "The investigator prepared all study drugs using identical syringes before anesthesia. Each syringe was premixed with rocuronium 50 mg (5 ml) and 5 ml of study drugs (Group S; 0.9% normal saline, Group L; 2% lidocaine, Group B; 8.4% sodium bicarbonate, and Group LB; 2.5 ml of 4% lidocaine and 2.5 ml of 8.4% sodium bicarbonate) to become

Jung 2005 (*Continued*)

		an equivalent volume"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**On communication**: Quote: "The investigator prepared all study drugs using identical syringes before anesthesia. Each syringe was premixed with rocuronium 50 mg (5 ml) and 5 ml of study drugs (Group S; 0. 9% normal saline, Group L; 2% lidocaine, Group B; 8.4% sodium bicarbonate, and Group LB; 2.5 ml of 4% lidocaine and 2.5 ml of 8.4% sodium bicarbonate) to become an equivalent volume"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Jung 2005a

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 150 Age: mean 43.2, 39.5, 41.8, 40, 37, 40.9 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	1: (Control) 0.5 mg/kg lidocaine, 30 seconds before rocuronium 2: Tourniquet + 0.5 mg/kg lidocaine 30 seconds before rocuronium 3: (Control) 0.5 mg/kg lidocaine 60 seconds before rocuronium 4: Tourniquet + 0.5 mg/kg lidocaine 60 seconds before rocuronium 5: (Control) propofol 2 mg/kg + 0.5 mg/kg lidocaine 30 seconds before rocuronium 6: Propofol 2 mg/kg + tourniquet + 0.5 mg/kg lidocaine, 30 seconds before rocuronium
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Duration of treatment (intervention drug): 30 and 60 seconds Central/peripheral action of intervention drug assessed Pain assessed in awake/asleep patients
Risk of bias	

Jung 2005a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Jung 2005b

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 120 Age: mean 39.4, 38.2. 37.9, 33.4 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	1. 5 ml 2% lidocaine + 5 ml rocuronium 2. 5 ml 8.5% sodium bicarbonate + 5 ml rocuronium 3. 2.5 ml 4% lidocaine + 2.5 ml 8.4% sodium bicarbonate + 5 ml rocuronium Control: 5 ml saline + 5 ml rocuronium
Outcomes	Pain
Notes	Translation of article required, data extracted from abstract, figures and tables. Authors contacted Adult patients Pain assessment: 5-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application

Jung 2005b (*Continued*)

	Duration of treatment (intervention drug): not applicable Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Kaya 2004

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 90 Age: 18 to 65 years Gender: both male and female Inclusion criteria: ASA III Exclusion criteria: allergy to anaesthetic drug
Interventions	1. Lignocaine 1 ml 2. Dexmedetomidine 0.25 mg/kg Control: 1 ml saline
Outcomes	Pain

Kaya 2004 (*Continued*)

Notes	Article in Turkish, data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 1/8th of total dose 0.9 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. Authors could not be contacted.
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors could not be contacted.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. Authors could not be contacted.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Authors could not be contacted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kelsaka 2002

Methods	RCT, parallel design, 2 centres, Canada
Participants	Total patients: 60 Age: 20 to 60 years Gender: both male and female Inclusion criteria: ASA I and II Exclusion criteria: allergy to drugs, thin dorsal veins
Interventions	1. 2 cc ondansetron (4 mg) 2. 2 cc lidocaine (2%) Control: 2 cc 0.9% NS

Kelsaka 2002 (*Continued*)

Outcomes	Pain
Notes	**Authors cannot be contacted as no email ID available,** data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 15 seconds Duration of treatment (intervention drug): 15 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Translation required. Author could not be contacted.
Allocation concealment (selection bias)	Unclear risk	Translation required. Author could not be contacted.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Translation required. Author could not be contacted.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Translation required. Author could not be contacted.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No
Selective reporting (reporting bias)	Unclear risk	Translation required
Other bias	Unclear risk	Nothing suggestive

Ki 2005

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 80 Age: mean 41.6, 41.5, 41.2, 40.6 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required

Ki 2005 (*Continued*)

Interventions	Ondansetron 4 mg, 6 mg and 8 mg Control: 3 ml NS
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application Duration of treatment (intervention drug):translation required Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Kilicaslan 2010

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 60 Age: 18 to 65 years Gender: both male and female Inclusion criteria: ASA I and II Exclusion criteria: allergy to drugs, neurologic and psychiatric problems, those on long-term analgesics, thrombophlebitis, Parkinson's disease, thin veins
Interventions	Diphenhydramine: 2 mg in 2 ml Control: 2 ml saline
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 10 mg Tourniquet application for 30 seconds Duration of treatment (intervention drug): 30 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**On communication** Quote: "Allocation was performed by a computer-conducted randomization in which the code was sealed until the arrival of the patient in the operating room."
Allocation concealment (selection bias)	Low risk	**On communication** Quote: "Allocation was performed by a computer-conducted randomization in which the code was sealed until the arrival of the patient in the operating room."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**On communication** Quote: "The drugs were prepared by one of the investigators, with both the patient and an independent observer (a resident of anaesthesiology) blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**On communication** Quote: "The drugs were prepared by one of the investigators, with both the patient and an independent observer (a resident of anaesthesiology) blinded."

Kilicaslan 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kim 2002

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 42 Age: mean 5.2, 3.6 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	0.1 ml/kg 1% lidocaine Control: 0.1 ml/kg saline
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Paediatric patients Pain assessment: 5-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 5 seconds Duration of treatment (intervention drug): 5 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias)	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response

Kim 2002 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Kim 2004

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 240 Age: 20 to 65 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	Rocuronium cold (4 to 5 degrees centigrade) Control: rocuronium at ambient temperature (20 to 24 degrees centigrade)
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 5-point scale Rocuronium dose: 10 mg No tourniquet application Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response

Kim 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Kim 2006

Methods	RCT, parallel design, 2 centres, Korea
Participants	Total patients: 200 adults; 150 children Age: 19 to 63 years; 2 to 9 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: neurologic deficits, allergy to trial drugs, sedatives or analgesics within 24 hours
Interventions	Adults: lidocaine 1 mg/kg with and without (control) occlusion of intravenous flow Children: 1% lidocaine 1 mg/kg 1% rocuronium 0.8 mg/kg mixed with same volume of sodium bicarbonate 8.4%
Outcomes	Pain
Notes	Adult/paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg in adults; 0.8 mg/kg No tourniquet application Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque envelopes

Kim 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All syringes of the study solution were prepared by another investigator and covered so that the investigator who assessed the patient response was unaware of the nature of the solution."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All syringes of the study solution were prepared by another investigator and covered so that the investigator who assessed the patient response was unaware of the nature of the solution."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kim 2007

Methods	RCT, parallel design, 2 centres, Korea
Participants	Total patients: 70 Age: 3 to 10 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: allergy to opioids, asthma, neurological deficits and those who received sedatives or analgesics within previous 24 hours
Interventions	Remifentanil 1 µg/kg Control: 5 ml saline
Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 60 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Kim 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not mentioned. No response from author.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, anaesthesia providers and investigators who scored the movements were blinded to the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kim 2008

Methods	RCT, parallel design, multi-centre, Korea
Participants	Total patients: 120 Age: 3 to 10 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: allergy to opioid, asthma, neurological deficit, sedatives or analgesic within 24 hours, crying children on arrival in the operating room
Interventions	1. 0.5 µg/kg remifentanil 2. 1 µg/kg remifentanil 3. 15 µg/kg alfentanil Control: saline 5 ml
Outcomes	Pain Adverse events
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 60 seconds Central action of intervention drug assessed Pain assessed in asleep patients
Risk of bias	

Kim 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated into four groups to receive either iv remifentanil 0.5 mcg/kg, iv remifentanil 1 mcg/kg, iv alfentanil 15 mcg/kg or iv saline 5 ml using a sealed envelope system"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated into four groups to receive either iv remifentanil 0.5 mcg/kg, iv remifentanil 1 mcg/kg, iv alfentanil 15 mcg/kg or iv saline 5 ml using a sealed envelope system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, anaesthesia providers and investigators who scored the movement were blinded to the treatment group and an independent researcher prepared the study solution..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, anaesthesia providers and investigators who scored the movement were blinded to the treatment group and an independent researcher prepared the study solution...."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kim 2009

Methods	RCT, parallel design, multi-centre, South Korea
Participants	Total patients: 115 Age: Over 18 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: history of neurological deficits, allergies to opioids and local anaesthetics, asthma and those who had received analgesics or sedatives within the previous 24 hours
Interventions	1. Alfentanil 10 μg/kg (3 ml) 2. Remifentanil 1 μg/kg (3 ml) Control: 3 ml NS

Kim 2009 (*Continued*)

Outcomes	Pain Adverse events
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 90 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Using computer generated numbers patients were randomly assigned to one of the three treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "A nurse anaesthetist who was blinded to the study prepared and labelled the syringes, which contained a total volume of 3 ml"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A nurse anaesthetist who was blinded to the study prepared and labelled the syringes, which contained a total volume of 3 ml"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An investigator who was unaware of patient group assignment observed patient movement during and immediately after rocuronium administration"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kim 2010

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 90 Age: 18 to 65 years Gender: both male and female

Kim 2010 (*Continued*)

	Inclusion criteria: ASA I and II Exclusion criteria: allergy to nafamostat mesilate, chronic pain, pregnancy, analgesics/ sedatives within 24 hours
Interventions	Nafamostat 1.5 mg in 1.5 ml Control: 1.5 ml 5 % glucose solution
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application 60 seconds Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "90 patients, aged 18-65 years, with ASA I or II were allocated to one of the two groups by computer generated randomization"
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The syringes of the test solution were prepared by another investigator and covered so that the investigator who assessed each patients response was unaware of the solution administered."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An investigator blinded to the contents of the test solution was responsible for scoring the observed responses during rocuronium injection"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kirpit 2010

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 120 Age: 18 to 65 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: morbid obesity, expected difficult intubation, history of chronic pain, neuropsychiatric and neurologic disorders, history of allergy to study drugs, severe respiratory, cardiac, renal, hepatic and neuromuscular disease, sedatives in last 24 hours, unco-operative patients
Interventions	Lidocaine: 1 mg/kg diluted with 5 ml normal saline, over 30 seconds Ketamine: 0.2 mg/kg diluted with 5 ml normal saline, over 30 seconds Ephedrine: 70 mg/kg diluted with 5 ml normal saline, over 30 seconds Control: 5 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: dose of rocuronium in awake state: 0.06 mg/kg Dose of rocuronium in asleep state: 0.54 mg/kg No tourniquet application Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake and asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. No response from author.
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelope method...." Comment: not adequately explained. Probably opaque.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. No response from author.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. No response from author.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed

Kirpit 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Kwak 2004

Methods	RCT, parallel design, multi-centre, Korea
Participants	Total patients: 75 Age: mean 43.4, 40.9, 36.2 years Gender: both male and female Inclusion criteria: ASA I and III. Translation required. Exclusion criteria: translation required
Interventions	1. 3 ml saline + rocuronium mixed with 30 mg lidocaine 2. Lidocaine 30 mg before injecting rocuronium Control: 3 ml NS
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): not applicable Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response

Kwak 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Kwak 2010

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 66 Age: 5 to 12 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: allergy to LA, asthma, neurologic deficits, analgesic or sedative within 24 hours, those crying on arrival in the operating room
Interventions	(50%) Nitrous oxide + oxygen + lidocaine 1 mg/kg 1% Control: oxygen + lidocaine 1 mg/kg 1%
Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg of 0.1% rocuronium Tourniquet application for 15 seconds Duration of treatment (intervention drug): 15 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to two groups using a computer generated randomization table"
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, anesthesia providers, and investigators who scored the movements were blind to the gas mixture administered to patients (flowmeters were covered by cardboard)"

Kwak 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, anesthesia providers, and investigators who scored the movements were blind to the gas mixture administered to patients (flowmeters were covered by cardboard)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient in nitrous oxide group and 2 in oxygen group were excluded as they became excited and started crying and did not co-operate
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Lee 2004

Methods	RCT, parallel design, single centre, Korea	
Participants	Total patients: 150 Age: 18 to 60 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required	
Interventions	1. Lidocaine 30 mg 2. Lidocaine 50 mg 3. Fentanyl 100 μg 4. Ondansetron 4 mg Control: saline 3 ml	
Outcomes	Pain	
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Manual occlusion of forearm Duration of treatment (intervention drug):translation required Peripheral action of intervention drug assessed Pain assessed in awake patients	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lee 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.
Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Lee 2009

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 171 Age: 18 to 65 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: patients with neurologic deficits, opioids or local anaesthetic allergies, recent exposure to antihistaminics or antidepressants, asthma, pregnancy, analgesics within 24 hours, difficult venous access, those requiring rapid sequence induction
Interventions	Pheniramine maleate 2 ml (45.5 mg) as premedication Control: 2 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 30 minutes Central action of intervention drug assessed Pain assessed in asleep patients

Lee 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. No response from author.
Allocation concealment (selection bias)	Low risk	Sealed envelope method used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. No response from author.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. No response from author
Incomplete outcome data (attrition bias) All outcomes	High risk	Pain data for only 58/79 patients in control group and 62/92 in intervention group reported
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Lee 2009b

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 150 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: neurological deficits, or allergies to thiopental sodium, rocuronium or lidocaine
Interventions	1. 0.1 mg/kg 1% lidocaine + slow injection of rocuronium 1 mg/kg within 10 seconds 2. 0.1 ml/kg of saline + rapid injection of rocuronium 1 mg/kg within 1 seconds 3. 0.1 ml/kg of saline + slow injection of rocuronium 1 mg/kg within 10 seconds Control: 0.1 ml/kg of saline + slow injection of rocuronium 1 mg/kg within 10 seconds
Outcomes	Pain
Notes	Adults patients Pain assessment: 4-point scale Rocuronium dose: 1 mg/kg Tourniquet application for 15 seconds Duration of treatment (intervention drug): 15 seconds

Lee 2009b (*Continued*)

	Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A single anaesthesiologist with no knowledge of study protocol graded each patients response"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Lee 2009c

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 150 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: chronic pain syndromes, neurologic deficits, difficult venous access, drug allergies, sedatives or analgesics within 24 hours
Interventions	Lidocaine: 1 mg/kg diluted to 5 ml Rocuronium: 0.06 mg/kg diluted to 5 ml Control: 5 ml saline
Outcomes	Pain Heart rate Blood pressure

Lee 2009c (*Continued*)

Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 10 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. No response from authors.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All priming solutions were diluted with normal saline using 5 ml syringes and injected over 10 sec by an investigator who was blinded to the priming solution"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Lee 2011

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 194 Age: 20 to 70 years Gender: both male and female Inclusion criteria: ASA I and II, well controlled hypertension, elective gastric or colorectal surgery Exclusion criteria: known allergy to opioids, history of DM, asthma, neurologic deficit, pregnancy, use of analgesics within 24 hours
Interventions	1. Hydromorphone: 0.03 mg/kg 2. Fentanyl: 2 μg/kg Control: 5 ml NS

Lee 2011 (*Continued*)

Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 90 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Envelope method used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patient and 2 anaesthesiologists carrying out the induction and recording the outcome were all blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The patient and 2 anaesthesiologists carrying out the induction and recording the outcome were all blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 patients excluded in fentanyl group and 1 in control group
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Liou 2003

Methods	RCT, parallel design, single centre, Taiwan
Participants	Total patients: 100 Age: 1 to 6 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: history of neurologic deficit, drug allergy, asthma, analgesic or sedative within 24 hours
Interventions	Ketamine: 0.2 mg/kg diluted to 2 ml with normal saline Control: 2 ml NS

Liou 2003 (*Continued*)

Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.8 mg/kg of 0.1% rocuronium No tourniquet application Duration of treatment (intervention drug): 20 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization table used
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patient and nurse preparing the syringes were unaware of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator assessing the response was unaware of the nature of the study solution
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 patients excluded in ketamine group and 1 in placebo group
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Mahajan 2005

Methods	Quasi RCT, parallel design, single centre, India
Participants	Total patients: 150 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: history of allergy, convulsions, taking sedatives and analgesic medications, difficult venous access, those requiring rapid sequence induction
Interventions	Ketamine: 10 mg in 2 ml normal saline Ketamine: 20 mg in 2 ml saline

	Control: 2 ml saline
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Author's reply: by assigning according to sequential number: 1, 4, 7 for control; 2, 5, 8 for 10 mg ketamine; 3, 6, 9 for 20 mg ketamine Comment: quasi-randomization
Allocation concealment (selection bias)	Low risk	Author's reply: "It was the last digit of pt MRD (registration number) on the file. Drug was prepared by the pharmacy and delivered to us and the number on the syringe and drug was with pharmacy which was revealed to us at the end of study."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. No satisfactory response.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. No satisfactory response.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Mahajan 2010

Methods	RCT, parallel design, single centre, India
Participants	Total patients: 90 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I and II, elective spinal surgery Exclusion criteria: history of chronic pain, neurologic deficit, psychiatric illness, substance abuse, alcoholism, using sedatives or analgesics, difficult venous access
Interventions	Local warming at 40 degrees centigrade Control: no warming
Outcomes	Pain
Notes	Adults patients Pain assessment: 5-point scale Rocuronium dose: 10 mg No tourniquet application Duration of treatment (warming over injection site): 60 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	No standard method of concealment was used. Enrolled patients were sequentially allocated to the group based on randomization chart
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both aware of the study. Blinding not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The response was recorded according to five point scale by an investigator who was blinded to the group allocation of the patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No

Other bias	Unclear risk	Nothing suggestive

Memis 2002

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 250 Age: mean 37.3, 40.5, 38.6, 42.2, 41.6 years Gender: both male and female Inclusion criteria: ASA I and II, elective arthroscopy or hysteroscopy Exclusion criteria: opioid or local anaesthetic allergies, Parkinson's disease, weak or thin dorsal veins
Interventions	Ondansetron 4 mg Lidocaine 30 mg Tramadol 50 mg Fentanyl 100 µg Control: 3 ml NS
Outcomes	Pain
Notes	Adults patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized list was generated . .."
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Identical syringes containing each drug were prepared by personnel blinded to the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed

Memis 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Memis 2005

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 90 Age: adult patients Gender: both males and females Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Dexmedetomidine 0.1 μg/kg and 0.2 μg/kg diluted to 1 ml Control: 1 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.05 mg/kg No tourniquet application Duration of treatment (intervention drug): 5 minutes Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported. No response from author.
Allocation concealment (selection bias)	Unclear risk	Not reported. No response from author.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported. No response from author.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported. No response from author.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No

Memis 2005 (*Continued*)

Other bias	Unclear risk	Nothing suggestive

Oh 2007

Methods	RCT, parallel design, multi-centre, Korea
Participants	Total patients: 164 Age: 1 to 14 years Gender: both male and female Inclusion criteria: ASA I, II, undergoing general anaesthesia Exclusion criteria: history of neurologic deficit, opioid or local anaesthetic allergies, asthma, sedatives or analgesics within 24 hours
Interventions	Remifentanil: 1 μg/kg diluted to 3 ml Alfentanil: 10 μg/kg diluted to 3 ml Fentanyl: 2 μg/kg diluted to 3 ml Control: 3 ml NS
Outcomes	Pain Adverse events
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 90 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned, using computer-generated numbers to one of the four groups."
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Group C received saline 3 ml; group R, remifentanil 1 mcg/kg; group A, alfentanil 10 mcg/kg; and group F: fentanyl 2 mcg/kg, each diluted to 3ml with saline. A nurse anaesthetist, blinded to the study, prepared and labelled the syringes."

Oh 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An investigator who was unaware of the patient group assignments, observed the movements of the patients during and immediately after rocuronium administration"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Park 2005

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 90 Age: 16 to 69 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: specific response to thiopental in history, asthma, chronic obstructive pulmonary diseases, pregnant women, treated with analgesic drugs on the day of surgery
Interventions	2 ml (50 mg) thiopentone injected after tourniquet application Control: saline injected after tourniquet application
Outcomes	Pain
Notes	Adult/paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 30 seconds Duration of treatment (intervention drug): 30 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. No response from authors.
Allocation concealment (selection bias)	Unclear risk	Not mentioned. No response from authors.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Park 2006

Methods	RCT, parallel design, 2 centres, Korea
Participants	Total patients: 90 Age: 5 to 15 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	1. Rocuronium 0.6 mg/kg diluted with 0.9% NaCl to 1 mg/ml 2. Rocuronium 0.6 mg/kg diluted with 0.9% NaCl to 0.67 mg/ml Control: rocuronium 0.6 mg/kg
Outcomes	Pain
Notes	Data extracted from abstract, figures and tables Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug):translation required Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.

Park 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed, as evident from the results shown in tables
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Park 2011

Methods	RCT, parallel design, multi-centre, Korea
Participants	Total patients: 75 Age: 4 to 9 years Gender: both males and females Inclusion criteria: age 4 to 9 years with physical status I or II, undergoing a strabismus operation Exclusion criteria: children with contradictions to inhalational induction of anaesthesia (gastroesophageal reflux, myopathy, familial history of malignant hyperthermia or patient refusal), and children with neurological disease, or who had received analgesics or sedatives 24 hours before surgery were not included in the study
Interventions	Group S1.5: received rocuronium 0.4 mg/kg, 1.5 minutes after the start of induction with sevoflurane/once Group S2.0: received rocuronium 0.4 mg/kg, 2.0 minutes after the start of induction with sevoflurane/once Group S2.5: received rocuronium 0.4 mg/kg, 2.5 minutes after the start of induction with sevoflurane/once Group S3.5: received rocuronium 0.4 mg/kg, 3.0 minutes after the start of induction with sevoflurane/once Control: 2.5% thiopental 5 mg/kg
Outcomes	Withdrawal/pain

Park 2011 (*Continued*)

Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.04 mg/kg No tourniquet application Duration of treatment (intervention drug): 1.5, 2, 2.5 and 3 minutes Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization and sealed envelopes were used"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 patient were excluded
Selective reporting (reporting bias)	Unclear risk	Data for all possible complications mentioned in methodology are not reported
Other bias	Unclear risk	Nothing suggestive

Reddy 2001

Methods	RCT, parallel design, single centre, Singapore
Participants	Total patients: 60 Age: mean 33.5, 39.8, 41.4 years Gender: both male and female Inclusion criteria: ASA I, II, elective orthopaedic and gastrointestinal procedures
Interventions	1. Ondansetron 4 mg in 5 ml saline 2. Lidocaine 50 mg in 5 ml saline Control: 5 ml 0.9% NS

Reddy 2001 (*Continued*)

Outcomes	Pain Adverse events
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 60 seconds Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly allocated to one of the three groups by the drawing of lots"
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All syringes of test solution were prepared by another investigator and covered so that the investigator who assessed the patient response was unaware of the nature of the solution"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Sharma 2010

Methods	RCT, parallel design, single centre, India
Participants	Total patients: 80 Age: 18 to 55 years Gender: both male and female Inclusion criteria: ASA I, II, elective procedures Exclusion: chronic pain, anticipated difficult airway, pregnancy, contraindication to ni-

Sharma 2010 (*Continued*)

	trous oxide, patients receiving analgesics or sedatives
Interventions	Nitrous oxide (50%) in oxygen for 3 minutes Control: 100% oxygen for 3 minutes
Outcomes	Pain Adverse events
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.06 mg/kg diluted with saline to 5 ml No tourniquet application Duration of treatment (intervention drug): 3 minutes Central action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Drawing of lots
Allocation concealment (selection bias)	Low risk	Drawing blindly from the box that contained exactly 80 coded lots
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Screen was placed in front of the flow meters in such a fashion that the investigator collecting the data was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Shevchenko 1999

Methods	RCT, parallel design, single centre, USA
Participants	Total patients: 100 Age: 5 to 18 years Gender: both male and female

Shevchenko 1999 (*Continued*)

	Inclusion criteria: ASA I, II Exclusion criteria: neurologic deficits, allergy to thiopental, rocuronium or lidocaine drugs, patients receiving analgesics or sedatives within previous 24 hours
Interventions	1% lidocaine 0.1 ml/kg Control: saline
Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 1 mg/kg Tourniquet application for 15 seconds Duration of treatment (intervention drug): 15 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Card drawn method
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Possibly done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Shin 2011a

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 200 Age: mean 41.7, 41.8, 39.8, 40.9 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: prior use of calcium channel blockers, opioids and anticoagulants, pregnancy, non allergy to magnesium sulfate, disorders of cardiovascular, hepatic, renal, gastrointestinal and neurological diseases, morbid obesity and difficult airway
Interventions	1. 5 mg/kg magnesium sulfate diluted to 5 ml 2. 10 mg/kg magnesium sulfate diluted to 5 ml 3. 20 mg/kg magnesium sulfate diluted to 5 ml Control: 5 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 30 seconds Duration of treatment (intervention drug): 30 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Low risk	Sequentially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Shin 2011b

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 171 Age: 1 to 15 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: neurological deficits, known allergy to trial drugs, asthma, those receiving analgesics or sedatives within previous 24 hours
Interventions	1. Fast injection of non-diluted rocuronium (10 mg/ml) over 5 seconds 2. (Control) Slow injection of non-diluted rocuronium (10 mg/ml) over 60 seconds 3. Fast injection of diluted rocuronium (1 mg/ml) over 5 seconds 4. (Control) Slow injection of diluted rocuronium (1 mg/ml) over 60 seconds
Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg No tourniquet application Duration of treatment (intervention drug): 5 and 60 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Identical syringes were prepared by investigator and were covered to hide the nature and amount of solution"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The blinded observer stood outside the operating room during the preparation of syringes and assessed patient's response during and immediately after rocuronium injection"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No

Shin 2011b (*Continued*)

Other bias	Unclear risk	Nothing suggestive

Singh 2007

Methods	RCT, parallel design, single centre, India
Participants	Total patients: 80 Age: 20 to 75 years Gender: both male and female Inclusion criteria: ASA I, II, elective neurosurgery Exclusion criteria: difficult venous access, thin dorsal veins, requiring rapid sequence induction, allergy to any study drug, non-consenting patients
Interventions	1. Lidocaine 1 mg/kg diluted to 5 ml 2. Fentanyl 1 µg/kg diluted to 5 ml 3. Sufentanil 0.5 µg/kg diluted to 5 ml Control: 5 ml NS
Outcomes	Pain
Notes	Adult patients Pain assessment: 5-point scale Rocuronium dose: 10 mg Tourniquet application for 60 seconds Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated table
Allocation concealment (selection bias)	High risk	Not mentioned. No standard method of concealment was used. Enrolled patients were sequentially allocated to the group based on randomization chart
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mentioned

Singh 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Tuncali 2004

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 150 Age: mean 46.7, 51.5, 44.7 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: age < 18 years, allergy to any of the anaesthetic medications being administered
Interventions	1. Rocuronium 0.06 mg/kg diluted with normal saline (1 mg/ml) 2. Rocuronium 0.06 mg/kg diluted with normal saline (0.5 mg/ml) Control: rocuronium 0.06 mg/kg (10 mg/kg)
Outcomes	Pain Adverse effects
Notes	Adult patients Pain assessment: 5-point scale Rocuronium dose: 0.06 mg/kg No tourniquet application Duration of treatment (intervention drug): 10 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing mentioned about the personnel

Tuncali 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All syringes were prepared by another investigator and were covered so that the investigator who assessed the patients response was unaware of the nature of solution"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Turan 2003

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 250 Age: mean 39.4, 42.2, 40.3, 43.4, 38.3 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: patients with opioids and local anaesthetic allergies, Parkinson's disease and/or weak, thin dorsal veins
Interventions	1. 2.48 mmol MgSo4 in 3 ml 2. Lidocaine 30 mg in 3 ml 3. 8.4% sodium bicarbonate 2 ml 4. Alfentanil 1000 µg diluted with 3 ml saline Control: 3 ml saline
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Turan 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Identical syringe containing each drug were prepared by an anaesthetist blinded to the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Wee 2004

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 120 Age: mean 34.8, 33.1, 38.1, 38.1 years Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	1. Lidocaine 20 mg diluted in 3 ml solution 2. Lidocaine 40 mg diluted in 3 ml solution 3. Lidocaine 60 mg diluted in 3 ml solution Control: 3 ml NS
Outcomes	Pain Adverse events
Notes	Data extracted from abstract, figures and tables Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 20 seconds Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors contacted for details on randomization. No response.

Wee 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Authors contacted for details on allocation concealment. No response
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors contacted for detailed methodology to find out who was blinded during the study period. No response
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Authors contacted for details on blinding of outcome assessors. No response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Unclear risk	Translation required and so cannot be commented upon
Other bias	Unclear risk	Nothing suggestive but authors failed to respond to queries

Yavascaoglu 2007

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 120 Age: 18 to 72 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: non allergy to esmolol or lidocaine, chronic pain, pregnancy, patients receiving analgesics or sedatives
Interventions	1. Esmolol 0.05 mg/kg diluted with normal saline to 5 ml solution 2. Lidocaine 0.05 mg/kg diluted with normal saline to 5 ml solution Control: 5 ml NS
Outcomes	Pain Adverse events
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.05 mg/kg diluted to 5 ml with saline in awake state; 0.6 mg/kg over 10 seconds in asleep state No tourniquet application Duration of treatment (intervention drug): 30 seconds (in awake state) Central action of intervention drug assessed Pain assessed in awake/asleep patients
Risk of bias	

Yavascaoglu 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All syringes of test solution were prepared by an investigator who did not participate in the study evaluation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Injection pain response and withdrawal movements were assessed and graded by the same study blinded anaesthesiologist."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Yoon 2010

Methods	RCT, parallel design, multi-centre, Korea
Participants	Total patients: 96 Age: 3 to 10 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: asthma, neurologic deficits, psychiatric disorders, known allergies to opioids, sedatives or analgesics with 24 hours, rapid sequence induction
Interventions	1. 0.5 µg/kg remifentanil 1 minute before rocuronium 2. 0.5 µg/kg remifentanil after tourniquet application and over 10 seconds Control: 2 ml saline
Outcomes	Pain
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 30 seconds in one group Duration of treatment (intervention drug): 60 seconds and 30 seconds Peripheral and central action of intervention drug assessed Pain assessed in asleep patients

Yoon 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization schedule
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An investigator who did not know the purpose of the study graded the patient response to rocuronium"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Yoon 2011

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 86 Age: 18 to 69 years Gender: both male and female Inclusion criteria: ASA I-II, scheduled to undergo elective surgery with general anaesthesia Exclusion criteria: ASA III or greater, neurological deficits, pregnancy, anticipated difficult airway, body weight more than 20% of ideal weight, substance abuse, alcoholism and those receiving analgesics, sedatives, hypnotics, antidepressants, haemodynamic instabilities during induction
Interventions	Gabapentin 600 mg Control: placebo
Outcomes	Pain Adverse events
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg

Yoon 2011 (*Continued*)

	No tourniquet application Duration of treatment (intervention drug): 2 hours Central action of intervention drug assessed Pain assessed in asleep patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 patients were dropped from the study. Reason not mentioned
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

Zhang 2012

Methods	RCT, parallel design, single centre, China
Participants	Total patients: 160 Age: 18 to 50 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: neurological deficits, allergy to trial drugs, difficult venous access, patients receiving analgesics or sedatives
Interventions	1. Parecoxib 20 mg in 3 ml 2. Parecoxib 40 mg in 3 ml 3. Lidocaine 40 mg in 3 ml Control: 3 ml NS
Outcomes	Pain

Zhang 2012 (*Continued*)

Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 120 seconds Duration of treatment (intervention drug): 120 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All pretreatment drugs were prepared in 3 ml doses by personnel who were blinded to the study details"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Authors contacted. No response from authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	No
Other bias	Unclear risk	Nothing suggestive

ASA: American Society of Anesthesiologists (grade)
BMI: body mass index
DM: diabetes mellitus
HT: hypertension
ICP: intracranial pressure
IHD: ischaemic heart disease
IV: intravenous
LA: local anaesthetics
NaCl: sodium chloride
$NaHCO_3$: sodium bicarbonate
NMD: neuromuscular diseases
NS: normal saline
pt: patient
RCT: randomized controlled trial

SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kim 2008a	Not a RCT
Min 2011	Not a RCT
Shabana 2011	Not a RCT
Yoon 2010a	Not a RCT
Zeidan 2006	Not a RCT

RCT: randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Abu-Halaweh 2013

Methods	RCT, parallel design, single centre, Jordan
Participants	Total patients: 200 Age: adult patients, age not mentioned Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: not mentioned
Interventions	Control: 5 ml normal saline Lidocaine: 40 mg, diluted to 5 ml Remifentanil: 1 μg/kg diluted to 5 ml Fentanyl:1 μg/kg diluted to 5 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 60 seconds Duration of treatment (intervention drug): over 5 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Abu-Halaweh 2014

Methods	RCT, parallel design, single centre, Jordan
Participants	Total patients: 101 Age: child and adolescent patients 3 to 16 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: difficult intravenous access, a history of allergy to the study drugs, and receipt of analgesics or sedation in the preoperative period
Interventions	Control: 5 ml normal saline Lidocaine: 1% (0.5 mg/kg), diluted to 5 ml Remifentanil: 1 μg/kg diluted to 5 ml Fentanyl:1 μg/kg diluted to 5 ml
Outcomes	Pain Heart rate and mean arterial pressure
Notes	Paediatric patients Pain assessment: 4-point scale Rocuronium dose: 0.5 mg/kg Tourniquet application for 60 seconds Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Akcaboy 2012

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 120 Age:18 to 65 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: increased risk of pulmonary aspiration, neuromuscular disease, hypertension, anticipated difficulty with airway management, receiving analgesics and sedatives, having chronic pain and pregnancy
Interventions	Control: normal saline 5 ml Ephedrine: 70 μg/kg diluted to 5 ml Lidocaine: 0.5 mg/kg diluted to 5 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake patients

Ates 2014

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 180 Age: adult patients, 18 to 65 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: patients with chronic pain syndromes, neurological deficits, vascular diseases, difficult venous access, infection on the dorsum of their left hands, habituation to analgesics, sedatives or anti-anxiety drugs and patients who have a history of allergic reaction to the study drugs and who received analgesics or sedative drugs within the 24 hours before surgery
Interventions	Control: 5 ml normal saline Lidocaine: 40 mg, diluted to 5 ml Paracetamol: 50 mg diluted to 5 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet application for 120 seconds Duration of treatment (intervention drug): 120 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Aydin 2014

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 150 Age: adult patients, 18 to 75 years Gender: both male and female Inclusion criteria: ASA I, II, III elective surgery Exclusion criteria: patients having difficult venous access on the dorsum of the hand, an allergy to NSAIDs, hepatic renal and gastric disease, a history of peptic ulcer, coagulopathies, chronic pain or pregnancy, those who had used corticosteroids within the last 7 days or anticoagulants within the last month and those who had received analgesics or sedatives within the previous 24 hours were excluded from the study
Interventions	Control: oral starch tablets Dexketoprofen trometamol: oral 25 mg tablets
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg over 5 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Chiarella 2003

Methods	RCT, parallel design, single centre
Participants	Total patients: 250 Age: > 18 years Gender: both males and females Inclusion criteria: not specified Exclusion criteria: < 18 years, allergy to any anaesthetic medication, ASA IV-V, inability to provide consent
Interventions	Control: rocuronium 10 mg Rocuronium + 8.4% sodium bicarbonate 2 ml Rocuronium + fentanyl 100 µg Rocuronium + lidocaine 2%
Outcomes	Pain
Notes	Adult patients Pain assessment: 5-point scale Rocuronium dose: 10 mg No tourniquet application Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake patients **Included in 'studies awaiting classification' as data not provided in numbers or percentage for each pain score. Authors did not respond to queries sent via emails**

Cho 2014

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 80 Age: adult patients, 20 to 70 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: patients those who had been administered an analgesic or sedative on the day of the surgery were excluded, along with patients whose periphery veins were difficult to secure, patients with an allergic reaction to local anaesthetics, patients with chronic pain and pregnant patients
Interventions	Control: 1.5 ml normal saline Palonosetron: 0.075 mg
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg over 30 seconds Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Choi 2012

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 95 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: known allergy to propofol, rocuronium, lidocaine or remifentanil, or who had a neuromuscular disorder or cognitive impairment
Interventions	Control: saline Remifentanil: 1 μg/kg Lidocaine: 1.5 mg/kg
Outcomes	Pain
Notes	Adult patients Pain due to both propofol and rocuronium was assessed Pain assessment: 10-point verbal numeric rating scale Rocuronium dose: 0.6 mg/kg Tourniquet applied Duration of treatment (intervention drug): 60 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients for propofol and asleep state for rocuronium

Honca 2013

Methods	RCT, parallel design, multi-centre, Turkey
Participants	Total patients: 200 Age: 18 to 50 years Gender: females Inclusion criteria: ASA I, II, gynaecological surgery Exclusion criteria: patients with neurological deficits, thrombophlebitis, chronic pain syndrome, difficult venous access or clinical conditions that contraindicated the administration of any of the drugs used in the study
Interventions	Tramadol: 50 mg diluted to 3 ml Meperidine: 40 mg diluted to 3 ml Sufentanil: 10 μg diluted to 3 ml Lidocaine: 30 mg diluted to 3 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg Tourniquet was applied Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in awake patients

Hwang 2004

Methods	RCT, parallel design, Korea
Participants	Total patients: 62 Gender: both males and females Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	Control: rocuronium 0.6 mg/kg alone Rocuronium + lidocaine 2 ml Rocuronium + equivalent volume sodium bicarbonate
Outcomes	Pain
Notes	Insufficient data to determine inclusion eligibility. Authors to be contacted for further information

Jeon 2013

Methods	RCT, parallel design, multi-centre, Korea
Participants	Total patients: 140 Age: 20 to 75 years Gender: both males and females Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: patients with difficult venous access on the dorsum of the hand, a known allergy to lidocaine or ketorolac, chronic pain, pregnancy and those who had received analgesics or sedatives within the previous 24 hours
Interventions	Control: saline Lidocaine: 20 mg Ketorolac: 10 mg Lidocaine + ketorolac: 20 mg + 10 mg, respectively
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg, over 10 seconds Tourniquet was applied Duration of treatment (intervention drug): 20 seconds Peripheral action of intervention drug assessed Pain assessed in asleep patients

Jung 2014

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 120 Age: adult patients, 20 to 60 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: poor venous access, diabetes, allergies to anaesthetic medications, neurologic deficit, psychiatric disorder, vasculitis, thrombosis, prior administration of analgesics within 24 hours, or pregnancy
Interventions	Control: 3 ml normal saline Lidocaine: 40 mg diluted to 3 ml Ketamine: 0.5 mg/kg diluted to 3 ml Remifentanil: 1 μg/kg diluted to 3 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg over 10 seconds Duration of treatment (intervention drug): 60 seconds Central action of intervention drug assessed Pain assessed in asleep patients

Kim 2013

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 205 Age: adult patients, 18 to 68 years Gender: both male and female Inclusion criteria: ASA I, II, elective surgery Exclusion criteria: the regular use of sedatives or analgesics; an allergy to lidocaine; a pre-existing movement disorder; pre-existing drug abuse; inability to co-operate or give informed consent; any anticipated difficulty in obtaining an airway; thrombophlebitis (or any other pain-causing lesion); the presence of chronic obstructive pulmonary disease (COPD); or any contraindication to the administration of N_2O (e.g. pneumothorax)
Interventions	Control: 100% oxygen for 1 minute, 3 ml normal saline Lidocaine: 100% oxygen, 3 ml 0.5 mg/kg lidocaine Nitrous oxide: 67% nitrous oxide/oxygen
Outcomes	Pain
Notes	Adult patients Pain assessment: 4-point scale Rocuronium dose: 0.6 mg/kg over 10 seconds Tourniquet application for 1 minute Duration of treatment (intervention drug): 60 seconds Central action of intervention drug assessed

	Pain assessed in asleep patients

Lee 2009a

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 75 Age: adults Gender: both male and female Inclusion criteria: translation required Exclusion criteria: translation required
Interventions	Control: rocuronium 0.6 mg/kg Rocuronium 0.6 mg/kg plus 2 ml of 2% lidocaine Rocuronium 0.6 mg/kg plus same volume 8.4% sodium bicarbonate
Outcomes	Pain Mean arterial pressure Heart rate
Notes	Adults patients Pain assessment: in asleep state Rocuronium dose: 0.6 mg/kg In 'Studies awaiting classification' as translation needed to provide sufficient data

Lim 2006

Methods	RCT, parallel design, single centre, Korea
Participants	Total patients: 80 Age: adult Gender: females Inclusion criteria: ASA I and II, elective surgery Exclusion criteria: translation required
Interventions	Control: 2 ml normal saline 2 ml 2% lidocaine 2 ml remifentanil 0.5 μg/kg 2 ml remifentanil 1 μg/kg
Outcomes	Pain
Notes	Adult female patients undergoing gynaecological procedures Pain assessment: 4-point scale Rocuronium dose: 0.7 mg/kg In 'Studies awaiting assessment' as translation needed for sufficient data

Prasanna 2005

Methods	RCT, parallel design, single centre, India
Participants	Total patients: 120 Age: 18 to 60 years Gender: females Inclusion criteria: scheduled for elective surgery Exclusion criteria: history of allergy, major medical illness and difficult intravenous access
Interventions	Control: rocuronium 0.6 mg/kg diluted to 10 ml Lidocaine 40 mg + rocuronium 0.6 mg/kg diluted to 10 ml Lidocaine 20 mg + rocuronium 0.6 mg/kg diluted to 10 ml 2 cc sodium bicarbonate + rocuronium 0.6 mg/kg diluted to 10 ml
Outcomes	Pain
Notes	Adult patients Pain assessment: 5-point scale Rocuronium dose: 0.6 mg/kg Central action of intervention drug assessed Pain assessed in awake patients In 'Studies awaiting classification' as insufficient data for analysis

Sari 2008

Methods	RCT, parallel design, single centre, Turkey
Participants	Total patients: 102 Age: 18 to 60 years Gender: both male and female Inclusion criteria: ASA I, II, elective procedures under general anaesthesia Exclusion: anticipated difficult airway, BMI > 30 kg/m^2, or weighing less than 50 kg, chronic pain, severe chronic obstructive pulmonary disease, asthma, reactive airway disease, history of neuropsychiatric or neurologic disease, history of allergy to any study drug, pregnancy, patients requiring rapid induction, hepatic and renal dysfunction, history of thrombophlebitis, muscle disease, patients receiving analgesics or sedatives within last 24 hours
Interventions	Control: 2 ml saline Remifentanil: 2 ml (0.02 mg) Fentanyl: 2 ml (0.1 mg)
Outcomes	Pain
Notes	Adult patients Pain assessment: 5-point scale Rocuronium dose: 10 mg Duration of treatment (intervention drug): 30 seconds Central action of intervention drug assessed Pain assessed in awake patients In 'Studies awaiting classification' as insufficient data available for analysis

ASA: American Society of Anesthesiologists
BMI: body mass index
COPD: chronic obstructive pulmonary disease
NSAID: non-steroidal anti-inflammatory drug
RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Non-pharmacological interventions versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Bolus/speed	3	391	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.02, 2.75]
1.2 Compression versus no compression	2	214	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.08, 14.83]
1.3 Warming of injection site	1	90	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.72]

Comparison 2. Rocuronium admixtures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Dexmedetomidine plus lidocaine	1	90	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.59]
1.2 Rocuronium plus sodium bicarbonate	5	433	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.11, 0.32]
1.3 Rocuronium plus lidocaine	2	103	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.58, 1.25]
1.4 Rocuronium plus lidocaine plus sodium bicarbonate	2	101	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.08, 0.48]
1.5 Rocuronium plus saline	5	420	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.09, 0.74]
1.6 Rocuronium plus lidocaine plus saline	1	50	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.25, 0.88]

Comparison 3. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Fentanyl	7	514	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.26, 0.70]
1.2 Remifentanil	7	494	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.04, 0.26]
1.3 Sufentanil	1	40	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.16, 0.62]
1.4 Alfentanil	4	316	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.14, 0.31]
1.5 Hydromorphone	1	126	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.22]
1.6 Tramadol	3	220	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.12, 1.46]

Comparison 4. Anaesthetics versus placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Thiopentone	1	90	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.03, 0.51]
1.2 Ketamine	7	561	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.19, 0.63]
1.3 Sevoflurane	1	72	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.14, 0.49]
1.4 Nitrous oxide	2	143	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.06, 0.48]
1.5 Lidocaine	29	2256	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.17, 0.31]
1.6 Lidocaine in children	3	192	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.07, 0.77]

Comparison 5. Antiemetics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Ondansetron	6	380	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.33, 0.52]
1.2 Metoclopramide	2	82	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.15, 0.50]

Comparison 6. Analgesics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Ketorolac	1	54	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.45]
1.2 Acetaminophen	1	79	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.30, 1.09]
1.3 Parecoxib	1	120	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.15, 0.47]
1.4 Gabapentin	1	82	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.34, 1.07]

Comparison 7. Antihistamines versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Pheniramine	1	120	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.55, 0.92]
1.2 Diphenhydramine	1	60	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.03, 0.39]

Comparison 8. Miscellaneous drugs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Magnesium sulphate	2	300	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.04, 1.73]
1.2 Esmolol	1	80	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.87]
1.3 Dexmedetomidine	3	210	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.39, 0.77]
1.4 Sodium bicarbonate	1	100	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.03, 0.32]
1.5 Nafamostat	1	90	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.05, 0.37]
1.6 Ephedrine	1	60	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.25, 0.99]

Comparison 9. Adverse events

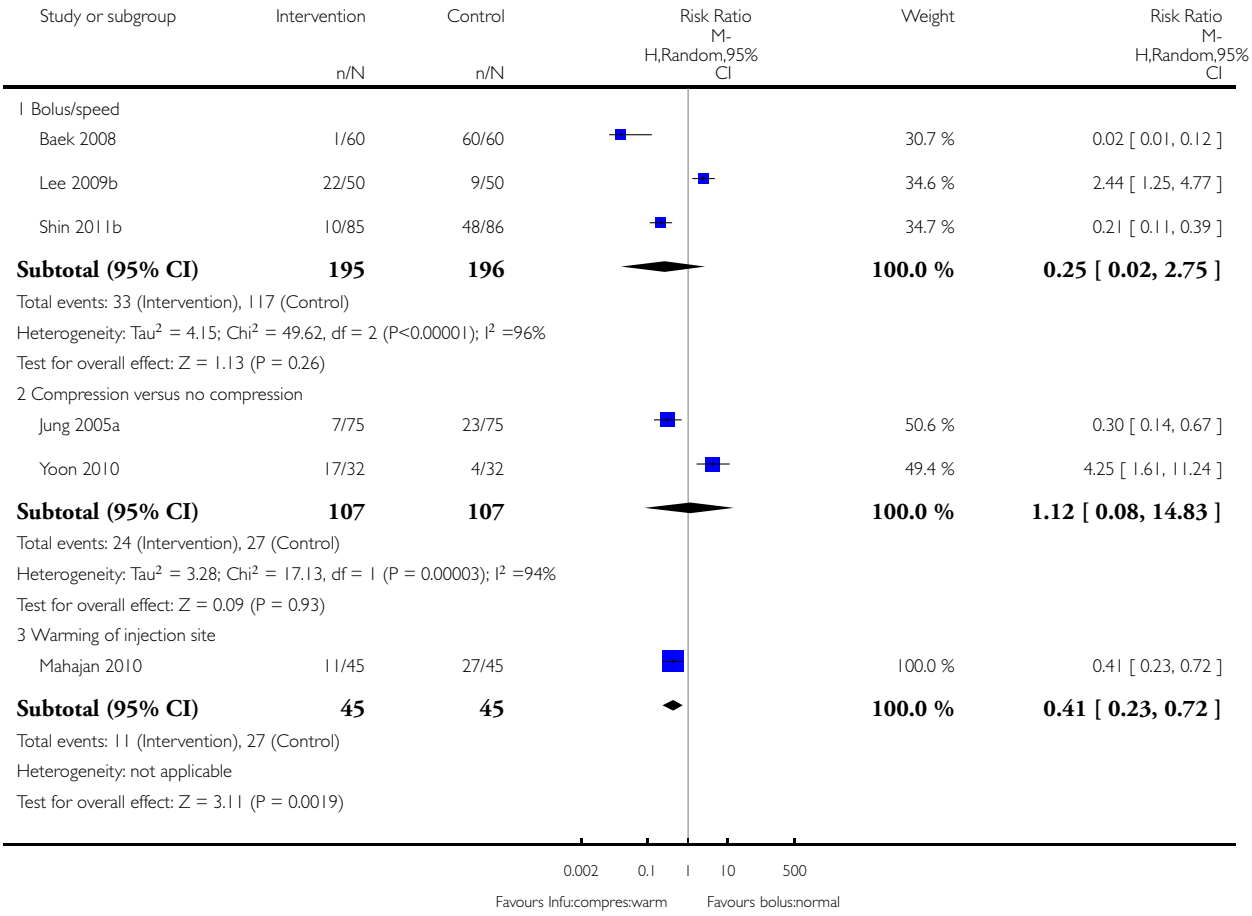
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breath holding	2	279	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.12, 11.65]
2 Chest tightness	1	90	Odds Ratio (M-H, Fixed, 95% CI)	2.61 [0.12, 56.03]
3 Cough	5	529	Odds Ratio (M-H, Fixed, 95% CI)	9.00 [2.77, 29.29]
4 Pain on injection	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.09, 2.46]

Analysis 1.1. Comparison 1 Non-pharmacological interventions versus placebo, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 1 Non-pharmacological interventions versus placebo

Outcome: 1 Pain

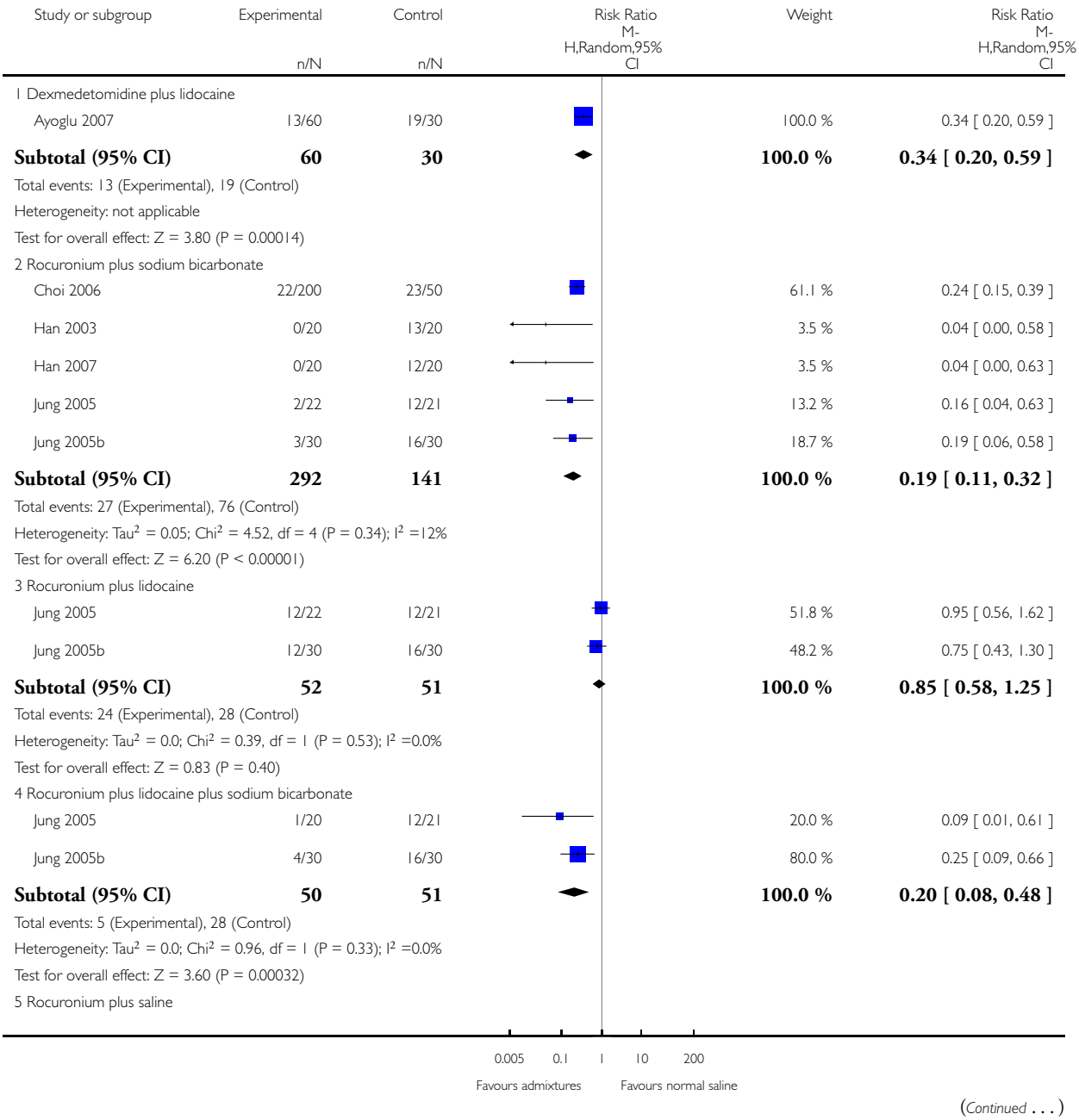


Analysis 2.1. Comparison 2 Rocuronium admixtures, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 2 Rocuronium admixtures

Outcome: 1 Pain



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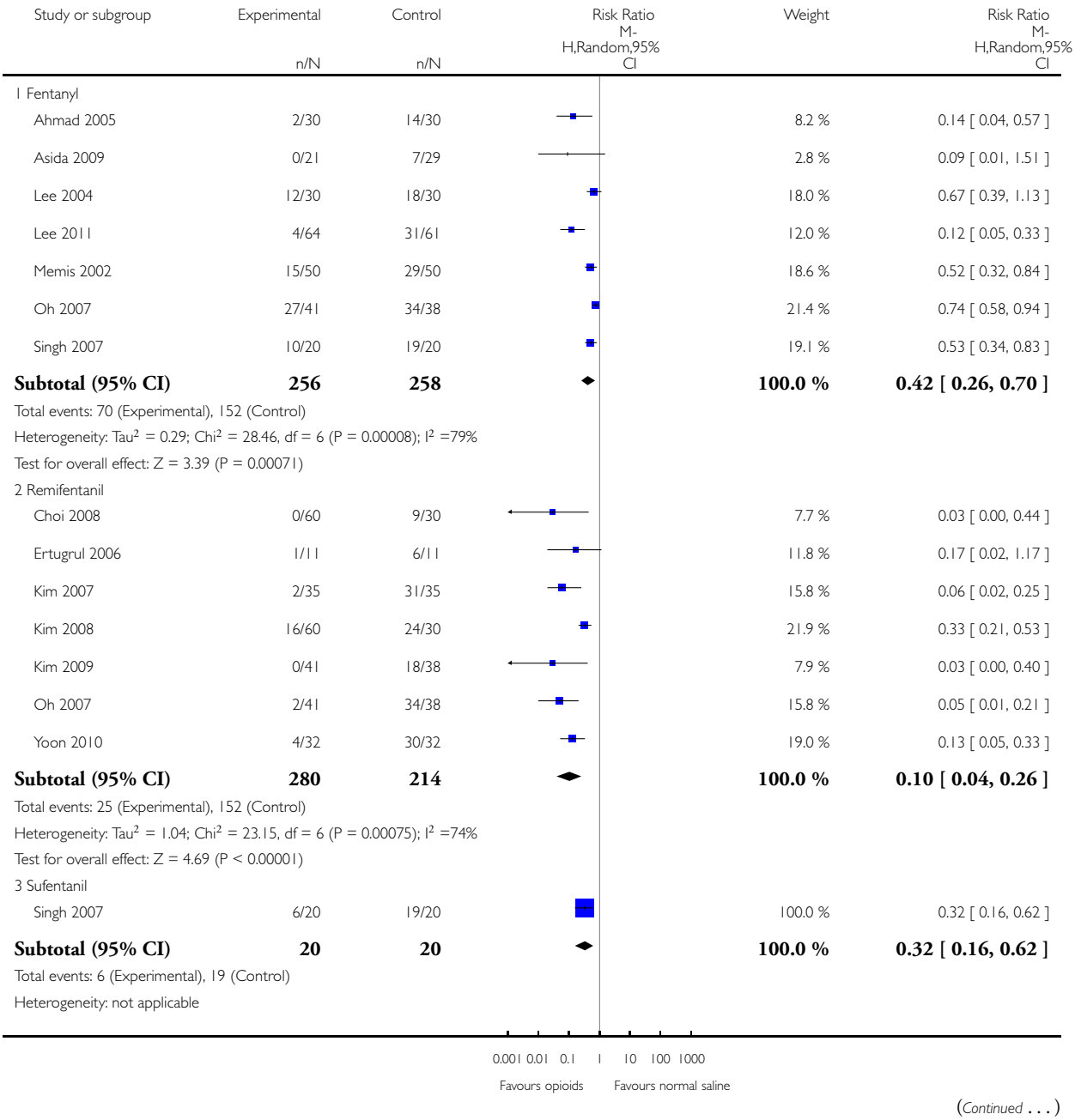
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Han 2003	9/20	13/20		21.3 %	0.69 [0.39, 1.24]
Han 2007	10/20	12/20		21.4 %	0.83 [0.47, 1.47]
Lee 2009c	4/50	17/50		18.8 %	0.24 [0.09, 0.65]
Park 2006	7/60	26/30		20.6 %	0.13 [0.07, 0.27]
Tuncali 2004	3/100	30/50		18.0 %	0.05 [0.02, 0.16]
Subtotal (95% CI)	**250**	**170**		**100.0 %**	**0.26 [0.09, 0.74]**
Total events: 33 (Experimental), 98 (Control)					
Heterogeneity: Tau^2 = 1.25; Chi^2 = 39.26, df = 4 (P<0.00001); I^2 =90%					
Test for overall effect: Z = 2.51 (P = 0.012)					
6 Rocuronium plus lidocaine plus saline					
Kwak 2004	8/25	17/25		100.0 %	0.47 [0.25, 0.88]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**0.47 [0.25, 0.88]**
Total events: 8 (Experimental), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.34 (P = 0.019)					

Analysis 3.1. Comparison 3 Opioids versus placebo, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 3 Opioids versus placebo

Outcome: 1 Pain



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Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 3.34 (P = 0.00085)					
4 Alfentanil					
Kim 2008	3/30	24/30		13.6 %	0.13 [0.04, 0.37]
Kim 2009	2/36	18/38		8.3 %	0.12 [0.03, 0.47]
Oh 2007	10/44	34/38		52.1 %	0.25 [0.15, 0.44]
Turan 2003	6/50	29/50		26.0 %	0.21 [0.09, 0.45]
Subtotal (95% CI)	**160**	**156**		**100.0 %**	**0.21 [0.14, 0.31]**
Total events: 21 (Experimental), 105 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.13, df = 3 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 7.74 (P < 0.00001)					
5 Hydromorphone					
Lee 2011	1/65	31/61		100.0 %	0.03 [0.00, 0.22]
Subtotal (95% CI)	**65**	**61**		**100.0 %**	**0.03 [0.00, 0.22]**
Total events: 1 (Experimental), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.50 (P = 0.00047)					
6 Tramadol					
Alanoglu 2007	3/30	16/30		29.3 %	0.19 [0.06, 0.58]
Eun 2005	18/30	16/30		36.4 %	1.13 [0.72, 1.75]
Memis 2002	8/50	29/50		34.3 %	0.28 [0.14, 0.54]
Subtotal (95% CI)	**110**	**110**		**100.0 %**	**0.41 [0.12, 1.46]**
Total events: 29 (Experimental), 61 (Control)					
Heterogeneity: Tau^2 = 1.09; Chi^2 = 19.55, df = 2 (P = 0.00006); I^2 =90%					
Test for overall effect: Z = 1.38 (P = 0.17)					

Analysis 4.1. Comparison 4 Anaesthetics versus placebo/control, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 4 Anaesthetics versus placebo/control

Outcome: 1 Pain

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Thiopentone					
Park 2005	2/45	16/45		100.0 %	0.13 [0.03, 0.51]
Subtotal (95% CI)	**45**	**45**		**100.0 %**	**0.12 [0.03, 0.51]**
Total events: 2 (Experimental), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.89 (P = 0.0039)					
2 Ketamine					
Abdusoglu 2011	10/27	11/27		14.8 %	0.91 [0.47, 1.78]
Akkaya 2008	25/40	33/40		17.4 %	0.76 [0.57, 1.00]
Cheong 2003	3/40	16/20		11.2 %	0.09 [0.03, 0.28]
Choi 2005	4/40	10/20		11.9 %	0.20 [0.07, 0.56]
Kirpit 2010	6/30	16/30		13.8 %	0.38 [0.17, 0.83]
Liou 2003	9/48	36/49		15.2 %	0.26 [0.14, 0.47]
Mahajan 2005	14/100	26/50		15.7 %	0.27 [0.15, 0.47]
Subtotal (95% CI)	**325**	**236**		**100.0 %**	**0.34 [0.19, 0.63]**
Total events: 71 (Experimental), 148 (Control)					
Heterogeneity: Tau^2 = 0.53; Chi^2 = 39.55, df = 6 (P<0.00001); I^2 =85%					
Test for overall effect: Z = 3.46 (P = 0.00055)					
3 Sevoflurane					
Park 2011	11/57	11/15		100.0 %	0.26 [0.14, 0.49]
Subtotal (95% CI)	**57**	**15**		**100.0 %**	**0.26 [0.14, 0.49]**
Total events: 11 (Experimental), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.27 (P = 0.000019)					
4 Nitrous oxide					
Kwak 2010	0/32	6/31		14.2 %	0.07 [0.00, 1.27]
Sharma 2010	3/40	16/40		85.8 %	0.19 [0.06, 0.59]
Subtotal (95% CI)	**72**	**71**		**100.0 %**	**0.16 [0.06, 0.48]**
Total events: 3 (Experimental), 22 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.36, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 3.31 (P = 0.00092)					

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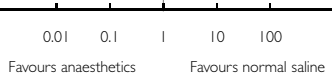
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
5 Lidocaine					
Ahmad 2005	8/30	14/30		4.9 %	0.57 [0.28, 1.16]
Akkaya 2008	5/40	33/40		4.4 %	0.15 [0.07, 0.35]
Alanoglu 2007	3/30	16/30		3.4 %	0.19 [0.06, 0.58]
Asida 2009	2/25	7/29		2.5 %	0.33 [0.08, 1.45]
Ayoglu 2007	6/30	19/30		4.7 %	0.32 [0.15, 0.68]
Byun 2005	7/30	27/30		5.1 %	0.26 [0.13, 0.50]
Cheong 2000	9/60	18/30		5.0 %	0.25 [0.13, 0.49]
Dogru 2002	0/30	8/30		1.0 %	0.06 [0.00, 0.98]
Ertugrul 2006	0/11	6/11		1.0 %	0.08 [0.00, 1.22]
Eun 2005	1/30	16/30		1.7 %	0.06 [0.01, 0.44]
Hwang 2003	31/200	33/50		6.1 %	0.23 [0.16, 0.34]
Ikram 2008	0/60	6/60		0.9 %	0.08 [0.00, 1.34]
Jeon 2010	9/39	17/39		5.0 %	0.53 [0.27, 1.04]
Kaya 2004	0/30	20/30		1.0 %	0.02 [0.00, 0.39]
Kelsaka 2002	2/20	14/20		2.8 %	0.14 [0.04, 0.55]
Kim 2002	4/21	21/21		4.4 %	0.21 [0.09, 0.48]
Kirpit 2010	2/30	16/30		2.7 %	0.13 [0.03, 0.50]
Kwak 2004	0/25	17/25		1.0 %	0.03 [0.00, 0.45]
Lee 2004	15/60	18/30		5.6 %	0.42 [0.25, 0.71]
Lee 2009b	6/50	22/50		4.5 %	0.27 [0.12, 0.61]
Lee 2009c	16/50	17/50		5.4 %	0.94 [0.54, 1.65]
Memis 2002	2/50	29/50		2.7 %	0.07 [0.02, 0.27]
Reddy 2001	2/20	18/20		2.9 %	0.11 [0.03, 0.42]
Shevchenko 1999	19/50	39/50		6.1 %	0.49 [0.33, 0.71]
Singh 2007	0/20	19/20		1.0 %	0.03 [0.00, 0.40]
Turan 2003	2/50	29/50		2.7 %	0.07 [0.02, 0.27]
Wee 2004	10/90	16/30		5.0 %	0.21 [0.11, 0.41]
Yavascaoglu 2007	5/40	9/40		3.8 %	0.56 [0.20, 1.51]
Zhang 2012	2/40	24/40		2.7 %	0.08 [0.02, 0.33]
Subtotal (95% CI)	**1261**	**995**		**100.0 %**	**0.23 [0.17, 0.31]**
Total events: 168 (Experimental), 548 (Control)					



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Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.34; Chi^2 = 80.36, df = 28 (P<0.00001); I^2 =65%					
Test for overall effect: Z = 9.63 (P < 0.00001)					
6 Lidocaine in children					
Kim 2002	4/21	21/21		39.7 %	0.21 [0.09, 0.48]
Kwak 2010	0/25	17/25		13.1 %	0.03 [0.00, 0.45]
Shevchenko 1999	19/50	39/50		47.1 %	0.49 [0.33, 0.71]
Subtotal (95% CI)	**96**	**96**		**100.0 %**	**0.24 [0.07, 0.77]**
Total events: 23 (Experimental), 77 (Control)					
Heterogeneity: Tau^2 = 0.71; Chi^2 = 9.21, df = 2 (P = 0.01); I^2 =78%					
Test for overall effect: Z = 2.40 (P = 0.016)					

Analysis 5.1. Comparison 5 Antiemetics versus placebo, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 5 Antiemetics versus placebo

Outcome: 1 Pain

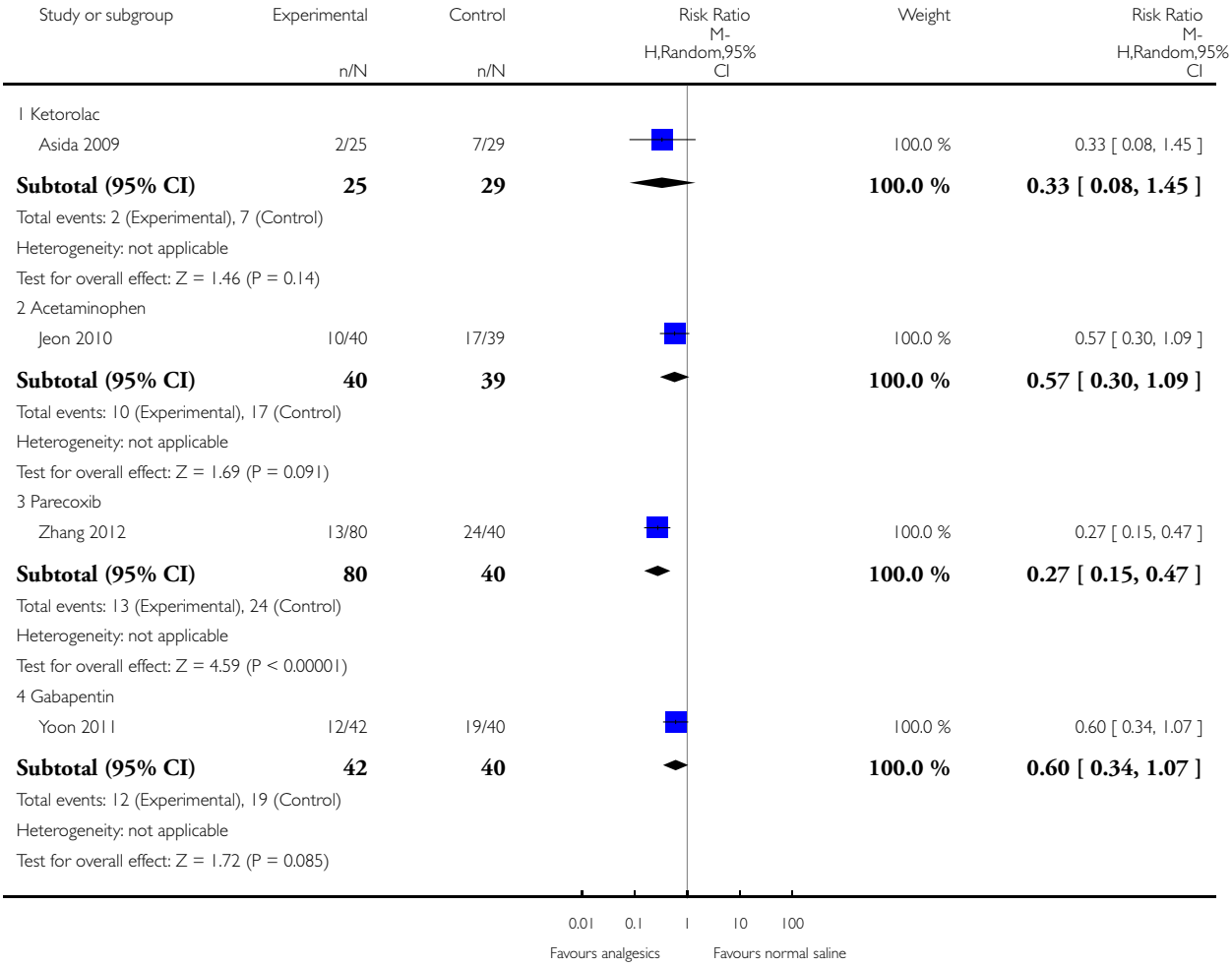
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Ondansetron					
Eun 2005	5/30	16/30		7.5 %	0.31 [0.13, 0.74]
Kelsaka 2002	8/20	14/20		15.2 %	0.57 [0.31, 1.05]
Ki 2005	21/60	17/20		36.7 %	0.41 [0.28, 0.61]
Lee 2004	10/30	18/30		16.4 %	0.56 [0.31, 1.00]
Memis 2002	8/50	29/50		12.2 %	0.28 [0.14, 0.54]
Reddy 2001	6/20	18/20		12.0 %	0.33 [0.17, 0.66]
Subtotal (95% CI)	**210**	**170**		**100.0 %**	**0.41 [0.33, 0.52]**
Total events: 58 (Experimental), 112 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.37$, df = 5 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 7.31 (P < 0.00001)					
2 Metoclopramide					
Byun 2005	8/30	27/30		95.4 %	0.30 [0.16, 0.54]
Ertugrul 2006	0/11	6/11		4.6 %	0.08 [0.00, 1.22]
Subtotal (95% CI)	**41**	**41**		**100.0 %**	**0.28 [0.15, 0.50]**
Total events: 8 (Experimental), 33 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 1 (P = 0.32); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.24 (P = 0.000023)					

Analysis 6.1. Comparison 6 Analgesics versus placebo, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 6 Analgesics versus placebo

Outcome: 1 Pain

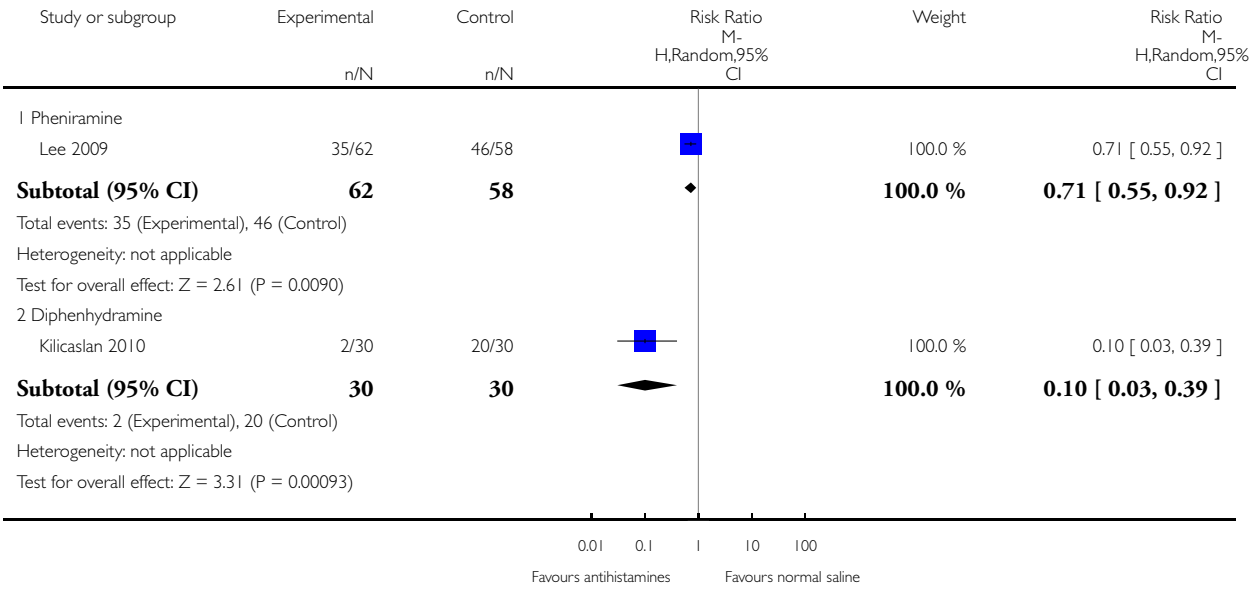


Analysis 7.1. Comparison 7 Antihistamines versus placebo, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 7 Antihistamines versus placebo

Outcome: 1 Pain

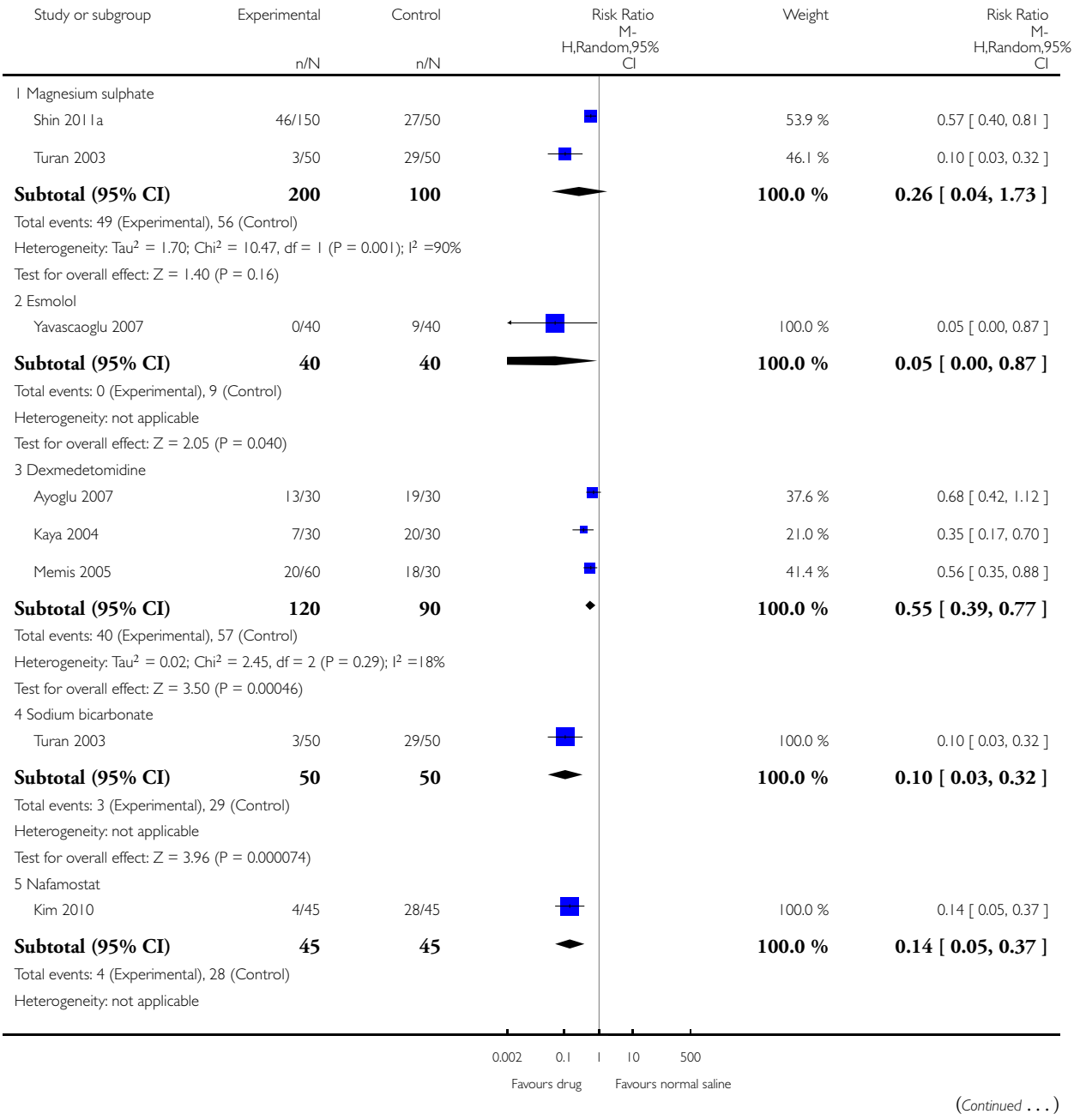


Analysis 8.1. Comparison 8 Miscellaneous drugs versus placebo, Outcome 1 Pain.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 8 Miscellaneous drugs versus placebo

Outcome: 1 Pain



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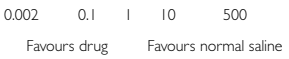
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 3.96 (P = 0.000074)					
6 Ephedrine					
Kirpit 2010	8/30	16/30		100.0 %	0.50 [0.25, 0.99]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**0.50 [0.25, 0.99]**
Total events: 8 (Experimental), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.99 (P = 0.046)					



Analysis 9.1. Comparison 9 Adverse events, Outcome 1 Breath holding.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 9 Adverse events

Outcome: 1 Breath holding

Study or subgroup	Remifentanil n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kim 2009	1/77	0/38		46.4 %	1.51 [0.06, 37.94]
Oh 2007	1/126	0/38		53.6 %	0.92 [0.04, 23.05]
Total (95% CI)	**203**	**76**		**100.0 %**	**1.19 [0.12, 11.65]**
Total events: 2 (Remifentanil), 0 (Control)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 0.15 (P = 0.88)					
Test for subgroup differences: Not applicable					

Analysis 9.2. Comparison 9 Adverse events, Outcome 2 Chest tightness.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 9 Adverse events

Outcome: 2 Chest tightness

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Choi 2008	2/60	0/30		100.0 %	2.61 [0.12, 56.03]
Total (95% CI)	**60**	**30**		**100.0 %**	**2.61 [0.12, 56.03]**

Total events: 2 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

Analysis 9.3. Comparison 9 Adverse events, Outcome 3 Cough.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 9 Adverse events

Outcome: 3 Cough

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Choi 2008	11/60	0/30		15.5 %	14.17 [0.81, 249.23]
Kim 2007	5/35	0/35		12.2 %	12.80 [0.68, 241.03]
Kim 2008	4/60	0/30		17.7 %	4.86 [0.25, 93.27]
Kim 2009	11/77	0/38		16.4 %	13.32 [0.76, 232.31]
Oh 2007	17/126	1/38		38.3 %	5.77 [0.74, 44.87]
Total (95% CI)	**358**	**171**		**100.0 %**	**9.00 [2.77, 29.29]**

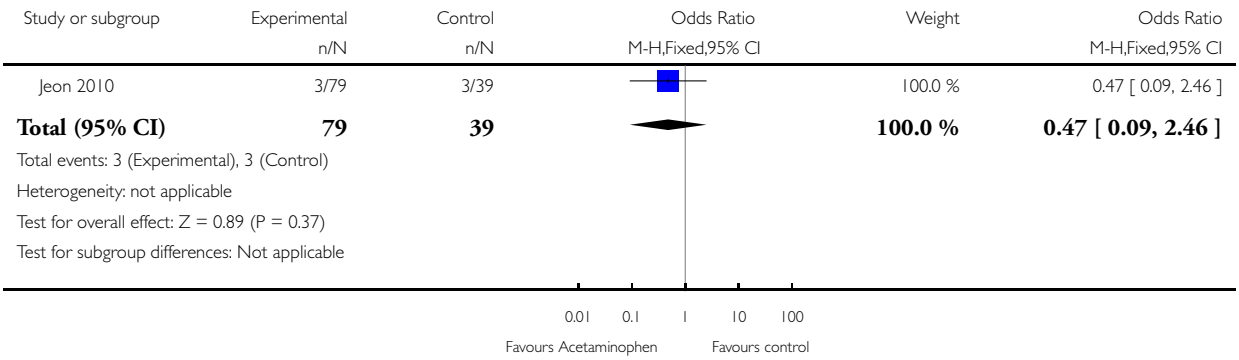
Total events: 48 (Experimental), 1 (Control)
Heterogeneity: Chi^2 = 0.57, df = 4 (P = 0.97); I^2 =0.0%
Test for overall effect: Z = 3.65 (P = 0.00026)
Test for subgroup differences: Not applicable

Analysis 9.4. Comparison 9 Adverse events, Outcome 4 Pain on injection.

Review: Pharmacological and non-pharmacological interventions for reducing rocuronium bromide induced pain on injection in children and adults

Comparison: 9 Adverse events

Outcome: 4 Pain on injection



APPENDICES

Appendix 1. Pharmacological and non-pharmacological interventions

Pharmacological

Opioids

- Fentanyl
- Alfentanil
- Sufentanil
- Remifentanil
- Tramadol
- Hydromorphone

Anaesthetics

- Lidocaine
- Thiopentone
- Ketamine
- Thiopentone
- Sevoflurane
- Nitrous oxide

Antiemetics

- Metoclopramide
- Ondansetron

Analgesics

- Ketorolac
- Acetaminophen
- Parecoxib
- Gabapentin

Antihistamines

- Pheniramine
- Diphenhydramine

Admixtures

- Rocuronium with lidocaine or saline or sodium bicarbonate and dexmedetomidine plus lidocaine

Miscellaneous

- Magnesium sulphate
- Esmolol
- Dexmedetomidine
- 8.4% sodium bicarbonate
- Nafamostat
- Ephedrine

Non-pharmacological

- Temperature
- Saline admixture or dilution
- Massaging or rubbing at the site of injection
- Speed of injection

Appendix 2. Pain scales used in various studies

Five-point scale for pain assessment (patient-reported pain)		
Pain score	Severity of pain	Patient's response
0	None	No pain or discomfort reported on questioning
1	Mild	Pain/discomfort reported as mild when questioned
2	Moderate	Pain/discomfort reported as moderate when questioned
3	Severe	Pain/discomfort reported spontaneously by patient and stated to be severe when questioned
4	Very severe	Pain/discomfort associated with strong vocal response, hand or arm withdrawal, facial grimacing, crying, reported to be very severe

Four-point scale for pain assessment (limb movement)	
Pain score	Patient's response
1	No response
2	Movement at wrist only
3	Movement/withdrawal involving arm only (elbow/shoulder)
4	Generalized response, movement/withdrawal in more than one extremity

Appendix 3. Search strategies

Database: Ovid MEDLINE(R) (1966 to date)

1 rocuronium.af.

2 pain/ or exp Injections/ae, co or ((injection or induced or alleviate or reduce) adj3 pain).mp. or pain.ti,ab. or (lidocaine* or lidocain* or fentanyl or alfentanil or sufentanil or remifentanil or ondansetron or metoclopramide or tramadol or magnesium sulphate or sodium bicarbonate or thiopental sodium or dexmedetomidine or esmolol or dilute*).mp. or ((drugs or ((pharmacological or non-pharmacological) adj3 intervention*)) and pain).mp.

3 1 and 2

4 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

5 1 and 4

6 3 or 5

Database: EMBASE (Ovid SP) (1980 to date)

1. exp rocuronium/ or rocuronium.af.
2. pain/ or exp Injections/ae, co or patient satisfaction/ or ((injection or induced or alleviate or reduce) adj3 pain).mp. or pain.ti,ab. or (lidocaine* or lidocain* or fentanyl or alfentanil or sufentanil or remifentanil or ondansetron or metoclopramide or tramadol or magnesium sulphate or sodium bicarbonate or thiopental sodium or dexmedetomidine or esmolol or dilute*).mp. or ((drugs or ((pharmacological or non-pharmacological) adj3 intervention*)) and pain).mp.
3. 1 and 2
4. ((((singl* or doubl* or tripl*) adj3 blind) or crossover).ti,ab. or multicenter.ab. or placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animal not (human and animal)).sh.
5. 3 and 4

Database: CENTRAL

#1 rocuronium
#2 MeSH descriptor Pain, this term only
#3 MeSH descriptor Injections explode all trees
#4 MeSH descriptor Patient Satisfaction explode all trees
#5 ((injection or induced or alleviate or reduce) near pain) or pain:ti,ab or (lidocaine* or lidocain* or fentanyl or alfentanil or sufentanil or remifentanil or ondansetron or metoclopramide or tramadol or magnesium sulphate or sodium bicarbonate or thiopental sodium or dexmedetomidine or esmolol or dilute*) or ((drugs or ((pharmacological or non-pharmacological) near intervention*)) and pain)
#6 (#2 OR #3 OR #4 OR #5)
#7 (#1 AND #6)

Appendix 4. Study selection and Study eligibility form

Study selection

First author	Journal/conference proceedings etc.	Year

Study eligibility

RCT	Relevant participants	Relevant interventions	Relevant outcomes
	(All age groups)	(Any pharmacological or non-pharmacological method used to reduce pain)	(Intensity of pain on rocuronium (Intensity of pain on rocuronium
	(Pain score defined)		(Incidence of pain)
			(Patient satisfaction)
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear

(*Continued*)

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the reviews, record below the information to be inserted into 'Tables of excluded studies'.

Appendix 5. Eligible trials form

Code of each paper	Author(s)	Journal /conference Proceedings etc.	Year
A			
B			
C			
D			

Appendix 6. Data extraction form

Outcomes	Reported in paper (circle)	Information available in paper
Primary outcome: pain score	Yes/No	Yes/No
Secondary outcome 1. Incidence of pain	Yes/No	Yes/No

For continuous data (with a separate copy for each subgroup)					
Code of paper	Outcome described in text	Unit of measurement	Intervention group	Control group	Details of outcome only
			n Mean (SD)	n Mean (SD)	

For dichotomous data (with a separate copy for each subgroup)					
Code of paper	Outcome described in text	Unit of measurement	Intervention group	Control group	Details of outcome only
			n (%)	n (%)	

Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by using a formula (this should be stated and the formula given). In general if results are not reported in paper(s) are obtained this should be made clear here to be cited in review.
Freehand space for writing actions such as contact with study author and changes.

Reference to other trials
Did this report include any reference to published reports of potentially eligible trials not identified for this review?

First author	Journal/conference proceeding etc.	Year of publication

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list of contact name and details.

Trial characteristics	Further details
Single centre/multi-centre	
Country/countries	
How was participant eligibility defined?	
How many people were randomized?	
Number of participants in each intervention group?	
Number of participants who received intended treatment	
Number of participants who were analysed	
Drug treatment(s) used	

(*Continued*)

Dose/frequency of administration	
Duration of treatment (state weeks/months, etc.; if cross-over trial give length of time in each arm)	
Median (range) length of follow-up reported in this paper (state weeks/months or years or if not stated)	
Time points when measurements were taken during the study	
Time points reported in the study	
Time points you are using in RevMan 5.3	
Trial design (e.g. parallel/cross-over)	
Other	

Appendix 7. Quality assessment of eligible trials form

Methodological quality	**Comments**	**Grade (circle)**
Random sequence generation		Low risk of bias (random) High risk of bias (e.g. alternate) Unclear
State here method used to generate allocation and reasons for grading		
Comment on allocation by review authors or included study quote concerning allocation		
Allocation concealment		Low risk of bias (random) High risk of bias (e.g. alternate) Unclear
State here method used to generate allocation and reasons for grading		
Comment on allocation by review authors or included study quote concerning allocation		
Blinding		

(*Continued*)

Participant	Yes/No	
Outcome assessor	Yes/No	
Other (please specify)	Yes/No	
Comment on blinding by review author or included study quote concerning allocation		
Intention-to-treat		
An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not		
All participants entering trial	15% or fewer excluded More than 15% excluded Not analysed as 'intention-to-treat'	
Were withdrawals described?	Yes/No/Unclear	
Discuss if appropriate		

CONTRIBUTIONS OF AUTHORS

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Co-ordinating the review: HP

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Screening retrieved papers against inclusion criteria: HP, GPS

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Extracting data from papers: HP, GPS, MAS

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Providing additional data about papers: HP, ZA

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RevMan statistical data: HP, MK

Other statistical analysis not using RevMan: HP, MK

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DECLARATIONS OF INTEREST

Hemanshu Prabhakar: none known

Gyaninder Pal Singh: none known

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Internal sources

- All India Institute of Medical Sciences, New Delhi, India.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We planned to search Google Scholar for relevant studies but did not do so.

2. We provided more detail in the Types of interventions section on how we defined non-pharmacological and pharmacological agents.

3. In the primary outcome section, we expanded on how we analysed pain as a dichotomous variable.

4. In the secondary outcomes section, we expanded on how we planned to measure the continuous outcomes of rise in blood pressure and increase in heart rate from their baseline values after administration of rocuronium.

5. We planned to judge the quality of the studies for the domains random sequence generation, allocation concealment and blinding and outcome. However, we also assessed the quality of studies for the domains of incomplete outcome data, selective reporting and any other bias.

6. We planned to report pain as dichotomous or as a continuous variable. However, we only reported pain as a dichotomous outcome.

7. We planned to perform subgroup analysis based on obvious clinical or statistical heterogeneity, and also to consider subgroup analysis based on gender, technique followed for rocuronium administration, intervention alleviating pain centrally or locally, age and dose of the rocuronium used. We carried this out but, with the exception of the use of lidocaine in children, we did not formally report this in the review, as we did not observe any change in our findings.

NOTES

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INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [therapeutic use]; Analgesics, Opioid [therapeutic use]; Androstanols [administration & dosage; *adverse effects]; Anesthetics, Local [therapeutic use]; Fentanyl [therapeutic use]; Lidocaine [therapeutic use]; Neuromuscular Depolarizing Agents [administration & dosage; *adverse effects]; Pain [etiology; *prevention & control]; Pain Measurement; Piperidines [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans