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Single, double or multiple-injection techniques for non-ultrasound guided axillary brachial plexus block in adults undergoing surgery of the lower arm (Review)

Chin KJ, Cubillos JE, Alakkad H

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[Intervention Review]

Single, double or multiple-injection techniques for non-ultrasound guided axillary brachial plexus block in adults undergoing surgery of the lower arm

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ABSTRACT

Background

Regional anaesthesia comprising axillary block of the brachial plexus is a common anaesthetic technique for distal upper limb surgery. This is an update of a review first published in 2006 and previously updated in 2011 and 2013.

Objectives

To compare the relative effects (benefits and harms) of three injection techniques (single, double and multiple) of axillary block of the brachial plexus for distal upper extremity surgery. We considered these effects primarily in terms of anaesthetic effectiveness; the complication rate (neurological and vascular); and pain and discomfort caused by performance of the block.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3), MEDLINE (1946 to April Week 1 2016), Embase (1947 to April 18 2016) and reference lists of trials. We contacted trial authors. The date of the last search was April 2016 (updated from March 2013).

Selection criteria

We included randomized controlled trials that compared double with single-injection techniques, multiple with single-injection techniques, or multiple with double-injection techniques for axillary block in adults undergoing surgery of the distal upper limb. We excluded trials using ultrasound-guided techniques.

Data collection and analysis

Independent study selection, 'Risk of bias' assessment and data extraction were performed by at least two investigators. We undertook meta-analysis.

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Main results

We included one new trial involving 45 participants in this updated review. In total we included 22 trials involving a total of 2193 participants who received regional anaesthesia for hand, wrist, forearm or elbow surgery. 'Risk of bias' assessment indicated that trial design and conduct were generally adequate; the most common areas of weakness were in blinding and allocation concealment.

Nine trials comparing double versus single injections showed a statistically significant decrease in primary anaesthesia failure (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.34 to 0.89, high-quality evidence). Subgroup analysis by method of nerve location showed that the effect size was greater when neurostimulation was used rather than the transarterial technique.

Nine trials comparing multiple with single injections showed a statistically significant decrease in primary anaesthesia failure (RR 0.25, 95% CI 0.14 to 0.42, high-quality evidence). Pooled data from five trials also showed a significant decrease in incomplete motor block (RR 0.61, 95% CI 0.39 to 0.96, high-quality evidence) in the multiple-injection group.

Twelve trials comparing multiple versus double injections showed a statistically significant decrease in primary anaesthesia failure (RR 0.27, 95% CI 0.19 to 0.39, high-quality evidence). Pooled data from six trials also showed a significant decrease in incomplete motor block (RR 0.55, 95% CI 0.36 to 0.85, high-quality evidence) in the multiple injection group.

Tourniquet pain was significantly reduced with multiple injections compared with double injections (RR 0.53, 95% CI 0.33 to 0.84, high-quality evidence). Otherwise there were no statistically significant differences between groups in any of the three comparisons on secondary analgesia failure, complications and patient discomfort. Compared with multiple injections, the time for block performance was significantly shorter for single injection (MD 3.33 minutes, 95% CI 2.76 to 3.90) and double injections (MD 1.54 minutes, 95% CI 0.80 to 2.29); however there was no difference in time to readiness for surgery.

Authors' conclusions

This review provides evidence that multiple-injection techniques using nerve stimulation for axillary plexus block produce more effective anaesthesia than either double or single-injection techniques. However, there was insufficient evidence to draw any definitive conclusions regarding differences in other outcomes, including safety.

PLAIN LANGUAGE SUMMARY

Anaesthesia for hand and forearm surgery via single, double or multiple injections placed close to nerves in the armpit

Review question

This review compared the effects of single, double and multiple (three or four) injections of local anaesthetic around the nerves in the armpit in providing regional anaesthesia for hand, wrist or forearm surgery in adults.

Background

A common method of regional anaesthesia for hand, wrist or forearm surgery is to inject local anaesthetic into the tissues surrounding nerves in the armpit. This is because in the armpit (axilla) the key nerves for the lower part of the arm are close together and are easier to locate. This type of anaesthesia is called axillary brachial plexus block. The nerves themselves are located with the needle using various methods including neurostimulation (where an electrical current is passed through the needle to stimulate the nerve and produce muscle movement), the fascial click approach (puncture of the sheath around the nerves), or the transarterial approach (puncture of the artery next to the nerves). Successful blocking of the nerves produces a numb and limp arm that enables pain-free surgery. These nerves may be blocked using single, double or multiple (three or four) injections of local anaesthetic, but it is not clear which technique is preferable.

Study characteristics

We searched the literature up until April 2016 and identified 22 randomized controlled trials for inclusion in the review. These trials involved a total of 2193 participants who were given regional anaesthesia for hand, wrist, forearm or elbow surgery. The trials used methods that were generally adequate and did not affect the validity of the findings.

Key results

Nine trials compared double versus single injections. These found that people in the double-injection group had a 45% reduction in their chance of needing additional anaesthesia. The effect was more certain in the four trials where the nerves were located using the more precise method of neurostimulation. In the nine trials comparing multiple with single injections, and the 12 trials comparing multiple with double injections, there were significant reductions in the chance of needing additional anaesthesia in the multiple-injection groups (75% and 73% reductions when compared to single and double injections respectively). In addition, people in the multiple-injection group were 47% less likely to experience pain from the surgical tourniquet compared to the double-injection group. There were no other statistically significant differences in complications or patient discomfort between the two groups for any of the three comparisons. Single and double injections took less time to perform than multiple injections, but this did not reduce the total time required for adequate surgical anaesthesia to be established.

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Overall, there is high-quality evidence showing that multiple injections of anaesthetic close to three or four nerves in the armpit provide more complete anaesthesia for hand and forearm surgery than one or two injections. There was, however, not enough evidence to determine if there was a significant difference in the other outcomes, including safety.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Double versus single-injection technique

Double-injection versus single-injection technique of axillary brachial plexus block for hand, wrist or forearm surgery in adults

Patient or population: adult patients undergoing hand, wrist or forearm surgery
Setting: hospitals in Central America, Europe, North America and South America
Intervention: double-injection technique of axillary brachial plexus block
Comparison: single-injection technique of axillary brachial plexus block

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with single-injection technique of axillary brachial plexus block	Risk with double-injection technique of axillary brachial plexus block				
Primary anaesthesia failure (incomplete sensory block)	Study population		RR 0.55 (0.34 to 0.89)	527 (9 RCTs)	⊕⊕⊕⊕ HIGH	—
	392 per 1000	216 per 1000 (133 to 349)				
	Moderate					
	360 per 1000	198 per 1000 (122 to 320)				
Secondary analgesia failure - intraoperative sedation required	Study population		RR 0.64 (0.31 to 1.31)	129 (2 RCTs)	⊕⊕⊕⊖ MODERATE[1]	—
	318 per 1000	204 per 1000 (99 to 417)				
	Moderate					
	242 per 1000	155 per 1000 (75 to 318)				
Secondary analgesia failure - tourniquet pain	Study population		RR 0.58 (0.22 to 1.52)	104 (2 RCTs)	⊕⊕⊕⊖ MODERATE[1]	—
	205 per 1000	119 per 1000 (45 to 311)				
	Moderate					

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	186 per 1000	108 per 1000 (41 to 283)				
Complete failure of block[3]	Study population		RR 1.29 (0.33 to 5.01)	368 (7 RCTs)	⊕⊕⊝⊝ LOW[1,2]	There were no events in 5 out of 7 studies.
	14 per 1000	18 per 1000 (5 to 72)				
Time to readiness for surgery[4]	Study population		Not estimable	(0 RCTs)		None of the included studies assessed this outcome.
	0 per 1000	0 per 1000 (0 to 0)				
Intravascular injection	Study population		RR 4.15 (0.46 to 37.13)	90 (2 RCTs)	⊕⊕⊝⊝ LOW[1]	Only 2 events occurred in total, both in the double-injection group.
	0 per 1000	0 per 1000 (0 to 0)				
Adverse effects lasting more than 24 hours[5]	Study population		Not estimable	119 (2 RCTs)	⊕⊕⊝⊝ LOW[1,2]	There were no events in 1 of the 2 studies, and only 7 events in total in the other study.
	Not pooled	Not pooled				
	Moderate					
	Not pooled	Not pooled				

*__The risk in the intervention group__ (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; **RCT:** randomized controlled trial; **RR:** risk ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the evidence by one level because of the small number of events and sample size.
[2]We downgraded the evidence by one level because of heterogeneity in the estimate of treatment effect.
[3]Complete failure of block is defined as the need for general anaesthesia or a new plexus block.
[4]Time to readiness for surgery is defined as the time required to perform the block plus the time from completion of the block to development of surgical anaesthesia.
[5]Adverse effects lasting more than 24 hours refers mainly to neurological symptoms or deficits in the arm that was blocked.

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Summary of findings 2. Multiple versus single-injection technique

Multiple-injection versus single-injection technique of axillary brachial plexus block for hand, wrist or forearm surgery in adults

Patient or population: adult patients undergoing hand, wrist or forearm surgery
Setting: hospitals in Central America, Europe, North America and South America
Intervention: multiple-injection technique of axillary brachial plexus block
Comparison: single-injection technique of axillary brachial plexus block

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with single-injection technique of axillary brachial plexus block	Risk with multiple-injection technique of axillary brachial plexus block				
Primary anaesthesia failure	Study population		RR 0.25 (0.14 to 0.42)	712 (9 RCTs)	⊕⊕⊕⊕ HIGH	—
	405 per 1000	101 per 1000 (57 to 170)				
	Moderate					
	442 per 1000	111 per 1000 (62 to 186)				
Secondary analgesia failure - intraoperative sedation required	Study population		RR 0.70 (0.41 to 1.19)	482 (5 RCTs)	⊕⊕⊕⊕ HIGH	—
	228 per 1000	160 per 1000 (94 to 272)				
	Moderate					
	217 per 1000	152 per 1000 (89 to 259)				
Secondary analgesia failure - tourniquet pain	Study population		RR 0.97 (0.30 to 3.11)	379 (4 RCTs)	⊕⊕⊕⊕ HIGH	—
	139 per 1000	135 per 1000 (42 to 432)				
	Moderate					

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	126 per 1000	123 per 1000 (38 to 393)				
Complete failure of block[1]	Study population		RR 0.31 (0.03 to 2.71)	484 (7 RCTs)	⊕⊕⊕⊖ MODERATE [2]	There were no events in 4 out of 7 studies and 6 events in total.
	22 per 1000	7 per 1000 (1 to 60)				
Time to readiness for surgery (minutes)[3]	The mean time to readiness for surgery (minutes) ranged from 14.3 to 38.5 minutes	The mean time to readiness for surgery (minutes) in the intervention group was 3.33 minutes fewer (23.23 fewer to 16.56 more)	-	206 (2 RCTs)	⊕⊕⊖⊖ LOW [2 4]	—
Intravascular injection	Study population		RR 1.35 (0.20 to 9.06)	352 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	—
	63 per 1000	84 per 1000 (13 to 566)				
	Moderate					
	14 per 1000	20 per 1000 (3 to 131)				
Adverse effects lasting more than 24 hours[5]	Study population		Not estimable	244 (3 RCTs)	⊕⊕⊖⊖ LOW [2 4]	There were no events in 2 out of the 3 studies that reported this outcome. There were a total of only 3 events in the 1 study that did.
	Not pooled	Not pooled				

*__The risk in the intervention group__ (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; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1]Complete failure of block is defined as the need for general anaesthesia or a new plexus block to provide surgical anaesthesia.
[2]We downgraded the evidence by one level because of the small number of events and sample size.
[3]Time to readiness for surgery is defined as the time required to perform the block plus the time from completion of the block to development of surgical anaesthesia.
[4]We downgraded the evidence by one level because of heterogeneity in the estimate of treatment effect.
[5]Adverse effects lasting more than 24 hours refers mainly to neurological symptoms or deficits in the arm that was blocked.

Summary of findings 3. Multiple versus double-injection technique

Multiple-injection versus double-injection technique of axillary brachial plexus block for hand, wrist or forearm surgery in adults

Patient or population: adult patients undergoing hand, wrist or forearm surgery
Setting: hospitals in Central America, Europe, North America and South America
Intervention: multiple-injection technique of axillary brachial plexus block
Comparison: double-injection technique of axillary brachial plexus block

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with double-injection technique of axillary brachial plexus block	Risk with multiple-injection technique of axillary brachial plexus block				
Primary anaesthesia failure	Study population		RR 0.27 (0.19 to 0.39)	966 (12 RCTs)	⊕⊕⊕⊕ HIGH	—
	268 per 1000	72 per 1000 (51 to 104)				
	Moderate					
	257 per 1000	69 per 1000 (49 to 100)				
Secondary analgesia failure - intraoperative sedation required	Study population		RR 0.75 (0.55 to 1.03)	716 (7 RCTs)	⊕⊕⊕⊕ HIGH	—
	190 per 1000	142 per 1000 (104 to 196)				
	Moderate					
	145 per 1000	109 per 1000 (80 to 149)				
	Study population		RR 0.53 (0.33 to 0.84)	719 (7 RCTs)	⊕⊕⊕⊕ HIGH	—

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Secondary analgesia failure - tourniquet pain	127 per 1000	68 per 1000 (42 to 107)				
	Moderate					
	140 per 1000	74 per 1000 (46 to 118)				
Complete failure of block[1]	Study population		RR 0.24 (0.04 to 1.41)	630 (9 RCTs)	⊕⊕⊖⊖ LOW [2 3]	There were no events in 7 out of 9 studies.
	16 per 1000	4 per 1000 (1 to 23)				
Time to readiness for surgery[4]	The mean time to readiness for surgery ranged from 8.8 to 38 minutes	The mean time to readiness for surgery in the intervention group was 0.08 minutes fewer (2.92 fewer to 2.77 more)	-	524 (5 RCTs)	⊕⊕⊕⊖ MODERATE [3]	—
Intravascular injection	Study population		RR 0.69 (0.32 to 1.49)	676 (7 RCTs)	⊕⊕⊕⊖ MODERATE [2]	—
	63 per 1000	44 per 1000 (20 to 94)				
	Moderate					
	100 per 1000	69 per 1000 (32 to 149)				
Adverse effects lasting more than 24 hours[5]	Study population		Not estimable	510 (6 RCTs)	⊕⊕⊖⊖ LOW [2 3]	There were no events in 5 out of the 6 studies reporting this outcome. Note that Fanelli 1999 observed a 1% risk of transient neurologic deficit in 1650 patients receiving multiple injection blocks.
	Not pooled	Not pooled				

*__The risk in the intervention group__ (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; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect

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Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1]Complete failure of block is defined as the need for general anaesthesia or a new plexus block to provide surgical anaesthesia.
[2]We downgraded the evidence by one level because of the small number of events and sample size.
[3]We downgraded the evidence by one level because of heterogeneity in the estimate of treatment effect.
[4]Time to readiness for surgery is defined as the time required to perform the block plus the time from completion of the block to development of surgical anaesthesia.
[5]Adverse effects lasting more than 24 hours refers mainly to neurological symptoms or deficits in the arm that was blocked.

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BACKGROUND

An increase in the use of ambulatory hand surgery has generated the need for a method of regional anaesthesia that is comparable to general anaesthesia. Most anaesthesiologists agree that the regional technique has to satisfy four criteria for inclusion in their clinical practice. It should be effective, fast, safe and cause the patient either no, or only minimal, pain.

Description of the condition

The three main nerves of the upper extremity (median, ulnar and radial) are enclosed in the axilla by the fascial neurovascular sheath. This limits the spread of fluid. Burnham 1958 discovered that filling this sheath with local anaesthetic could simplify the blocking procedure to a single axillary injection. The fourth main nerve of the upper extremity, the musculocutaneous nerve, usually leaves the brachial plexus more proximally, at the cord level in the infraclavicular area. De Jong 1961, using the mathematical formula for a cylinder and assuming equal proximal and distal spread from the injection site, calculated that 42 ml of local anaesthetic was sufficient to reach this area and thus anaesthetize the whole arm in the average adult. Thompson and Rorie were the first to show (by computed tomograms) that the median, ulnar and radial nerves lie in separate fascial compartments within the neurovascular sheath (Thompson 1983). Small septae divide the neurovascular sheath and limit the circumferential spread of local anaesthetic. This provided a rational explanation for incomplete blocks. The anatomical study by Lassale and Ang, based on plaster injection into the axillary perivascular space, did not confirm the existence of a true neurovascular sheath (Lassale 1984). In a similar study, Vester-Andersen et al did not find the fascial septae separating the nerves but noticed that in all dissections only the median and ulnar nerves were engulfed by injected gelatine (Vester-Andersen 1986a). The musculocutaneous and radial nerves had either a partial contact or none at all. Partridge et al found interneural septae that were easily broken by injection of dyed latex (Partridge 1987). They therefore concluded that the septae did not limit fluid spread and had no clinical significance for anaesthesia. All these reports were based on either personal experience in a small number of patients or on cadaver studies, and none of them were controlled.

Description of the intervention

Before the 1960s, the prevalent block techniques were double or multiple axillary injections. After De Jong's report in 1961, the single-injection technique, being the simplest, became standard. Entry into the fascial neurovascular sheath was signalled either by a fascial 'click' or elicitation of paraesthesiae in the arm. The proximal spread of local anaesthetic was considered mandatory for success. The incomplete blocks were explained by insufficient volume of local anaesthetic. In the 1980s, however, Vester-Andersen et al repeatedly showed that, in spite of increased local anaesthetic volumes or concentrations, the rate of incomplete axillary blocks was high (Vester-Andersen 1984a; Vester-Andersen 1984b; Vester-Andersen 1986a). In the early 1990s, the double-injection transarterial technique using high doses of local anaesthetic gained popularity in the USA (Stan 1995; Urban 1994). In this technique, transfixion of the axillary artery was deliberately achieved to confirm entry into the neurovascular sheath; local anaesthetic was then injected behind (posterior to) as well as in front of (anterior to) the artery, in anticipation that this would increase the chance of spread to all components of the plexus.

At approximately the same time, technical development of peripheral nerve stimulators and insulated blunt needles allowed electrolocation of the individual plexus nerves. While electrolocation (also known as neurostimulation) may be applied to single and double-injection techniques, its greatest advantage is that it allows targeted injection around three or more of the main nerves to the arm. This is known as the multiple-injection technique. Lavoie et al and Koscielniak-Nielsen et al reported that this technique was superior to the single-injection method (K-Nielsen 1997a; Lavoie 1992a), and Koscielniak-Nielsen et al reported its superiority over the transarterial technique (K-Nielsen 1998a; K-Nielsen 1999c). Coventry et al and Sia et al drew similar conclusions when comparing triple injection with double injection (Coventry 2001a; Sia 2001a).

Why it is important to do this review

The first version of our review reported that no recommendations were available as to which of these techniques (single, double or multiple injection) were preferable, and that the choice is left to the personal preferences of the anaesthesiologist (Handoll 2006). The findings of the systematic review were in favour of multiple-injection techniques using nerve stimulation for axillary plexus block in terms of providing more effective anaesthesia than either double or single-injection techniques. It emphasized, however, that there was insufficient evidence for other outcomes, especially longer-term outcomes and safety.

We updated this review in 2011 (Chin 2011), with data from eight newly identified studies, and again in 2013 with data from one additional study (Chin 2013), and confirmed our previous findings. In 2011 we also clarified the scope of this review. We explicitly excluded ultrasound-guided axillary block techniques as these are clinically very different from the landmark and neurostimulation-guided techniques described above. Our review noted that ultrasound-guided axillary block was "a multiple injection technique where each of the four individual nerves are identified and targeted under direct vision" (Chin 2011). While there has been investigation since then comparing single, double and multiple-injection ultrasound-guided techniques of axillary block (Bernucci 2012; Huynh 2012; Tran 2012), this remains a separate question from that addressed in this review.

Despite the fact that scientific research into peripheral nerve blockade is now focused primarily on ultrasound-guided techniques, this review remains clinically relevant as there are areas in the world, particularly developing countries, where ultrasound technology is not readily available to anaesthesia practitioners. This updated review therefore sought to determine which of the non-ultrasound guided techniques (single, double or multiple injection) are preferable in performing axillary block of the brachial plexus.

OBJECTIVES

To compare the relative effects (benefits and harms) of three injection techniques (single, double and multiple) of axillary block of the brachial plexus for distal upper extremity surgery. We considered these effects primarily in terms of anaesthetic effectiveness; the complication rate (neurological and vascular); and pain and discomfort caused by performance of the block.

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METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that compared single with double or multiple-injection techniques, or double with multiple-injection techniques, for axillary block.

Types of participants

We included adults (generally over 18 years of age) undergoing surgery of the distal upper extremity: the hand, wrist, forearm, elbow or some combination thereof. We excluded trials that focused on children only.

Types of interventions

1. Single injection in the axilla (including injection through a catheter)
2. Double injection in the axilla (transarterial, elicitation of two paraesthesiae, electrolocation of two nerves, insertion of two needles)
3. Multiple-injection techniques in the axilla (three or more paraesthesiae or electrolocations) regardless of the local anaesthetic, pH adjustment or additives

In this review, multiple-injection techniques, in particular nerve stimulator guided multiple-injection techniques, were the 'experimental' intervention. Single-injection and double-injection techniques represented 'standard' interventions. For comparisons of single versus double-injection techniques, the single injection was the 'standard'.

We distinguished between 'guided' (neurostimulation as the endpoint for nerve location) and 'blind' (fascial clicks, paraesthesia or arterial puncture as the endpoints for nerve location) injection techniques.

Exclusions: ultrasound-guided techniques of nerve location; and routine supplementary analgesia (local anaesthetic infiltration of the surgical site; general anaesthetics and systemic opioids), with the exception of systemic opioids when used as a component of sedation (for example, small doses of opioids used in combination with benzodiazepines).

Types of outcome measures

Primary outcomes

Primary analgesia or anaesthesia failure. This was represented by the use of any additional anaesthetic or surgical intervention to ensure adequate surgical anaesthesia. This outcome can be measured or defined in various ways. It can be: a) incomplete overall sensory block or analgesia; or b) incomplete or inadequate sensory block or analgesia for the specific surgery undertaken at an appropriate (generally 30 minutes) time interval after completion of the blocking procedure.

Failure is also indicated by one or more of the following: use of supplementary analgesia either to ensure a) complete overall analgesia or b) analgesia for the surgical site; change in anaesthesia method, such as recourse to general anaesthesia; and the curtailment or modification of the planned surgical procedure due to inadequate anaesthesia. We also reported incomplete motor block.

Secondary outcomes

1. Secondary analgesia failure, such as surgical site pain, tourniquet pain or need for intraoperative sedation.
2. Timing, primarily time to achieve readiness for surgery.
3. Complications and adverse effects: these included vascular complications such as haematoma; accidental intravascular injection and its sequelae (tachycardia, dizziness, loss of consciousness, seizures); and neurological complications, including residual neurapraxias not related to surgical site, which were present for more than 24 hours.
4. Pain and discomfort during block performance.

Search methods for identification of studies

In the first version of this review (Handoll 2006), one author (Zbigniew J Koscielniak-Nielsen (ZK-N)) undertook the search (to August 2004) and Karen Hovhannisyan (KH) (former Trials Search Co-ordinator, Cochrane Anaesthesia, Critical and Emergency Care Group (ACE)) supplemented this search (to March 2005).

In the second (Chin 2011), and third versions (Chin 2013), of this review, KH updated the database search strategies that had been used in the first version of this review and ran these for the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase.

In this updated review we searched CENTRAL (2016, Issue 3), MEDLINE (1946 to April Week 1 2016) and Embase (1947 to April 18 2016) databases using the same search strategy (see Appendix 1) up to April 2016. As before, we applied no language restrictions.

The search strategy used in the first version of this review may be viewed in Appendix 2.

Data collection and analysis

Selection of studies

In the first version of the review, one review author (ZK-N) compiled a set of reports of controlled trials testing various aspects of axillary brachial plexus neural blockade for surgery of the distal upper limb, using the author-performed search strategy, supplemented by his personal reference collection. ZK-N provided the second author, Helen Handoll (HH), with copies of the first pages (or more as required) of each report. Both authors independently selected a set of potentially eligible trials and then, based on full-text versions, independently selected trials that met the review inclusion criteria. All disagreements were resolved by discussion.

HH checked through the supplementary search results (March 2005) from three databases and put forward eligible trials for selection and future consideration.

In the second version of the review, both of the review authors (Ki Jinn Chin (K-JC) and HH) independently selected potentially eligible trials from the search downloads of CENTRAL, MEDLINE and Embase that were provided by Karen Hovhannisyan. Then, upon discussion and clarification of the inclusion criteria (*see* Differences between protocol and review), we independently selected trials from full-text versions.

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In the third version and this updated version of the review, the review authors (K-JC, Husni Alakkad (HA) and Javier Enrique Cubillos (JEC)) independently selected potentially eligible trials from the search downloads of CENTRAL, MEDLINE and Embase. We obtained full-text versions of these potentially eligible studies and independently selected trials based on the inclusion and exclusion criteria.

Data extraction and management

In the first version of the review, three people (the two review authors and one other, Saúl Rugeles) performed data collection. For all versions, two people independently extracted trial information and results using a piloted data extraction form. Where available, we collected information on the following: trial methods (including methods of randomization and outcome assessment); details of the injection technique; the local anaesthetic agent; drugs used for sedation; baseline characteristics of the trial population (including sex, age, mental status and surgical interventions); and outcome measures such as pain and complications of the blocking procedure, as listed above. We resolved any differences by discussion via email correspondence. We contacted trial authors for further details of their trials.

In the first version of the review, because ZK-N was the lead investigator of four included trials, the other review authors undertook independent data entry into Review Manager (RevMan 4.2) and performed the presentation and interpretation of these four trials. However, we took note of feedback, particularly corrections, from ZK-N.

In the second version of the review, both of the review authors (K-JC and HH) independently extracted trial information and results using a piloted data extraction form as described above. We resolved any differences by discussion via email correspondence. We contacted trial authors for further details of their trials. Both authors undertook independent data entry into RevMan 5.1.

In both the third and current versions of the review, two of the review authors (K-JC and Javier Cubillos (JC)) independently extracted trial information and results. Any differences were resolved by discussion, via email correspondence or video-conference. We contacted trial authors for further details of their trials. Two of the three review authors independently entered data from newly included trials into Review Manager 5.3.

Assessment of risk of bias in included studies

For the first version of the review, two people independently assessed adequacy of study design using an adaptation of the eight-item scoring scheme (*see* Appendix 3) formerly developed by ACE. We assessed the following items: allocation concealment; description of study inclusion and exclusion criteria; intention-to-treat analysis (description of withdrawals); description of baseline characteristics of the trial population (in particular age, sex, mental status and type of surgery); comparability of care programmes other than the trial interventions (including anaesthetist experience with technique); outcome assessor blinding; and timing of outcome measurement (minimum 24 hours). As ZK-N was the lead investigator of four of the included trials in the first version of the review, these trials were reviewed independently of him. We resolved any differences by discussion.

In subsequent versions of the review, as well as this update, we assessed risk of bias using the tool outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This tool incorporates assessment of randomization (sequence generation and allocation concealment), blinding (of participants, treatment providers and outcome assessors), completeness of outcome data, selection of the outcomes reported and other sources of bias. We considered all outcomes in our assessment of blinding and completeness of outcome data. We assessed two additional sources of bias: selection bias resulting from major imbalances in key baseline characteristics (age, sex, type of surgery, mental status); and performance bias, such as that resulting from a lack of comparability in the experience of the anaesthetist with the interventions being compared.

In the second version of the review, one author (HH) assessed risk of bias of the already included trials, drawing on the previous assessments. Both authors independently assessed the newly included trials. We resolved any differences by discussion.

In the subsequent versions of the review, all three authors (KJ-C, JC and HA) independently assessed the newly included trials. We resolved any differences by discussion.

Measures of treatment effect

We calculated risk ratios and 95% confidence intervals for dichotomous outcomes, and mean differences and 95% confidence intervals for continuous outcomes.

Unit of analysis issues

We analysed studies with more than two intervention groups by making the appropriate pair-wise comparisons between all possible pairs of intervention groups. We treated each pair-wise comparison as a separate trial for data entry and analysis. The same intervention group was not included more than once in any meta-analysis of outcomes.

Dealing with missing data

We assumed any missing data to be missing at random and only analysed available data. We contacted trial authors to obtain missing data where possible.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plot (the analysis) along with consideration of the Chi^2 test for heterogeneity and the I^2 statistic (Higgins 2003).

Assessment of reporting biases

We searched the ClinicalTrials.gov website using the term 'axillary nerve block'. All relevant listed and completed trials were accounted for. Testing for funnel plot asymmetry is not recommended for meta-analyses involving fewer than 10 studies and was not performed (Higgins 2011).

Data synthesis

We reviewed the data from the included studies qualitatively and then, where possible and appropriate, presented data in the analysis and combined the data quantitatively. We pooled results of comparable groups of trials using the fixed-effect model and 95% confidence intervals. Where there was significant and unexplained

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heterogeneity among studies (P < 0.10 using Q statistics), we applied the random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses on the method of nerve location (paraesthesia, transarterial, nerve stimulation) and broad location of the surgery (hand, wrist, forearm and elbow). To test whether the subgroups were statistically significantly different from one another, we tested the interaction using the technique outlined by Altman and Bland (Altman 2003).

Sensitivity analysis

Where possible, we planned or undertook sensitivity analyses examining various aspects of trial and review methodology, including the effects of missing data and study quality (specifically allocation concealment and outcome assessor blinding).

Summary of findings

We assessed the following outcomes in the 'Summary of findings' table:

1. primary anaesthesia failure;
2. the need for intraoperative sedation (secondary analgesia failure);
3. tourniquet pain (secondary analgesia failure);
4. complete block failure;
5. time to readiness for surgery;
6. intravascular injection;
7. adverse effects lasting more than 24 hours.

We used the GRADE approach to interpret findings and assess the quality of evidence for each outcome. We downgraded the evidence from 'high quality' by one level for serious (or by two for very serious) concerns regarding any one of five factors: risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. We used the GRADE profiler (GRADEpro) to import data from Review Manager (Review Manager 5.3) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence, the magnitude of effect of the interventions examined and the sum of available data on the main outcomes we considered.

RESULTS

Description of studies

Results of the search

In the first version of this review (Handoll 2006), 73 studies were initially identified all of which involved investigation of some aspect of brachial plexus blockade for surgery of the distal upper limb. We rejected 55 studies at the first screening. The majority of rejected studies compared different types or doses of anaesthetic; the others investigated various physical aspects such as arm position, the use of digital pressure, and different techniques and approaches. We included 12 of the 18 remaining studies; the other six were excluded for reasons given in the Characteristics of excluded studies table.

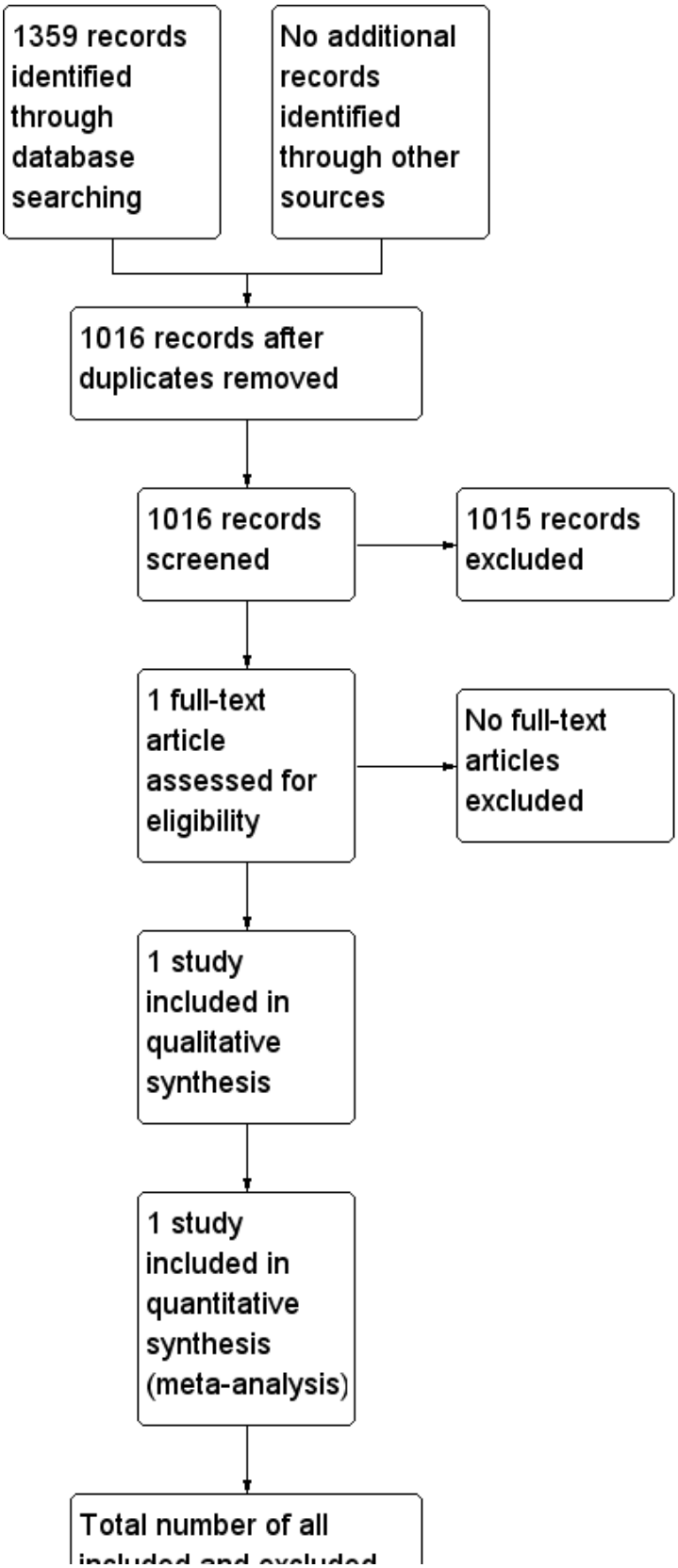
In the second version of this review, we identified 18 articles that were related to new studies for potential inclusion, of which we excluded 10 after reviewing the full-text reports or after some reconsideration or clarification of the inclusion criteria of the review (Chin 2011). We included six new articles related to eight trials (Hickey 1993; Imbelloni 2005; Rodriguez 2005; Rodriguez 2008; Sia 2010a; Sia 2010b; Sia 2010c; Turkan 2002). Three trials were run concurrently and reported in the same article (Sia 2010a; Sia 2010b; Sia 2010c). Of the remaining two articles, one was a letter (Geier 2006) commenting on Imbelloni 2005 and was hence excluded. The other was not included as it was awaiting translation and classification (Ramirez-Gomez 2010).

In the third version of this review, we identified three articles related to new studies for potential inclusion (Bernucci 2012; Huynh 2012; Tran 2012), but excluded all three after reviewing the full-text reports as they involved ultrasound-guided axillary block techniques and therefore fell outside the scope of the review (Chin 2013). We included the study that had been awaiting classification in the previous version (Ramirez-Gomez 2010).

In the current update of this review, all three authors independently screened 1359 citations retrieved by the electronic search from three databases: CENTRAL (174 citations), MEDLINE (390 citations), Embase (795 citations). There were 1016 unique citations after removal of duplicates, from which we identified one new study for inclusion (Kjelstrup 2014) (*see* Figure 1).

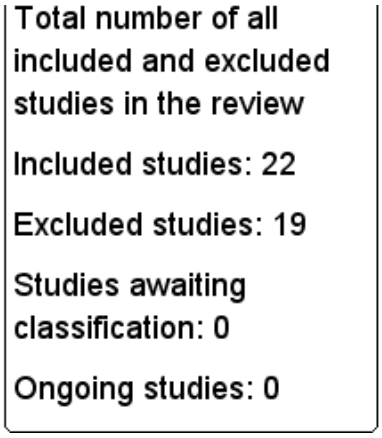
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Figure 1. Study flow diagram for updated search March 2013 to April 2016.



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Figure 1. (Continued)



Included studies

We included a total of 22 trials in this update, one of which was new (Kjelstrup 2014). Details of individual trials are provided in the Characteristics of included studies table. All 22 included trials were reported in full. We obtained a translation for the two trials not reported in the English language (Ramirez-Gomez 2010; Serradell Catalan 2001).

Setting

Each of the 22 trials took place in one of 10 countries (Brazil: 1; Canada: 1; Denmark: 5; Finland: 2; Italy: 4; Mexico: 1; Spain: 3; Turkey: 1; UK: 2; USA: 2). Four Danish trials had the same lead investigator (Koscielniak-Nielsen) and shared many trial characteristics. All four Italian trials also had the same lead investigator (Sia); three of these trials were run concurrently and were published together (Sia 2010a; Sia 2010b; Sia 2010c).

Participants

The 22 trials included a total of 2193 participants; the number of participants in individual trials ranged from 45 (Kjelstrup 2014) to 138 (Sia 2010a; Sia 2010b; Sia 2010c). Fourteen patients in the three concurrent trials conducted by Sia were excluded after randomization because of the inability to locate the desired nerves; the distribution of these 14 participants between the three trials is not known (Sia 2010a; Sia 2010b; Sia 2010c). The percentage of male participants ranged from 2% to 75% in the 18 trials providing this information. The mean ages of trial participants, reported by 20 trials, ranged between 37 and 58 years; the inclusion of exclusively adult participants was confirmed in 11 trials providing age-range data, or from their inclusion criteria. Nineteen trials reported the requirement for informed consent.

Five trials gave no exclusion criteria relating to anaesthesia (Baranowski 1990; Goldberg 1987; Inberg 1999; Lavoie 1992; Ramirez-Gomez 2010). Of the other 17 trials, 10 excluded people with an American Society of Anaesthesiologists (ASA) score greater than two (Imbelloni 2005; K-Nielsen 1999a; K-Nielsen 1999b; Kjelstrup 2014; Pere 1993; Sia 2001; Sia 2010a; Sia 2010b; Sia 2010c; Turkan 2002), and seven excluded people with an ASA score greater than three (Coventry 2001; Hickey 1993; K-Nielsen 1997; K-Nielsen 1998; Rodriguez 2005; Rodriguez 2008; Serradell Catalan 2001).

The description of the types of surgery, including location or site and whether elective or acute, was generally limited in the trial reports but it was usually enhanced on receipt of further information from trialists. Details of the types of or indications for surgery were given for 12 trials (Coventry 2001; Goldberg 1987; Imbelloni 2005; Kjelstrup 2014; K-Nielsen 1997; K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b; Ramirez-Gomez 2010; Sia 2010a; Sia 2010b; Sia 2010c), but were quantified in full in only three trials (Coventry 2001; Goldberg 1987; Ramirez-Gomez 2010), and split by treatment group in only one trial (Coventry 2001). Surgery was explicitly restricted to the hand or wrist, or both, in five trials (Goldberg 1987; K-Nielsen 1997; Sia 2010a; Sia 2010b; Sia 2010c), and was probably limited to the same locations in Baranowski 1990. Eight trials also included forearm and elbow surgery (Inberg 1999; K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b; Lavoie 1992; Pere 1993; Ramirez-Gomez 2010; Rodriguez 2008). While including forearm surgery, elbow surgery was not mentioned for four trials (Imbelloni 2005; Kjelstrup 2014; Serradell Catalan 2001; Sia 2001). There was no indication of location in Coventry 2001, although specific hand and wrist operations were listed. Surgery was referred to as 'elective' in three trials (Coventry 2001; K-Nielsen 1997; Sia 2001); 'scheduled' in another three trials (Baranowski 1990; Goldberg 1987; Inberg 1999); and 'post-traumatic' in Serradell Catalan 2001. Mixed elective and acute surgery were undertaken in three trials (K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b), and, probably, also in Lavoie 1992 and Ramirez-Gomez 2010. There was no information on the urgency of the operation in 10 trials (Hickey 1993; Imbelloni 2005; Kjelstrup 2014; Pere 1993; Rodriguez 2005; Rodriguez 2008; Sia 2010a; Sia 2010b; Sia 2010c; Turkan 2002).

Interventions

Fourteen trials had two intervention groups (Coventry 2001; Imbelloni 2005; Inberg 1999; K-Nielsen 1997; K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b; Pere 1993; Ramirez-Gomez 2010; Rodriguez 2008; Sia 2001; Sia 2010a; Sia 2010b; Sia 2010c). Five trials had three intervention groups (Baranowski 1990; Goldberg 1987; Hickey 1993; Kjelstrup 2014; Turkan 2002). Rodriguez 2005 had four intervention groups. The remaining two trials had five intervention groups (Lavoie 1992; Serradell Catalan 2001). The trials made the following comparisons according to the aims of this review.

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Double versus single-injection technique

Nine trials made this comparison (Goldberg 1987; Hickey 1993; Inberg 1999; Kjelstrup 2014; Lavoie 1992; Pere 1993; Rodriguez 2005; Serradell Catalan 2001; Turkan 2002).

Multiple versus single-injection technique

Nine trials made this comparison (Baranowski 1990; Kjelstrup 2014; K-Nielsen 1997; K-Nielsen 1999b; Lavoie 1992; Ramirez-Gomez 2010; Rodriguez 2005; Serradell Catalan 2001; Sia 2010a).

Multiple versus double-injection technique

Twelve trials made this comparison (Coventry 2001; Imbelloni 2005; Kjelstrup 2014; K-Nielsen 1998; K-Nielsen 1999a; Lavoie 1992; Rodriguez 2005; Rodriguez 2008; Serradell Catalan 2001; Sia 2001; Sia 2010b; Sia 2010c).

The method of nerve location varied among the studies (*see* Table 1) and can be broadly grouped into the following four methods:

1. transarterial (eight trials);
2. Winnie's perivascular (two trials);
3. paraesthesia (two trials); and
4. neurostimulation (19 trials).

Outcomes

We have documented the length of follow-up and the types of outcomes assessed in individual trials in the Characteristics of included studies table. Further details of the methods used to assess and define sensory and motor blockade are presented in Appendix 4.

With the exception of six trials (Lavoie 1992; Ramirez-Gomez 2010; Sia 2010a; Sia 2010b; Sia 2010c; Turkan 2002), the included trials provided separate data on anaesthesia outcomes (for example sensory blockade) for named individual nerves. We have not presented these data in this review because our focus is on overall measures of incomplete or inadequate anaesthesia.

Monitoring of longer-term effects (24 hours or over), particularly adverse effects, was conducted in 11 trials.

Excluded studies

We excluded 19 studies upon full-text review for the reasons given in the Characteristics of excluded studies table; six of these were identified in the first version of this review (Bouaziz 1997; Singelyn 1992; Tuominen 1987; Vester-Andersen 1984; Vester-Andersen 1986; Youssef 1988), 10 in the second version (Bloc 2010; Carre 2000; Gianesello 2010; Imasogie 2010; Kjelstrup 2006; K-Nielsen 2000; Liu 2005; Sia 2001b; Sites 2006; Yu 2007), and three in the third version (Bernucci 2012; Huynh 2012; Tran 2012). In this update, we excluded all non-relevant citations on review of title and abstract.

Awaiting classification

There are no studies awaiting classification in this update.

Ongoing studies

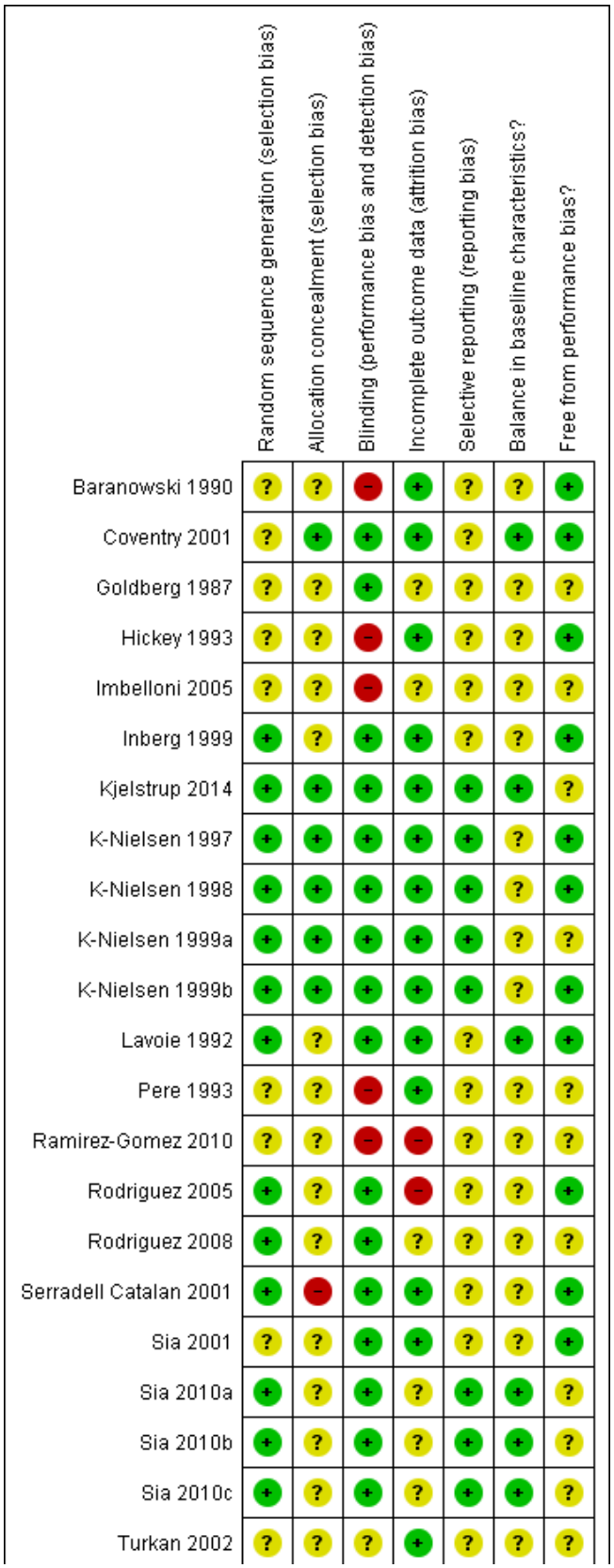
There were no ongoing studies identified in this update.

Risk of bias in included studies

The risk of bias judgements on seven items for the individual trials are summarized in Figure 2 and Figure 3, and described in the 'Risk of bias' tables in Characteristics of included studies. We judged items as having a low, high or 'unclear' risk of bias. An 'unclear' verdict often reflected a lack of information upon which to judge the item. Successful contact with trial investigators usually resulted in an improved assessment of one or more items. We always took lack of information on blinding, primarily assessor blinding, to imply that there was no blinding and rated this as high risk of bias. We gave a high risk of bias rating for single items in six trials; this related to a lack of assessor blinding in four of these. We gave a high risk of bias for two items in Ramirez-Gomez 2010.

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Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Figure 2. (Continued)

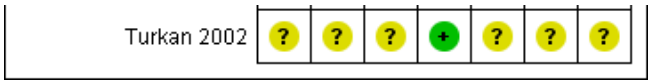
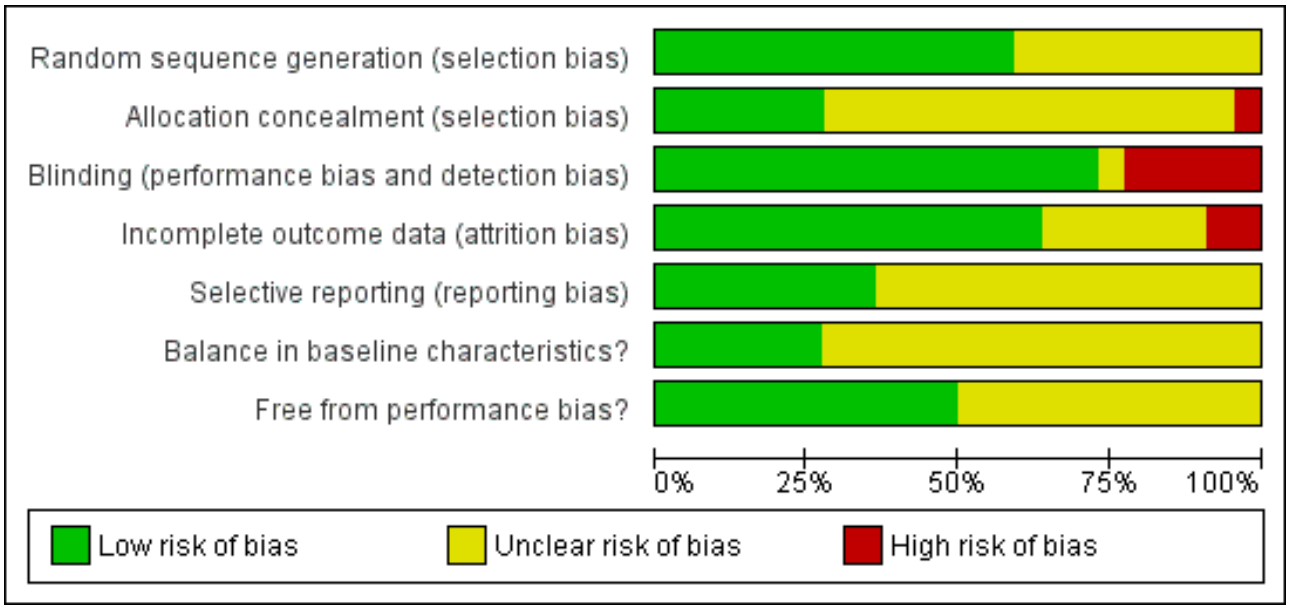


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

There was a general lack of detail on the method of randomization and measures taken to conceal treatment allocation in the included trials. We judged only five trials at low risk of bias, resulting from adequate sequence generation and allocation concealment (Kjelstrup 2014; K-Nielsen 1997; K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b). We judged allocation as concealed in Coventry 2001 but there were insufficient details on the shuffling of the envelopes to confirm the generation of an adequate randomization sequence. The use of an open randomization list by Serradell Catalan 2001 meant that we judged this trial at high risk of selection bias.

Blinding

Assessor blinding for the primary outcome was absent in Ramirez-Gomez 2010 and was not mentioned in four trials (Baranowski 1990; Hickey 1993; Imbelloni 2005; Pere 1993), which we thus judged at high risk of bias for this item. Blinding was incomplete for Turkan 2002, which we judged as 'unclear' for this item. While safeguards were rarely described, we considered the risk of bias low for those trials that reported blinding.

Incomplete outcome data

The short follow-up in most of these trials prevented loss of follow-up for the primary outcome being a serious issue and we judged that all trials performed intention-to-treat analysis in that there was no cross-over. 'Unclear' ratings generally resulted from post-randomization exclusions but we noted also that none of the trials that followed up people after surgery explicitly reported that all trial participants attended their surgical follow-up. Unaddressed reporting inconsistencies in Ramirez-Gomez 2010 and Rodriguez 2005 were the reason behind the high risk of bias judgement for this item in these trials.

Selective reporting

The lack of protocols or trial registration entries hampered the assessment of risk of bias from selective reporting. However, we judged that selective reporting bias was avoided by virtue of the consistent approach taken in the planning of two series of trials headed by Koscielniak-Nielsen (K-Nielsen 1997; K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b), and Sia (Sia 2010a; Sia 2010b; Sia 2010c), and the provision of additional data on request.

Other potential sources of bias

We judged risk of bias resulting from major imbalances in baseline characteristics as low in five trials and 'unclear' in the remainder. Generally the lack of information on the distribution in the types of surgery undertaken (and implicated nerves) in the intervention groups was the reason for uncertainty. We judged the risk of performance bias, primarily based on an assessment of reported operator experience and comparability of this between intervention groups, as low in 11 trials and 'unclear' in the rest. While we also based our judgement on an interpretation of individual trial procedures, we did not think the lack of reporting by trials on comparability of care programmes impacted on trial validity.

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Effects of interventions

See: **Summary of findings for the main comparison** Double versus single-injection technique; **Summary of findings 2** Multiple versus single-injection technique; **Summary of findings 3** Multiple versus double-injection technique

The 22 included trials involved a total of 2193 participants who received regional anaesthesia for hand, wrist, forearm or elbow surgery.

Where data were available, we summed the results of the two or three intervention groups that fell into the same category (for example single injection) for the eight trials with more than two intervention groups (Baranowski 1990; Goldberg 1987; Hickey 1993; Kjelstrup 2014; Lavoie 1992; Rodriguez 2005; Serradell Catalan 2001; Turkan 2002). As stated a priori, we performed subgroup analysis according to the method of nerve location. We limited this to the outcome of primary analgesia failure and subgrouped according to whether nerves were located by nerve stimulation (or, more rarely, paraesthesia) or not, as in the transarterial method. Due to lack of data, we were unable to perform subgroup analyses according to the site of surgery. We were also unable to undertake sensitivity analyses to test aspects of trial methodology.

For primary analgesia or anaesthesia failure, we also presented data subgrouped according to whether this outcome was defined as incomplete overall sensory block, as determined by the individual trials, or incomplete sensory block as indicated by the need for supplementation at the surgical site.

Double versus single-injection technique

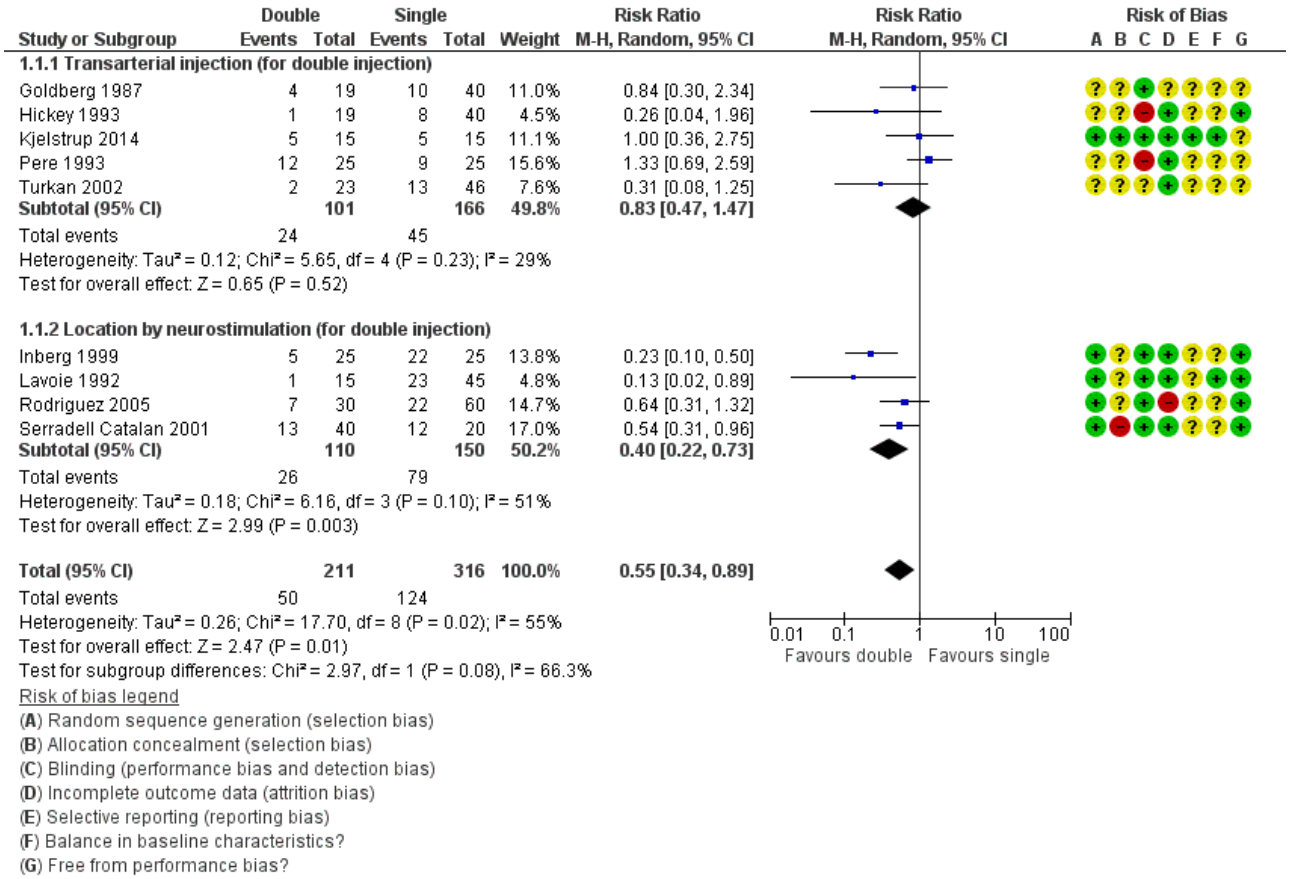
Nine trials made this comparison in a total of 528 participants (Goldberg 1987; Hickey 1993; Inberg 1999; Lavoie 1992; Pere 1993; Rodriguez 2005; Serradell Catalan 2001; Turkan 2002). One person was excluded from Hickey 1993 following an aborted axillary block in which tachycardia and lightheadedness occurred during injection. The three incomplete procedures that occurred in the double-injection group of Rodriguez 2005 were included in an intention-to-treat analysis.

Primary analgesia or anaesthesia failure (Comparison 1; Outcomes 1.1 to 1.4)

The pooled results, using the random-effects model because of significant (P = 0.02) and substantial (I^2 = 55%) heterogeneity, showed a statistically significant decrease in primary analgesia or anaesthesia failure (incomplete sensory block) in the double-injection group (*see* Figure 4) (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.34 to 0.89) (Analysis 1.1). Figure 4 also presents the results for the trials subgrouped according to the technique used for double-injection (transarterial versus neurostimulation). The results of the five trials using transarterial injection showed no statistically significant difference between the double and single-injection groups (failure: RR 0.83, 95% CI 0.47 to 1.47) (Goldberg 1987; Hickey 1993; Kjelstrup 2014; Pere 1993; Turkan 2002), whereas a double injection was superior in those trials where location was by neurostimulation in both groups (failure: RR 0.40, 95% 0.22 to 0.73). A test of interaction based on fixed-effect model risk ratios showed that statistically the results of the two subgroups were significantly different from each other (two-tailed z-test = 0.0261). However, this was not the case for the random-effects model results (two-tailed z-test = 0.243) and the results in the two subgroups were also heterogeneous, hence, the differences in the method of nerve location do not appear to explain fully the heterogeneity of the overall result.

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Figure 4. Forest plot of comparison: 1 Double versus single-injection technique, outcome: 1.1 Primary anaesthesia failure (incomplete sensory block).



Analysis 1.2 presented the results subgrouped according to the definition of primary analgesia failure: incomplete overall sensory block (RR 0.50, 95% CI 0.29 to 0.86) or supplemental blocks required for surgical site anaesthesia (RR 0.43, 95% CI 0.17 to 1.11). The results for Inberg 1999 illustrated the difference in these two definitions. In the first, complete anaesthesia (sensory block) was sought, and supplemental blocks were performed if necessary to achieve this. In the second, only anaesthesia of the anticipated surgical site was sought and, as a result, the extent of supplementation was generally less.

The plexus block failed totally in seven people, six of whom had general anaesthesia and one (in Inberg 1999) had a new plexus block; there was no difference between the two groups in this outcome (*see* Analysis 1.3) (RR 1.29, 95% CI 0.33 to 5.01). We downgraded the quality of evidence from high to low based on the imprecision resulting from the small numbers of events and inconsistency of the direction of effect in the two trials that reported events. There was no statistically significant difference between the two injection groups in the numbers of participants with incomplete motor block (*see* Analysis 1.4) (RR 0.78, 95% CI 0.58 to 1.03).

Secondary analgesia failure, timing, complications and other outcomes (Comparison 1; Outcomes 1.5 to 1.9)

None of the pooled differences between the two injection groups for secondary analgesia failure (surgical site pain, tourniquet pain or intraoperative sedation) were statistically significant *(see* Analysis 1.5). Two trials reported the time to perform the nerve block and found that the double-injection block took significantly more time to perform (mean difference (MD) 2.05 minutes, 95% CI 1.18 to 2.93 minutes) (Kjelstrup 2014; Serradell Catalan 2001). None of the other differences in duration of operation, duration of tourniquet use and duration of block were statistically significant between the two groups (*see* Analysis 1.6). Time to readiness for surgery was not reported in any of the included trials. There were no significant differences between groups in complications of the block (*see* Analysis 1.7) but we graded the quality of evidence as low because of imprecision associated with low event rates. Only five cases of venous puncture occurred in the three trials reporting this outcome (Inberg 1999; Kjelstrup 2014; Serradell Catalan 2001). There were two cases of tachycardia and lightheadedness (signifying probable intravascular injection), both occurring during a double-injection block. None of the differences between the two groups were statistically significant, however we downgraded the quality of evidence from high to low because of imprecision associated with low event rates. The seven instances of adverse effects lasting more then 24 hours were all persistent paraesthesias in Serradell Catalan 2001 (*see* Analysis 1.8). The

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only persistent adverse effect that was noted in the 22 included trials, and recorded at three months in Serradell Catalan 2001, was described as neurological dysfunction. This occurred in one participant of one of the two double-injection groups. Serradell Catalan 2001 found no statistically significant difference between the double and single-injection groups in patient discomfort or their dissatisfaction with the anaesthetic method (*see* Analysis 1.9).

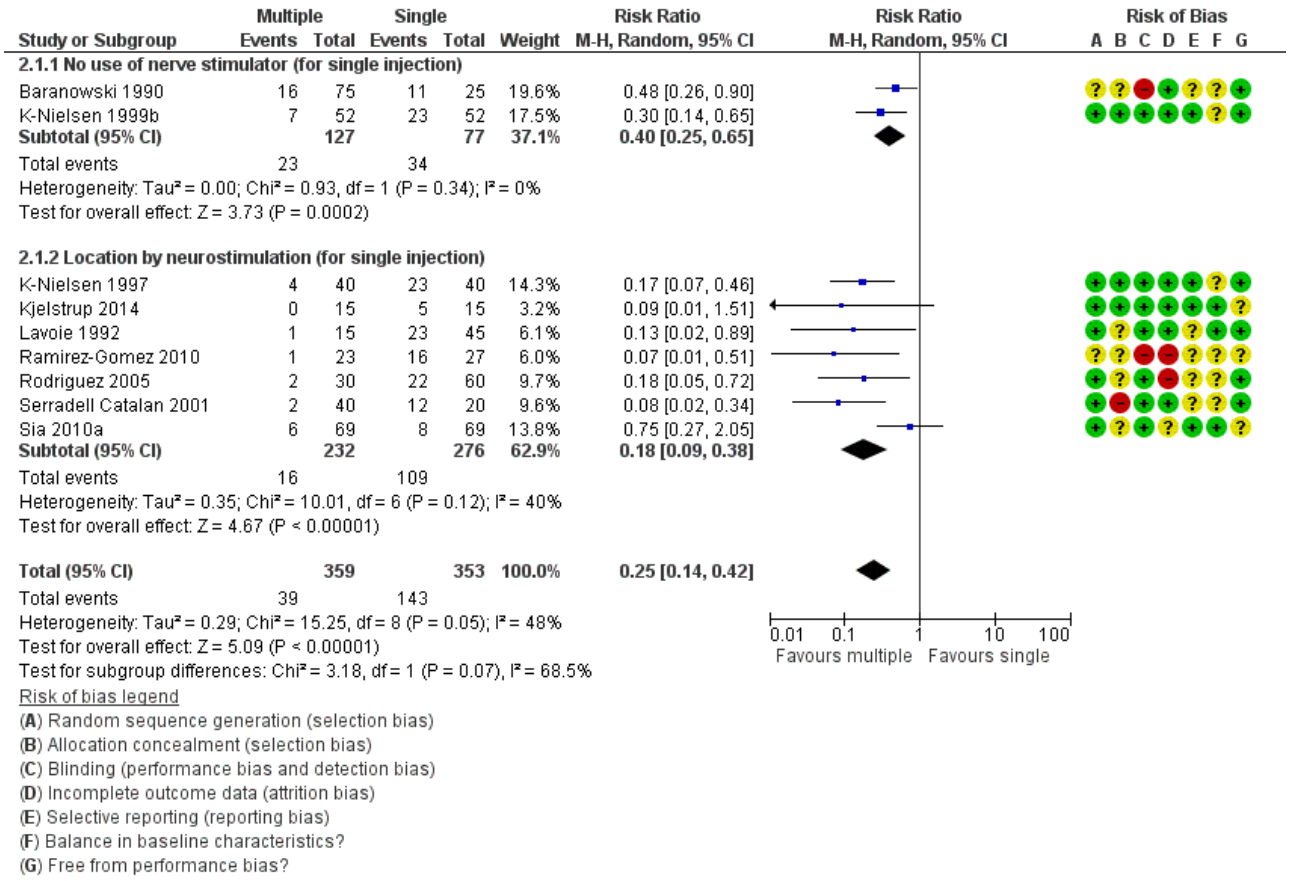
Multiple versus single-injection technique

Nine trials made this comparison in a total of 714 participants (Baranowski 1990; K-Nielsen 1997; K-Nielsen 1999b; Lavoie 1992; Ramirez-Gomez 2010; Rodriguez 2005; Serradell Catalan 2001; Sia 2010a). Two participants were excluded from K-Nielsen 1999b; one because of lack of comprehension of trial procedures and the other because of chest pain resulting in cancelled surgery. The one incomplete procedure that occurred in the multiple-injection group of Rodriguez 2005 was included in an intention-to-treat analysis.

Primary analgesia or anaesthesia failure (Comparison 2; Outcomes 2.1 to 2.4)

The pooled results, using the random-effects model because of significant (P = 0.05) and substantial heterogeneity (I^2 = 48%), showed a statistically significant decrease in primary analgesia or anaesthesia failure (incomplete sensory block) in the multiple-injection group (*see* Figure 5) (RR 0.25, 95% CI 0.14 to 0.42) (Analysis 2.1). Figure 5 also presents the trials subgrouped according to the technique used for single injection (neurostimulation versus no neurostimulation). The results of both groups of trials showed that multiple injections, all located via nerve stimulation, provided more complete sensory block than single injections located with (failure: RR 0.18, 95% CI 0.09 to 0.38) or without (failure: RR 0.40, 95% CI 0.25 to 0.65) the use of a nerve stimulator. A test of interaction showed that statistically the results of the two subgroups were not significantly different from each other (two-tailed z-test = 0.190).

Figure 5. Forest plot of comparison: 2 Multiple versus single-injection technique, outcome: 2.1 Primary anaesthesia failure (incomplete sensory block).



Analysis 2.2 shows the results subgrouped according to the definition of primary analgesia failure: incomplete overall sensory block (RR 0.26, 95% CI 0.12 to 0.57), or supplemental blocks required for surgical site (RR 0.23, 95% CI 0.10 to 0.52). It should be noted that K-Nielsen 1997 was placed in the second category on the basis that it stipulated that supplementation of the musculocutaneous nerve was done only if necessary for surgery.

The plexus block failed totally in six people, all of whom then received general anaesthesia (*see* Analysis 2.3) (RR 0.31, 95% CI 0.03 to 2.71). We graded the quality of evidence as low based on the imprecision resulting from the small numbers of events and inconsistency of the direction of effect in the three trials that reported events. The pooled results for incomplete motor block, using the random-effects model because of significant (P = 0.03) and substantial heterogeneity (I^2 = 66%), showed a statistically

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significant increase in incomplete motor block in the single-injection group (*see* Analysis 2.4) (RR 0.61, 95% CI 0.39 to 0.96).

Secondary analgesia failure, timing, complications and other outcomes (Comparison 2; Outcomes 2.5 to 2.9)

None of the pooled differences between the two injection groups for secondary analgesia failure (surgical site pain, tourniquet pain or intraoperative sedation) were statistically significant (*see* Analysis 2.5). Pooled analysis (using the random-effects model because of significant heterogeneity) of the four trials reporting the time to perform the nerve block (Kjelstrup 2014; K-Nielsen 1997; Serradell Catalan 2001; Sia 2010a), found that the multiple-injection block took significantly more time to perform (*see* Analysis 2.6) (mean difference (MD) 3.30 minutes, 95% CI 2.66 to 3.90 minutes). There were conflicting findings in the two trials that measured the time from the start of the block until readiness for surgery (*see* Analysis 2.6). K-Nielsen 1997 found that this time period was significantly shorter in the multiple-injection group (MD -13.50 minutes, 95% CI -16.36 to -10.64 minutes) whereas Sia 2010a found it to be significantly longer in the multiple-injection group (MD 6.80 minutes, 95% CI 4.53 to 9.07 minutes). We graded the quality of evidence as low because of the inconsistency in the direction of effect and imprecision resulting from the limited sample size. None of the differences in duration of tourniquet use, duration of the block or length of surgery were statistically significant between the two groups (*see* Analysis 2.6). Using the random-effects model because of significant (P = 0.01) and substantial heterogeneity (I^2 = 72% and 69% respectively) for the pooled results for paraesthesia and tachycardia, Analysis 2.7 showed that none of the differences between the two groups in the six listed complications occurring during nerve block were statistically significant. However, we downgraded the quality of evidence for acute complications of the nerve block to moderate based on inconsistency in direction and magnitude of effect. The statistically significant excess of paraesthesia and tachycardia as well as the two serious episodes of local anaesthetic toxicity reported in the single-injection group of K-Nielsen 1999b should not be disregarded given that these may reflect the risks of the method used for performing the single injection in this group (that is, transarterial). The three instances of adverse effects lasting more than 24 hours were all persistent paraesthesias in Serradell Catalan 2001 (*see* Analysis 2.8). Serradell Catalan 2001 found no statistically significant difference between the multiple and single-injection groups in patient discomfort. Pooled data from Serradell Catalan 2001 and Sia 2010a showed no statistically significant difference between the two groups in dissatisfaction with the anaesthetic method (*see* Analysis 2.9). K-Nielsen 1999b found no difference between the two groups in the pain experienced by the trial participants during performance of the block.

Multiple versus double-injection technique

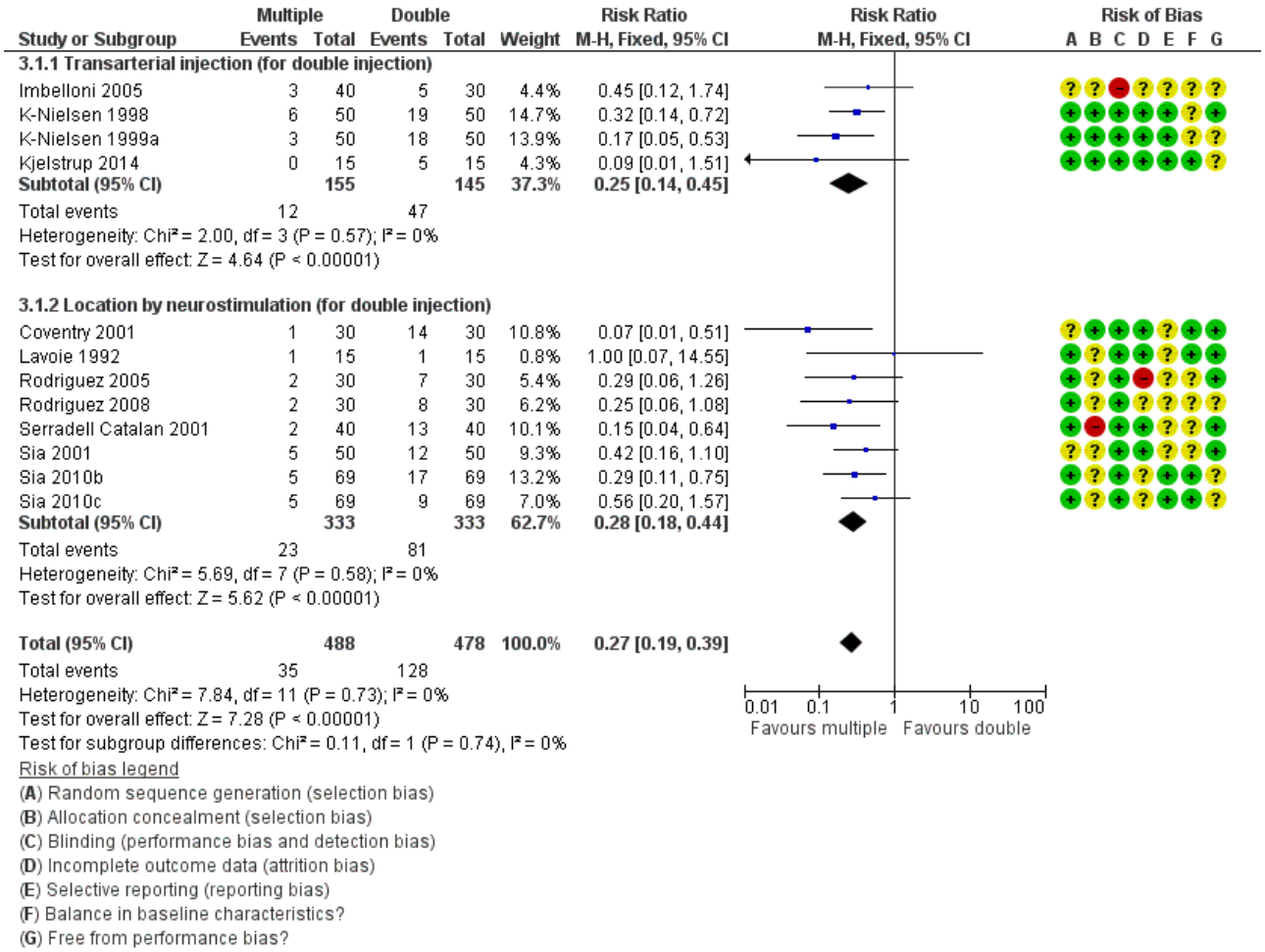
Twelve trials made this comparison in a total of 967 participants (Coventry 2001; Imbelloni 2005; Kjelstrup 2014; K-Nielsen 1998; K-Nielsen 1999a; Lavoie 1992; Rodriguez 2005; Rodriguez 2008; Serradell Catalan 2001; Sia 2001; Sia 2010b; Sia 2010c). One participant in the multiple-injection group of K-Nielsen 1999a (who was taking cardiovascular medication) was excluded due to a severe reaction including loss of consciousness.

Primary analgesia or anaesthesia failure (Comparison 3; Outcomes 3.1 to 3.4)

The pooled results, using the fixed-effect model, showed a statistically significant decrease in primary analgesia or anaesthesia failure (incomplete sensory block) in the multiple-injection group (*see* Figure 6) (RR 0.27, 95% CI 0.19 to 0.39) (Analysis 3.1). Figure 6 also presents the trials subgrouped according to the technique used for double injection (transarterial versus neurostimulation). The clearly similar results of both groups of trials showed that multiple injections, all located via neurostimulation, provided more complete sensory block than double injections located with (failure: RR 0.28, 95% CI 0.18 to 0.44) or without (failure: RR 0.25, 95% CI 0.14 to 0.45) the use of a nerve stimulator.

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Figure 6. Forest plot of comparison: 3 Multiple versus double-injection technique, outcome: 3.1 Primary anaesthesia failure (incomplete sensory block).



Analysis 3.2 shows the results subgrouped according to the definition of primary analgesia failure (incomplete overall sensory block or supplemental blocks required for surgical site). While the results for both groups were in favour of multiple injections (incomplete overall sensory block: RR 0.23, 95% CI 0.15 to 0.36; supplemental blocks required for surgical site: RR 0.40, 95% CI 0.24 to 0.66), it was noteworthy that there were proportionately fewer participants in the double-injection group with primary anaesthesia failure when this outcome was defined according to the need for supplemental blocks for the surgical site rather than incomplete overall sensory blockade.

Six people required general anaesthesia for block failure (*see* Analysis 3.3) (RR 0.24, 95% CI 0.04 to 1.41). The pooled results for incomplete motor block, using the random-effects model because of significant (P = 0.02) and substantial heterogeneity (I^2 = 62%), showed a statistically significant decrease in incomplete motor block in the multiple-injection group (*see* Analysis 3.4) (RR 0.55, 95% CI 0.36 to 0.85).

Secondary analgesia failure, timing, complications and other outcomes (Comparison 3; Outcomes 3.5 to 3.9)

There was high-quality evidence for a statistically significant decrease in tourniquet pain in the multiple-injection group (RR 0.53, 95% CI 0.33 to 0.84) but not in the other outcomes of secondary analgesia failure (surgical site pain and intraoperative sedation), although both favoured the multiple-injection group (*see* Analysis 3.5). Pooled results (using the random-effects model due to highly significant heterogeneity) from six trials reporting the time to perform the nerve block (Kjelstrup 2014; K-Nielsen 1998; Serradell Catalan 2001; Sia 2001; Sia 2010b; Sia 2010c), found that the multiple-injection block took significantly more time to perform (*see* Analysis 3.6) (MD 1.54 minutes, 95% CI 0.80 to 2.29 minutes). In contrast, the time from the start of the block until readiness for surgery was similar between the multiple-injection and double-injection groups (MD -0.08 minutes, 95% CI -2.92 to 2.77 minutes) (*see* Analysis 3.6). Analysis 3.6 showed no statistically significant differences between the two groups for duration of tourniquet use, length of surgery or duration of block. Using the random-effects model because of significant (P = 0.01) and substantial heterogeneity (I^2 = 63%) in the pooled results for paraesthesia, Analysis 3.7 showed that there were no statistically significant differences between the two injection groups in the

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eight listed complications occurring during nerve block. It should be noted though that the more frequent occurrence of tachycardia (resulting from intravascular injection) and axillary haematoma, when the results of K-Nielsen 1998 and K-Nielsen 1999a were pooled, were consistent with the method of double injection used (transarterial without neurostimulation). The six instances of adverse effects lasting more than 24 hours were all persistent paraesthesias in Serradell Catalan 2001 (*see* Analysis 3.8). The only persistent adverse effect, recorded at three months in Serradell Catalan 2001, was neurological dysfunction that occurred in one participant in one of the two double-injection groups. There was no statistically significant difference between the multiple and double-injection groups in patient discomfort or their dissatisfaction with the anaesthetic method (*see* Analysis 3.9).

DISCUSSION

Summary of main results

The ideal regional anaesthetic technique should meet four criteria: it should be effective, fast, safe and cause the patient little or no pain. All 22 included trials reported on and provided high-quality evidence for differences in anaesthetic effectiveness (primary anaesthesia) between single, double or multiple-injection techniques of axillary brachial plexus blocks. However, the reporting of timing (block performance time, onset time, time to readiness for surgery), safety (early and late complications), and pain during block performance was less complete and the quality of evidence therefore ranged from low to moderate due mainly to imprecision as well as some inconsistency in direction of effect. Though the latter three criteria are described as secondary outcomes in this review, they are as important as the primary outcome of anaesthetic effectiveness when considering the choice of anaesthetic technique. We summarize the findings of the three comparisons in turn and then provide some overall comments.

Double versus single-injection technique

We found high-quality evidence from nine studies in 527 participants for a reduced risk of primary anaesthesia failure in the double-injection group compared to the single-injection group (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.34 to 0.89). This was true regardless of whether failure was defined as incomplete sensory block of all nerves or incomplete anaesthesia of the surgical site. However, when we subgrouped the data according to the technique used for double injection, double injections were significantly more effective than single injections only when neurostimulation was used in both intervention groups, and not when the transarterial technique was used. It should be noted that in the original review a test of interaction showed the results of these two subgroups to be significantly different from each other. This was not the case in the updated review (based on random-effects model risk ratios) and, given that the method of nerve location by itself does not explain the heterogeneity within the two subgroups, we have therefore pooled the data and reported the summary statistic for all trials. There were no statistically significant differences between the double and single-injection groups in the other reported outcomes (incomplete motor block, secondary analgesia failure, timings, complications and patient discomfort).

Multiple versus single-injection technique

We found high-quality evidence from nine studies in 712 participants for a reduced risk of primary anaesthesia failure in the multiple-injection group compared to the single-injection group (RR 0.25, 95% CI 0.14 to 0.42) and this held true across all subgroup analyses. Pooled data from four trials also showed a statistically significant decrease in incomplete motor block in the multiple-injection group. It took 3.3 minutes longer on average to perform the block in the multiple-injection group. Although this difference is clinically significant, it is unclear if this has any impact on the time to readiness for surgery as only two trials reported this outcome and had conflicting results. There were no statistically significant overall differences in the other reported outcomes (secondary analgesia failure, other timings, complications and patient discomfort). In one study there was a statistically significant excess of paraesthesia and tachycardia and two serious episodes of local anaesthetic toxicity in the single-injection group, which can be attributed to the transarterial technique used (K-Nielsen 1999b).

Multiple versus double-injection technique

There was high-quality evidence from 12 studies in 966 participants for a reduced risk of primary anaesthesia failure in the multiple-injection group compared to the double-injection group (RR 0.27, 95% CI 0.19 to 0.39); again, this held true across all subgroup analyses. In particular, it was irrespective of whether the double injections involved the transarterial injection technique or neurostimulation. Incomplete motor block and tourniquet pain were also significantly less likely in the multiple-injection group compared to the double-injection group. It took 1.7 minutes longer on average to perform the block in the multiple-injection group which, although statistically significant, is not clinically important. This was supported by the pooled data from five trials showing no overall difference in the time to readiness for surgery. There were no other statistically significant differences between the multiple and double-injection groups in the pooled results of other reported outcomes (secondary analgesia failure, other timings, complications and patient discomfort). The more frequent occurrence of tachycardia (resulting from intravascular injections) and axillary haematoma when the results of K-Nielsen 1998 and K-Nielsen 1999a were pooled are likely to reflect the method of double injection used (transarterial without neurostimulation) in these trials.

Overview

The results of this update confirm the original review's conclusion that a multiple-injection technique (using neurostimulation) of non-ultrasound guided axillary block provides more effective anaesthesia than either a double or a single-injection technique. The question of whether three or four injections should be performed, or which nerves should be targeted in the multiple-injection technique, is not addressed in this review. The multiple-injection technique also appears to have other advantages, including more complete motor block and a reduced risk of tourniquet pain. Its primary disadvantage is that locating and injecting around three or more nerves in the axillary brachial plexus is much more complex, as reflected in the longer time required for performance of the multiple-injection technique compared to the single and double-injection techniques. Interestingly, this did not appear to significantly increase the time to readiness for surgery, although this is not necessarily conclusive given the limited data. The most likely explanation is that the increased anaesthetic efficacy of the multiple-injection technique offsets the longer block performance time.

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The method of nerve location used in the single or double-injection techniques appears to influence the effectiveness and safety of anaesthesia. Double injections are more effective than single injections when neurostimulation is used in both interventions, but not when double injection is performed using the transarterial method and single injection is performed using neurostimulation. There was also some evidence of a greater risk of short-term complications related to vascular puncture, such as intravascular injection and axillary haematoma, when the transarterial method was used. Taken together, this suggests that neurostimulation should be the method of choice when performing a double-injection axillary block.

While there were no significant differences observed in many of the other outcomes related to secondary anaesthesia, complications, and patient pain and discomfort, this cannot be regarded as conclusive due to the limited data and thus low quality of available evidence. In particular, the safety of multiple-injection methods remains an important unresolved issue given the low complication event rates reported in this review. The inevitable increase in needle passes while searching for other nerves after the first or second injection carries an increased risk of vascular puncture and trauma to nerves that is difficult to quantify. However, one large, multicentre prospective study of multiple-injection techniques for upper and lower limb blockade found generally reassuring evidence for axillary brachial plexus block (Fanelli 1999). Although 17% (278/1650) of these multiple-injection axillary blocks elicited unintentional paraesthesiae prompting needle withdrawal, all 17 (1%) people sustaining transient neurological dysfunction recovered fully at an average of six weeks. The same study also found some evidence that neurological dysfunction was associated with high tourniquet pressure rather than multiple injections (Fanelli 1999).

Overall completeness and applicability of evidence

In this update we identified and included one new trial, bringing the total to 22 trials. There are almost 2200 participants in the updated review, although the numbers of participants for each of the three comparisons are fewer and range from 527 to 966. The distinction between no evidence of an effect and evidence of no effect still needs to be considered where there are apparently comparable findings as data were limited for many of these outcomes. Application of trial results to clinical practice is hampered where there is an inadequate description of trial inclusion and exclusion criteria (six trials) and the types of surgery undertaken (10 trials). Another common shortcoming (10 trials) was the failure to monitor longer-term effects, particularly adverse effects.

Quality of the evidence

The risk of bias varied in the 22 trials but the included trials were generally well conducted and either at low or unclear risk of bias for the seven aspects rated in our assessment (*see* Figure 2). We rated only seven trials at high risk of bias and this in one domain only (mainly lack of blinding) for six of the seven trials. We rated the quality of evidence underlying the primary outcome of primary analgesic or anaesthetic failure as high. We downgraded the quality of evidence to low or moderate for several of the secondary outcomes, particularly the risk of complications such as intravascular injection and longer-term adverse effects, due mainly to imprecision and inconsistency (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Potential biases in the review process

Publication bias

We may have missed trials that are not indexed in MEDLINE or Embase. In particular, we may have missed trials that remain unpublished in journals by not searching conference proceedings and other 'grey literature'. We did, however, approach trialists and contacts in the industry for information on existing trials. While the possibility of publication bias cannot be ruled out, we consider that a well-conducted trial on this topic would have stood a good chance of being published in specialist journals irrespective of its results. Our trial selection procedure was systematic and, after an initial filtering of the results from the electronic searches, each author carried out independent selection.

Pooling and heterogeneity

We chose to pool data from trials testing the same comparisons; however, no two trials were identical. There were notable differences in the interventions, such as in the method of location of nerves and selection of specific nerves (*see* Table 1), study populations and definitions of outcomes (*see* Appendix 4). We performed subgroup analyses of the outcome of primary anaesthesia failure according to the method of nerve location and the definition of adequate sensory blockade; however, the data were insufficient to examine the effects of the other methodological differences.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides high-quality evidence that multiple-injection techniques using neurostimulation for axillary brachial plexus block provide more effective anaesthesia than either double or single-injection techniques. There is insufficient evidence to determine the relative effects of single, double and multiple-injection techniques on the complication rate, secondary analgesia failure, patient discomfort and pain during the procedure.

Implications for research

Since the second version of the review was published, the use of ultrasound to guide peripheral nerve blockade has become widespread and has largely supplanted neurostimulation techniques, particularly in developed countries with access to the technology. Hence while the maintenance of this review in the light of any new evidence from randomized trials is required, we do not consider that conducting further randomized trials on this subject is a priority. We however suggest that the systematic surveillance of people undergoing these injections to ascertain the incidence of rare adverse effects, in particular serious and permanent neurological injuries, should be ongoing.

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CHARACTERISTICS OF STUDIES

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* Indicates the major publication for the study

Baranowski 1990

Methods	Method of randomization: not stated

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Baranowski 1990 *(Continued)*

	No blinding indicated No loss to follow-up
Participants	London, UK Period of study: not stated 100 people scheduled for outpatient hand surgery. Informed consent Male: not stated; mean age: 49 years Excluded: no details
Interventions	Multiple (neurostimulation method) versus multiple (paraesthesia method) versus single injection All received local anaesthetic (LA) solution: up to 40 ml lignocaine 1.5% with adrenaline 200 µg No premedication. No sedation or IV analgesia. All blocks performed or supervised by 1 of the 2 trial authors 1. Multiple injection using neurostimulator: unsheathed block needle. Attempts made to locate 3 to 4 main branches of brachial plexus; nerve specific muscle twitches. Incremental LA injections 2. Multiple injection using paraesthesia: 22 gauge regional block needle. Attempts made to locate 3 to 4 main peripheral nerves. Incremental LA injections. Distal pressure applied 3. Single injection via catheter on its insertion (introduction with 18 gauge needle) in brachial plexus sheath. Fascial 'click' and easy insertion used to identify sheath. Distal pressure applied
Outcomes	Length of follow-up: 30 minutes Sensory blockade Motor blockade (no data) Anaesthesia failure (fewer than 3 nerves fully blocked, general anaesthesia, failure to penetrate brachial plexus sheath)
Notes	Request for details of methods, types of surgery and results, including adverse effects, sent to Dr Baranowski on 2 December 2004. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“One hundred patients ... were randomly allocated”. No details of method
Allocation concealment (selection bias)	Unclear risk	No details of method
Blinding (performance bias and detection bias) All outcomes	High risk	No mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up seemed likely
Selective reporting (reporting bias)	Unclear risk	Possible but no protocol available
Balance in baseline characteristics?	Unclear risk	Incomplete information to judge: no gender or type of surgery. Single injection group was 6 years younger (not statistically significant)
Free from performance bias?	Low risk	"All of the blocks were performed or supervised by one of the two authors.” There was a register and a consultant. Other treatment (none) seemed comparable

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Coventry 2001

Methods	Method of randomization: "Technique written on card and placed in envelope. Envelopes sealed, shuffled and numbered 1-60." "Envelope opened immediately pre-op by 'regional anaesthetist'" Double-blind: anaesthetist carrying out assessments and surgeon were blind to injection technique Blinded outcome assessor No loss to follow-up
Participants	Dundee, UK Period of study: 1995 60 people undergoing elective upper limb surgery: Dupuytren's, carpal tunnel, tendon surgery, arthrodesis/arthroplasty, wrist arthroscopy and miscellaneous Male: 45%; age range: 20 to 85 years Excluded: patients refusing a local anaesthetic technique, dementia; age < 17 years; peripheral neuropathy, sensitivity to amide local anaesthetics; ASA physical status > 3 (see notes)
Interventions	Multiple versus double injection (both groups using the neurostimulation method) All received LA solution: 30 ml lidocaine 15 mg/ml with epinephrine 5 µg/ml. Nerve blockade facilitated using 22G insulated short-bevelled needle and peripheral nerve stimulator. All blocks carried out by one operator Initial sedation with midazolam. Skin anaesthetized with 1 ml to 2 ml plain lidocaine 10 mg/ml. Musculocutaneous nerve was first located and 5 ml LA solution injected 1. Multiple injection: 15 ml LA to median nerve followed by 10 ml LA to radial nerve 2. Double injection: single injection of 25 ml LA to median nerve
Outcomes	Length of follow-up: 30 minutes (and duration of surgery) Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia) Duration of surgery Tourniquet discomfort Problems (all nerves located; no problems indicated)
Notes	Reply to request for details of methods and adverse effects received from Dr Coventry on 13 October 2004 The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“randomly allocated”, “Technique written on card and placed in envelope. Envelopes sealed, shuffled and numbered 1-60.” Unclear how well shuffled
Allocation concealment (selection bias)	Low risk	Sealed "Envelope opened immediately pre-op by 'regional anaesthetist"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Blinded investigator anaesthetist then carried out all assessments. This investigator was totally blind as was the surgeon. No assessment was carried out by the regional anaesthetists thus ensuring blinding
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up

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Coventry 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Likely but no protocol available and took 6 years to publish
Balance in baseline characteristics?	Low risk	Baseline characteristics including types of surgery detailed and appeared balanced
Free from performance bias?	Low risk	All blocks carried out by one operator. No cause for concern

Goldberg 1987

Methods	Method of randomization: not stated Blinded outcome assessor: operating surgeon No loss to follow-up
Participants	Philadelphia, USA Period of study: not stated 59 people scheduled for upper extremity surgery, wrist or more distal, amenable to brachial plexus block outpatient hand surgery: carpal tunnel repair/median nerve release; Dupuytren's contracture release; arthroplasty of interphalangeal joint; ganglion excision; distal radial and/or ulnar plating; foreign body excision; miscellaneous finger operations. Consenting. Male: not stated; mean age: 50 years, age 18+ years Excluded: no details
Interventions	Double versus single (neurostimulation method) versus single (paraesthesia method) injection All received local anaesthetic (LA) solution: 40 ml/70 kg mepivacaine 1.5% No mention of premedication, sedation or IV analgesia. All blocks performed by first or second year anaesthesiology residents supervised by staff anaesthesiologist (usually first author) 1. Double transarterial injection: 22 gauge short bevel needle inserted transarterial fixation - half of LA volume administered posterior to axillary artery and half anterior to artery 2. Single injection using nerve stimulator: 23 gauge insulated needle connected to stimulator. Whole volume of LA injected when maximum stimulation no longer produced muscle activity 3. Single injection using paraesthesia: 22 gauge short bevel needle inserted until hand paraesthesia elicited - whole volume of LA injected
Outcomes	Length of follow-up: hand clinic (timing not specified) Sensory blockade Anaesthesia failure (non-blocked nerves) Adverse effects (none at hand clinic)
Notes	Request for details of methods, types of surgery and results, including adverse effects, sent to Prof Goldberg on 15 December 2004. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Three methods of blockade were randomly selected.” No details of method
Allocation concealment (selection bias)	Unclear risk	No details of method

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Goldberg 1987 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Pain was tested "by a surgeon (with an Allis clamp) unaware of the method utilized"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Possible but no protocol available
Balance in baseline characteristics?	Unclear risk	Incomplete information to judge: no gender or type of surgery. Single injection groups were 6 and 11 years younger than transarterial groups
Free from performance bias?	Unclear risk	No difference in "the level of training of the residents who performed the blocks, which ranged from 1-19 months". No other problems detected - blinded surgeon

Hickey 1993

Methods	Method of randomization: not specified No blinding of patient, care-giver or outcome assessor described No loss to follow-up
Participants	Texas, USA Period of study: not stated 60 adults scheduled for surgery of the upper extremity (not otherwise specified) Male: 1.7%; mean age 56 years Excluded: ASA physical status > 3 (see notes)
Interventions	Double versus single posterior versus single anterior injection (transarterial method in all groups) All received local anaesthetic (LA) solution: 1.5% mepivacaine with 5 µg/ml epinephrine; total volume 50 ml. Transarterial technique in all cases with a 22G short-bevel block needle. All blocks performed by residents supervised by one staff anaesthesiologist Sedative premedication with IV midazolam: up to 3 mg 1. Double injection: injection of half of LA volume (25 ml) anterior to axillary artery, injection of other half (25 ml) posterior to axillary artery 2. Single posterior injection: injection of all of LA volume (50 ml) posterior to axillary artery 3. Single anterior injection: injection of all of LA volume (50 ml) anterior to axillary artery Subcutaneous injection of 3 ml of LA over the axillary artery to block the intercostobrachial nerve
Outcomes	Length of follow-up: 30 minutes Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; general anaesthesia) Onset of analgesia and anaesthesia in individual nerve territories Complications during block injection and operation
Notes	One double injection patient excluded from the analyses because of an aborted block The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease,

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Hickey 1993 *(Continued)*

	3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized study". No further details
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding stated (seems unlikely given the supervisory aspect)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol. Insufficient information to judge this
Balance in baseline characteristics?	Unclear risk	Insufficient information to judge this in terms of lack of details on surgical interventions. Double injection group on average 8 years older
Free from performance bias?	Low risk	All blocks performed by residents directly supervised by the same member of staff

Imbelloni 2005

Methods	Method of randomization: not stated No blinding of patient, care-giver or outcome assessor described No loss to follow-up
Participants	Sao Jose do Rio Preto, Brazil Period of study: not stated 70 adults scheduled for orthopaedic surgery of the forearm and hand. Informed consent Male: 56%; mean age 38 years Exclusions: ASA physical status > 2 (see notes); age < 20 years or > 60 years
Interventions	Multiple (neurostimulation method) versus double injection (transarterial method) All received local anaesthetic (LA) solution: 1.6% lidocaine with 5 µg/ml epinephrine; total volume 50 ml. The identity and experience level of the operator performing the blocks was not stated No premedication given 1. Multiple injection: neurostimulation-guided, injection of 20 ml to ulnar or distal radial nerve response, 20 ml to median nerve, 10 ml to musculocutaneous nerve 2. Double injection: transarterial technique, injection of 30 ml posterior to axillary artery, injection of 20 ml anterior to artery Incomplete blocks were supplemented but the definition of incomplete blocks and the timing of supplementation were not specified

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Imbelloni 2005 *(Continued)*

Outcomes	Length of follow-up: sensory and motor block follow-up duration was not specified. Patients were followed up for 48 hours postoperatively to assess for complications Sensory blockade Analgesic failure (use of supplementary anaesthesia; general anaesthesia, pain at surgical site) Time to readiness for surgery Tourniquet discomfort and pain Complications during block injection and operation, and up to 48 hours after Block duration Patient satisfaction
Notes	Block outcomes were vaguely defined, and assessment timing not specified The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"prospective study"; "who were randomly distributed in two groups (group MNS= 40 patients and group TA = 30 patients) according to the technique." Unexplained imbalance
Allocation concealment (selection bias)	Unclear risk	No details of method
Blinding (performance bias and detection bias) All outcomes	High risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Likely that all participants accounted for, but not stated explicitly
Selective reporting (reporting bias)	Unclear risk	No prior protocol and vague in the definition of outcomes
Balance in baseline characteristics?	Unclear risk	Balanced for sex, age, weight and height but no information on surgery
Free from performance bias?	Unclear risk	Insufficient information to judge this

Inberg 1999

Methods	Method of randomization: computer-based, organized by the statistical department Patient blinded Blinded outcome assessor No loss to follow-up
Participants	Tampere, Finland Period of study: 1996 to 1997 50 adults scheduled for upper limb surgery under axillary block anaesthesia. Informed consent Male: 74%; mean age: 44.5 years

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Inberg 1999 *(Continued)*

	Excluded: weight < 50 kg or > 100 kg; surgery proximal from the elbow joint
Interventions	Double versus single injection (both groups using neurostimulation method) All received local anaesthetic (LA) solution: prilocaine 1% and bupivacaine 0.5% in 1:1 ratio; total volume 0.7 ml/kg body weight. Nerve blockade facilitated using 22G insulated needle and nerve stimulator. All blocks carried out by one operator Initial sedation with diazepam. Initial subcutaneous injection of 2 to 3 ml LA 1. Double injection: injection (half volume) LA to median nerve followed by injection (rest of volume) LA to radial nerve (14 cases) or ulnar (11 cases) 2. Single injection: single injection of LA to median nerve (23 cases); radial nerve (1 case) or ulnar nerve (1 case) Subcutaneous injection of 5 ml LA to block medial cutaneous nerves of the arm
Outcomes	Length of follow-up: 40 minutes (and duration of surgery) Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; new plexus block, general anaesthesia; use of opioids for tourniquet pain or pain in operation area) Duration of surgery Duration of tourniquet use Tourniquet discomfort and pain Problems (during operation)
Notes	Reply to request for details of methods, type of surgery and details of participants receiving general and another full plexus block received from Dr Annila on 21 December 2004. Original patient papers are now missing. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-based randomization", organized by the statistical department
Allocation concealment (selection bias)	Unclear risk	No information on concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	“The evaluation of the sensory and motor blocks was blinded, and the patient was unaware of the method used, which makes the study double blind”
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Information supplied by trial author on the particular circumstances of 2 patients, who received respectively a new plexus block and general anaesthesia
Selective reporting (reporting bias)	Unclear risk	Possible but no protocol available
Balance in baseline characteristics?	Unclear risk	No information on type of surgery or mental status. No statistically significant differences between the 2 groups in age, gender, weight or height
Free from performance bias?	Low risk	Seemingly so: same experienced operator and anaesthetic procedures. "All blocks were performed by the first author, who is experienced in axillary block"

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K-Nielsen 1997

Methods	Method of randomization: computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room. Blinded outcome assessor No loss to follow-up
Participants	Copenhagen, Denmark Period of study: 1995 to 1996 80 people undergoing elective hand surgery: arthrodeses, arthroplasties, osteosyntheses (K-wire, Herbert screw etc), nerve sutures, finger amputations, neuroma or ganglion removals, hardware removals, wrist arthroscopies. Informed consent Male: 66%; mean age: 46 years, range: 18 to 75 years Excluded: ASA physical status > 3 (see notes). Allergy to amide type LA, pregnancy, inability to communicate, neurological disorders affecting peripheral nerves and resulting sensory loss and/or motor weakness (e.g. advanced neuropathies - uraemic or diabetic)
Interventions	Multiple versus single injection (both groups using neurostimulation method) All received local anaesthetic (LA) solution: 1% mepivacaine with adrenaline 5 µg/ml Nerve blockade facilitated using 22G insulated short-bevelled needle and nerve stimulator. All blocks carried out by one operator Initial sedation with diazepam. Initial subcutaneous injection of 5 ml LA to anaesthetize medial cutaneous nerves of arm or forearm 1. Multiple injection: injection of 10 ml LA cephalad to artery, then injection below artery - 20 ml at point of maximum stimulation OR if 2 nerves located: 15 ml close to each nerve. If just one located then final 10 ml into coracobrachial muscle 2. Single injection: injection of 40 ml LA to one nerve: median nerve (32), ulnar (6), radial (2); then 20 ml to radial nerve
Outcomes	Length of follow-up: surgical follow-up (not stated) for adverse neurological outcomes; onset of sensory block assessed every 10 minutes (and duration of surgery) Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; general anaesthesia; use of opioids for tourniquet pain in operation area) Time to be ready for surgery Duration of tourniquet use Tourniquet discomfort and pain Problems (during injection and operation) Long-term complications (none)
Notes	Reply to request for details of types of surgery, exclusion criteria and so on received from Dr Koscielniak-Nielsen on 11 November 2004 The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand ...."

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K-Nielsen 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room"
Blinding (performance bias and detection bias) All outcomes	Low risk	“All the blocks were performed by the first author [who left the room] and assessed by the others. .. The [randomization] envelope was then resealed and attached to the assessment form”
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Unclear risk	Yes, aside from the distribution of the various elective hand operations
Free from performance bias?	Low risk	All the blocks were performed by the first author [an experienced anaesthetist]. Other care seemed comparable

K-Nielsen 1998

Methods	Method of randomization: computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room Blinded outcome assessor No loss to follow-up
Participants	Copenhagen, Denmark Period of study: 1996 to 1997 100 people undergoing acute (nerve and/or tendon sutures, K-wire or Hoffmann osteosynthesis) or elective hand, wrist or forearm surgery. Informed consent Male: 64%; mean age: 47 years, range: 18 to 80 years Excluded: ASA physical status > 3 (see notes). Allergy to amide type LA, pregnancy, inability to co-operate, diseases affecting sensory or motor function of the upper extremity
Interventions	Multiple (neurostimulation method) versus double injection (transarterial method) All received local anaesthetic (LA) solution: 1% mepivacaine with adrenaline 5 µg/ml Nerve blockade facilitated using 22G or 24G insulated short-bevelled needle with nerve stimulator in place. All blocks carried out by one operator Initial sedation with diazepam. Initial subcutaneous injection of 5 ml LA to anaesthetize medial cutaneous nerves of arm or forearm 1. Multiple injection: injection of 10 ml LA to 4 terminal motor nerves (musculocutaneous, median, radial and ulnar). Connected to nerve stimulator, current = 1.5 mA 2. Double injection "transarterial": injection of 20 ml LA deep to and 20 ml superficial to axillary artery. Connected to nerve stimulator but current = 0 mA
Outcomes	Length of follow-up: surgical follow-up (not stated) for adverse neurological outcomes; onset of sensory block assessed every 10 minutes (and duration of surgery) Sensory blockade Motor blockade

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K-Nielsen 1998 *(Continued)*

	Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area) Time to be ready for surgery Duration of tourniquet use Tourniquet discomfort and pain Problems (during injection and operation) Long-term complications (none)
Notes	Reply to request for details of types of surgery received from Dr Koscielniak-Nielsen on 15 November 2004 The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand ...."
Allocation concealment (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room"
Blinding (performance bias and detection bias) All outcomes	Low risk	“All the blocks were performed by the first author [who left the room] and assessed by the others, who were unaware of the applied nerve block"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Unclear risk	Yes, aside from the distribution of the various operations, which were elective or acute hand, wrist or forearm surgery
Free from performance bias?	Low risk	All the blocks were performed by the first author [an experienced anaesthetist]. Other care seemed comparable

K-Nielsen 1999a

Methods	Method of randomization: computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room. Blinded outcome assessor(s) No loss to follow-up but 1 excluded due to serious adverse effect
Participants	Copenhagen, Denmark Period of study: 1998 101 people undergoing acute (nerve and/or tendon sutures, fracture osteosyntheses, amputations, wound revisions etc) or elective (Dupuytrens, arthroplasties, arthrodeses, ligament reconstructions,

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K-Nielsen 1999a *(Continued)*

	Hunter I or II, caput ulnae resections, scaphoideum osteosyntheses, neuroma or ganglion removals, carpal tunnel surgery etc) hand, wrist or forearm surgery. Informed consent. Male: 64%; mean age: 49.5 years, range: 18 to 80 years Excluded: ASA physical status > 2 (see notes). Allergy to amide type LA, pregnancy, inability to co-operate, diseases affecting sensory or motor function of the upper extremity
Interventions	Multiple (neurostimulation method) versus double injection (transarterial method) All received local anaesthetic (LA) solution: 2% mepivacaine with adrenaline 5 µg/ml Nerve blockade facilitated using 22G or 24G insulated short-bevelled needle with nerve stimulator in place. Blocks carried out by one operator or under his supervision Initial sedation with diazepam. Initial subcutaneous injection of 5 ml LA (1% mepivacaine) to anaesthetize medial cutaneous nerves of arm or forearm 1. Multiple injection: injection of 10 ml LA to 4 terminal motor nerves (musculocutaneous, median, radial and ulnar). Connected to nerve stimulator, current = 1.5 mA 2. Double injection "transarterial": injection of 20 ml LA deep to and 20 ml superficial to axillary artery. Connected to nerve stimulator but current = 0 mA
Outcomes	Length of follow-up: surgical follow-up (5 to 10 days, then 3 to 4 weeks after) for adverse neurological outcomes; onset of sensory block assessed every 10 minutes Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area) Time to be ready for surgery Pain during block Duration of tourniquet use Tourniquet discomfort and pain Problems (during injection and operation) Long-term complications (none)
Notes	Excluded patient was a cardiovascularly medicated participant of the multiple-injection group who developed hypertension, atrial fibrillation, became agitated and lost consciousness 12 minutes after block performance. After intravenous administration of labetol, metoprolol and midazolam his condition improved and he woke up 15 minutes later Details of types of surgery, study period received from Dr Koscielniak-Nielsen on 2 December 2004. The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand ...."
Allocation concealment (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room"
Blinding (performance bias and detection bias) All outcomes	Low risk	“All blocks were assessed by the anaesthetists, who were unaware of the applied nerve block technique"

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K-Nielsen 1999a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up but 1 excluded due to serious adverse effect
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Unclear risk	Yes, aside from the distribution of the various operations, which were elective or acute hand, wrist or forearm surgery
Free from performance bias?	Unclear risk	While 38% versus 32% of blocks were done by residents and other staff members (rather than the first author [an experienced anaesthetist], the first author supervised all blocks. Other care seemed comparable

K-Nielsen 1999b

Methods	Method of randomization: computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room Blinded outcome assessor No loss to follow-up
Participants	Copenhagen, Denmark Period of study: 1998 106 people undergoing acute (nerve and/or tendon sutures, fracture osteosyntheses, amputations, wound revisions etc) or elective (Dupuytrens, arthroplasties, arthrodeses, ligament reconstructions, Hunter I or II, caput ulnae resections, scaphoideum osteosyntheses, neuroma or ganglion removals, carpal tunnel surgery etc) hand, wrist or forearm surgery. Informed consent Male: 57%; mean age: 45.5 years, range: 18 to 80 years Excluded: ASA physical status > 2 (see notes). Allergy to amide type local anaesthetic (LA), pregnancy, inability to co-operate, diseases affecting sensory or motor function of the upper extremity
Interventions	Multiple (neurostimulation method) versus single injection (transarterial/paraesthesia method) Blocks carried out by first author - consultant anaesthetist - other staff members or supervised residents Initial sedation with diazepam to apprehensive patients. Initial subcutaneous injection of 5 ml mepivacaine 1% with adrenaline 5 µg/ml to anaesthetize medial cutaneous nerves of arm or forearm 1. Multiple injection: injection using 24 gauge, 25 mm long insulated short-bevelled cannula of 5 ml mepivacaine 1% with adrenaline 5 µg/ml to 4 terminal motor nerves (musculocutaneous, median, radial and ulnar). Connected to nerve stimulator, current = 1.5 mA 2. Single injection: injection with 25 gauge, 35 mm long hypodermic needle of 80 ml mepivacaine 1% with adrenaline 2.5 µg/ml LA behind transfixed axillary artery (beforehand if hand paraesthesia elicited). Connected to nerve stimulator but current = 0 mA
Outcomes	Length of follow-up: surgical follow-up (5 to 10 days, then 3 to 4 weeks after) for adverse neurological outcomes; onset of sensory block assessed every 10 minutes Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area; use of propofol for restlessness caused by tourniquet) Time to be ready for surgery Pain during block Duration of tourniquet use Tourniquet discomfort and pain Problems (during injection and operation)

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K-Nielsen 1999b *(Continued)*

	Long-term complications (none)
Notes	One of the 2 excluded trial participants was an Inuit who did not understand trial procedures. The other participant, who already had coronary artery disease, developed chest pain - the surgery was cancelled Details of types of surgery, study period and other clarification received from Dr Koscielniak-Nielsen on 14 December 2004 The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand ...."
Allocation concealment (selection bias)	Low risk	"A computer-generated random allocation assuring an equal number of patients in both groups was obtained beforehand and sealed in numbered envelopes. An envelope containing the random assignment was opened after the patient's arrival at the anaesthesia room"
Blinding (performance bias and detection bias) All outcomes	Low risk	“The anaesthetist performing the block ... restarted the stopwatch and left the room. The blocks were ...assessed by an anaesthesiologist unaware of the applied technique"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up although 2 were excluded; because of language and heart problems respectively
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Unclear risk	Yes, aside from the distribution of the various operations, which were elective or acute hand, wrist or forearm surgery
Free from performance bias?	Low risk	Blocks carried out by first author - consultant anaesthetist - other staff members or supervised residents. Other care seemed comparable

Kjelstrup 2014

Methods	Method of randomization: patients were randomized using random digits; group allocation was sealed in envelopes opened just before the axillary block Blinding: only block assessors were blinded. Patients and staff performing the block were not blinded Loss to follow-up: none
Participants	Oslo, Norway Period of study: January 2009 to February 2011 45 adult people undergoing day surgery of the hand or forearm Male:female ratio: 33:12; mean age 42 to 49 years, range 18 to 75 years; ASA 1-2

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Kjelstrup 2014 *(Continued)*

Interventions	Multiple (triple) versus double versus single injection Single injection: median nerve was located by percutaneous mapping, and a catheter was inserted parallel to the median nerve and anterior to the axillary artery, using neurostimulation guidance, motor response (not specified) sought at 0.2 mA to 0.8 mA. Total local anaesthetic volume was injected through the catheter Double injection: transarterial injection with 25G hypodermic needle, injecting 30 ml of local anaesthetic lateral (deep) to the artery and 10 ml medial (superficial) to the artery Triple injection: combination of single-injection technique with insertion of catheter and transarterial injection. Median nerve was located by percutaneous mapping, and a catheter was inserted parallel to the median nerve and anterior to the axillary artery, using neurostimulation guidance, motor response (not specified) sought at 0.2 mA to 0. 8 mA. 10 ml of local anaesthetic was injected through the catheter, followed by 20 ml lateral (deep) to the artery and 10 ml medial (superficial to the artery) All patients received 40 ml of local anaesthetic mixture: 20 ml of 2% lidocaine + 20 ml 0.5% bupivacaine + 2.5 µg/ml of epinephrine All patients received premedication of oral paracetamol (acetaminophen) 1 g to 1.5 g and block sedation of intravenous midazolam 3.5 mg Patients received a supplementary peripheral nerve block at the elbow if sensory block was inadequate (0 to 1 on a 0 to 3 scale) at the time of testing (not standardized but mean time across groups was 52 to 57 minutes after block completion)
Outcomes	MRI pattern of spread Sensory blockade of all terminal nerves of brachial plexus (axillary, median, ulnar, radial, musculocutaneous, medial brachial cutaneous, medial antebrachial cutaneous, intercostobrachial) Motor blockade of 5 main terminal nerves of brachial plexus (axillary, median, ulnar, radial, musculocutaneous) Block performance time Need for local anaesthetic supplementation Adverse events: paraesthesia, intravascular injection, haematoma formation
Notes	Block testing was done only once, and after the MRI scan, so the interval between block completion and sensory/motor testing varied from patient to patient. There was, however, no significant difference in this interval between groups. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomised...using random digits."
Allocation concealment (selection bias)	Low risk	"Group allocation was sealed in envelopes opened just before the axillary block"
Blinding (performance bias and detection bias) All outcomes	Low risk	Block assessors were "anaesthetists who were blinded to the block method and MR images"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up

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Kjelstrup 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All major outcomes were defined and reported
Balance in baseline characteristics?	Low risk	Patient demographic and anaesthetic data were similar between groups
Free from performance bias?	Unclear risk	The technique is relatively complex and is prone to performance bias. It was not explicitly stated who performed the blocks

Lavoie 1992

Methods	Method of randomization: use of random number table. "The 75 patients were blocked in 15 groups of 5 patients each (group 1, group 2 etc allocated in a random way into each one of the 15 groups)." Double-blind: anaesthetist carrying out assessments and patients were blind to injection technique No loss to follow-up
Participants	Sherbrooke, Quebec, Canada Period of study: 1991 75 people undergoing upper limb surgery including the elbow down to the hand: fractures, soft tissues. Informed consent Male: 55%; mean age: 41 years Excluded: no details
Interventions	Multiple versus double versus single (radial nerve) versus single (median nerve) versus single (ulnar nerve) injection All received local anaesthetic (LA) solution: 30 ml/square metre body surface (approximately 50 ml/70 kg body weight) lidocaine 1% with adrenaline 5 µg/ml. A tourniquet was used in all cases. No premedication, sedation or IV analgesia mentioned. Anaesthetist performing the blocks was aware of the surgical site. After locating, by palpation, the axillary nerve in the axilla, 2 ml of 2% lidocaine injected subcutaneously to block medial cutaneous nerves of the arm. A 22 gauge insulated needle connected to peripheral nerve stimulator used to locate the nerves (0.5 mA current) 1. Multiple injection: to musculocutaneous, radial, median and ulnar nerves. LA volume equally divided between the 4 injections 2. Double injection: to musculocutaneous and one of radial, median or ulnar nerves directly related to surgical site. LA volume equally divided between the 2 injections 3. Single injection: to radial nerve of full volume of LA 4. Single injection: to median nerve of full volume of LA 5. Single injection: to ulnar nerve of full volume of LA
Outcomes	Length of follow-up: 30 minutes Sensory blockade Motor blockade Anaesthesia failure (incomplete sensory blockade, general anaesthesia: none) Adverse effects (none recalled by contact trialist)
Notes	Reply to request for details of methods, types of surgery and results, including adverse effects, received from Dr Martin on 5 January 2005. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement

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Lavoie 1992 *(Continued)*

Random sequence generation (selection bias)	Low risk	"We used a random number table. The 75 patients were blocked in 15 groups of 5 patients each (group 1, group 2 etc allocated in a random way into each one of the 15 groups)"
Allocation concealment (selection bias)	Unclear risk	No information, but some predictability may have occurred at the end of each block
Blinding (performance bias and detection bias) All outcomes	Low risk	"The anaesthetist performing the block was aware of the surgery but another anaesthetist unaware of the patients' group evaluated the sensory and motor blocks ..", ".. the patient did not know what aspect of his axillary block was studied specifically .."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Possible but no protocol available
Balance in baseline characteristics?	Low risk	Fine. Although no details of surgery, there was balance in the implicated nerves
Free from performance bias?	Low risk	Seems likely and the author suggested that the "technique of randomization by blocks allows that the learning of the technique is uniform on the 5 groups of patients"

Pere 1993

Methods	Method of randomization: not stated No blinding indicated No loss to follow-up (assumed for 3 hours follow-up)
Participants	Helsinki, Finland Period of study: not stated 50 people undergoing hand, forearm or elbow surgery. Informed consent Male:female ratio: not stated; mean age: 37 years Excluded: ASA physical status > 2 (see notes)
Interventions	Double (transarterial method) versus single injection (neurostimulation method) All received LA solution: mepivacaine 1% with adrenaline 5 µg/ml Premedication with diazepam and oxycodone 1. Double injection "transarterial": injection using 0.7 x 50 mm needle advanced through the artery. Injection of half of 45 ml LA deep to and half superficial to axillary artery 2. Single "perivascular" injection: injection using 0.7 x 50 mm needle and facilitated by nerve stimulator of 45 ml LA after location of axillary brachial plexus Neurovascular sheath compressed during the injection and for 3 minutes afterwards
Outcomes	Length of follow-up: 3 hours Sensory blockade - 8 nerves Motor blockade Analgesic failure (use of supplementary blocks; general anaesthesia; use of opioids) Duration of tourniquet use

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Pere 1993 *(Continued)*

Notes	Subsidiary radiological study of 16 people also performed. It was not clear if the people were randomized to the same comparison as the clinical trial. Need for supplementary blocks (2/8 versus 2/8) and more than 1 dose of opoid (1 versus 1) was the same in both groups Response from Dr Pere, received 10 February 2005, indicated, with regret, that there was now no more information available on this trial The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were allocated randomly to two groups"
Allocation concealment (selection bias)	Unclear risk	No details of method
Blinding (performance bias and detection bias) All outcomes	High risk	No mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seemed fine
Selective reporting (reporting bias)	Unclear risk	Protocol not available. No mention of complications
Balance in baseline characteristics?	Unclear risk	"There were no differences between the groups in patient age, height or weight.." However, no details of type of surgery or gender
Free from performance bias?	Unclear risk	No details of who administered the anaesthesia

Ramirez-Gomez 2010

Methods	Method of randomization: not stated No blinding of outcome assessor No loss to follow-up; excluded 3 patients who received general anaesthesia from certain outcome assessments based on assumed block failure
Participants	Tamaulipas, Mexico Period of study: not stated 50 adult patients undergoing surgery of the elbow, forearm, wrist and hand Male:female ratio 27:23. ASA 1-3. Age not stated
Interventions	Multiple versus single injection, both neurostimulation guided, motor response sought at 0.4 mA or less

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Ramirez-Gomez 2010 *(Continued)*

	Multiple injection: radial nerve + one or more of the following: median, ulnar, musculocutaneous Single injection: any motor response All patients received 30 ml of local anaesthetic mixture: 20 ml of 1.5% lidocaine + 10 ml 0.25% bupivacaine All patients received pre-operative ketorolac 1 mg/kg and block sedation of midazolam 0.1 mg/kg and nalbuphine 0.1 mg/kg Patients received local anaesthetic supplementation if sensory and motor block was inadequate after 30 minutes, and general anaesthesia if there was intraoperative pain
Outcomes	Need for local anaesthetic supplementation Need for general anaesthesia Duration of motor and sensory block Surgical site pain score at 8 hours and 24 hours postoperatively
Notes	Study was published in Spanish and translated by co-author (JC). The methods state that patients were undergoing trauma surgery of the lower arm, however the data supplied indicate that the majority underwent surgery for non-traumatic conditions.There were inconsistencies in the paper between data reported in the text and in the tables. The authors were contacted for clarification of methodology and data; a response was received which provided some additional information but did not answer all queries. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding (personal communication from lead author)
Incomplete outcome data (attrition bias) All outcomes	High risk	The reported denominators for each group vary between the text and the tables. The authors clarification also contains inconsistencies in the numbers. It is unclear if this is simple error or reflects incomplete outcome data. Communication with the authors was unhelpful in clarifying this
Selective reporting (reporting bias)	Unclear risk	They appear to have collected data that were not reported, e.g. onset of block in the various dermatomes. Complication data were not reported. Communication with the authors was unhelpful in clarifying this
Balance in baseline characteristics?	Unclear risk	There was a high proportion of minor surgery, e.g. carpal tunnel release. The distribution of this surgery between groups was not stated
Free from performance bias?	Unclear risk	Multiple-injection group: the proportion of patients receiving 2, 3 or 4 injections was not stated, which could have an influence on the results. It was not clear how skilled the investigators were at performing the more complex multiple-injection technique

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Rodriguez 2005

Methods	Method of randomization: computer-generated randomization list Blinded outcome assessor No loss to follow-up. 4 incomplete procedures included in intention-to-treat analysis
Participants	Santiago, Spain Period of study: not stated 120 people undergoing surgery of the upper limb (not otherwise specified). Informed consent Male: 27%; mean age: 51 years Excluded: ASA physical status > 3 (see notes)
Interventions	Multiple versus double versus single (median nerve) versus single (radial nerve) injection All received local anaesthetic (LA) solution: 1.5% mepivacaine; total volume 40 ml. All blocks were neurostimulation-guided with a 22G insulated block needle. All blocks were performed by one of 2 senior anaesthesiologists Sedative premedication with 1 mg to 3 mg of IV midazolam according to clinical judgement 1. Multiple injection: injection of 15 ml to radial nerve, 15 ml to median nerve, 10 ml to musculocutaneous nerve 2. Double injection: injection of 35 ml on radial nerve, injection of 5 ml on musculocutaneous nerve. 3. Single injection (median): injection of 40 ml on median nerve 4. Single injection (radial): injection of 40 ml on radial nerve Blocks were supplemented preoperatively if the operative nerve distributions did not have complete sensory block before operation; timing of this was not specified Intraoperative pain was treated with infiltration of local anaesthetic at the site, or with injection of 50 µg to 100 µg of fentanyl. General anaesthesia was used if pain was persistent
Outcomes	Length of follow-up: sensory and motor block assessed at 5 and 20 minutes. No follow-up detailed beyond that Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; general anaesthesia; pain in operative field) Block performance time
Notes	Request for additional information on method of randomization, blinding and results sent to Dr Rodriguez on 13 July 2010; no reply received The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assignment was performed by means of a computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants - not blinded. Caregivers - not blinded. Outcome assessors - blinded. No mention of safeguards, but plausible. Blinding is within study limitations and unlikely to influence outcome

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Rodriguez 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis was done and there were none lost to follow-up. However, the length of follow-up was only 20 minutes, yet authors state "we had the clinical impression that many incomplete blocks progressed until 30 minutes." It is unclear if they supplemented the blocks after 20 minutes, or later, yet this is reported as an outcome
Selective reporting (reporting bias)	Unclear risk	Protocol not available. No reporting of complications, which is unusual for this type of study
Balance in baseline characteristics?	Unclear risk	No details of type of surgery performed
Free from performance bias?	Low risk	Blocks were administered by one of 2 senior anaesthesiologists

Rodriguez 2008

Methods	Method of randomization: computer-generated randomization list Blinded outcome assessor Loss for follow-up: one patient in the double group excluded after randomization and block performance as assessment was not possible
Participants	Santiago, Spain Period of study: not stated 60 people undergoing surgery of the hand (49), forearm (3), elbow (8). Informed consent Male: 48.3%; mean age: 58 years Excluded: ASA physical status > 3 (see notes)
Interventions	Multiple versus double injection (both groups using neurostimulation method) All received local anaesthetic (LA) solution: 2% mepivacaine of volume 30 ml, and 1% mepivacaine of volume 5 ml (to musculocutaneous nerve); total volume 35 ml. All blocks were neurostimulation-guided with a 22G insulated block needle. Identity and experience level of operators performing block were not specified. Sedative premedication with 1 mg to 3 mg of IV midazolam 1. Multiple injection: injection of 15 ml to radial nerve, 15 ml to median nerve, 5 ml to musculocutaneous nerve 2. Double injection: injection of 30 ml on radial nerve, injection of 5 ml on musculocutaneous nerve
Outcomes	Length of follow-up: sensory and motor block assessed at 10, 20 and 30 minutes Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; general anaesthesia; pain in operative field) Block performance time (reported as median and ranges) Acute complications during block procedure
Notes	Request for additional information on method of randomization, blinding and results sent to Dr Rodriguez on 13 July 2010; no reply received The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

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Rodriguez 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assignment was performed by computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants - not blinded. Caregivers - not blinded. Outcome assessors - blinded. No mention of safeguards, but plausible. Blinding is within study limitations and unlikely to influence outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Mostly: 4 incomplete procedures were included - but there is slight concern over the 1 excluded patient; the percentages in Table 4 imply the patient was included in the analysis
Selective reporting (reporting bias)	Unclear risk	No protocol and side effects not reported
Balance in baseline characteristics?	Unclear risk	Baseline characteristics balanced but no details of distribution of types of surgery
Free from performance bias?	Unclear risk	The identity and experience of care providers was not stated

Serradell Catalan 2001

Methods	Method of randomization: use of a computer-generated table of random numbers to generate a randomization list Blinded outcome assessor No loss to follow-up
Participants	Barcelona, Spain Period of study: 1999 to 2000 100 adults (> 18 years) undergoing upper limb (forearm, wrist or hand) post-traumatic orthopaedic surgery. ASA physical status 1-3 (see notes). Informed consent Male: 56%; mean age: 55 years Excluded: usual contraindications for axillary nerve blockade and regional anaesthesia. Motor or sensory disease of limb involved in surgical procedure. Non-palpable axillary artery pulse
Interventions	Multiple (musculocutaneous, radial, median and ulnar nerves) versus multiple (triple: musculocutaneous + 2 of radial/median/ulnar nerves) versus double (2 of radial/median/ulnar nerves) versus double (musculocutaneous + radial/median/ulnar nerve) versus single (radial/ median/ ulnar nerve) injection All received local anaesthetic (LA) solution: 40 ml mepivacaine 1% Oral premedication with lorazepam 1 mg and sedation with IV midazolam. One anaesthetist performed all the blocks. After locating the axillary artery in the axilla, lidocaine 1%was injected subcutaneously over the arterial pulse. A 22 gauge 50 mm long insulated needle connected to nerve stimulator was used to locate the nerves 1. Multiple injection: to musculocutaneous, radial, median and ulnar nerves 2. Multiple injection: to musculocutaneous nerve (10 ml LA) and either to the radial and median nerves or the radial and ulnar nerves or the median and ulnar nerves 3. Double injection: to the radial and median nerves or the radial and ulnar nerves or the median and ulnar nerves

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Serradell Catalan 2001 *(Continued)*

	4. Double injection: to musculocutaneous nerve (10 ml LA) and either to the radial, median or ulnar nerve 5. Single injection: to the radial or median or ulnar nerve
Outcomes	Length of follow-up: 3 months surgical follow-up (also 24 hours) for adverse neurological outcomes; onset of sensory block assessed every 10 minutes, 40 minutes; also duration of block Sensory blockade Motor blockade Anaesthesia failure (incomplete sensory blockade, incomplete motor blockade) Time for block Duration of sensory blockade Duration of tourniquet use Tourniquet discomfort Problems (during injection) Long-term neurological complication Participant opinion of technique
Notes	Part translation from Spanish provided by co-author (SR) Response to request for details of methods, trial setting and use of intraoperative opioids and sedatives received from Dr Serradell Catalan on 3 February 2005 The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated table of random numbers"
Allocation concealment (selection bias)	High risk	"read off the allocation from a list"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Single blind". Blinded doctor for motor and sensory block evaluation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Possible but no protocol available. There was a sample size calculation
Balance in baseline characteristics?	Unclear risk	Yes, aside from the distribution of the various operations, which were upper limb (forearm, wrist or hand) post-traumatic orthopaedic surgery
Free from performance bias?	Low risk	All blocks were performed by the same doctor. Other care seemed comparable

Sia 2001

Methods	Method of randomization: not stated Double-blind

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Sia 2001 *(Continued)*

	Blinded outcome assessor No loss to follow-up (assumed for 30 days follow-up)
Participants	Florence, Italy Period of study: 2000 100 people undergoing elective upper limb surgery in hand, wrist or forearm. Informed consent Male: 55%; mean age: 41.5 years Excluded: ASA physical status > 2 (see notes)
Interventions	Multiple versus double injection (both groups using neurostimulation method) All received local anaesthetic (LA) solution: lidocaine 2% and bupivacaine 0.5% in 1:1 ratio. Nerve blockade facilitated using 22G insulated short-bevelled needle and nerve stimulator. All blocks carried out by one operator All received IV midazolam (sedation) and fentanyl 5 minutes before block. Initial subcutaneous injection of 4 ml LA to anaesthetize medial cutaneous nerves of arm or forearm 1. Multiple (triple) injection: injection of 10 ml LA to musculocutaneous nerve; then 10 ml to median nerve and 20 ml to radial nerve 2. Double injection: injection of 20 ml LA to median nerve; then 20 ml to radial nerve
Outcomes	Length of follow-up: nerve injury at 48 hours, neurological sequelae at 10 and 30 days; 30 minutes or until sensory block (and duration of surgery) Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area) Duration of anaesthesia Duration of surgery Duration of tourniquet use Tourniquet discomfort and pain Problems (during injection and operation) Long-term neurological complication (none)
Notes	Request for details of method of randomization, types of surgery and some of the results sent to Dr Sia on 9 November 2004 The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"One hundred patients were randomly allocated to 2 groups." No details of method
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind study"; "All blocks .... were assessed by an investigator unaware of group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up apparent for block performance

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Sia 2001 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Possible but no protocol available. The selection of primary outcome for sample size calculation of the blocking of the musculocutaneous nerve is unusual
Balance in baseline characteristics?	Unclear risk	Yes, aside from the distribution of the various operations, which were elective forearm, wrist or hand surgery
Free from performance bias?	Low risk	"All blocks were performed or supervised by the first author." Other care seemed comparable

Sia 2010a

Methods	Method of randomization: computer-generated randomization list Blinded outcome assessor No loss to follow-up (14 patients - distributed between the 3 trials Sia 2010a, b + c - were excluded after randomization because of inability to locate the desired nerves)
Participants	Florence, Italy Period of study: 2005 to 2008 138 people undergoing surgery on the fifth finger (fractures, neoformations, tendon injuries) and on the fifth metacarpal bone. Informed consent Male: 56.5%; mean age: 44 years Excluded: ASA physical status > 2 (see notes)
Interventions	Multiple (triple) versus single (ulnar) injection (both groups using neurostimulation method) All received local anaesthetic (LA) solution: lidocaine 2% and bupivacaine 0.5% in 1:1 ratio; total volume 40 ml. Nerve blockade facilitated using 22G insulated short-bevelled needle and nerve stimulator. All blocks carried out by one experienced operator All received IV midazolam 20 µg/kg and fentanyl 1 µg/kg 5 minutes before block. Initial subcutaneous injection of 4 ml LA over the axillary artery to anaesthetize medial cutaneous nerves of arm and forearm. 1. Multiple (triple) injection: injection of 10 ml LA to median nerve; 6 ml to musculocutaneous nerve and 20 ml to radial nerve 2. Single injection: injection of 36 ml LA to ulnar nerve
Outcomes	Length of follow-up: 30 minutes for sensory and motor block; 48 hours for nerve injury; neurological sequelae at 10 and 30 days Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area) Block performance time Block onset time Time to readiness for surgery Duration of surgery Duration of tourniquet use Tourniquet discomfort and pain Need for intraoperative sedation Problems (during injection and operation) Long-term neurological complication (none)
Notes	Request for clarification on patient enrolment and additional data on complications sent to Dr Salvatore Sia on 14 October 2010; reply received 6 November 2010 Although the Results section for the 3 trials states that 6 patients were excluded in the triple injections groups (TNS) and 8 patients in single injection groups (SEL), Dr Sia clarified in a personal communication that these were treated as "pre-operative" dropouts and were replaced by other patients

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Sia 2010a *(Continued)*

	The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients undergoing each type of surgery were randomly assigned by a computer-generated list ..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients - not blinded. Caregiver - unblinded. Assessors - blinded. “All the blocks were... assessed by a blinded investigator.” Blinding is within study limitations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Six patients in group TNS and 8 in group SEL were excluded from the study because all the prearranged nerves were not located by nerve stimulation.” Personal communication from the author indicates that these were post-randomization exclusions.
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Low risk	Balanced
Free from performance bias?	Unclear risk	All the blocks were performed or supervised by the first author, however the number and experience level of supervised care providers is not stated

Sia 2010b

Methods	Method of randomization: computer-generated randomization list Blinded outcome assessor No loss to follow-up (14 patients - distributed between the 3 trials Sia 2010a, b + c were excluded after randomization because of inability to locate the desired nerves)
Participants	Florence, Italy Period of study: 2005 to 2008 138 people undergoing superficial surgery (without bone involvement) on the palm (e.g. Dupuytren contracture, tendons or nerve injuries, neoformations) or on the dorsum of the hand (e.g. cysts, neoformations, pathologies of extensor tendons). Informed consent Male: 45%; mean age: 49.5 years Excluded: ASA physical status > 2 (see notes)
Interventions	Multiple (triple) versus double (median and ulnar) injection All received local anaesthetic (LA) solution: lidocaine 2% and bupivacaine 0.5% in 1:1 ratio; total volume 40 ml. Nerve blockade facilitated using 22G insulated short-bevelled needle and nerve stimulator. All blocks carried out by one experienced operator All received IV midazolam 20 µg/kg and fentanyl 1 µg/kg 5 minutes before block. Initial subcutaneous injection of 4 ml LA over the axillary artery to anaesthetize medial cutaneous nerves of arm and forearm

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Sia 2010b *(Continued)*

	1. Multiple (triple) injection: injection of 10 ml LA to median nerve; 6 ml to musculocutaneous nerve and 20 ml to radial nerve 2. Double injection: injection of 18 ml LA to ulnar nerve, injection of 18 ml LA to median nerve
Outcomes	Length of follow-up: 30 minutes for sensory and motor block; 48 hours for nerve injury; neurological sequelae at 10 and 30 days Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area) Block performance time Block onset time Time to readiness for surgery Duration of surgery Duration of tourniquet use Tourniquet discomfort and pain Need for intraoperative sedation Problems (during injection and operation) Long-term neurological complication (none)
Notes	Request for clarification on patient enrolment and additional data on complications sent to Dr Salvatore Sia on 14 October 2010; reply received 6 November 2010 Although the Results section for the 3 trials states that 6 patients were excluded in the triple injections groups (TNS) and 8 patients in single injection groups (SEL), Dr Sia clarified in a personal communication that these were treated as "pre-operative" dropouts and were replaced by other patients The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients undergoing each type of surgery were randomly assigned by a computer-generated list ..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients - not blinded. Caregiver - unblinded. Assessors - blinded. “All the blocks were... assessed by a blinded investigator.” Blinding is within study limitations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Six patients in group TNS and 8 in group SEL were excluded from the study because all the prearranged nerves were not located by nerve stimulation.” Personal communication from the author indicates that these were post-randomization exclusions
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Low risk	Balanced

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Sia 2010b *(Continued)*

Free from performance bias?	Unclear risk	All the blocks were performed or supervised by the first author, however the number and experience level of supervised care providers is not stated

Sia 2010c

Methods	Method of randomization: computer-generated randomization list Blinded outcome assessor No loss to follow-up (14 patients - distributed between the 3 trials Sia 2010a, b + c - were excluded after randomization because of inability to locate the desired nerves)
Participants	Florence, Italy Period of study: 2005 to 2008 138 people undergoing any surgery on the first 3 fingers in which only 1 or 2 nerves were involved. Informed consent Male: 52%; mean age: 45.5 years Excluded: ASA physical status > 2 (see notes)
Interventions	Multiple (triple) versus double (median and radial) injection All received local anaesthetic (LA) solution: lidocaine 2% and bupivacaine 0.5% in 1:1 ratio; total volume 40 ml. Nerve blockade facilitated using 22G insulated short-bevelled needle and nerve stimulator. All blocks carried out by one experienced operator All received IV midazolam 20 µg/kg and fentanyl 1 µg/kg 5 minutes before block. Initial subcutaneous injection of 4 ml LA over the axillary artery to anaesthetize medial cutaneous nerves of arm and forearm 1. Multiple (triple) injection: injection of 10 ml LA to median nerve; 6 ml to musculocutaneous nerve and 20 ml to radial nerve 2. Double injection: injection of 18 ml LA to median nerve and injection of 18 ml LA to radial nerve
Outcomes	Length of follow-up: 30 minutes for sensory and motor block; 48 hours for nerve injury; neurological sequelae at 10 and 30 days Sensory blockade Motor blockade Analgesic failure (use of supplementary anaesthesia; use of opioids for tourniquet pain in operation area) Block performance time Block onset time Time to readiness for surgery Duration of surgery Duration of tourniquet use Tourniquet discomfort and pain Need for intraoperative sedation Problems (during injection and operation) Long-term neurological complication (none)
Notes	Request for clarification on patient enrolment and additional data on complications sent to Dr Salvatore Sia on 14 October 2010; reply received 6 November 2010 Although the Results section for the 3 trials states that 6 patients were excluded in the triple injections groups (TNS) and 8 patients in single injection groups (SEL), Dr Sia clarified in a personal communication that these were treated as "pre-operative" dropouts and were replaced by other patients The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

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Sia 2010c *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients undergoing each type of surgery were randomly assigned by a computer-generated list ..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients - not blinded. Caregiver - unblinded. Assessors - blinded. “All the blocks were... assessed by a blinded investigator.” Blinding is within study limitations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Six patients in group TNS and 8 in group SEL were excluded from the study because all the prearranged nerves were not located by nerve stimulation.” Personal communication from the author indicates that these were post-randomization exclusions
Selective reporting (reporting bias)	Low risk	No protocol but same plan for series of trials. Clearly reported primary outcomes. Ethics committee acceptance reported
Balance in baseline characteristics?	Low risk	Balanced
Free from performance bias?	Unclear risk	All the blocks were performed or supervised by the first author, however the number and experience level of supervised care providers is not stated

Turkan 2002

Methods	Method of randomization: not stated Blinded outcome assessor No loss to follow-up apparent
Participants	Ankara, Turkey Period of study: not stated 69 people undergoing orthopaedic or trauma surgery of the upper extremity (not otherwise specified). Informed consent Male: 75%; mean age: 49 years Excluded: ASA physical status > 2 (see notes)
Interventions	Double versus single (Winnie's technique) versus single (transarterial) injection All received local anaesthetic (LA) solution: 2% prilocaine and 0.5% bupivacaine in 1:1 ratio; total volume 40 ml. Identity of operators performing block were not specified; but they were described as experienced Sedative premedication with 0.15 mg/kg of IM midazolam 1. Double injection: injection of 20 ml using Winnie's technique (endpoint of fascial click and paraesthesia in hand or forearm), and injection of 20 ml using transarterial technique posterior to the axillary artery 2. Single injection: injection of 40 ml using Winnie's technique (endpoint of fascial click and paraesthesia in hand or forearm) 3. Single injection: injection of 40 ml using transarterial technique posterior to the axillary artery

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Turkan 2002 *(Continued)*

	When patient in extreme anxiety or block was incomplete, propofol (≤ 3 mg/kg) and/or fentanyl (≤ 1µg/kg) was administered intraoperatively
Outcomes	Length of follow-up: sensory and motor block assessed at 10, 20 and 30 minutes Sensory blockade Analgesic failure (use of supplementary anaesthesia) Tourniquet discomfort and pain
Notes	The ASA (American Society of Anesthesiologists) physical status classification is a system for assessing the fitness of patients before surgery. It has 5 categories (1 to 5): 1 = healthy, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe disease that is a constant threat to life, 5 = moribund. Funding sources and declarations of author interests: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were divided randomly into three groups..". No further details given
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated for participants, operators. It is mentioned that part of sensory testing was done by a blinded surgeon, but no detail given for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not evident
Selective reporting (reporting bias)	Unclear risk	A bit vague in definition of outcomes and some of the P values seem excessive
Balance in baseline characteristics?	Unclear risk	Balanced for sex, age, weight and height but no information on surgery
Free from performance bias?	Unclear risk	Insufficient detail given regarding operator experience. “Experienced hands” implied in Discussion but no information to judge this

ASA = American Society of Anaesthesiologists; G = gauge; IM = intramuscular; IV = intravenous; kg = kilogram; LA = local anaesthetic; mA = milliampere; mg = milligram; ml = millilitre; MRI = magnetic resonance imaging; SEL = selective single nerve stimulation; TA = transarterial; TNS = triple nerve stimulation; µg = microgram

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

Study	Reason for exclusion
Bernucci 2012	Not in scope of review: use of ultrasound-guided method
Bloc 2010	Not in scope of review: use of ultrasound-guided method
Bouaziz 1997	Not in scope of review: comparison of 2 approaches: midhumeral versus axillary
Carre 2000	Not in scope of review: children only

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Study	Reason for exclusion
Gianesello 2010	Not in scope of review: review of full text revealed that the study compared 2 different multiple-injection methods
Huynh 2012	Not in scope of review: use of ultrasound-guided method
Imasogie 2010	Not in scope of review: use of ultrasound-guided method
K-Nielsen 2000	Not in scope of review: comparison of 2 approaches: subcoracoid versus axillary
Kjelstrup 2006	Non-randomized study
Liu 2005	Not in scope of review: use of ultrasound-guided method
Sia 2001b	Not in scope of review: both interventions tested belonged to the multiple-injection group
Singelyn 1992	Not in scope of review: single injection in both groups
Sites 2006	Not in scope of review: use of ultrasound-guided method
Tran 2012	Not in scope of review: use of ultrasound-guided method
Tuominen 1987	Not in scope of review: review of the full text revealed that these were both single-injection techniques
Vester-Andersen 1984	Not in scope of review: single injection into the same site via indwelling catheter
Vester-Andersen 1986	Not in scope of review: single injection into the same site via indwelling catheter
Youssef 1988	Not in scope of review: review of the full text revealed that these were both single-injection techniques
Yu 2007	Not in scope of review: use of ultrasound-guided method

DATA AND ANALYSES

Comparison 1. Double versus single-injection technique

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary anaesthesia failure (incomplete sensory block)	9	527	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.34, 0.89]
1.1 Transarterial injection (for double injection)	5	267	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.47, 1.47]
1.2 Location by neurostimulation (for double injection)	4	260	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.22, 0.73]

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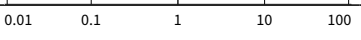
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Primary anaesthesia failure - subgrouped by outcome definition	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Incomplete overall sensory block	5	268	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.29, 0.86]
2.2 Supplemental blocks for surgical area	5	309	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.11]
3 Complete failure of block: general anaesthesia or new plexus block	7	368	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.33, 5.01]
4 Incomplete motor block	4	229	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.03]
5 Secondary analgesia failure	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Pain in surgical site/operative field	3	160	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.25, 1.25]
5.2 Tourniquet pain	2	104	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.22, 1.52]
5.3 Intraoperative sedatives	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.31, 1.31]
6 Timing (in minutes)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Time for block	2	90	Mean Difference (IV, Fixed, 95% CI)	2.05 [1.18, 2.93]
6.2 Duration of operation	1	50	Mean Difference (IV, Fixed, 95% CI)	9.0 [-8.19, 26.19]
6.3 Duration of tourniquet	3	154	Mean Difference (IV, Fixed, 95% CI)	2.44 [-5.24, 10.13]
6.4 Duration of block	2	129	Mean Difference (IV, Fixed, 95% CI)	11.98 [-6.73, 30.68]
7 Complications during nerve block	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Arterial puncture	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Venous puncture	3	140	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.16, 4.78]
7.3 Paraesthesia	3	140	Risk Ratio (M-H, Fixed, 95% CI)	5.91 [1.25, 28.03]
7.4 Tachycardia (intravascular injections)	2	90	Risk Ratio (M-H, Fixed, 95% CI)	4.15 [0.46, 37.13]
8 Adverse effects (> 24 hours)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Patient discomfort and dissatisfaction with method	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Patient uncomfortable	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Patient would not have method again	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

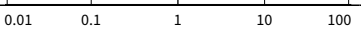
Analysis 1.1. Comparison 1 Double versus single-injection technique, Outcome 1 Primary anaesthesia failure (incomplete sensory block).

Study or subgroup	Double n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Transarterial injection (for double injection)					
Goldberg 1987	4/19	10/40		10.98%	0.84[0.3,2.34]
Hickey 1993	1/19	8/40		4.46%	0.26[0.04,1.96]
Kjelstrup 2014	5/15	5/15		11.1%	1[0.36,2.75]
Pere 1993	12/25	9/25		15.65%	1.33[0.69,2.59]
Turkan 2002	2/23	13/46		7.57%	0.31[0.08,1.25]
Subtotal (95% CI)	**101**	**166**		**49.76%**	**0.83[0.47,1.47]**
Total events: 24 (Double), 45 (Single)					
Heterogeneity: Tau^2=0.12; Chi^2=5.65, df=4(P=0.23); I^2=29.18%					
Test for overall effect: Z=0.65(P=0.52)					
1.1.2 Location by neurostimulation (for double injection)					
Inberg 1999	5/25	22/25		13.76%	0.23[0.1,0.5]
Lavoie 1992	1/15	23/45		4.8%	0.13[0.02,0.89]
Rodriguez 2005	7/30	22/60		14.7%	0.64[0.31,1.32]
Serradell Catalan 2001	13/40	12/20		16.98%	0.54[0.31,0.96]
Subtotal (95% CI)	**110**	**150**		**50.24%**	**0.4[0.22,0.73]**
Total events: 26 (Double), 79 (Single)					
Heterogeneity: Tau^2=0.18; Chi^2=6.16, df=3(P=0.1); I^2=51.27%					
Test for overall effect: Z=2.99(P=0)					
Total (95% CI)	**211**	**316**		**100%**	**0.55[0.34,0.89]**
Total events: 50 (Double), 124 (Single)					
Heterogeneity: Tau^2=0.26; Chi^2=17.7, df=8(P=0.02); I^2=54.81%					
Test for overall effect: Z=2.47(P=0.01)					
Test for subgroup differences: Chi^2=2.97, df=1 (P=0.08), I^2=66.3%					

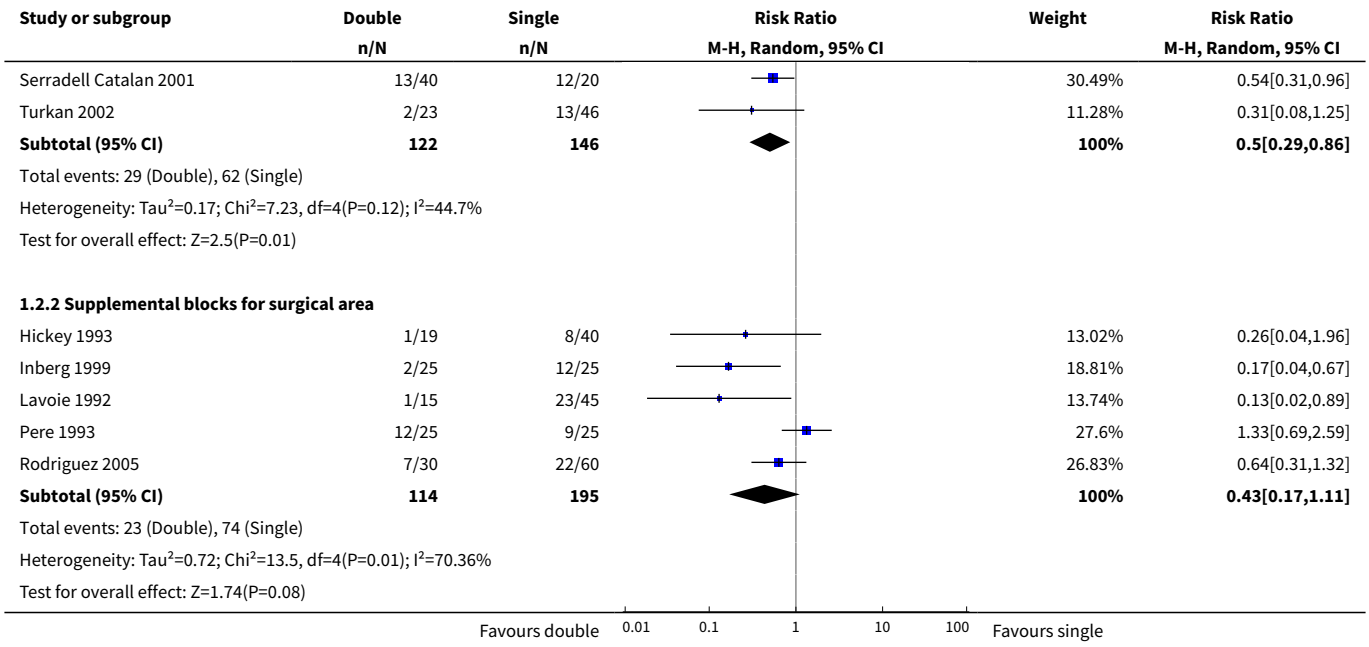


Analysis 1.2. Comparison 1 Double versus single-injection technique, Outcome 2 Primary anaesthesia failure - subgrouped by outcome definition.

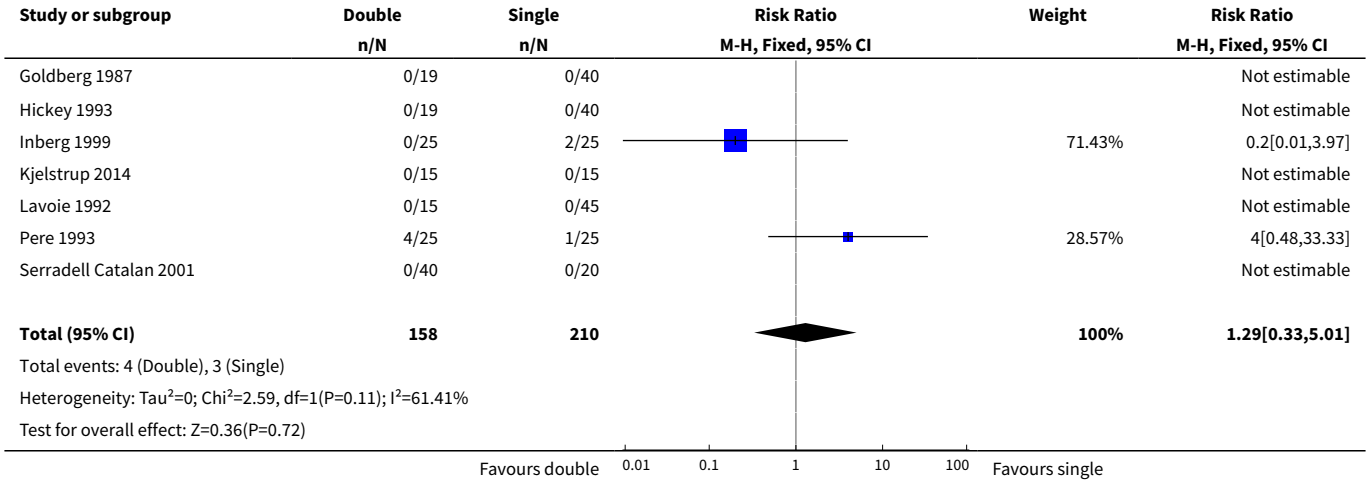
Study or subgroup	Double n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Incomplete overall sensory block					
Goldberg 1987	4/19	10/40		17.45%	0.84[0.3,2.34]
Inberg 1999	5/25	22/25		23.09%	0.23[0.1,0.5]
Kjelstrup 2014	5/15	5/15		17.68%	1[0.36,2.75]



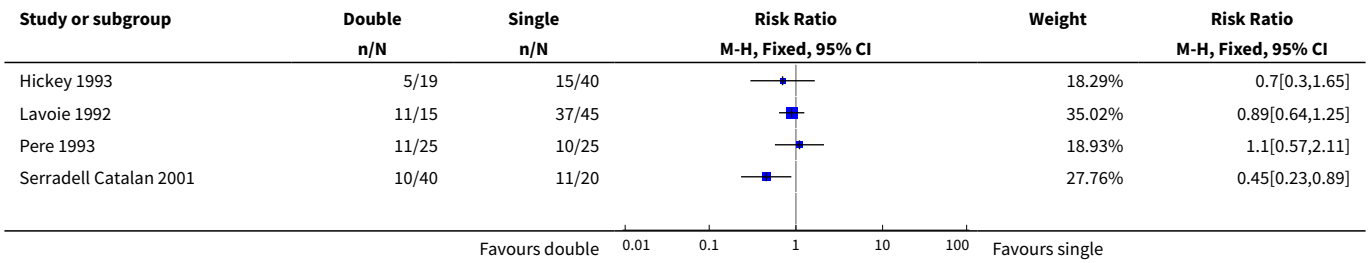
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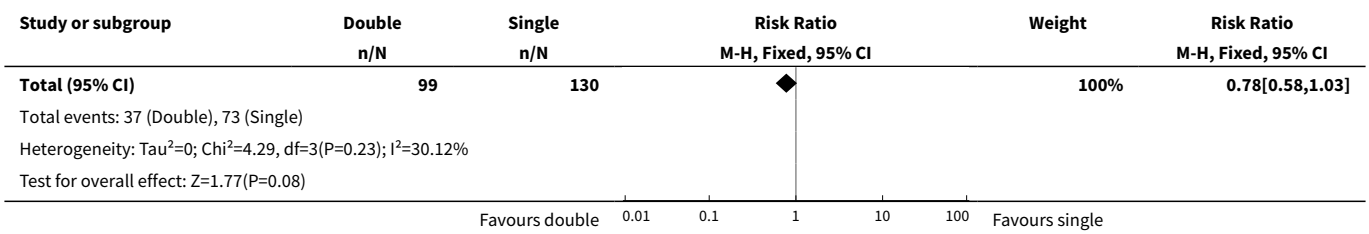
Analysis 1.3. Comparison 1 Double versus single-injection technique, Outcome 3 Complete failure of block: general anaesthesia or new plexus block.



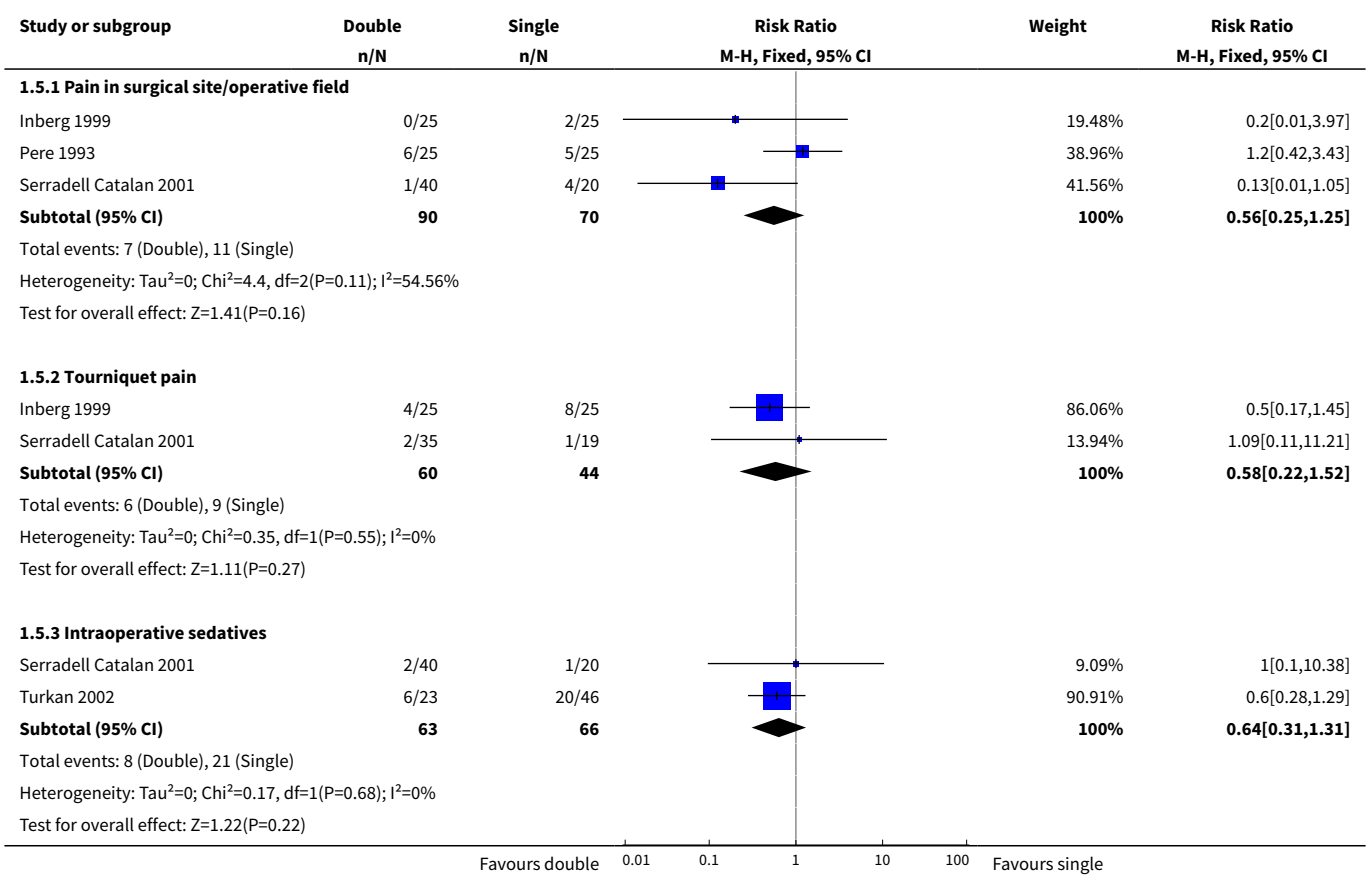
Analysis 1.4. Comparison 1 Double versus single-injection technique, Outcome 4 Incomplete motor block.



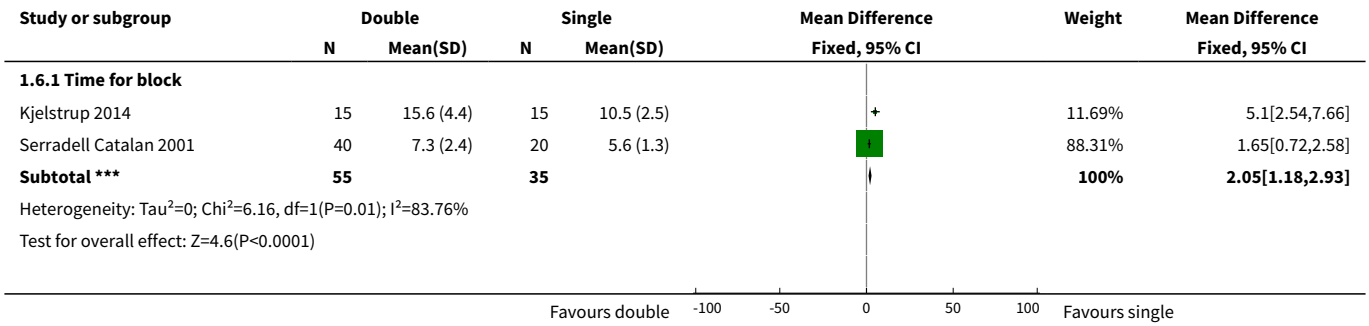
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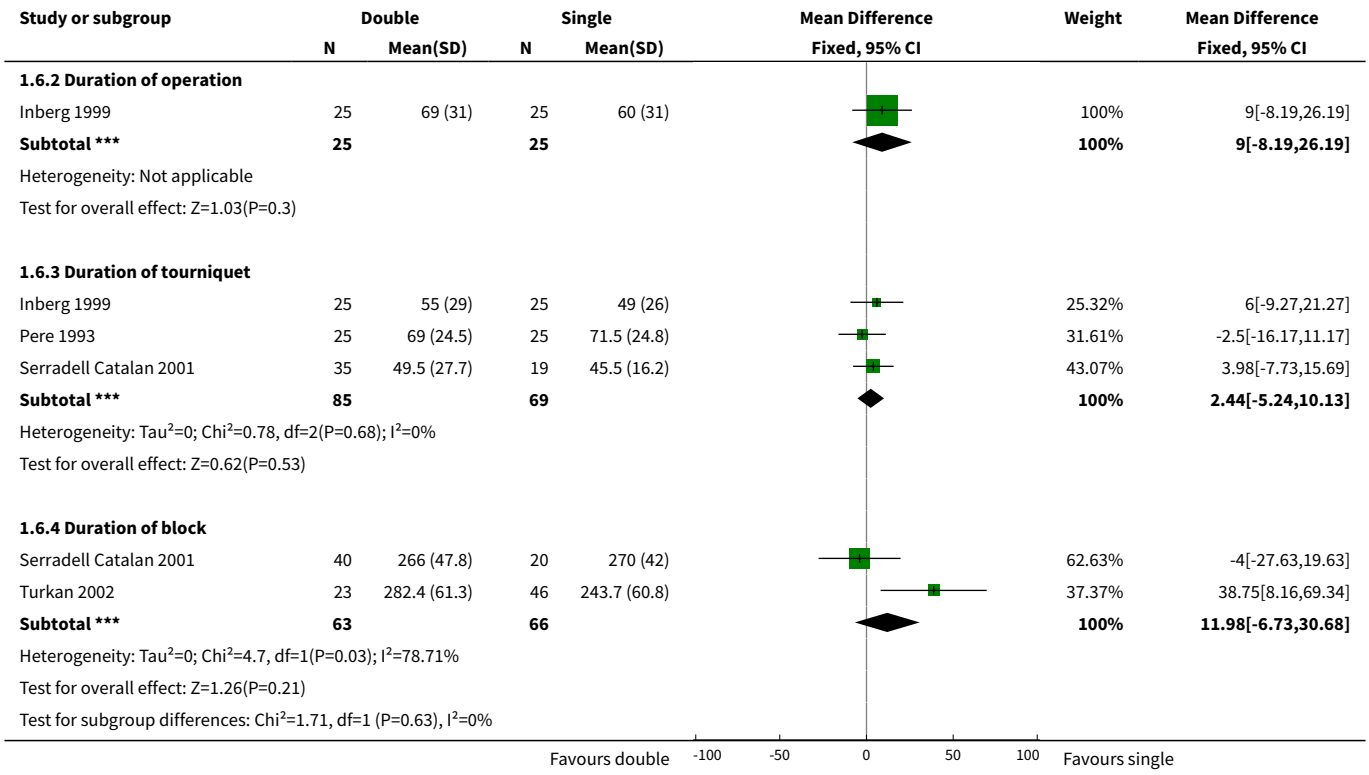
Analysis 1.5. Comparison 1 Double versus single-injection technique, Outcome 5 Secondary analgesia failure.



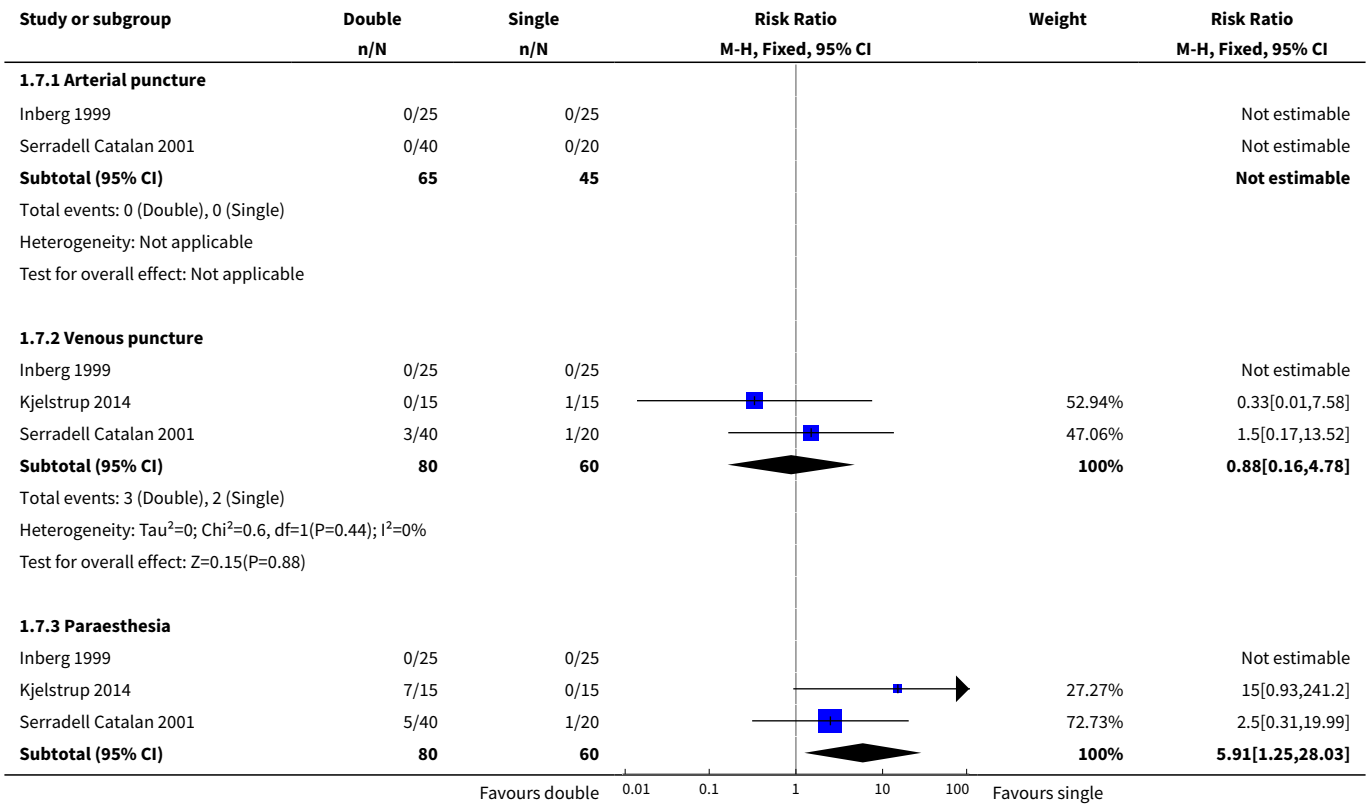
Analysis 1.6. Comparison 1 Double versus single-injection technique, Outcome 6 Timing (in minutes).



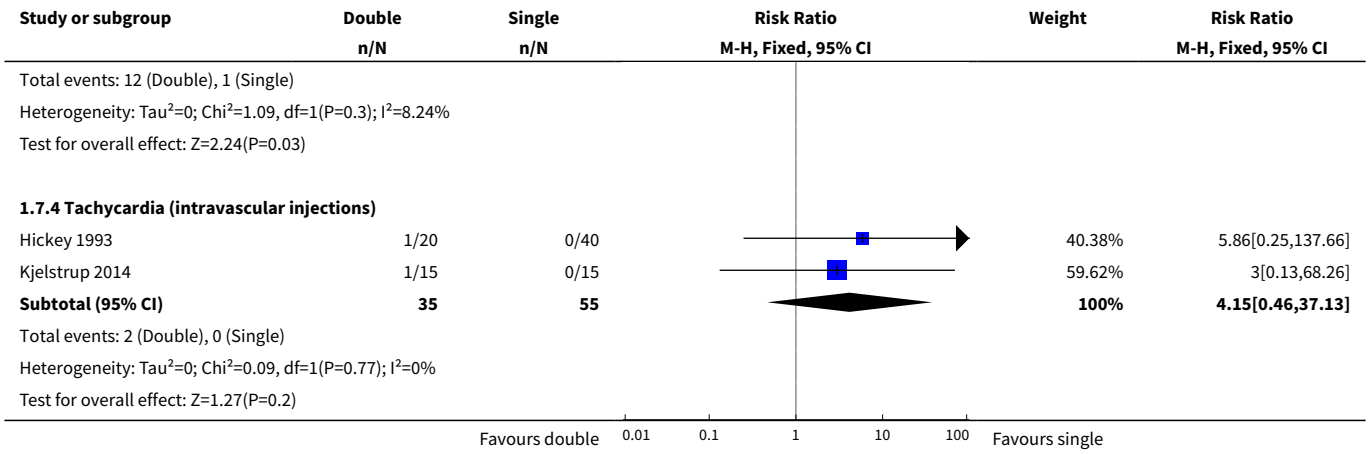
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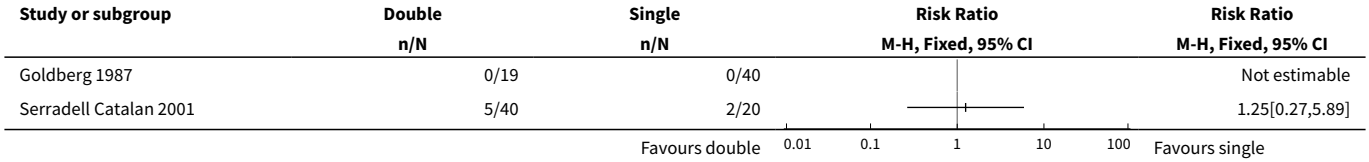
Analysis 1.7. Comparison 1 Double versus single-injection technique, Outcome 7 Complications during nerve block.



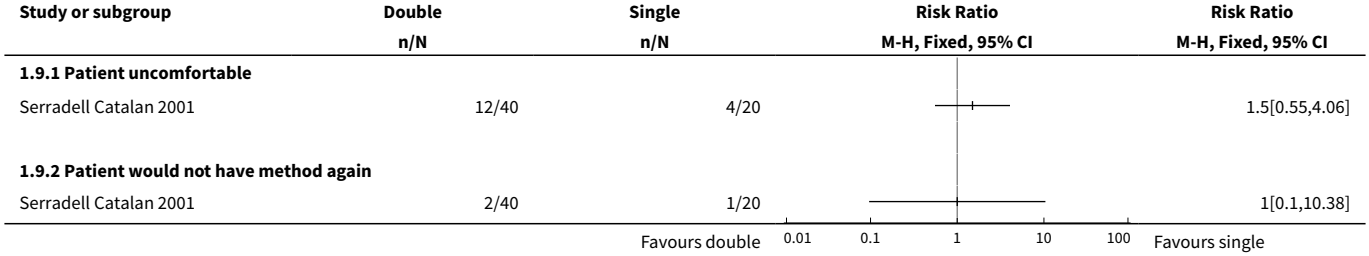
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Analysis 1.8. Comparison 1 Double versus single-injection technique, Outcome 8 Adverse effects (> 24 hours).



Analysis 1.9. Comparison 1 Double versus single-injection technique, Outcome 9 Patient discomfort and dissatisfaction with method.



Comparison 2. Multiple versus single-injection technique

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary anaesthesia failure (incomplete sensory block)	9	712	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.14, 0.42]
1.1 No use of nerve stimulator (for single injection)	2	204	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.25, 0.65]

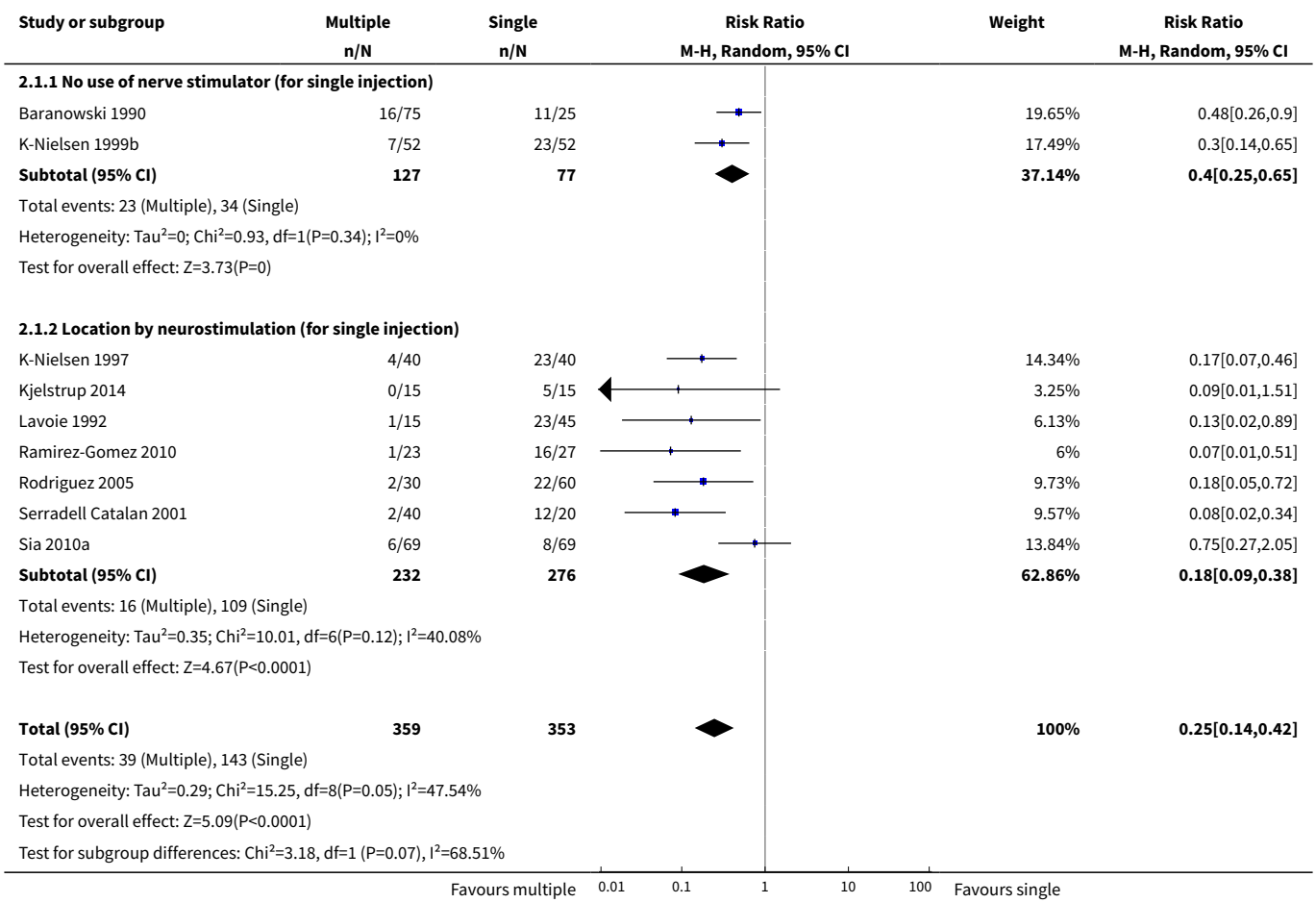
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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Location by neurostimulation (for single injection)	7	508	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.09, 0.38]
2 Primary anaesthesia failure - subgrouped by outcome definition	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Incomplete overall sensory block	4	294	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.12, 0.57]
2.2 Supplemental blocks for surgical area	5	418	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.10, 0.52]
3 Complete failure of block: general anaesthesia or new plexus block	7	484	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.03, 2.71]
4 Incomplete motor block	4	304	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.39, 0.96]
5 Secondary analgesia failure	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Pain in surgical site/operative field	3	244	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.05, 5.37]
5.2 Tourniquet pain	4	379	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.30, 3.11]
5.3 Intraoperative sedatives	5	482	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.41, 1.19]
6 Timing (in minutes)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Time for block	4	308	Mean Difference (IV, Random, 95% CI)	3.33 [2.76, 3.90]
6.2 Time for readiness for surgery	2	206	Mean Difference (IV, Random, 95% CI)	-3.33 [-23.23, 16.56]
6.3 Duration of tourniquet	4	379	Mean Difference (IV, Random, 95% CI)	2.30 [-2.22, 6.82]
6.4 Duration of block	2	107	Mean Difference (IV, Random, 95% CI)	-7.22 [-22.91, 8.47]
6.5 Length of surgery	1	138	Mean Difference (IV, Random, 95% CI)	2.0 [-3.53, 7.53]
7 Complications during nerve block	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Arterial puncture	3	278	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.64, 5.66]
7.2 Venous puncture	4	308	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.76, 5.71]
7.3 Paraesthesia	5	412	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.27, 3.27]
7.4 Tachycardia (intravascular injections)	4	352	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.20, 9.06]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 Local anaesthesia toxicity (intra-arterial injections)	2	134	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.05, 10.72]
7.6 Subcutaneous/axillary haematoma	3	214	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.95]
8 Adverse effects > 24 hours	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Patient discomfort and dissatisfaction with method	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Patient uncomfortable	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.77, 5.20]
9.2 Patient would not have method again	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.43, 2.77]

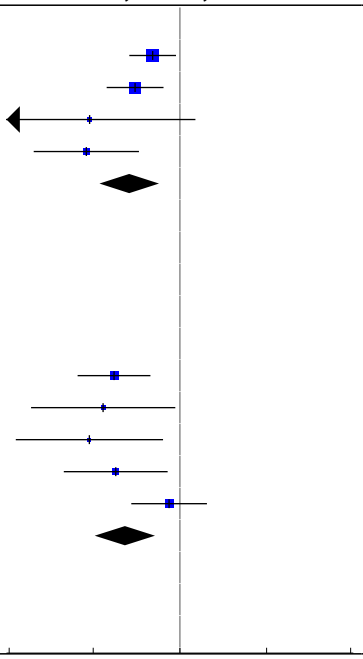
Analysis 2.1. Comparison 2 Multiple versus single-injection technique, Outcome 1 Primary anaesthesia failure (incomplete sensory block).



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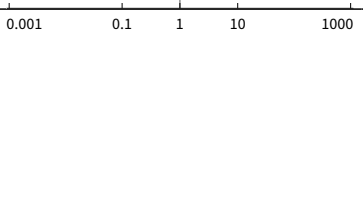
Analysis 2.2. Comparison 2 Multiple versus single-injection technique, Outcome 2 Primary anaesthesia failure - subgrouped by outcome definition.

Study or subgroup	Multiple n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Incomplete overall sensory block					
Baranowski 1990	16/75	11/25		38.73%	0.48[0.26,0.9]
K-Nielsen 1999b	7/52	23/52		34.77%	0.3[0.14,0.65]
Kjelstrup 2014	0/15	5/15		6.85%	0.09[0.01,1.51]
Serradell Catalan 2001	2/40	12/20		19.65%	0.08[0.02,0.34]
Subtotal (95% CI)	**182**	**112**		**100%**	**0.26[0.12,0.57]**
Total events: 25 (Multiple), 51 (Single)					
Heterogeneity: Tau²=0.32; Chi²=6.66, df=3(P=0.08); I²=54.95%					
Test for overall effect: Z=3.34(P=0)					
2.2.2 Supplemental blocks for surgical area					
K-Nielsen 1997	4/40	23/40		28.04%	0.17[0.07,0.46]
Lavoie 1992	1/15	23/45		12.76%	0.13[0.02,0.89]
Ramirez-Gomez 2010	1/23	13/27		12.36%	0.09[0.01,0.64]
Rodriguez 2005	2/30	22/60		19.68%	0.18[0.05,0.72]
Sia 2010a	6/69	8/69		27.16%	0.75[0.27,2.05]
Subtotal (95% CI)	**177**	**241**		**100%**	**0.23[0.1,0.52]**
Total events: 14 (Multiple), 89 (Single)					
Heterogeneity: Tau²=0.35; Chi²=7.1, df=4(P=0.13); I²=43.65%					
Test for overall effect: Z=3.58(P=0)					



Analysis 2.3. Comparison 2 Multiple versus single-injection technique, Outcome 3 Complete failure of block: general anaesthesia or new plexus block.

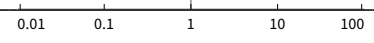
Study or subgroup	Multiple n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baranowski 1990	0/75	2/25		33.66%	0.07[0,1.38]
K-Nielsen 1997	1/40	0/40		31.36%	3[0.13,71.51]
K-Nielsen 1999b	0/52	0/52			Not estimable
Kjelstrup 2014	0/15	0/15			Not estimable
Lavoie 1992	0/15	0/45			Not estimable
Ramirez-Gomez 2010	0/23	3/27		34.99%	0.17[0.01,3.07]
Serradell Catalan 2001	0/40	0/20			Not estimable
Total (95% CI)	**260**	**224**		**100%**	**0.31[0.03,2.71]**
Total events: 1 (Multiple), 5 (Single)					
Heterogeneity: Tau²=1.33; Chi²=3.11, df=2(P=0.21); I²=35.77%					
Test for overall effect: Z=1.07(P=0.29)					



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Analysis 2.4. Comparison 2 Multiple versus single-injection technique, Outcome 4 Incomplete motor block.

Study or subgroup	Multiple n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
K-Nielsen 1997	16/40	23/40		28.93%	0.7[0.44,1.11]
K-Nielsen 1999b	24/52	32/52		32.77%	0.75[0.52,1.08]
Lavoie 1992	9/15	37/45		30.03%	0.73[0.47,1.13]
Serradell Catalan 2001	2/40	11/20		8.27%	0.09[0.02,0.37]
Total (95% CI)	**147**	**157**		**100%**	**0.61[0.39,0.96]**
Total events: 51 (Multiple), 103 (Single)					
Heterogeneity: Tau^2=0.13; Chi^2=8.93, df=3(P=0.03); I^2=66.4%					
Test for overall effect: Z=2.13(P=0.03)					



Favours multiple — Favours single

Analysis 2.5. Comparison 2 Multiple versus single-injection technique, Outcome 5 Secondary analgesia failure.

Study or subgroup	Multiple n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Pain in surgical site/operative field					
K-Nielsen 1997	1/40	1/40		35.66%	1[0.06,15.44]
K-Nielsen 1999b	1/52	0/52		30.41%	3[0.13,71.99]
Serradell Catalan 2001	0/40	4/20		33.93%	0.06[0,1.01]
Subtotal (95% CI)	**132**	**112**		**100%**	**0.53[0.05,5.37]**
Total events: 2 (Multiple), 5 (Single)					
Heterogeneity: Tau^2=1.98; Chi^2=3.78, df=2(P=0.15); I^2=47.07%					
Test for overall effect: Z=0.54(P=0.59)					
2.5.2 Tourniquet pain					
K-Nielsen 1997	8/40	8/40		32.69%	1[0.42,2.4]
K-Nielsen 1999b	11/52	2/52		24.68%	5.5[1.28,23.61]
Serradell Catalan 2001	0/38	1/19		10.21%	0.17[0.01,4.01]
Sia 2010a	6/69	14/69		32.42%	0.43[0.17,1.05]
Subtotal (95% CI)	**199**	**180**		**100%**	**0.97[0.3,3.11]**
Total events: 25 (Multiple), 25 (Single)					
Heterogeneity: Tau^2=0.89; Chi^2=9.82, df=3(P=0.02); I^2=69.46%					
Test for overall effect: Z=0.06(P=0.95)					
2.5.3 Intraoperative sedatives					
Baranowski 1990	0/75	0/25			Not estimable
K-Nielsen 1997	11/40	11/40		31.93%	1[0.49,2.04]
K-Nielsen 1999b	17/52	20/52		43.34%	0.85[0.51,1.43]
Serradell Catalan 2001	0/40	1/20		2.76%	0.17[0.01,4.01]
Sia 2010a	5/69	15/69		21.96%	0.33[0.13,0.87]
Subtotal (95% CI)	**276**	**206**		**100%**	**0.7[0.41,1.19]**
Total events: 33 (Multiple), 47 (Single)					
Heterogeneity: Tau^2=0.1; Chi^2=4.61, df=3(P=0.2); I^2=34.96%					
Test for overall effect: Z=1.32(P=0.19)					

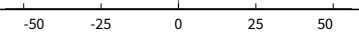


Favours multiple — Favours single

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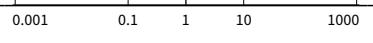
Analysis 2.6. Comparison 2 Multiple versus single-injection technique, Outcome 6 Timing (in minutes).

Study or subgroup	Multiple N	Multiple Mean(SD)	Single N	Single Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.6.1 Time for block							
K-Nielsen 1997	40	9.5 (2.2)	40	5.5 (0.9)		32.04%	4[3.26,4.74]
Kjelstrup 2014	15	13.7 (3.2)	15	10.5 (2.5)		6.92%	3.2[1.14,5.26]
Serradell Catalan 2001	40	8.6 (2.7)	20	5.6 (1.3)		21.72%	3[1.99,4.01]
Sia 2010a	69	7.1 (2.1)	69	4.1 (1.4)		39.32%	3[2.4,3.6]
Subtotal ***	**164**		**144**			**100%**	**3.33[2.76,3.9]**
Heterogeneity: Tau^2=0.12; Chi^2=4.78, df=3(P=0.19); I^2=37.24%							
Test for overall effect: Z=11.46(P<0.0001)							
2.6.2 Time for readiness for surgery							
K-Nielsen 1997	40	25 (6)	40	38.5 (7)		49.92%	-13.5[-16.36,-10.64]
Sia 2010a	63	21.1 (7)	63	14.3 (6.6)		50.08%	6.8[4.42,9.18]
Subtotal ***	**103**		**103**			**100%**	**-3.33[-23.23,16.56]**
Heterogeneity: Tau^2=204.25; Chi^2=114.65, df=1(P<0.0001); I^2=99.13%							
Test for overall effect: Z=0.33(P=0.74)							
2.6.3 Duration of tourniquet							
K-Nielsen 1997	40	73 (30)	40	73 (31)		11.44%	0[-13.37,13.37]
K-Nielsen 1999b	52	65 (25)	52	65 (28)		19.63%	0[-10.2,10.2]
Serradell Catalan 2001	38	52.6 (55.3)	19	45.5 (16.2)		5.64%	7.1[-11.94,26.14]
Sia 2010a	69	45 (16)	69	42 (18)		63.29%	3[-2.68,8.68]
Subtotal ***	**199**		**180**			**100%**	**2.3[-2.22,6.82]**
Heterogeneity: Tau^2=0; Chi^2=0.61, df=3(P=0.89); I^2=0%							
Test for overall effect: Z=1(P=0.32)							
2.6.4 Duration of block							
Ramirez-Gomez 2010	23	336 (25)	24	338 (18)		70.18%	-2[-14.5,10.5]
Serradell Catalan 2001	40	250.5 (55.2)	20	270 (42)		29.82%	-19.5[-44.62,5.62]
Subtotal ***	**63**		**44**			**100%**	**-7.22[-22.91,8.47]**
Heterogeneity: Tau^2=50.66; Chi^2=1.49, df=1(P=0.22); I^2=33.08%							
Test for overall effect: Z=0.9(P=0.37)							
2.6.5 Length of surgery							
Sia 2010a	69	52 (18)	69	50 (15)		100%	2[-3.53,7.53]
Subtotal ***	**69**		**69**			**100%**	**2[-3.53,7.53]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.71(P=0.48)							

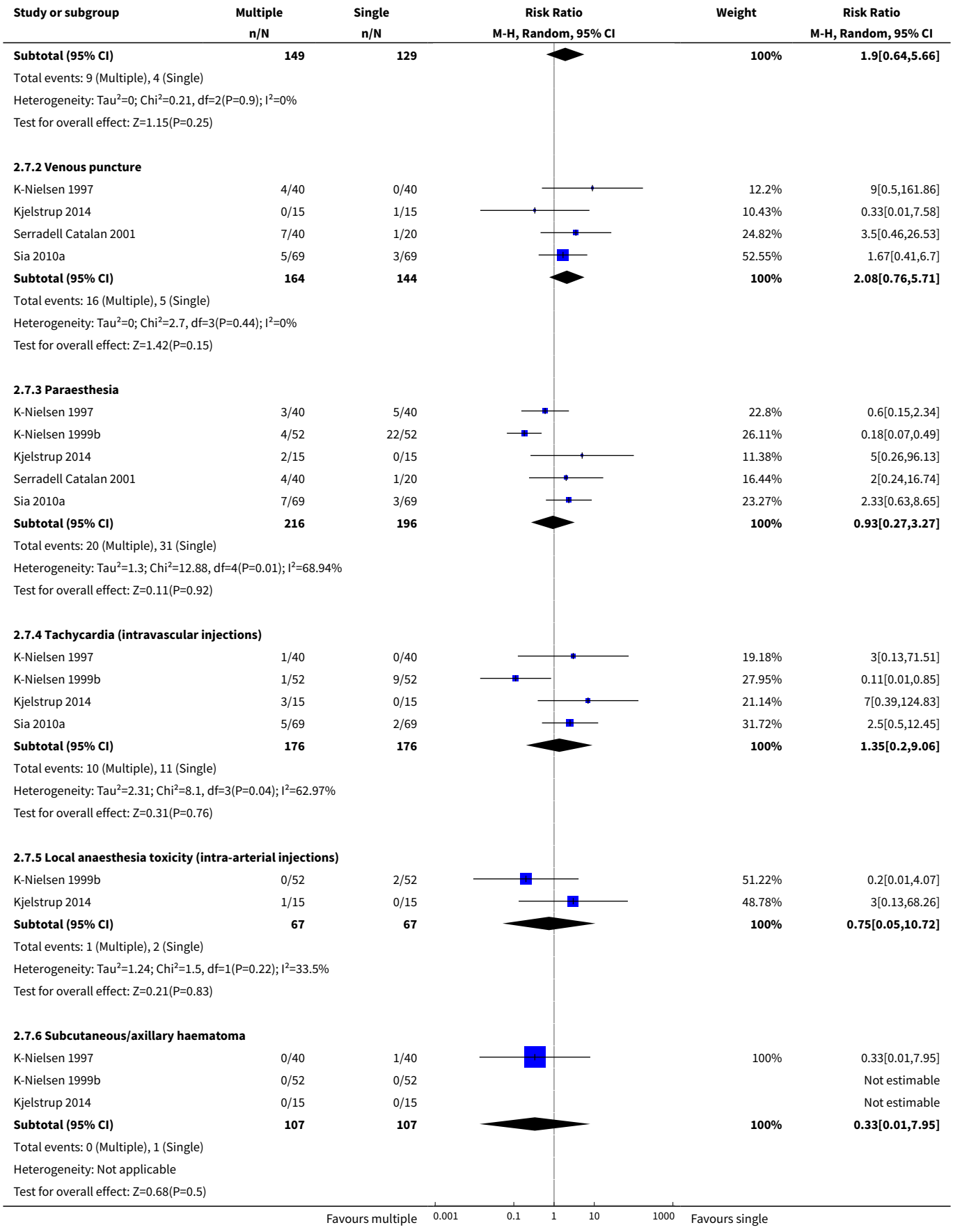


Analysis 2.7. Comparison 2 Multiple versus single-injection technique, Outcome 7 Complications during nerve block.

Study or subgroup	Multiple n/N	Single n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Arterial puncture					
K-Nielsen 1997	5/40	3/40		64.23%	1.67[0.43,6.51]
Serradell Catalan 2001	1/40	0/20		11.97%	1.54[0.07,36.11]
Sia 2010a	3/69	1/69		23.8%	3[0.32,28.14]

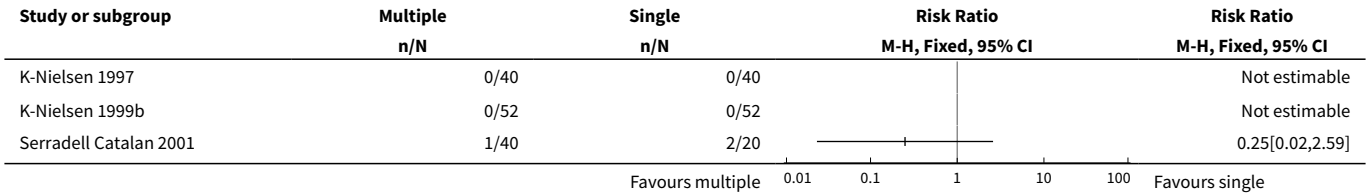


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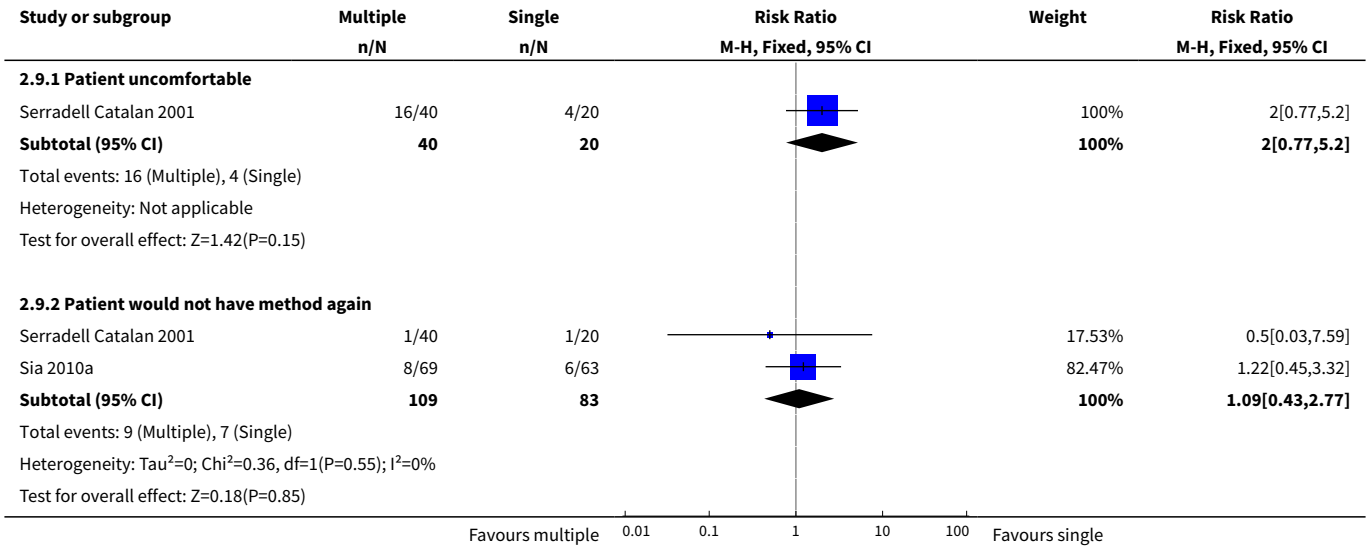


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Analysis 2.8. Comparison 2 Multiple versus single-injection technique, Outcome 8 Adverse effects > 24 hours.



Analysis 2.9. Comparison 2 Multiple versus single-injection technique, Outcome 9 Patient discomfort and dissatisfaction with method.



Comparison 3. Multiple versus double-injection technique

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary anaesthesia failure (incomplete sensory block)	12	966	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.19, 0.39]
1.1 Transarterial injection (for double injection)	4	300	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.14, 0.45]
1.2 Location by neurostimulation (for double injection)	8	666	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.18, 0.44]
2 Primary anaesthesia failure - subgrouped by outcome definition	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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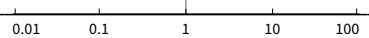
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incomplete overall sensory block	8	600	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.15, 0.36]
2.2 Supplemental blocks for surgical area	7	586	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.24, 0.66]
3 Complete failure of block: general anaesthesia or new plexus block	9	630	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.04, 1.41]
4 Incomplete motor block	6	470	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.36, 0.85]
5 Secondary analgesia failure	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Pain in surgical site/operative field	5	450	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.14]
5.2 Tourniquet pain	7	719	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.33, 0.84]
5.3 Intraoperative sedatives	7	716	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.03]
6 Timing (in minutes)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Time for block	6	586	Mean Difference (IV, Random, 95% CI)	1.54 [0.80, 2.29]
6.2 Time for readiness for surgery	5	524	Mean Difference (IV, Random, 95% CI)	-0.08 [-2.92, 2.77]
6.3 Duration of tourniquet	5	549	Mean Difference (IV, Random, 95% CI)	2.99 [-1.03, 7.01]
6.4 Duration of surgery	3	376	Mean Difference (IV, Random, 95% CI)	0.63 [-4.97, 6.24]
6.5 Duration of block	2	150	Mean Difference (IV, Random, 95% CI)	0.89 [-27.95, 29.73]
7 Complications during nerve block	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Arterial puncture	6	616	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.66, 2.84]
7.2 Venous puncture	7	646	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.76, 2.13]
7.3 Paraesthesia	8	746	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.30, 1.34]
7.4 Tachycardia (intravascular injections)	5	506	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.32, 1.49]
7.5 Local anaesthesia toxicity (intra-arterial injections)	3	200	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.26, 6.94]
7.6 Axillary haematoma/bruises	4	290	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 1.06]
7.7 Accidental intravascular injection	2	200	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.20, 3.26]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.8 Transient bradycardia	1	100	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.99]
8 Adverse effects > 24 hours	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Patient discomfort and dissatisfaction with method	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Patient uncomfortable	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.73, 2.45]
9.2 Patient would not have method again	3	356	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.59, 2.13]
9.3 Patient dissatisfied	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 5.98]

Analysis 3.1. Comparison 3 Multiple versus double-injection technique, Outcome 1 Primary anaesthesia failure (incomplete sensory block).

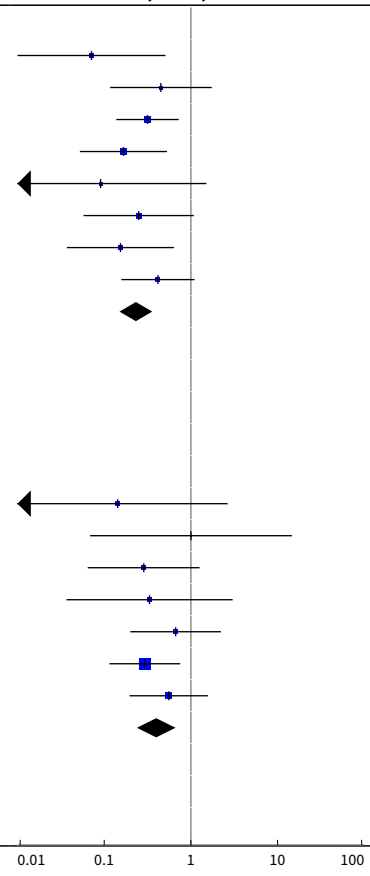
Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Transarterial injection (for double injection)					
Imbelloni 2005	3/40	5/30		4.42%	0.45[0.12,1.74]
K-Nielsen 1998	6/50	19/50		14.7%	0.32[0.14,0.72]
K-Nielsen 1999a	3/50	18/50		13.93%	0.17[0.05,0.53]
Kjelstrup 2014	0/15	5/15		4.26%	0.09[0.01,1.51]
Subtotal (95% CI)	**155**	**145**		**37.31%**	**0.25[0.14,0.45]**
Total events: 12 (Multiple), 47 (Double)					
Heterogeneity: Tau^2=0; Chi^2=2, df=3(P=0.57); I^2=0%					
Test for overall effect: Z=4.64(P<0.0001)					
3.1.2 Location by neurostimulation (for double injection)					
Coventry 2001	1/30	14/30		10.83%	0.07[0.01,0.51]
Lavoie 1992	1/15	1/15		0.77%	1[0.07,14.55]
Rodriguez 2005	2/30	7/30		5.42%	0.29[0.06,1.26]
Rodriguez 2008	2/30	8/30		6.19%	0.25[0.06,1.08]
Serradell Catalan 2001	2/40	13/40		10.06%	0.15[0.04,0.64]
Sia 2001	5/50	12/50		9.29%	0.42[0.16,1.1]
Sia 2010b	5/69	17/69		13.16%	0.29[0.11,0.75]
Sia 2010c	5/69	9/69		6.97%	0.56[0.2,1.57]
Subtotal (95% CI)	**333**	**333**		**62.69%**	**0.28[0.18,0.44]**
Total events: 23 (Multiple), 81 (Double)					
Heterogeneity: Tau^2=0; Chi^2=5.69, df=7(P=0.58); I^2=0%					
Test for overall effect: Z=5.62(P<0.0001)					
Total (95% CI)	**488**	**478**		**100%**	**0.27[0.19,0.39]**
Total events: 35 (Multiple), 128 (Double)					
Heterogeneity: Tau^2=0; Chi^2=7.84, df=11(P=0.73); I^2=0%					
Test for overall effect: Z=7.28(P<0.0001)					
Test for subgroup differences: Chi^2=0.11, df=1 (P=0.74), I^2=0%					



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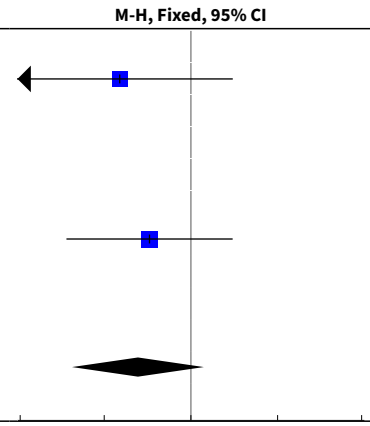
Analysis 3.2. Comparison 3 Multiple versus double-injection technique, Outcome 2 Primary anaesthesia failure - subgrouped by outcome definition.

Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Incomplete overall sensory block					
Coventry 2001	1/30	14/30		14.7%	0.07[0.01,0.51]
Imbelloni 2005	3/40	5/30		6%	0.45[0.12,1.74]
K-Nielsen 1998	6/50	19/50		19.95%	0.32[0.14,0.72]
K-Nielsen 1999a	3/50	18/50		18.9%	0.17[0.05,0.53]
Kjelstrup 2014	0/15	5/15		5.78%	0.09[0.01,1.51]
Rodriguez 2008	2/30	8/30		8.4%	0.25[0.06,1.08]
Serradell Catalan 2001	2/40	13/40		13.65%	0.15[0.04,0.64]
Sia 2001	5/50	12/50		12.6%	0.42[0.16,1.1]
Subtotal (95% CI)	**305**	**295**		**100%**	**0.23[0.15,0.36]**
Total events: 22 (Multiple), 94 (Double)					
Heterogeneity: Tau^2=0; Chi^2=5.32, df=7(P=0.62); I^2=0%					
Test for overall effect: Z=6.6(P<0.0001)					
3.2.2 Supplemental blocks for surgical area					
Coventry 2001	0/30	3/30		7.53%	0.14[0.01,2.65]
Lavoie 1992	1/15	1/15		2.15%	1[0.07,14.55]
Rodriguez 2005	2/30	7/30		15.05%	0.29[0.06,1.26]
Rodriguez 2008	1/30	3/30		6.45%	0.33[0.04,3.03]
Sia 2001	4/50	6/50		12.9%	0.67[0.2,2.22]
Sia 2010b	5/69	17/69		36.56%	0.29[0.11,0.75]
Sia 2010c	5/69	9/69		19.35%	0.56[0.2,1.57]
Subtotal (95% CI)	**293**	**293**		**100%**	**0.4[0.24,0.66]**
Total events: 18 (Multiple), 46 (Double)					
Heterogeneity: Tau^2=0; Chi^2=2.64, df=6(P=0.85); I^2=0%					
Test for overall effect: Z=3.52(P=0)					



Analysis 3.3. Comparison 3 Multiple versus double-injection technique, Outcome 3 Complete failure of block: general anaesthesia or new plexus block.

Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Coventry 2001	0/30	0/30			Not estimable
Imbelloni 2005	0/40	2/30		48.69%	0.15[0.01,3.04]
K-Nielsen 1998	0/50	0/50			Not estimable
K-Nielsen 1999a	0/50	0/50			Not estimable
Kjelstrup 2014	0/15	0/15			Not estimable
Lavoie 1992	0/15	0/15			Not estimable
Rodriguez 2008	1/30	3/30		51.31%	0.33[0.04,3.03]
Serradell Catalan 2001	0/40	0/40			Not estimable
Sia 2001	0/50	0/50			Not estimable
Total (95% CI)	**320**	**310**		**100%**	**0.24[0.04,1.41]**
Total events: 1 (Multiple), 5 (Double)					

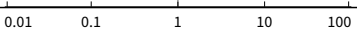


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Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.17, df=1(P=0.68); I²=0%					
Test for overall effect: Z=1.58(P=0.11)					

Analysis 3.4. Comparison 3 Multiple versus double-injection technique, Outcome 4 Incomplete motor block.

Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Coventry 2001	5/30	21/30		13.87%	0.24[0.1,0.55]
K-Nielsen 1998	26/50	34/50		25.3%	0.76[0.55,1.06]
K-Nielsen 1999a	8/50	19/50		15.9%	0.42[0.2,0.87]
Lavoie 1992	9/15	11/15		20.74%	0.82[0.49,1.37]
Serradell Catalan 2001	2/40	10/40		6.64%	0.2[0.05,0.86]
Sia 2001	12/50	15/50		17.54%	0.8[0.42,1.53]
Total (95% CI)	**235**	**235**		**100%**	**0.55[0.36,0.85]**
Total events: 62 (Multiple), 110 (Double)					
Heterogeneity: Tau²=0.16; Chi²=13.15, df=5(P=0.02); I²=61.98%					
Test for overall effect: Z=2.73(P=0.01)					



Analysis 3.5. Comparison 3 Multiple versus double-injection technique, Outcome 5 Secondary analgesia failure.

Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Pain in surgical site/operative field					
Imbelloni 2005	0/40	0/30			Not estimable
K-Nielsen 1998	0/50	0/50			Not estimable
K-Nielsen 1999a	0/50	1/50		50%	0.33[0.01,7.99]
Serradell Catalan 2001	0/40	1/40		50%	0.33[0.01,7.95]
Sia 2001	0/50	0/50			Not estimable
Subtotal (95% CI)	**230**	**220**		**100%**	**0.33[0.04,3.14]**
Total events: 0 (Multiple), 2 (Double)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%					
Test for overall effect: Z=0.96(P=0.34)					
3.5.2 Tourniquet pain					
Imbelloni 2005	2/40	2/30		4.98%	0.75[0.11,5.02]
K-Nielsen 1998	6/50	7/50		15.26%	0.86[0.31,2.37]
K-Nielsen 1999a	2/50	8/50		17.43%	0.25[0.06,1.12]
Serradell Catalan 2001	0/38	2/35		5.67%	0.18[0.01,3.72]
Sia 2001	3/50	2/50		4.36%	1.5[0.26,8.6]
Sia 2010b	5/69	13/69		28.33%	0.38[0.14,1.02]
Sia 2010c	6/69	11/69		23.97%	0.55[0.21,1.39]
Subtotal (95% CI)	**366**	**353**		**100%**	**0.53[0.33,0.84]**
Total events: 24 (Multiple), 45 (Double)					
Heterogeneity: Tau²=0; Chi²=4.21, df=6(P=0.65); I²=0%					

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Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=2.68(P=0.01)					
3.5.3 Intraoperative sedatives					
K-Nielsen 1998	19/50	12/50		17.52%	1.58[0.86,2.91]
K-Nielsen 1999a	15/50	19/50		27.74%	0.79[0.45,1.37]
Rodriguez 2008	1/30	3/30		4.38%	0.33[0.04,3.03]
Serradell Catalan 2001	0/40	2/40		3.65%	0.2[0.01,4.04]
Sia 2001	4/50	6/50		8.76%	0.67[0.2,2.22]
Sia 2010b	6/69	16/69		23.36%	0.38[0.16,0.9]
Sia 2010c	6/69	10/69		14.6%	0.6[0.23,1.56]
Subtotal (95% CI)	**358**	**358**		**100%**	**0.75[0.55,1.03]**
Total events: 51 (Multiple), 68 (Double)					
Heterogeneity: Tau^2=0; Chi^2=9.75, df=6(P=0.14); I^2=38.45%					
Test for overall effect: Z=1.75(P=0.08)					

Favours multiple — Favours double

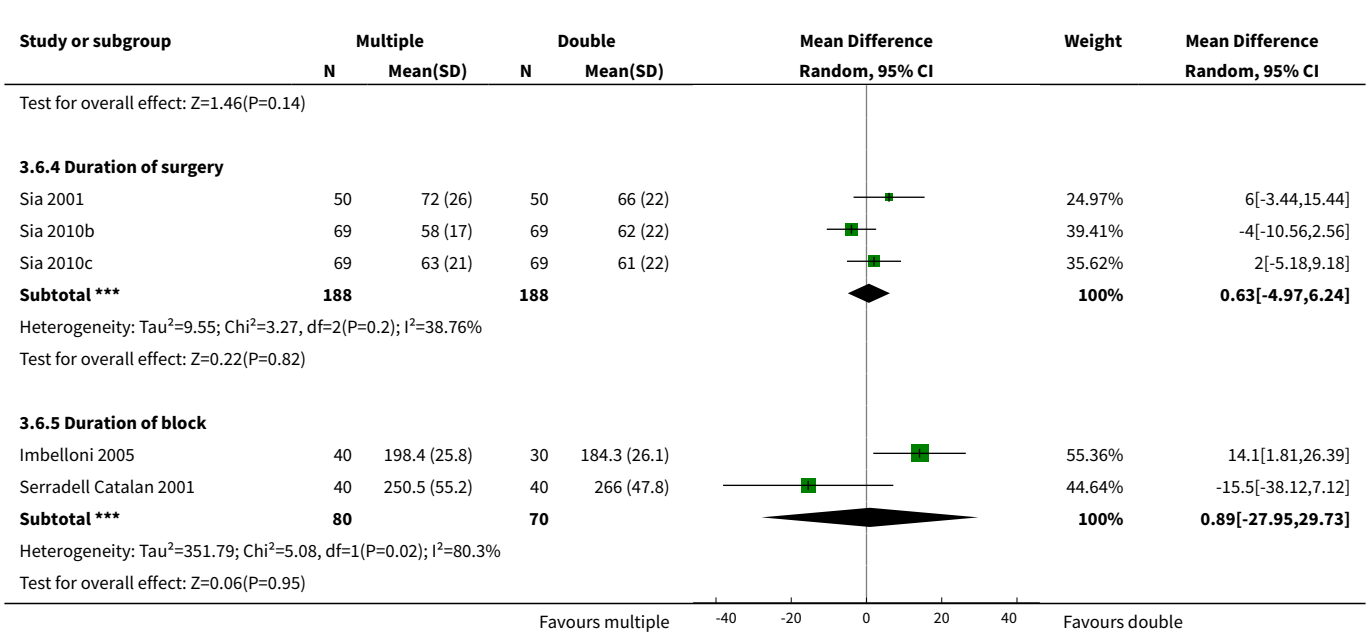
Analysis 3.6. Comparison 3 Multiple versus double-injection technique, Outcome 6 Timing (in minutes).

Study or subgroup	Multiple N	Multiple Mean(SD)	Double N	Double Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.6.1 Time for block							
K-Nielsen 1998	50	10 (2)	50	7 (2)		18.13%	3[2.22,3.78]
Kjelstrup 2014	15	13.7 (3.2)	15	15.6 (4.4)		5.56%	-1.9[-4.65,0.85]
Serradell Catalan 2001	40	8.6 (2.7)	40	7.3 (1.3)		16.78%	1.35[0.42,2.28]
Sia 2001	50	6 (1)	50	5 (1)		21.32%	1[0.61,1.39]
Sia 2010b	69	7.3 (2)	69	5.9 (1.9)		19.33%	1.4[0.75,2.05]
Sia 2010c	69	8.1 (2.2)	69	6 (2)		18.88%	2.1[1.4,2.8]
Subtotal * **	**293**		**293**			**100%**	**1.54[0.8,2.29]**
Heterogeneity: Tau^2=0.64; Chi^2=29.11, df=5(P<0.0001); I^2=82.83%							
Test for overall effect: Z=4.05(P<0.0001)							
3.6.2 Time for readiness for surgery							
Imbelloni 2005	40	10.2 (2.4)	30	8.8 (2.3)		23.93%	1.4[0.29,2.51]
K-Nielsen 1998	50	30 (10)	50	38 (10)		16.89%	-8[-11.92,-4.08]
Sia 2001	50	25 (10)	50	26 (11)		16.34%	-1[-5.12,3.12]
Sia 2010b	64	22.7 (6.3)	63	18.7 (6)		21.78%	4[1.86,6.14]
Sia 2010c	64	21.9 (7.1)	63	20.8 (6.8)		21.06%	1.1[-1.32,3.52]
Subtotal * **	**268**		**256**			**100%**	**-0.08[-2.92,2.77]**
Heterogeneity: Tau^2=8.5; Chi^2=28.96, df=4(P<0.0001); I^2=86.19%							
Test for overall effect: Z=0.05(P=0.96)							
3.6.3 Duration of tourniquet							
K-Nielsen 1998	50	78 (36)	50	72 (28)		9.21%	6[-6.64,18.64]
Serradell Catalan 2001	38	52.6 (55.3)	35	49.5 (27.7)		3.95%	3.12[-16.72,22.96]
Sia 2001	50	60 (20)	50	52 (19)		21.85%	8[0.35,15.65]
Sia 2010b	69	51 (17)	69	53 (17)		33.92%	-2[-7.67,3.67]
Sia 2010c	69	54 (20)	69	50 (16)		31.08%	4[-2.04,10.04]
Subtotal * **	**276**		**273**			**100%**	**2.99[-1.03,7.01]**
Heterogeneity: Tau^2=4.01; Chi^2=4.92, df=4(P=0.3); I^2=18.76%							

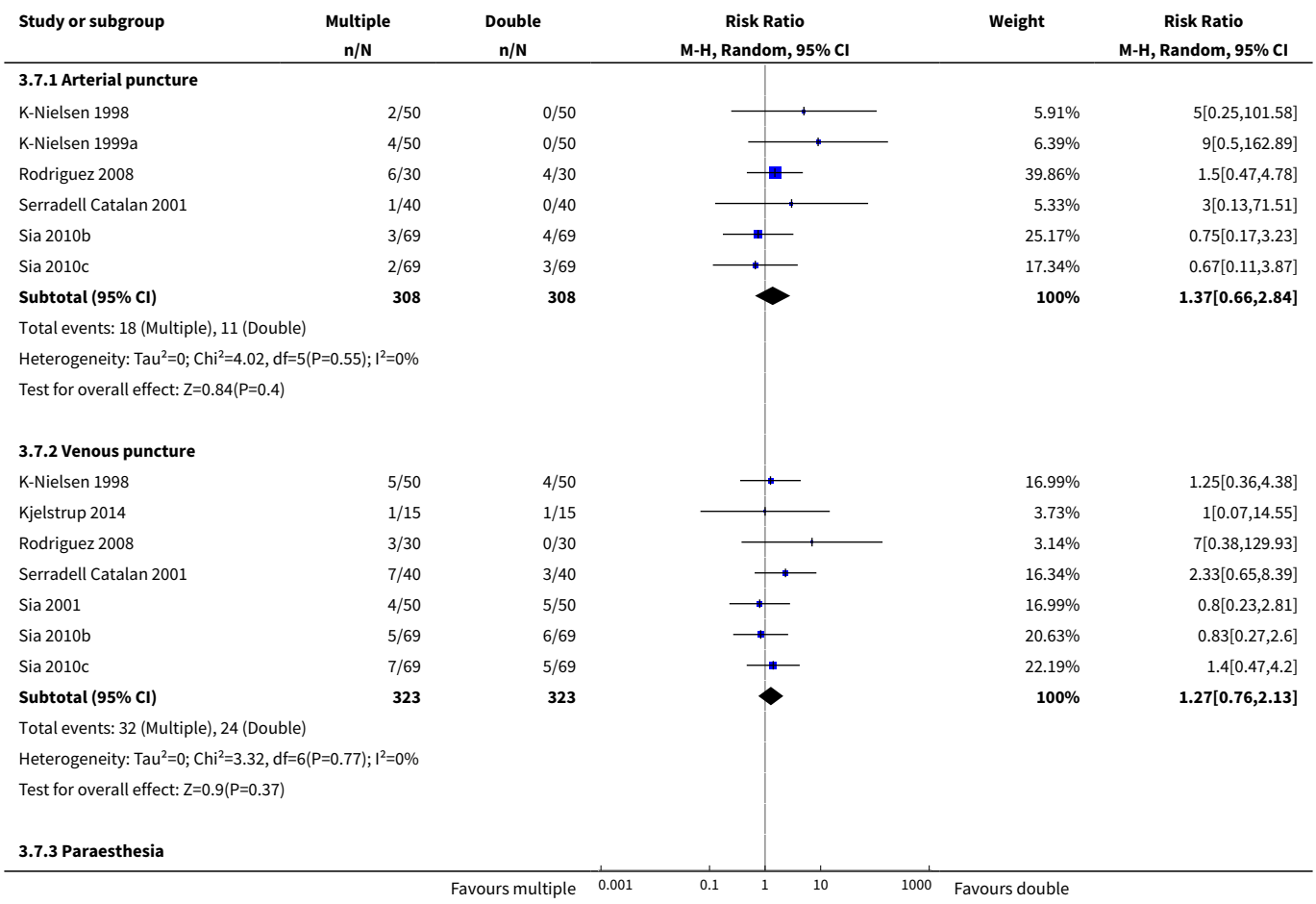


Favours multiple — Favours double

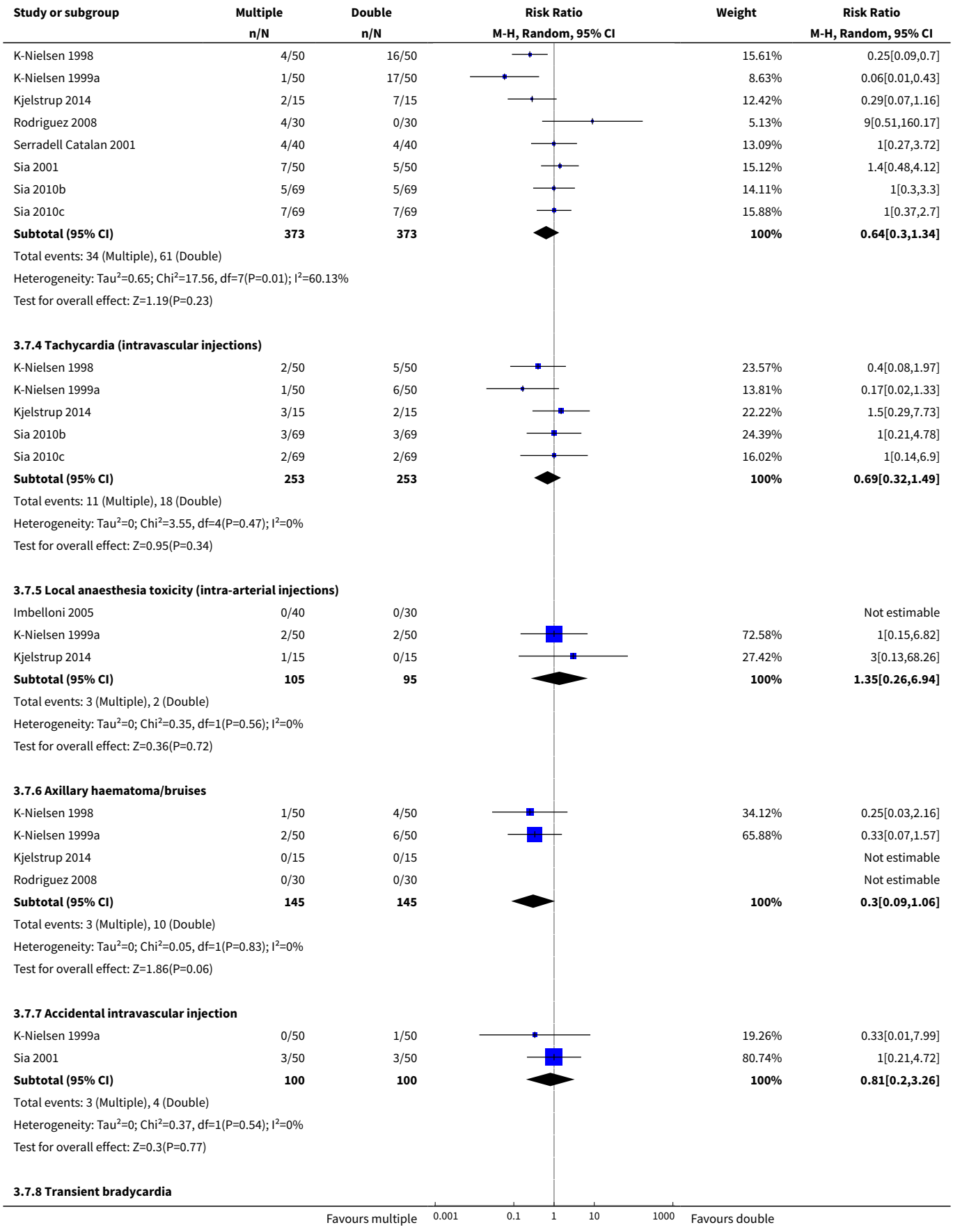
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Analysis 3.7. Comparison 3 Multiple versus double-injection technique, Outcome 7 Complications during nerve block.

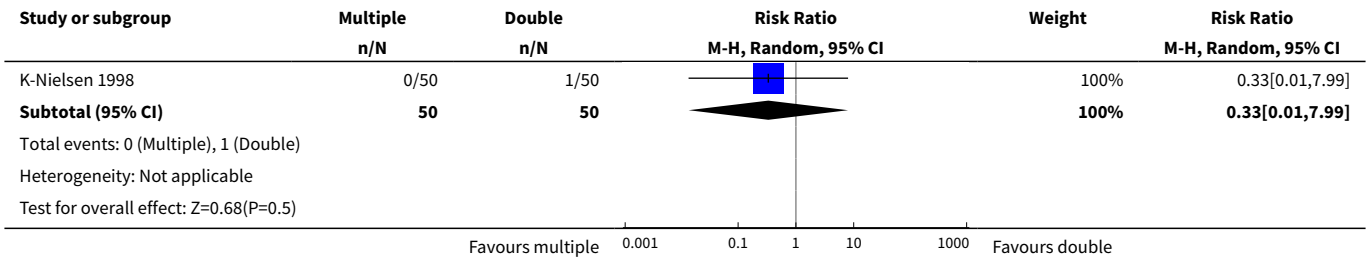


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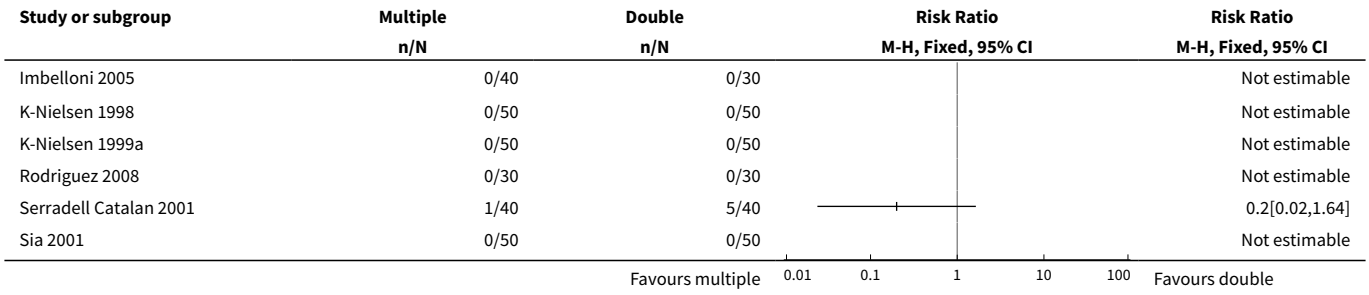


Study or subgroup	Multiple n/N	Double n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
K-Nielsen 1998	4/50	16/50		15.61%	0.25[0.09,0.7]
K-Nielsen 1999a	1/50	17/50		8.63%	0.06[0.01,0.43]
Kjelstrup 2014	2/15	7/15		12.42%	0.29[0.07,1.16]
Rodriguez 2008	4/30	0/30		5.13%	9[0.51,160.17]
Serradell Catalan 2001	4/40	4/40		13.09%	1[0.27,3.72]
Sia 2001	7/50	5/50		15.12%	1.4[0.48,4.12]
Sia 2010b	5/69	5/69		14.11%	1[0.3,3.3]
Sia 2010c	7/69	7/69		15.88%	1[0.37,2.7]
Subtotal (95% CI)	**373**	**373**		**100%**	**0.64[0.3,1.34]**
Total events: 34 (Multiple), 61 (Double)					
Heterogeneity: Tau^2=0.65; Chi^2=17.56, df=7(P=0.01); I^2=60.13%					
Test for overall effect: Z=1.19(P=0.23)					
3.7.4 Tachycardia (intravascular injections)					
K-Nielsen 1998	2/50	5/50		23.57%	0.4[0.08,1.97]
K-Nielsen 1999a	1/50	6/50		13.81%	0.17[0.02,1.33]
Kjelstrup 2014	3/15	2/15		22.22%	1.5[0.29,7.73]
Sia 2010b	3/69	3/69		24.39%	1[0.21,4.78]
Sia 2010c	2/69	2/69		16.02%	1[0.14,6.9]
Subtotal (95% CI)	**253**	**253**		**100%**	**0.69[0.32,1.49]**
Total events: 11 (Multiple), 18 (Double)					
Heterogeneity: Tau^2=0; Chi^2=3.55, df=4(P=0.47); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
3.7.5 Local anaesthesia toxicity (intra-arterial injections)					
Imbelloni 2005	0/40	0/30			Not estimable
K-Nielsen 1999a	2/50	2/50		72.58%	1[0.15,6.82]
Kjelstrup 2014	1/15	0/15		27.42%	3[0.13,68.26]
Subtotal (95% CI)	**105**	**95**		**100%**	**1.35[0.26,6.94]**
Total events: 3 (Multiple), 2 (Double)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					
3.7.6 Axillary haematoma/bruises					
K-Nielsen 1998	1/50	4/50		34.12%	0.25[0.03,2.16]
K-Nielsen 1999a	2/50	6/50		65.88%	0.33[0.07,1.57]
Kjelstrup 2014	0/15	0/15			Not estimable
Rodriguez 2008	0/30	0/30			Not estimable
Subtotal (95% CI)	**145**	**145**		**100%**	**0.3[0.09,1.06]**
Total events: 3 (Multiple), 10 (Double)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%					
Test for overall effect: Z=1.86(P=0.06)					
3.7.7 Accidental intravascular injection					
K-Nielsen 1999a	0/50	1/50		19.26%	0.33[0.01,7.99]
Sia 2001	3/50	3/50		80.74%	1[0.21,4.72]
Subtotal (95% CI)	**100**	**100**		**100%**	**0.81[0.2,3.26]**
Total events: 3 (Multiple), 4 (Double)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.3(P=0.77)					
3.7.8 Transient bradycardia					

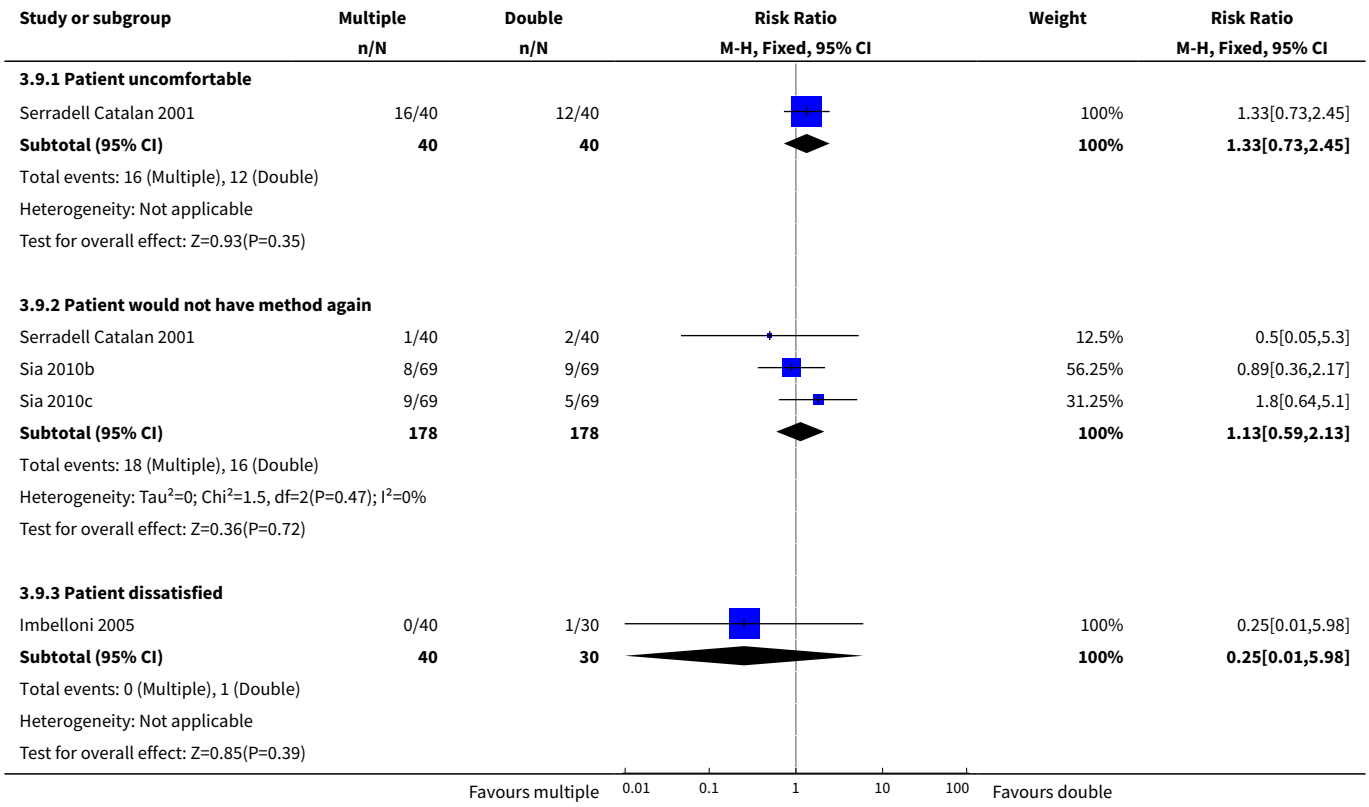
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Analysis 3.8. Comparison 3 Multiple versus double-injection technique, Outcome 8 Adverse effects > 24 hours.



Analysis 3.9. Comparison 3 Multiple versus double-injection technique, Outcome 9 Patient discomfort and dissatisfaction with method.



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ADDITIONAL TABLES

Table 1. Methods of nerve location

Method of nerve location	Number of injections	Trials
Transarterial The axillary artery is palpated and deliberately transfixed with a needle. The needle is then either withdrawn to inject LA anterior (superficial) to the artery, or inserted deeper to inject LA posterior to the artery, or both.	Single - anterior	Hickey 1993
	Single - posterior	Hickey 1993; K-Nielsen 1999b
	Double	Goldberg 1987; Hickey 1993; Imbelloni 2005; Kjelstrup 2014; K-Nielsen 1998; K-Nielsen 1999a; Pere 1993
Winnie's perivascular technique A needle is inserted adjacent to the axillary artery until a fascial click is felt, signifying penetration of the neurovascular fascial sheath. A catheter may be also inserted proximally within the sheath. LA is then injected, usually as a single bolus, while applying distal pressure to promote proximal spread of the LA.	Single	Baranowski 1990; Turkan 2002
Paraesthesia A needle is inserted adjacent to the axillary artery and manipulated to elicit paraesthesia in the distribution of one or more of the 4 terminal nerves. LA is then injected at these locations.	Single	Goldberg 1987
	Multiple	Baranowski 1990
Neurostimulation (electrolocation) A needle is inserted adjacent to the axillary artery and manipulated until it comes into close proximity to one or more of the 4 terminal nerves. An electric current is passed through the needle and needle-nerve proximity is signalled by an appropriate movement (motor response) of the forearm or hand, usually at currents of ≤ 0.5 mA. LA is injected at these locations.	Single	Inberg 1999; Kjelstrup 2014; K-Nielsen 1997; Pere 1993; Ramirez-Gomez 2010; Rodriguez 2005; Serradell Catalan 2001; Sia 2010a
	Double	Coventry 2001; Inberg 1999; Lavoie 1992; Rodriguez 2005; Rodriguez 2008; Serradell Catalan 2001; Sia 2001; Sia 2010b; Sia 2010c
	Multiple	Baranowski 1990; Coventry 2001; Imbelloni 2005; Kjelstrup 2014; K-Nielsen 1997; K-Nielsen 1998; K-Nielsen 1999a; K-Nielsen 1999b; Lavoie 1992; Ramirez-Gomez 2010; Rodriguez 2005; Rodriguez 2008; Serradell Catalan 2001; Sia 2001; Sia 2010a; Sia 2010b; Sia 2010c

LA = local anaesthetic; mA = milliamperes

APPENDICES

Appendix 1. Search strategies for current update

CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Anesthesia, Conduction, this term only
#2 MeSH descriptor Anesthesia, Local, this term only
#3 MeSH descriptor Nerve Block, this term only

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#4 ((analg* or an?esth*) adj3 (local* or regional)).ti,ab.
#5 (pain adj3 (per?operativ* or post?operativ*)).ti,ab.
#6 (par?esthes* or dys?esthes* or h?ematom* or seizur*).ti,ab.
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 (surg* adj3 (hand* or wrist* or forearm* or elbow*)).ti,ab.
#9 (#7 AND #8)
#10 (((brachial or axillary) adj3 (block* or an?esthesia)) or midhumer*).ti,ab.
#11 (#9 OR #10)

EMBASE (OvidSP)

1 regional anesthesia/ or local anesthesia/ or nerve block/ or ((exp brachial plexus/ or exp axilla/) and block*.mp.) or ((analg* or an?esth*) adj3 (local* or regional)).ti,ab. or (par?esthes* or dys?esthes* or h?ematom* or seizur*).ti,ab. or (pain adj3 (per?operativ* or post?operativ*)).ti,ab.
2 exp hand surgery/ or (surg* adj3 (hand* or wrist* or forearm* or elbow*)).ti,ab.
3 1 and 2
4 (((brachial or axillary) adj3 (block* or an?esthesia)) or midhumer* or mid-humer*).ti,ab.
5 3 or 4

Ovid MEDLINE(R)

1 Anesthesia Conduction/ or Anesthesia Local/ or Nerve Block/ or ((exp Brachial Plexus/ or exp Axilla/) and block*.mp.) or ((analg* or an?esth*) adj3 (local* or regional)).ti,ab. or Postoperative Complications/ or Pain, Postoperative/ or (par?esthes* or dys?esthes* or h?ematom* or seizur*).ti,ab. or (pain adj3 (per?operativ* or post?operativ*)).ti,ab.
2 (exp Surgical Procedures, Operative/ and exp Hand/) or (surg* adj3 (hand* or wrist* or forearm* or elbow*)).ti,ab.
3 1 and 2
4 (((brachial or axillary) adj3 (block* or an?esthesia)) or midhumer* or mid-humer*).ti,ab.
5 3 or 4

Appendix 2. Search strategies in first version of review (Handoll 2006)

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE.

Author-led literature search

One author (ZK-N) performed literature searches up to August 2004 and identified RCTs using the following strategy.

1. Searching MEDLINE (Ovid-Web) from 1966 to August 2004 using a series of free-text and MESH terms (*see* below). The results from each term were inspected in turn.
2. Using similar search terms (free text and MESH) for EMBASE (Ovid-Web) from 1988 to August 2004, and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2004).
3. Checking reference lists of RCTs identified through the electronic searches.
4. Contacting trial authors and the medical industry.
5. Scrutiny of article titles of the following anaesthesia journals for mention of axillary or midhumeral block:

- *Acta Anaesthesiologica Scandinavica* (1980 to 2004);
- *Anaesthesia* (1980 to 2004);
- *Anaesthesia and Intensive Care* (1980 to 2004);
- *Anesthesia and Analgesia* (1980 to 2004);
- *Anesthesiology* (1980 to 2004);
- *British Journal of Anaesthesia* (1980 to 2004);
- *Canadian Journal of Anaesthesia* (1980 to 2004);
- *European Journal of Anaesthesiology* (1990 to 2004);
- *Regional Anesthesia/Regional Anesthesia and Pain Medicine* (1985 to 2004).

Supplementary search

Karen Hovhannisyan ((KH) Trials Search Co-ordinator, Cochrane Anaesthesia Review Group (CARG)) supplemented these searches up to March 2005 on CENTRAL, MEDLINE and EMBASE.

- CENTRAL (Issue 1, 2005).
- SilverPlatter MEDLINE (WebSPIRS) (up to April Week 3 2005/04).
- SilverPlatter EMBASE (WebSPIRS) (up to 2005/03).

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KH combined the subject-specific terms for MEDLINE and EMBASE with optimal search strategies for RCTs for these databases.

We applied no language restrictions.

MEDLINE (Ovid-Web) search terms

Search number	Search term
#1 (Free terms)	Search axillary or midhumeral block Field: All Fields, Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#2 (Free terms)	Search anesthesia and axillary or midhumeral block Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#3 (Free terms)	Search plexus anesthesia and axillary or midhumeral Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#4 (Free terms)	Search anesthesia and brachial plexus and surgery Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#5 (Free terms)	Search anesthesia and brachial plexus and injection Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#6 (Free terms)	Search nerve block and brachial plexus and injection technique Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#7 (Free terms)	Search axillary or midhumeral block and injection technique Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#8 (Mesh)	Search anesthesia,conduction and brachial plexus Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#9 (Mesh)	Search anesthesia,conduction and brachial plexus and axilla Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#10 (Mesh)	Search anesthesia,conduction and surgery,hand Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#11 (Mesh)	Search nerve block and surgery,hand Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#12 (Mesh)	Search nerve block and brachial plexus Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#13 (Mesh)	Search nerve block and axilla

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(Continued)

	Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans
#14 (Mesh)	Search nerve block and axilla and surgery Limits: All Adult: 19+ years, Publication Date from 1966 to 2004, only items with abstracts, Randomized Controlled Trial, Humans

Appendix 3. Former methodological quality assessment tool

Item	Score
1. Was the assigned treatment adequately concealed prior to allocation?	3 = allocation was concealed (e.g. sequentially numbered, sealed, opaque envelopes) 2 = small but possible chance of disclosure of assignment 1 = states random but no description 0 = quasi-randomized or open list/tables
2. Were the inclusion and exclusion criteria for entry clearly defined?	1 = clearly defined (including contra-indications) 0 = inadequately or not defined
3. Were the outcomes of patients who withdrew described and included in the analysis (intention-to-treat)?	1 = Outcomes of patients who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention-to-treat analysis OR the text stated there were no withdrawals 0 = Outcomes of patients who withdrew or were excluded after allocation were NEITHER detailed separately NOR included in an intention-to-treat analysis
4. Were important baseline characteristics reported?	1 = Intervention groups were adequately described at entry. A minimum of 3 admission details were described: age, sex, type of surgery, mental status 0 = Intervention groups were NOT adequately described at entry
5. Were care programmes, other than the trial options, identical? (Example of a clinically important difference is anaesthetist experience)	1 = The text stated that the care programmes other than trial options were identical (or clear from the text) 0 = The text stated that the care programmes other than trial options were NOT identical
6. Were the outcome measures used clearly defined?	1 = Outcome measures were clearly defined in the text 0 = Outcome measures were NOT clearly defined in the text
7. Were the outcome assessors blinded to treatment status?	1 = Outcome assessors were blind to the allocation of patients 0 = Not mentioned or outcome assessors were NOT blind to the allocation of patients
8. Was the timing (e.g. duration of surveillance) clinically appropriate?	1 = The timing of the measurement of the outcomes was appropriate (e.g. at least 24 hours) 0= The timing of the measurement of the outcomes was NOT appropriate

Appendix 4. Measurement of sensory and motor blockade

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Study ID	Sensory: method	Sensory: timing	Sensory: rating	Nerve areas tested	Nerves: block Y/N?	Motor: rating	Nerves tested
Baranowski 1990	Use of blunt end of a 27 gauge dental needle	Every 5 minutes for 30 minutes	0 = no sensory loss 1 = loss of pinprick 2 = loss of touch	Axillary Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Success = 3 or 4 of the following 4 nerves were blocked to sensory loss score of 2 (loss of touch) at 30 minutes: Median Musculocutaneous Radial Ulnar	Not reported	Not reported
Coventry 2001	Use of a short-bevelled 27 gauge needle	Every 10 minutes for 30 minutes	Complete sensory loss	Medial cutaneous nerve of arm Medial cutaneous nerve of fore arm Median Musculocutaneous Radial Ulnar	Success = sensory blockade of 6 nerves: Median Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Musculocutaneous Radial Ulnar	Inability to move relevant muscle groups against gravity	Blockade of 4 nerves reported: Median Musculocutaneous Radial Ulnar
Goldberg 1987	Skin pinched with Allis clamp	Not stated	No pain on pinching the skin	Median Musculocutaneous Radial Ulnar	Success = sensory blockade (no pain) for all 4 nerves: Median Musculocutaneous Radial Ulnar	Not reported	Not reported
Hickey 1993	Pinprick	2, 5, 10, 15, 20, 25 and 30 minutes following injection	0 = no loss of sensation to pinprick 1 = analgesia (patient felt touch but not sharp) 2 = anaesthesia (patient did not feel touch)	Axillary Musculocutaneous Median Radial Ulnar Medial brachial cutaneous Medial antebrachial cutaneous Intercostobrachial	Overall block success was not strictly defined. Instead they looked primarily at anaesthesia and analgesia in individual nerve territories	Hand grip 0 = no weakness 1 = paresis 2 = paralysis	Not reported

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Imbelloni 2005	Skin clamp and "observing patients' pain manifestations"	Not stated	Not stated. The term "analgesia" is used.	Musculocutaneous Median Ulnar Radial	"Blockade was considered complete if all nerves were blocked" Incomplete = "need for additional injection" Failure = "need for general anesthesia"	Not reported	Not reported
Inberg 1999	Skin pinched	40 minutes	0 = normal sensation 1 = hypalgesia 2 = analgesia 3 = anaesthesia	Axillary Lateral cutaneous Medial cutaneous Median Musculocutaneous Radial Ulnar	Success = sensory blockade (no pain: score 2 or 3) and motor blockade (little or no power: score 2 or 3) for all 4 nerves: Median Musculocutaneous Radial Ulnar	0 = normal muscular function 1 = slight depression of power 2 = weak function without power 3 = no muscular function	Median Musculocutaneous Radial Ulnar
K-Nielsen 1997	Painful pinch with a plastic clamp	Every 10 minutes until ready for surgery; supplementation from 20 minutes	0 = no analgesia/anaesthesia 1 = loss of pain 2 = loss of sensation	Axillary Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Success = no need to supplement any of 4 nerves: Median Musculocutaneous (only if necessary for surgery) Radial Ulnar	Poor = no obvious relaxation Satisfactory = minor movement of digits Good = completely limp hand	Not reported
K-Nielsen 1998	Painful pinch with a plastic clamp	Every 10 minutes until ready for surgery; supplementation from 30 minutes	0 = no analgesia/anaesthesia 1 = loss of pain 2 = loss of sensation	Axillary Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Success = no need to supplement. No pain felt in any area below elbow. Incompletely blocked nerves were: Axillary Median Musculocutaneous Radial Ulnar	Poor = no obvious relaxation Satisfactory = minor movement of digits Good = completely limp hand	Not reported
K-Nielsen 1999a	Painful pinch with	Every 10 minutes until ready	0 = no analgesia/anaesthesia 1 = loss of pain	Axillary Medial cutaneous nerve of arm	Success = no need to supplement. No pain	Poor = no obvious relaxation Satisfactory = minor movement of digits	Not reported

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(Continued)

	a plastic clamp	for surgery; supplementation from 30 minutes	2 = loss of sensation	Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	felt in any area below elbow. Incompletely blocked nerves were: Axillary Medial cutaneous nerve of arm Median Musculocutaneous Radial Ulnar	Good = completely limp hand	
K-Nielsen 1999b	Painful pinch with a plastic clamp	Every 10 minutes until ready for surgery; supplementation from 30 minutes	0 = no analgesia/anaesthesia 1 = loss of pain 2 = loss of sensation	Axillary Median Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Musculocutaneous Radial Ulnar	Success = no need to supplement. No pain felt in any area below elbow. Incompletely blocked nerves were: Axillary Medial cutaneous nerve of arm Median Musculocutaneous Radial Ulnar	Poor = no obvious relaxation Satisfactory = minor movement of digits Good = completely limp hand	Not reported
Lavoie 1992	Use of Wartenberg pinwheel	Every 5 minutes up to 30 minutes	Needles of pinwheel no longer felt	"Each dermatome of the upper limb". Nerves not listed but would be: Axillary Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Success = "dermatomes of the nerves implicated in the surgical site were anaesthetized". (All nerves at surgical site: skin, muscles and bones)	0% = flexion/extension movements in hand and arm against resistance 33% = flexion/extension movements in hand and arm against gravity but not against resistance 66% = flexion/extension movements in hand only 100% = no movement of upper limb against gravity	Not reported
Pere 1993	Pinprick	5, 10, 20 and 30 minutes and 3 hours; supplementation from 20 minutes	Painful pinprick/pinprick analgesia	Axillary Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median	Success = no supplementation of nerves at site of planned surgery Incompletely blocked nerves were: Axillary	Strength of extensors and flexors: No reduction in strength/reduced strength/no muscular movement Grip strength (kg/cm^2): 0/0.1 to 0.4/> 0.4	Not reported

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				Musculocutaneous Radial (Supraclavicular) Ulnar	Median Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Musculocutaneous Radial Supraclavicular Ulnar		
Ramirez-Gomez 2010	Pinprick with a sterile needle	Every 10 minutes until 30 minutes after block completion	0 = normal sensation of pinprick 1 = reduced sensation of pinprick 2 = sensation to touch only 3 = absence of sensation	Musculocutaneous Radial Median Ulnar	Criteria for successful block not clearly defined	0 = normal muscle power 1 = slight decrease in muscle power 2 = very weak muscle power 3 = absence of muscle power	Musculocutaneous Radial Median Ulnar
Rodriguez 2005	Pinprick with 18G long bevel needle	5, 20 minutes after block completion	0 = painful 1 = analgesia to pinprick 2 = anaesthesia to pinprick (no perception) Global quality scale = sum of scores for all 6 nerves (0 to 12)	Musculocutaneous Radial Median Ulnar Medial brachial cutaneous (arm?) Medial antebrachial cutaneous (forearm?)	Not specifically stated. Blocks were supplemented pre-operatively if there was absence of complete anaesthesia in surgical sites	Elbow flexion/extension Wrist flexion/extension Fingers flexion/extension Thumb adduction 0 = no paresis 1 = paresis 2 = complete paralysis Global quality scale = sum of scores for all 7 areas (0 to 14)	Not reported
Rodriguez 2008	Pinprick with 18G long bevel needle	10, 20 and 30 minutes after injection of the total dose of LA (time zero)	0 points = pinprick perceived as painful 1 point = analgesia to pinprick (tactile sensation) 2 points = anaesthesia to pinprick (no perception)	Musculocutaneous Radial Median Ulnar Medial cutaneous	Global quality scores for both sensory block (minimum, 0 point; maximum, 12 points) and motor block (minimum, 0 point; maximum, 14 points) were based on the sum of the individual scores obtained at 10, 20, and at 30 minutes in each cutaneous nerve distri-	Motor block was assessed for flexion and extension of the elbow, flexion and extension of the wrist, flexion and extension of the fingers, and adduction of the thumb 0 points = no paresis 1 point = paresis 2 points = complete paralysis	Not reported

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					bution or joint movement. "Blocks were supplemented preoperatively with additional peripheral nerve blocks when the cutaneous nerve distributions corresponding to the operative area did not have complete anesthesia (i.e., score < 2) before the operation"		
Serradell Catalan 2001	Pinprick	Every 10 minutes up to 40 minutes	None: normal sensation Partial: analgesia Total: anaesthesia	Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Success = sensory blockade for all 5 nerves: Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	None: normal movements Partial: reduced movements Total: flaccid hand and forearm	Median Musculocutaneous Radial Ulnar
Sia 2001	Used 22 gauge needle	Every 10 minutes up to 30 minutes	Analgesia: loss of pinprick Anaesthesia: loss of touch	Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Success = complete block of all 6 nerves: Medial cutaneous nerve of arm Medial cutaneous nerve of forearm Median Musculocutaneous Radial Ulnar	Absent: no block Satisfactory: minor movements of digits possible Complete: no movements against gravity	Not reported
Sia 2010a	Cold test	5, 10, 15, 20, 25 and 30 minutes after end of procedure	Yes = "I feel cold" No = "I do not feel cold"	Musculocutaneous Median Radial Ulnar Medial cutaneous	Loss of cold sensation at 30 minutes sufficient for surgery. Unblocked nerves implicated in the surgical site were blocked by the anaesthesiologist. Intraoperatively, if the patient complained of pain at the surgical	Motor block was assessed for wrist extension, forearm flexion, index flexion, little finger flexion Grade 1 = no loss of force Grade 2 = reduced force compared with contralateral arm Grade 3 = complete motor block	Not reported

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(Continued)

					field, supplementation with LA was done by the surgeon.		
Sia 2010b	Cold test	5, 10, 15, 20, 25 and 30 minutes after end of procedure	Yes = "I feel cold" No = "I do not feel cold"	Musculocutaneous Median Radial Ulnar Medial cutaneous	Loss of cold sensation at 30 minutes sufficient for surgery. Unblocked nerves implicated in the surgical site were blocked by the anaesthesiologist. Intraoperatively, if the patient complained of pain at the surgical field, supplementation with LA was done by the surgeon.	Motor block was assessed for wrist extension, forearm flexion, index flexion, little finger flexion Grade 1 = no loss of force Grade 2 = reduced force compared with contralateral arm Grade 3 = complete motor block	Not reported
Sia 2010c	Cold test	5, 10, 15, 20, 25 and 30 minutes after end of procedure	Yes = "I feel cold" No = "I do not feel cold"	Musculocutaneous Median Radial Ulnar Medial cutaneous	Loss of cold sensation at 30 minutes sufficient for surgery. Unblocked nerves implicated in the surgical site were blocked by the anaesthesiologist. Intraoperatively, if the patient complained of pain at the surgical field, supplementation with LA was done by the surgeon.	Motor block was assessed for wrist extension, forearm flexion, index flexion, little finger flexion Grade 1 = no loss of force Grade 2 = reduced force compared with contralateral arm Grade 3 = complete motor block	Not reported
Turkan 2002	Pinprick Testing with an Allis clamp by surgeon also mentioned	Sensory testing every 3 minutes following injection. No other details.	Quality of analgesia 1 = no pain 2 = discomfort 3 = pain	Musculocutaneous Median Radial Ulnar	Overall block success was when the patient felt no pain in all 4 nerve distributions when tested by a surgeon (with an Allis clamp).	Not reported	Not reported

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WHAT'S NEW

Date	Event	Description
19 April 2016	New citation required but conclusions have not changed	This review is an update of the previous Cochrane systematic review (Chin 2013). The conclusions are unchanged.
19 April 2016	New search has been performed	We updated the review as follows. 1. We updated the literature search from August 2013 to April 2016 and retrieved 1359 citations from three databases (1016 unique citations) 2. We included one new study (Kjelstrup 2014).

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 1, 2006

Date	Event	Description
7 August 2013	New citation required but conclusions have not changed	This review is an update of the previous Cochrane systematic review (Chin 2011). There is a change in authorship: Helen Handoll has been replaced by Husni Alakkad and Javier Cubillos.
7 August 2013	New search has been performed	We updated the review as follows. 1. The title was amended to make it explicit that the scope of the review is restricted to non-ultrasound guided techniques of axillary brachial plexus blockade. 2. We updated the literature search from March 2011 to March 2013. 3. We included one study that was identified and awaiting classification in the previous review (Ramirez-Gomez 2010). We excluded three newly identified studies on the basis of the use of ultrasound guidance.
14 March 2011	New search has been performed	We updated the review as follows. 1. The title was changed to make it explicit that the scope is restricted to adults. 2. The inclusion criteria were revised to exclude children and trials using ultrasound-guided techniques of nerve location. 3. We now assess risk of bias; this replaced the previous methodological quality assessment. 4. We updated our literature search from March 2005 (date of last search in the previous review) to March 2011. 5. We included eight new trials (Hickey 1993; Imbelloni 2005; Rodriguez 2005; Rodriguez 2008; Sia 2010a; Sia 2010b; Sia 2010c; Turkan 2002). We excluded a further seven newly identified studies (Carre 2000; Liu 2005; Sites 2006; Tuominen 1987; Youssef

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Date	Event	Description
		1988; Yu 2007). One trial is currently awaiting translation and classification (Ramirez-Gomez 2010). 6. We added 'Summary of findings' tables for the three comparisons.
14 March 2011	New citation required but conclusions have not changed	This review is an update of the previous Cochrane systematic review (Handoll 2006). There is a change in authorship, including the lead author and the contact author: Zbigniew J Koscielniak-Nielsen has been replaced by Ki Jinn Chin.
14 March 2011	Amended	The review was amended to the format of RevMan 5.1.
31 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Updated review

Ki Jinn Chin (KJC), Husni Alakkad (HA), Javier E Cubillos (JEC)

Conceiving the review: KJC
Co-ordinating the review: KJC
Screening search results: KJC, HA, JEC
Organizing retrieval of papers: KJC
Screening retrieved papers against inclusion criteria: KJC, HA, JEC
Appraising quality of papers: KJC, JEC
Abstracting data from papers: KJC, JEC
Data management for the review: KJC, JEC
Entering data into Review Manager (Review Manager 5.3): KJC, HA
RevMan statistical data: KJC
Interpretation of data: KJC, JEC
Writing the review: KJC, HA, JEC
Performing previous work that was the foundation of the present study: KJC
Guarantor for the review (one author): KJC
Person responsible for reading and checking review before submission: KJC

Previous updates

See Chin 2013.

Dr KJ Chin, Dr Husni Alakkad, Dr Javier Cubillos updated the review.

See Chin 2011.

Dr KJ Chin and Dr H Handoll updated the review.

Original review

See Handoll 2006

Dr ZJ Koscielnak-Nielsen conceived the idea for the review and wrote the protocol.
Dr H Handoll and Dr ZJ Koscielnak-Nielsen wrote the review.

DECLARATIONS OF INTEREST

Ki Jinn Chin is employed as a clinical and academic anaesthesiologist with a clinical and research focus on regional anaesthesia. He has received funding from Smiths Medical from 2013 to 2014 for a clinical research project unrelated to this review that examines different local anaesthetic infusion protocols in continuous popliteal sciatic nerve block. The grant was paid to his institution directly and he did

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not benefit directly. Smiths Medical is a global manufacturer of medical devices and thus has no vested interest in the intervention and comparators in this study, which are variations on a clinical technique

Husni Alakkad: Husni Alakkad is employed as a clinical anaesthesiologist in a university hospital and his scope of practice includes regional anaesthesia.

Javier E Cubillos: Javier Cubillos is employed as a clinical anaesthesiologist in a university hospital and his scope of practice includes regional anaesthesia.

SOURCES OF SUPPORT

Internal sources

- Department of Anesthesia, University of Toronto, Toronto, Canada.
- Department of Anaesthesia and Operative Services, HOC, Rigshospital, Copenhagen, Denmark.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes made for the current update of the review

1. We clarified our handling of studies with more than two intervention groups (e.g. Sia 2010a; Sia 2010b; Sia 2010c) in a new Methods section dealing with unit of analysis issues.
2. We described our methods for dealing with missing data.
3. We described our methods for assessment of reporting biases.
4. We included 'Summary of findings' tables for each of the three comparisons of interest: single versus double-injection techniques, single versus multiple-injection techniques, double versus multiple-injection techniques.

Changes made for the second update of the review (Chin 2013)

The title of the review was changed to make it explicit that the review is restricted to non-ultrasound guided techniques of nerve location.

Changes made for the first update of the review (Chin 2011)

Changes made to the inclusion criteria and methods before processing the included trials were as follows.

1. We clarified that we would exclude trials focusing on children only ('Types of participants'). The restriction to adults was made explicit in the title of the review.
2. We excluded trials that used ultrasound-guided techniques of nerve location.

'Risk of bias' assessment replaced the eight-item methodological quality assessment scoring scheme.

Changes made for the first version of the review (Chin 2011)

Important changes made to the protocol before processing the included trials were as follows.

1. The midhumeral approach was no longer specified as included ('Types of studies').
2. The exclusion of trials involving supplementary anaesthesia was moderated to allow for trials using systemic opioids as a component of sedation ('Types of interventions').
3. The addition of a third primary outcome, failed anaesthesia ('Types of outcome measures').
4. Adjustments to the methods to accommodate the change in review authorship ('Methods').
5. The expansion of the quality assessment of the included trials to include all eight items suggested in the generic scoring scheme of CARG ('Methods').
6. The prior specification of sensitivity and subgroup analyses.

Before publication of the review (Handoll 2006), the name was changed from that in the protocol: 'Single, double or multiple injection techniques for axillary brachial plexus block for surgery of the distal upper extremity'.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Brachial Plexus; Anesthetics, Local [*administration & dosage]; Axilla [innervation]; Elbow [surgery]; Forearm [*surgery]; Hand [*surgery]; Intraoperative Complications [prevention & control]; Nerve Block [*methods]; Pain [prevention & control]; Randomized Controlled Trials as Topic; Tourniquets [adverse effects]; Wrist [surgery]

MeSH check words

Adult; Humans

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