Systematic review

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Efficacy and safety of epidural, continuous perineural infusion and adjuvant analgesics for acute postoperative pain after major limb amputation – a systematic review

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Abstract

Background and aims: Treatment of pain following major limb amputations is often a clinical challenge in a patient population consisting mainly of elderly with underlying diseases. Literature on management of acute post-amputation pain is scarce. We performed a systematic review on this topic to evaluate the efficacy and safety of analgesic interventions for acute pain following major limb amputation.

Methods: A literature search was performed in PubMed, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews using the following key words: [(amputation) AND (pain OR analgesi* OR pain relief)] AND (acute OR postoperative). Randomized controlled studies (RCTs) and observational studies investigating treatment of acute pain following major amputations for any indication (peripheral vascular disease, malignant disease, trauma) were included. The review was performed according to the standards described in the PRISMA statement. The Cochrane quality assessment tool was used to evaluate the risk of bias in the RCTs.

Results: Nineteen studies with total of 949 patients were included. The studies were generally small and heterogeneous on outcomes, study designs and quality. There were 16 studies on epidural or continuous perineural analgesia (CPI). Based on five RCTs ($n=268$) and two observational studies ($n=49$), epidural analgesia decreased the intensity of acute stump pain as compared to systemic analgesics, during the first 24 h after the operation. Based on one study epidural analgesia caused more adverse effects like sedation, nausea and motor block than continuous perineural local anesthetic infusion. Based on one RCT ($n=21$) and eight observational studies ($n=501$) CPI seemed to decrease opioid consumption as compared to systemic analgesics only, on the first three postoperative days, and was well tolerated. Only three trials investigated systemic analgesics (oral memantine, oral gabapentine, iv ketamine). Ketamine did not decrease acute pain or opioid consumption after amputation as compared to other systemic analgesics. Gabapentin did not decrease acute pain when combined to epidural analgesia as compared to epidural analgesia and opioid treatment, and caused adverse effects.

Conclusions: The main finding of this systematic review is that evidence regarding pain management after major limb amputation is very limited. Epidural analgesia may be effective, but firm evidence is lacking. Epidural causes more adverse effects than CPI. The results on efficacy of CPI are indecisive. The data on adjuvant medications combined to epidural analgesia or CPI is limited. Studies on efficacy and adverse effects of systemic analgesics for amputation pain, especially concentrating on elderly patients, are needed.

Keywords: amputation; acute pain; phantom pain; stump pain; analgesia; acute pain treatment.

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1 Introduction

The most common indication for lower limb amputation is peripheral vascular disease, which causes chronic infections, chronic ischemic pain, chronic ulcers and necrosis. A minority of amputations are performed because of cancer, trauma, septic infections or for congenital reasons. A majority of amputations are performed in the lower limb [1, 2].

Management of acute and chronic post amputation pain is challenging, because large nerve, bone, and soft tissue damage is involved, and also due to the vulnerability of the patient population. Eighty percent of the patients are over 65 years of age, many with underlying diseases and polypharmacy, and the mortality after major amputation is high [3–5]. Selection of suitable analgesics for this patient group is limited due to factors like renal insufficiency, anticoagulative medications and the risk of adverse effects increasing with age. Various degrees of dementia, postoperative confusion and delirium are common, making evaluation of pain and drug effects difficult. Many patients have acute or chronic pain of the limb that will be amputated, or other chronic pain conditions [1]. There is a minor group of young patients with landmine or combat-related injuries that are treated with amputation [6].

Phantom limb pain is a painful or unpleasant sensation of the lost body part. It can be localized to the entire limb or a region of the missing limb. Phantom sensation is a non-painful perception emanating from the lost limb. The incidence of phantom limb pain in major limb amputations of both upper and lower limb is 80%, of which 75% develops during the first postoperative days [7–9]. Stump pain or residual limb pain is localized to the remaining body part after the amputation. Stump pain is common immediately after the operation, and usually diminishes with wound healing. However, it may also persist and increase over time [10–12]. Chronic phantom limb pain after amputation is common, and the pharmacological interventions seem to have only minor effect [13, 14].

The aim of this systematic review is to evaluate the efficacy and safety of various analgesic techniques on acute postoperative pain after major limb amputation.

2 Methods

This review was performed according to the standards described in the PRISMA statement [15].

2.1 Search strategy

Randomized controlled studies (RCTs) and observational studies investigating treatment of acute pain following major amputations were included. A literature search was performed in PubMed (1964–2017), Cochrane Central Register of Controlled Trials (April 2017) and Cochrane Database of Systematic Reviews (2005–2017) using the following key words: [(amputation) AND (pain OR analgesi* OR pain relief)] AND (acute OR postoperative).

PubMed automatic e-mail alert for new studies published during preparation of the review was used for follow-up of papers published after the initial search. The references of retrieved trials, review articles and meta-analyses were checked. Authors were not contacted for original data. Abstracts or unpublished observations were not considered. There was no language restriction.

2.2 Selection criteria

Criteria for including studies in this review were: studies on analgesics and regional analgesia for acute postoperative pain following major limb amputations. Major limb amputation was defined as amputation above knee or below knee but proximal to the ankle, or upper limb amputations proximal to the wrist. Amputations performed for any indications were included (peripheral vascular disease, malignant disease, trauma). Study period for acute pain was defined as beginning immediately after the operation and lasting up to 2 weeks after the operation, based on the clinical experience about the postoperative pain after amputation. Data from studies on treatment of chronic pain following amputation were included, if results during the immediate postoperative period of 2 weeks were reported. Studies reporting on any type of acute postoperative pain, stump pain or phantom pain were included. We included all RCTs, and the observational studies that had a minimum of 10 patients, clearly described methods and a control group. Case series and case reports were excluded.

2.3 Data extraction and analysis

Two authors (HP, KH) performed the searches and excluded papers not related to the topic, independently assessed studies for inclusion and extracted data using a standard form. The results were compared and a third author (VK) was consulted in case of disagreement.

Data was collected on study design, patient demographics including age, indication and type of amputation, diabetes and study intervention. The primary outcomes were the incidence and intensity of acute stump and phantom pain, and the secondary outcomes were the incidence and intensity of preoperative pain, opioid consumption in the first 72 h, the incidence and intensity of chronic stump and phantom pain and adverse effects.

The literature search was focused on acute postoperative pain following major limb amputations. However, if the included studies on acute pain reported the effect on chronic pain, this was evaluated.

The data was collected on a standard form. A meta-analysis was planned, but was not performed because of the heterogeneity of the data.

To evaluate the risk of bias in the RCTs the Cochrane Collaborations bias tool was used [16, 17]. The quality of the cohort studies was evaluated using the GRACE checklist [18].

3 Results

3.1 Description of included studies

The primary search produced 1,159 articles, of which 1,047 articles were not related to the topic. Of the remaining 112 articles 93 were excluded for reasons described in Fig. 1. In one study the randomization was performed by the year of birth, which is not considered proper randomisation and the study was not considered as a RCT. Types of study interventions and number of RCTs for each type of intervention are listed in Table 1. The quality of the 19 included studies was generally low, the majority being observational studies (Tables 1 and 2, Fig. 2, Supplemental Table 1).

Nineteen studies (nine RCTs, 10 observational studies) with 949 patients were included. The studies were generally small, number of patients varied typically between 11 and 65. The largest trial was an observational study of 198 patients with continuous peripheral local anesthetic infusions (CPI). The usual follow-up time was 6 months

Table 1: Study types of the 20 studies included in the analysis.

Intervention	Total amount of studies	Amount of RCTs
Epidural	6	4
Continuous nerve block	9	1
Comparison of epidural and continuous nerve block	1	1
Medication	3	3
Total	19	9

RCT = randomized controlled study.

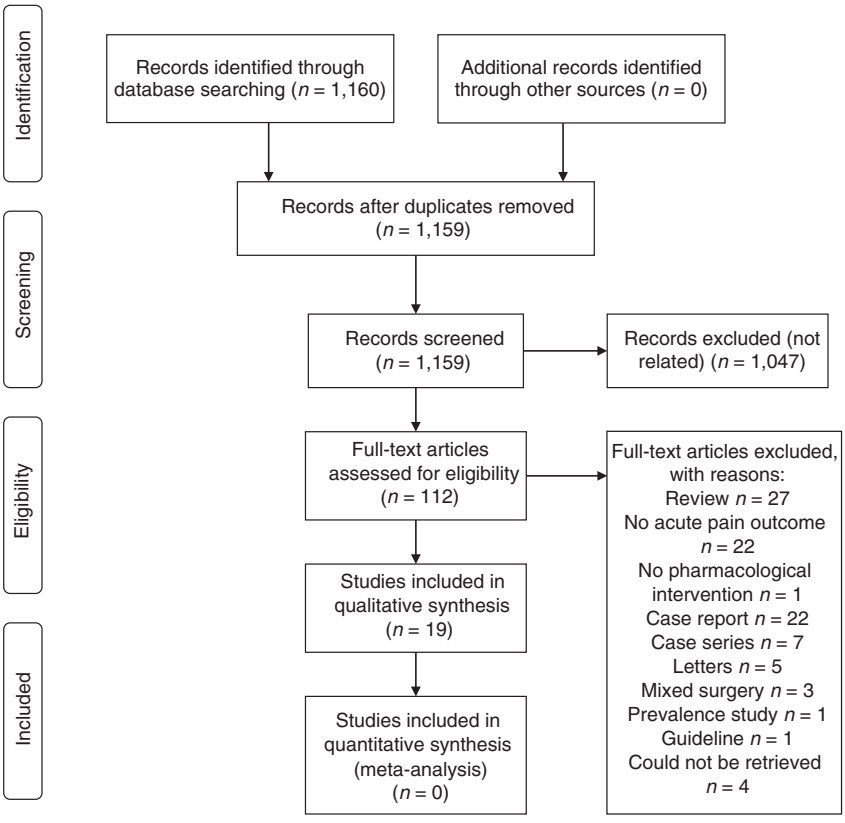

Fig. 1: PRISMA 2009 flow diagram.

Table 2: Risk of bias summary of the nine randomized controlled trials included in the analysis.

RCT:s	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hayes et al. [19]	+	?	+	+	+	?	+
Karanikolas et al. [20]	+	+	–	+	+	+	+
Lambert et al. [21]	+	–	–	–	+	?	+
Nikolajsen et al. [22]	?	?	+	+	+	+	+
Nikolajsen et al. [23]	+	+	+	+	+	?	+
Pinzur et al. [24]	+	?	+	+	?	?	+
Schley et al. [25]	?	?	?	?	–	?	+
Wilson et al. [26]	+	+	+	+	+	+	+
Yousef and Aborahma [27]	+	+	+	+	?	?	+

RCT = randomized controlled trial; + = low risk of bias; ? = unclear risk of bias; – = high risk of bias.

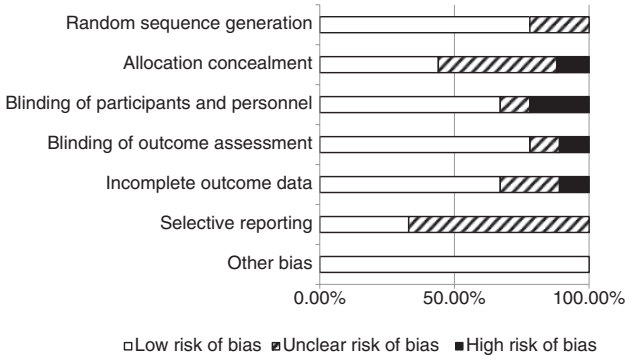

Fig. 2: Risk of bias of the included randomized controlled trials.

on chronic pain and 1 week on acute pain. Age of patients varied between 36 and 92 years. The incidence of diabetes was reported in eight studies presenting data on total number of 178 patients. Sixteen studies reported the incidence (10 studies) or intensity (six) of preoperative pain: six of these studies reported that all patients experienced preoperative pain (Tables 1 and 2, Fig. 2).

3.2 Interventions and outcomes

Six studies investigated continuous epidural analgesia [20, 22, 26–29] and one study compared epidural analgesia and CPI [21] (Table 3, Supplemental Table 2). Nine trials studied CPI (Table 4, Supplemental Table 3) [24, 30–37]. Only three trials studied systemic analgesics (oral memantine, oral gabapentin and i.v. ketamine) [19, 23, 25].

Only four studies stated the primary outcome of the study in the study methods.

There was extensive variation in the methods, interventions, outcome measures and scales, follow-ups, data analyses and reporting and presenting of results. This limited the pooling of the results and the comparison between the studies. Time points for measurement of pain intensity varied between studies (Tables 3 and 4).

The results of the literature search were divided into three groups, epidural analgesia, CPI and systemic medications.

3.3 Efficacy

3.3.1 Epidural analgesia

Characteristics and results of epidural studies are summarized in Table 3 and in detail in Supplemental Table 1. Acute pain as an outcome was reported in all seven epidural studies. Two out of seven epidural studies reported statistically less pain in the intervention group compared to control group in the first 48 h, one compared to systemic analgesics and one compared to continuous perineural infusion [20, 21]. One study showed a decrease in phantom pain at 7 days compared to opioid analgesics [29]. Because of the small number and clinical heterogeneity of the studies meta-analysis on the efficacy of epidural analgesia was not appropriate.

Rescue opioid consumption was reported as an outcome in two of the epidural studies on different time points, but there were no differences between the study groups [21, 22]. Five epidural studies did not report on opioid consumption [20, 26–29].

Results on the incidence of chronic pain 6 months after the amputation were conflicting. Three out of seven epidural studies found a decrease in chronic pain at

Table 3: Characteristics of the included studies on epidural analgesia.

Study/authors	Study design	Patients[a]	Intervention	Comparison	Outcomes			
					Acute postoperative stump pain[b]	Acute postoperative phantom pain[b]	Analgesic requirements[c]	Adverse effects
Randomized controlled trials								
Karanikolas et al. [20]	RCT	$n=65$ AKA and BKA	A: Preoperative epidural bupivacaine 2 mg/mL + fentanyl 2 µg/mL 4–8 mL/h for 48 h, epidural anesthesia, postoperative epidural analgesia as preop for 48 h ($n=13$) B: Preoperative i.v.-PCA fentanyl for 48 h, epidural anesthesia, postoperative epidural infusion as in A for 48 h ($n=13$) C: Preoperative i.v.-PCA fentanyl for 48 h, epidural anesthesia, postoperative i.v.-PCA fentanyl for 48 h ($n=13$) D: Preoperative i.v.-PCA fentanyl for 48 h, general anesthesia, postoperative i.v.-PCA fentanyl for 48 h ($n=13$)	E: Preoperative and postoperative analgesia with pethidine 50 mg i.m. 4–6 times per day + codeine 30 mg/paracetamol 500 mg 3–5 times per day p.o., general anesthesia ($n=13$)	24 and 48 h: VAS and MPQ RLP scores significantly lower in all intervention groups ($p<0.05$)	VAS median (range) 24 h: A: 0 (0–20) B: 23 (0–30) C: 18 (0–40) D: 0 (0–40) E: 50 (20–76) ($p<0.001$) 4 days: A: 0 (0–70) B: 22.5 (0–40) C: 40 (0–70) D: 5 (0–50) E: 45 (0–80) ($p=0.081$) 10 days: A: 0 (0–60) B: 20 (0–50) C: 40 (0–60) D: 0 (0–50) E: 45 (0–80) ($p=0.002$)	NA	Of all patients: Nausea 24%, vomiting 18%, drowsiness 16%, motor deficits 14%, dizziness 12%, pruritus 11%, constipation 9%, mild hypotension 8% (Adverse effects for each group not available)
Lambert et al. [21]	RCT	$n=30$ AKA, BKA	A: Epidural bupivacaine 0.166% 2–8 mL/h, diamorphine 0.2–0.8 mg/h 24 h preop and 72 h postoperatively ($n=14$)	B: Continuous sciatic (AKA) or tibial or common peroneal (BKA) nerve block with bupivacaine 0.25% 10 mL/h 72 h postoperatively ($n=16$)	VAS mean (range): 6 h: A: 1 (0–5) B: 5 (0–10) ($p=0.01$) 1 day: A: 1 (0–6) B: 4 (0–8) ($p=0.005$)	3 days A: $n=4/14$ B: $n=7/16$ ($p=0.32$)	72 h: A: 20 (5–42) mg B: 30 (0–143) mg NS	NA

Table 3 (continued)

Study/authors	Study design	Patients[a]	Intervention	Comparison	Outcomes			
					Acute postoperative stump pain[b]	Acute postoperative phantom pain[b]	Analgesic requirements[c]	Adverse effects
					2 days: A: 1 (0–6) B: 4 (0–10) ($p=0.01$) 3 days: A: 1 (0–3) B: 4 (0–9) ($p=0.005$)			
Nikolajsen et al. [22]	RCT	$n=60$ AKA, BKA, through knee joint	A: Epidural bupivacaine 0.25% 4–7 mL/h, morphine 0.16–0.28 mg/h median 18 h preoperatively and median 166 h postoperatively ($n=29$)	B: Epidural saline 4–7 mL/h + i.m./po morphine median 18.5 h preoperatively and epidural analgesia with bupivacaine 0.25% 4–7 mL/h, morphine 0.16–0.28 mg/h median 166 h postoperatively ($n=31$)	VAS median (range) 7 days: A: 16 (8–25) B: 15 (10–23) ($p=1.0$)	7 days: A: $n=14/27$ B: $n=15/27$ ($p=0.9$) VAS A: 4 (0–27) B: 10 (0–26) ($p=1.0$)	7 days: A: 80 (40–118) mg B: 80 (40–120) mg ($p=0.9$)	One meningitis, one subcutaneous abscess
Wilson et al. [26]	RCT	$n=53$ AKA, BKA	A: Epidural bolus ketamine 0.5 mg/kg and bupivacaine 0.5% 1 mg/kg preoperatively, continuous ketamine 3.3 mg/kg/L and bupivacaine 0.125% 10–20 mL/h with the aim of VAS <30 48–72 h postoperatively ($n=24$)	B: Epidural bolus saline + bupivacaine 0.5% 1 mL/kg before start of operation, continuous infusion saline + bupivacaine 0.125% 15 mL/h 48–72 h postoperatively ($n=29$)	8 days: A: $n=11/17$ B: $n=15/26$ ($p=0.9$) VAS median (quartiles): 8 days: A: 0 (0–17) B: 17 (0–35) ($p=0.031$)	8 days: A: $n=6/17$ B: $n=3/26$ NS	NA, no opioids given per protocol only epidural	Motor block, nausea and vomitimg, sedation, confusion, hallucinations: NS
Yousef and Aborahma [27]	RCT	$n=60$ AKA, BKA, minor amputations below ankle	A: Epidural bolus bupivacaine 0.5% 10 mL and fentanyl 0.1 mg and calcitonin 100 I. U. preoperatively, and once a day 2 days postoperatively	B: Epidural bolus bupivacaine 0.5% 10 mL and fentanyl 0.1 mg and saline 1 mL preoperatively, and once a day 2 days postoperatively	VAS mean ± SD 12 h: A: 2 ± 0.5 B: 2 ± 0.8 ($p=0.920$) 24 h: A: 2.4 ± 0.5 B: 2.9 ± 1.2 ($p=0.153$)	NA	NA	NA

Table 3 (continued)

Study/authors	Study design	Patients[a]	Intervention	Comparison	Outcomes			
					Acute postoperative stump pain[b]	Acute postoperative phantom pain[b]	Analgesic requirements[c]	Adverse effects
					36 h: A: 3.4 ± 1 B: 3.2 ± 1 ($p = 0.494$) 48 h: A: 3.3 ± 0.7 B: 3.6 ± 1.2 ($p = 0.223$)			
Other studies								
Bach et al. [28]	Prospective, controlled trial	$n = 25$ BKA	A: Epidural bupivacaine 0.25% and morphine 72 h preoperatively until amputation ($n = 11$)	B: Various analgesics: paracetamol, NSAID:s, opioids starting 72 h before amputation ($n = 14$)	7 days: A: $n = 1/11$ B: $n = 1/14$	7 days: A: $n = 3/11$ B: $n = 9/14$ ($p < 0.10$)	NA	NA
Jahangiri et al. [29]	Prospective, controlled trial	$n = 24$ AKA, BKA	A: Epidural bupivacaine 75 mg, clonidine 150 µg, diamorphine 5 mg in 60 mL of saline 1–4 mL/h 24–48 h preoperatively and 72 h postoperatively ($n = 13$)	B: Opioid analgesia as needed ($n = 11$)	7 days: A: $n = 3/13$ B: $n = 6/11$ NS	7 days: A: $n = 3/13$ B: $n = 9/11$ ($p < 0.01$)	NA	Two urinary retention and two faecal incontinence, in the epidural group

[a]Total number of patients (n) and type of amputation; [b]incidence (n of pts) and/or intensity (VAS); [c]morphine mg equivalent.
RCT = randomized controlled trial; AKA = above knee amputation; BKA = below knee amputation; PCA = patient controlled analgesia; VAS = visual analogue scale; pts = patients; MPQ = McGill Pain Questionnaire; RLP = residual limb pain; mo = months; NA = not available; NS = not significant.

Table 4: Characteristics of the included studies on continuous perineural local anesthetic infusion.

Study/ authors	Study design	Patients[a]	Intervention	Comparison	Outcomes			
					Acute postoperative stump pain[b]	Acute postoperative phantom pain[b]	Analgesic requirements[c]	Adverse effects
Randomized controlled trials								
Pinzur et al. [24]	RCT	$n=21$ AKA, BKA	A: Sciatic or tibial nerve block with bupivacaine 0.5% 1 mL/h + 10 mL bolus, for 72 h postoperatively and PCA opioid ($n=11$)	B: Continuous nerve block with placebo (saline) 1 mL/h + 10 mL placebo bolus, for 72 h postoperatively and PCA opioid ($n=10$)	NA	NA	1 day: A: 6.8 ± 1.1 mg B: 8.9 ± 1.2 mg ($p<0.001$) 2 days: A: 5.8 ± 1.0 mg B: 6.0 ± 0.9 mg ($p<0.001$) 3 days: A: 2.4 ± 0.6 mg B: 1.9 ± 0.5 mg NS	No complications related to catheters, no wound infections
Other studies								
Ayling et al. [30]	Retrospective comparison	$n=198$ AKA, BKA	A: Sciatic or tibial nerve block + various analgesics ($n=102$)	B: Various analgesics including i.v.-PCA opioids and gabapentin ($n=96$)	VAS (mean ± SD): 24 h: A: 3.0 ± 2.1 B: 3.4 ± 2.1 NS		72 h opioid consumption (mean ± SD): A: 81.2 ± 90.8 mg B: 134.5 ± 145.5 mg ($p=0.03$) No. of patients using postoperative gabapentinoids: A: 40/102 B: 35/96 NS	Delirium, sedation and nausea NS Catheter failure 8.8% Death NS
Borghi et al. [31]	Observational study, no comparative group	$n=62$ AKA, BKA	A: Various nerve blocks (sciatic, femoral, posterior lumbar) with ropivacaine 0.5% 5 mL/h (perineural sciatic, femoral, lumbar plexus), prolonged postoperative infusions for median 30 (4–83) days ($n=62$)	No comparative group	1 day: 62/62 1 week: 62/62 VRS (median): 1 day: 3 (distribution of patients by VRS 0:0, 1:0, 2:6, 3:47, 4:9) 1 week: 2 (distribution of patients by VRS: 0:8, 1:16, 2:32, 3:6, 4:0)	1 day: 58/62 1 week: 38/62 VRS (median): 1 day: 3 (distribution of patients by VRS 0:0, 1:0, 2:6, 3:47, 4:9) 1 week: 2 (distribution of patients by VRS: 0:8, 1:16, 2:32, 3:6, 4:0)	NA	NA

Table 4 (continued)

Study/ authors	Study design	Patients[a]	Intervention	Comparison	Outcomes			
					Acute postoperative stump pain[b]	Acute postoperative phantom pain[b]	Analgesic requirements[c]	Adverse effects
Elizaga et al. [32]	Observational study, historical control group	$n=59$ AKA, BKA	A: Sciatic or tibial nerve block with bupivacaine 0.5% 2–6 mL/h + bolus 10–20 mL, 3–7 days or boluses + analgesics ($n=19$)	B: Various analgesics, opioids ($n=40$)	NA		72 h Opioid consumption (mean ± SD): A: 132.7 ± 92.8 mg B: 151.3 ±124.3 mg ($p=0.564$)	Pruritus, drowsiness, NS
Fisher and Meller [33]	Observational study, historical control group	$n=31$ AKA, BKA	A: Sciatic or tibial nerve block with bupivacaine 0.25% 10 mL/h for 72 h + bolus 20 mL + pethidine i.m. ($n=11$)	B: Parenteral opioids ($n=20$)	NA	NA	72 h Opioid consumption [mean (range)]: A: 1.4 (0–10) mg B: 18.4 (10–45) mg ($p=0.0001$)	No wound infections, no intoxications, no urinary retention
Grant and Wood [34]	Retrospective comparison	$n=64$ AKA 34 BKA 30	A: Sciatic or tibial nerve block postoperatively for 1–8 days (3.4) with bupivacaine 0.5% 3–4 mL/h and various analgesics ($n=33$)	B: Various analgesics as paracetamol, dihydrocodeine, morphine ($n=31$)	NA	NA	Mean opioid required: (time point not reported) A: 74 mg B: 10 mg No. of patients not requiring opioid: A: 12/33 B: 4/31	Deep venous thrombosis, pulmonary embolism, chest infection, death, 3 catheters blocked and 8 pulled out
Malawer et al. [35]	Observational, historical comparative group	$n=34$ AKA, BKA, partial resection, hemi-pelvectomy	A: Sciatic, femoral or lumbar nerve block with bupivacaine 0.25% 2–4 mL/h and 0.25%–0.5%, bolus 10–20 mL for 72 h postoperatively ($n=23$)	B: Parenteral opioid analgesia and/or epidural opioid ($n=11$)	NA	NA	72 h Opioid consumption: A: 25 mg B: 123 mg No. of patients not requiring opioid: A: 11/23	Motor weakness 4, no infections, 2 catheters pulled out
Uhl et al. [36]	Observational study, divided to groups according to the side amputated	$n=42$ AKA	A: Sciatic nerve block with 0.375% ropivacaine 5 mL/h for 72 h ($n=20$)	B: Opioids, acetaminophen, oral metamizol ($n=22$)	VAS (mean): 1 day: A: 4.6, B: 6.5 ($p=0.001$) 2 days: A: 2.7, B: 5.3 ($p=0.001$) 3 days: A: 2.4, B: 4.3 ($p=0.002$) 4 days: A: 2.1, B: 4.0 ($p=0.001$)	NA	1 day: A: 42.1 mg B: 73.5 mg ($p=0.001$) 2 days: A: 27.7 mg B: 52.5 mg ($p=0.012$) 3 days: A: 23.9 mg B: 53.5 mg ($p=0.002$)	Wound complications A: 5% B: 10%

Table 4 (continued)

Study/ authors	Study design	Patients[a]	Intervention	Comparison	Outcomes			
					Acute postoperative stump pain[b]	Acute postoperative phantom pain[b]	Analgesic requirements[c]	Adverse effects
					5 days: A: 1.7, B: 3.7 ($p=0.001$)		4 days: A: 15.7 mg B: 48.3 mg ($p=0.003$) 5 days: A: 13.3 mg B: 49.9 mg ($p=0.001$)	
van Geffen et al. [37]	Observational	$n=11$ AKA, BKA	A: Sciatic, femoral or brachial nerve block preoperatively with ropivacaine 0.75% 0.3+0.1 mL/kg bolus, bupivacaine 0.25% (or 0.125% if two catheters) 0.1 mL/kg/h max 6 mL/h under ultrasound guidance for 5 days ($n=5$)	B: Postoperative neural blockade for 5 days as in A ($n=6$)	VAS 1 day: A: 2–4 B: 3–4	NA	NA	NA

[a]Total number of patients (n) and type of amputation; [b]incidence (n of pts) and/or intensity (VAS or VRS); [c]morphine mg equivalent.
RCT = randomized controlled trial; pts = patients; AKA = above knee amputation; BKA = below knee amputation; PCA = patient controlled analgesia; VAS = visual analogue scale; NA = information not reported, not available; NS = not significant.
Lambert et al. [21] is reported in Table 3 (Comparison of epidural analgesia and continuous perineural local anesthetic infusion).

6 months [20, 28, 29], but there were some methodological problems in two of these studies.

3.3.2 Continuous perineural local anesthetic infusion (CPI)

Characteristics and results on CPI are described in Table 4 and in detail in Supplemental Table 2. To summarize, acute pain as an outcome was reported in four out of the nine CPI studies [30, 31, 36, 37]. Only one study showed a decrease in acute pain at 24 h [36]. Rescue opioid consumption was reported in seven out of nine CPI studies. In three of these studies (one RCT, two observational studies) opioid consumption at early postoperative period was decreased in the intervention group compared to control group [24, 30, 33].

The incidence of chronic pain was reported in three CPI studies [24, 31, 32]. Only one of these studies was randomized and controlled [24]. CPI did not have an effect on chronic pain.

3.3.3 Systemic analgesics

Nikolajsen et al. [23] performed an RCT on the effect of gabapentin as an adjuvant analgesic on patients treated with epidural analgesia after major lower limb amputation. Gabapentin did not decrease acute pain intensity or opioid consumption, neither did it reduce the incidence or severity of phantom limb pain. However, the intensity of postamputation pain was low in both groups most likely due to epidural analgesia. There were no studies of gabapentinoids combined to CPI. Hayes et al. [19] found that perioperative and postoperative intravenous ketamine did not have an effect on acute postoperative pain incidence or intensity on lower limb amputees. There were no significant between-group differences in the adverse effects attributable to ketamine. Schley et al. [25] studied the effect of oral memantine as an adjuvant analgesic on phantom limb pain in upper limb amputation patients who had a continuous perineural local anesthetic infusion. Memantine did not have an effect on acute pain intensity.

3.4 Adverse effects

Only few of the studies reported adverse effects, and when available, data on adverse effects was inconsistent.

Four out of the seven epidural studies reported on adverse effects [20, 22, 26, 29]. When epidural analgesia was compared to systemic opioid analgesia, there were no significant differences found in motor block, nausea, vomiting, sedation, confusion or hallucinations. There were two cases of transient urinary retention and faecal incontinence reported in a study of 24 patients, all in the epidural group [29]. In a study of 60 amputees one case of meningitis and one subcutaneous abscess was reported [22].

Of the nine studies investigating the efficacy of CPI seven reported adverse effects [24, 30, 32–36]. One study reported catheter failure in nine patients (8.8%): five were blocked, two disconnected, one kinked and one was incompletely inserted [30]. Another study reported that catheter was pulled out in two out of 23 patients [35] and an other eight out of 33 patients [34]. No wound infections related to catheters were reported. It was generally reported that the amount of pruritus, drowsiness, delirium, sedation, nausea, vomiting, deep venous thrombosis, pulmonary embolism, chest infection, or death did not increase.

In a study on gabapentin, the study medication was either reduced or temporarily stopped in seven out of 46 patients (gabapentin five, placebo two) because of adverse effects [23]. Seventeen patients reported nausea, stomachache, fatigue, confusion, nightmares, but there were no significant differences between the groups (gabapentin nine, placebo eight). In Schley et al. [25] nausea, dizziness, headache and agitation were observed when the dose of memantine was increased.

4 Discussion

The main finding of this systematic review is the paucity and variability of published data on this topic. The evidence originates mainly from few small trials, and studies in which acute pain was not the primary outcome. The studies included were heterogeneous in terms of study interventions, methodology, outcomes and reporting. We found only nine randomized controlled trials. Judged by the criteria presented in the PRISMA statement and in the Cochrane risk of bias assessment tool, the study quality was generally low. We decided against performing any meta-analyses because the majority of these studies were non-randomized and clinically heterogeneous.

4.1 Implications for clinical practice

Despite the fact that vascular surgery techniques have developed during the last years, amputations are still a

common procedure among the patients suffering from peripheral vascular disease. However, in line with our conclusions, there is very little data to support the choice of postoperative analgesia for patients undergoing major amputation [3, 38, 39].

There is ethical and practical imperative for effective and safe management of acute postoperative pain also in this patient group.

In the studies reporting rescue opioid consumption, the amount of rescue opioid in the first 72 h (20–151 mg in morphine equivalents) shows that the postoperative pain following major limb amputations is severe. There also is a wide range in the opioid use in the included studies. Elderly patients are especially vulnerable to opioid related adverse effects and there is a genuine need for interventions that could decrease postoperative opioid consumption.

4.2 Epidural analgesia

Data from four RCTs and two observational studies with 257 patients showed that epidural analgesia may be effective in decreasing the intensity of stump and phantom pain during the first postoperative days but there is a lack of sound evidence. There was no difference in the consumption of rescue opioids during the first 72 h after the operation. Epidural analgesia seems to be efficient and safe in amputee patients, but the widespread use of anticoagulative medication in atherosclerosis patients often prevents effective use of this technique. There were various combinations of medications used in the included epidural studies. It is also noteworthy, that failure of epidural analgesia occurs in up to 30% in clinical practice [40].

4.3 Continuous perineural local anesthetic infusion

Based on studies on other types of surgery, such as knee arthroplasty and open shoulder surgery, there is relatively strong evidence that CPI or single shot nerve blocks decrease the intensity of postoperative pain and consumption of postoperative opioids [41, 42]. On the other hand, continuous wound infiltration with local anesthetic does not seem to diminish opioid consumption or acute pain after different types of surgery [43]. In major amputations, the CPI is a technique that might be considered to be something in between these two: the catheter is placed in the wound area, distal to the injured nerve, and usually placed into the nerve sheath or next to the nerve. It most likely provides better analgesia than wound infiltration catheters. The different nerves targeted with the continuous infusion were sciatic nerve in above the knee amputations and common peroneal nerve or tibial nerve in below the knee amputations.

Based on the scarce data from the non-randomized observational studies CPI seems to decrease the opioid consumption of amputee patients in the first 72 h. There was only a single RCT with total of 21 patients investigating CPI compared to placebo. The results showed that opioid consumption of the first two postoperative days was decreased in patients treated with CPI of sciatic nerve for 72 h with 0.5% bupivacaine 1 mL/h compared to a saline infusion.

4.4 Systemic analgesics

There are only three studies evaluating the efficacy of systemic analgesics in acute pain after major limb amputations. Gabapentin administered on top of epidural analgesia did not improve postoperative analgesia, but the postoperative pain scores in all patients were relatively low affecting the sensitivity of the trial [23]. A recent review summarized that there is lack of firm evidence of the benefit of gabapentin as a part of multimodal postoperative analgesia [44]. The routine use of gabapentinoids in postamputation pain is probably not advisable, but it may be beneficial in some patients after careful consideration.

Perioperative intravenous ketamine infusion continuing for 3 days after the operation did not have any effect on postoperative stump or phantom pain or central sensitisation, measured as allodynia for touch [19]. In other types of surgery, ketamine has been shown to be effective in reducing opioid requirement and pain scores in the first 24 h after surgery in subanesthetic doses [45–49].

4.5 Prevention of chronic pain

Many amputee patients experience acute or chronic pain before the operation. Preoperative pain and persistent acute postoperative pain are risk factors for increased postoperative pain and opioid consumption [50–55]. There is a significant correlation between the level of pain preceding amputation and chronic pain after the amputation, and it has been suggested that adequate analgesia before amputation and in the acute phase after amputation could prevent chronic pain [9, 10]. No firm

conclusions on prevention of chronic pain can be drawn based on the present review.

4.6 Limitations

The main limitation of this review is, that all except for one of the included studies had small sample sizes, used a short treatment and follow up period and were of relatively low quality overall, which made it problematic to form generalizations and conclusions.

4.7 Implications for clinical research

Studying elderly patients undergoing amputations is challenging: dementia, postoperative confusion and delirium are common, making evaluation of pain and drug effects difficult. However, treatment of pain should be improved especially in this vulnerable patient group. Pragmatic protocols with large numbers of patients and well-defined and clinically feasible outcome measures are urgently needed. Studies concentrating on the features of epidural analgesia are needed, taking in to account the location of the epidural catheter and the composure of the epidural infusion. Separate studies should address different patient groups: fragile elderly patients undergoing amputations for complications of peripheral vascular disease, amputations following traumatic injury, amputations for malignant diseases, and patients with preoperative pain in the limb to be amputated.

5 Conclusions

Based on this systematic review, epidural analgesia may be efficient, but the treatment regimes are too heterogenous for firm evaluation and the quality of data low. CPI probably decreases the acute pain levels after major amputation, but the evidence is scarce. We cannot state that there are efficient, safe ways of treating acute postoperative pain after major amputation, without clinically significant side-effects and with the benefit of preventing chronic pain. Overall, there seems to be very little data supporting the current clinical practice on pain management in acute pain after amputation.

Authors' statements

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