Do We Have the Tools to Prevent Phantom Limb Pain?

PERSISTENT pain after limb amputation is common, most often taking the form of phantom limb pain or localized pain in the residual portion of the limb (stump pain). The conflicts in Afghanistan and Iraq have brought this to the forefront: in a report[1] appearing in 2008, of the 8,058 reported military casualties in US military personnel, 5,684 (70.5%) had major limb injuries; and 423 (7.4%) of patients with major limb injuries underwent amputation. In a recent nationwide survey[2] of more than 1,088 amputees in Germany, 14.8% were pain free, 74.5% had phantom limb pain, 45.2% had stump pain, and 35.5% had a combination of both types of pain. This pain led to sleep disorders in most of those affected[1] and has been linked with long-term adverse health outcomes, including acceleration in onset of cardiovascular disease, obesity, and chronic joint and low-back pain.[3] Not all amputees experience persistent pain, and the reasons for this are unclear. One of the risk factors that seem to be associated with a higher prevalence of persistent pain is severe and poorly controlled pain before surgery,[4] raising the possibility that providing good analgesia before amputation may well decrease the risk of developing chronic pain. In this issue of ANESTHESIOLOGY, Karanikolas *et al.*[5] present the results of a small randomized controlled trial in patients undergoing amputation; the results further support the notion that providing for good pain control before amputation may be one of our best hopes of minimizing the risk of persistent pain after amputation.

The concept of "preemptive analgesia" (*i.e.*, the idea that central sensitization might be mitigated or prevented altogether by reducing or eliminating the barrage of nociceptive input reaching the central nervous system and thereby decreasing the degree of central sensitization) arose more than a decade ago.[6] Anesthesiologists embraced the concept that establishing neural blockade in the area of surgery before the surgical insult might improve pain treatment. The idea that preoperative epidural blockade could be used preemptively to provide analgesia before amputation and reduce the prevalence of persistent postamputation pain in the first 12 months after surgery was first tested by Bach *et al.*[7] in 1988. In this study, 11 patients received a continuous lumbar epidural block so that they were pain free for 3 days before the operation; however, patients who received epidural analgesia and remained in pain were excluded from the trial, a significant shortcoming in this small study. The control group of 14 patients all had preoperative limb pain. Seven days after the operation, 3 (27%) of 11 patients in the preoperative epidural group and 9 (64%) of 14 patients in the control group had phantom limb pain. After 6 months, all patients in the epidural group were pain free, whereas 5 (36%) of 14 patients in the control group had pain. After 1 yr, all the patients in the epidural group were still pain free; 3 (21%) of 14 patients in the control group had phantom limb pain. Despite these promising early results, numerous studies have ensued and the true benefit of preemptive analgesia in and of itself appears to be limited.[8] Nevertheless, severe pain after amputation is clearly associated with a higher prevalence of postamputation pain,[9,10] suggesting that aggressive efforts to control pain before surgery may have the potential of decreasing the prevalence of chronic pain. The outcomes in previous trials of preemptive analgesia and phantom limb pain in comparison with the new trial appearing in this issue are shown in Table 1.

In the study by Karanikolas *et al.*,[5] which appears in this issue of ANESTHESIOLOGY, 65 patients with severe lower-limb ischemic pain from peripheral vascular disease underwent amputation and were assigned to one of five analgesic regimens, including preoperative, intraoperative, and/or postoperative use of epidural analgesia or intravenous opioids, delivered by a patient-controlled analgesia device to provide adequate pain relief. Small groups of patients receiving these interventions were compared against standard means of providing preoperative analgesia using intermittent nurse-administered doses of intramuscular opioid. The analysis reveals consistent and striking differences between the control group receiving intramuscular opioid and all other treatment groups: the patient groups whose pain was well controlled perioperatively using combinations of intravenous patient-controlled analgesic opioid and/or epidural analgesia had a dramatically decreased prevalence of phantom limb pain 6 months after amputation compared with the opioid analgesia alone group (15 [28.8%] of 52 patients *vs.* 9 [75.0%] of 12 patients). In addition to decreasing the prevalence of phantom limb pain, the severity of symptoms in those who did develop phantom limb pain was lower in the groups with better pain control before surgery than in the control group. Therefore, providing good perioperative pain control before and after amputation was enough to dramatically reduce the prevalence and severity of postamputation pain.

The means used to control pain preoperatively in the control group in this study deserve special attention. Those receiving "conventional" preoperative analgesia (*i.e.*, the control group) were given intramuscular meperidine or codeine/acetaminophen orally and had much higher pain scores (of a total 100) before surgery. This group of control

◆ This Editorial View accompanies the following article: Karanikolas M, Aretha D, Tsolakis J, Monantera G, Kiekkas P, Papadoulas S, Swarm RA, Filos KS: Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: A prospective, randomized, clinical trial. ANESTHESIOLOGY 2011; 114:1144–54.

Accepted for publication January 4, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2011; 114:1021–4

Table 1. Studies Examining the Rate of PLP after Perioperative Treatment with Epidural Analgesia or Continuous Perineural Infusion of a Local Anesthetic

Source	Type	Study Group Anesthetic	Mode	Control Group Analgesic	No. of Patients		Rate of PLP at 6 Months, %		Level of Significance, *P*	Rate of PLP at 1 yr, %		Level of Significance, *P*	LTFU, %
					Study Group	Control Group	Study Group	Control Group		Study Group	Control Group		
Studies Comparing Opioids on Demand with Epidural Analgesia													
Bach *et al.*,[7] 1988	PCC	BUP, M, or BUP/M	EPID	Various analgesics	11	14	0	28	<0.05	0	27	<0.20	24.0
Jahangiri *et al.*,[11] 1994	PCC	BUP/DM/C	EPID	Opioids on demand	13	11	8	73	<0.002	8	73	<0.002	0.0
Nikolajsen *et al.*,[12] 1997	RCT	BUP/M	EPID	Opioids on demand	29	30	81	55	NS	75	69	NS	52.5
Nikolajsen *et al.*,[13] 1998	RCT	BUP/M	EPID	Opioids on demand	23	22	79	59	NS				31.1
Studies Comparing Other Analgesic Regimens													
Fisher and Meller,[14] 1991	POC/HS	BUP	PN	Opioids on demand	11	20	0			0			28.8
Lambert *et al.*,[15] 2001	RCT	BUP/DM *vs.* BUP	EPID *vs.* PN	Opioids on demand	14	16	63	88	NS	38	50	NS	10.7
Nikolajsen *et al.*,[16] 2006	RCT	GABAPENT + BUP (EPID)	PO	BUPI (EPID)	23	23	58	50	NS				28.3
Wilson *et al.*,[17] 2008	RCT	KETA/BUP	EPID	BUP	24	29	40	19	NS	50	40	NS	43.3
Borghi *et al.*,[18] 2010	POC	BUP	PN	No control group	71		17			17			12.7
Current Study													
Karanikolas *et al.*,[5] 2011	RCT	EPID/EPID/EPID	EPID and/or IV PCA	Nurse-administered opioids on demand	13	12	8	75	0.001				11.1*
		PCA/EPID/EPID			13		31		0.027				
		PCA/EPID/PCA			12		58		NS				
		PCA/GA/PCA			13		23		0.009				

Adapted with permission from Ypsilantis and Tang.[8]

* The range was from 0% to 23.1%. Patients lost to follow-up in the study by Karanikolas *et al.* were as follows: control, 0 (0%) of 12; EPID/EPID/EPID, 3 (23.1%) of 13; PCA/EPID/EPID, 2 (15.4%) of 13; PCA/EPID/PCA, 1 (8.3%) of 12; and PCA/GA/PCA, 1 (7.7%) of 13.

BUP = bupivacaine; C = clonidine; DM = diamorphine; EPID = epidural; GA = general anesthesia; GABAPENT = gabapentin; IV = intravenous; KETA = ketamine; LTFU = initial patient population lost to end follow-up; M = morphine; NS = nonsignificant; PCA = patient-controlled analgesia; PCC = prospective case-controlled study; PLP = phantom limb pain; PN = perineural block; PO = orally; POC/HS = prospective observational cohort study with historical control; RCT = randomized controlled trial.

patients had severe and ongoing pain (median pain score, 70) at the end of the 48-h preoperative observation period just before amputation. In comparison, patients receiving either intravenous patient-controlled analgesic opioids or epidural analgesia preoperatively had little or no pain just before amputation (median pain score range, 0–20). Is this really conventional treatment? A brief glance at the baseline pain scores in available published trials (table 2) demonstrates that the baseline pain scores in the current study were not atypical; however, the pain scores in the treatment group once pain treatment had been initiated remained higher than would be expected with free access to opioid analgesics on demand. It is unlikely in most developed nations that patients would be allowed to continue for 48 h with reports indicating severe and ongoing pain without more aggressive treatment of some kind. Karanikolas *et al.*[5] note, "The high perioperative pain scores in the control group raise the concern that analgesic doses and/or frequency was inadequate. However, unfortunately, analgesia, as provided in the control group, was the norm in our hospital and probably in many other hospitals."

Table 2. Comparison of Baseline Pain Scores in Studies Examining the Rate of Limb Pain (PLP) after Perioperative Treatment with Epidural Analgesia or Continuous Perineural Infusion of a Local Anesthetic

Source	Type	Study Group Anesthetic	Mode	Control Group Analgesic	Baseline Pain Scores*		Scores after Analgesic Treatment (before Amputation)*		No. of Patients		Rate of PLP at 6 Months, %		Level of Significance, *P*
					Study Group	Control Group	Study Group	Control Group	Study Group	Control Group	Study Group	Control Group	
Nikolajsen *et al.*,[12] 1997	RCT	BUP/M	EPID	Opioids on demand	51 (24–78)	44 (25–68)	0 (0–0)	31 (21–51)	27	29	81	55	NS
Nikolajsen *et al.*,[13] 1998	RCT	BUP/M	EPID	Opioids on demand	62 ± 31†	46 ± 29†	0 (0–31)	29 (0–80)	23	22	79	59	NS
Wilson *et al.*,[17] 2008	RCT	KETA/BUP	EPID	BUP	50 (40–50)	70 (50–83)	NR	NR	24	29	40	19	NS
Lambert *et al.*,[15] 2001	RCT	BUP/DM *vs.* BUP	EPID *vs.* PN	Opioids on demand	60 (10–80)	50 (0–90)	NR	NR	14	16	63	88	NS
Nikolajsen *et al.*,[16] 2006	RCT	GABAPENT + BUP (EPID)	PO	BUP (EPID)	80 (20–100)	80 (10–100)	NR	NR	23	23	58	50	NS
Karanikolas *et al.*,[5] 2011	RCT	EPID/EPID/EPID	EPID or IV PCA	Nurse-administered opioids on demand	90 (70–100)	70 (70–100)	0 (0–30)	60 (20–80)	13	12	8	75	0.001
		PCA/EPID/EPID			82 (25–100)		20 (0–30)		13		31		0.027
		PCA/EPID/PCA			90 (70–100)		20 (0–30)		12		58		NS
		PCA/GA/PCA			80 (50–100)		10 (0–35)		13		23		0.009

Only those studies that reported baseline pain scores and/or pain scores after analgesic treatment but before amputation were included.

* Data are given as median (range) visual analog scale score unless otherwise indicated. The possible score was from 0 to 100. † Data are given as mean ± SD.

BUP = bupivacaine; DM = diamorphine; EPID = epidural; GA = general anesthesia; GABAPENT = gabapentin; IV = intravenous; KETA = ketamine; M = morphine; NS = nonsignificant; NR = not reported; PCA = patient-controlled analgesia; PLP = phantom limb pain; PN = perineural block; PO = orally; RCT = randomized controlled trial.

The current study is plagued by the same limitations apparent in previous trials; the most worrisome of these limitations is the small sample size in the groups. Because of the few patients in each treatment group, it is difficult to interpret the results between the treatment subgroups receiving different intraoperative and postoperative analgesic regimens (*i.e.*, the relative role of epidural *vs.* patient-controlled analgesia). Nevertheless, the conclusions of this and many previous studies seem to be similar. Simply providing good pain control in the hours leading up to limb amputation and continued postoperatively with whatever means are available might well decrease the probability and severity of phantom limb pain. Sadly, poor control of pain before amputation likely remains more the rule than the exception. We can do better with the simple tools that are readily available to us today. What once passed for conventional perioperative analgesia should no longer be acceptable practice: the long-term well-being of our patients undergoing limb amputation is in our hands.

James P. Rathmell, M.D.,* Henrik Kehlet, M.D., Ph.D.† *Division of Pain Medicine, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts. jrathmell@partners.org. †Division of Surgical Pathophysiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark.

References

1. Stansbury LG, Lalliss SJ, Branstetter JG, Bagg MR, Holcomb JB: Amputations in U.S. military personnel in the current conflicts in Afghanistan and Iraq. J Orthop Trauma 2008; 22: 43–6
2. Kern U, Busch V, Rockland M, Kohl M, Birklein F: Prevalence and risk factors of phantom limb pain and phantom limb sensations in Germany: A nationwide field survey. Schmerz 2009; 23:479–88
3. Robbins CB, Vreeman DJ, Sothmann MS, Wilson SL, Oldridge NB: A review of the long-term health outcomes associated with war-related amputation. Mil Med 2009; 174:588–92
4. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367:1618–25
5. Karanikolas M, Aretha D, Tsolakis I, Monantera G, Kiekkas P, Papadoulas S, Swarm RA, Filos KS: Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: A prospective, randomized, clinical trial. Anesthesiology 2011; 114:1144–54
6. Woolf CJ, Chong MS: Preemptive analgesia: Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993; 77:362–79
7. Bach S, Noreng MF, Tjéllden NU: Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988; 33:297–301
8. Ypsilantis E, Tang TY: Pre-emptive analgesia for chronic limb pain after amputation for peripheral vascular disease: A systematic review. Ann Vasc Surg 2010; 24:1139–46
9. Jensen TS, Krebs B, Nielsen J, Rasmussen P: Immediate and

long-term phantom limb pain in amputees: Incidence, clinical characteristics and relationship to pre-amputation limb pain. Pain 1985; 21:267–78

10. Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS: The influence of preamputation pain on postamputation stump and phantom pain. Pain 1997; 72:393–405
11. Jahangiri M, Jayatunga AP, Bradley JW, Dark CH: Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann R Coll Surg Engl 1994; 76:324–6
12. Nikolajsen L, Ilkjaer S, Christensen JH, Krøner K, Jensen TS: Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet 1997; 350:1353–7
13. Nikolajsen L, Ilkjaer S, Jensen TS: Effect of preoperative extradural bupivacaine and morphine on stump sensation in lower limb amputees. Br J Anaesth 1998; 81: 348–54
14. Fisher A, Meller Y: Continuous postoperative regional analgesia by nerve sheath block for amputation surgery: A pilot study. Anesth Analg 1991; 72:300–3
15. Lambert AW, Dashfield AK, Cosgrove C, Wilkins DC, Walker AJ, Ashley S: Randomized prospective study comparing preoperative epidural and intraoperative perineural analgesia for the prevention of postoperative stump and phantom limb pain following major amputation. Reg Anesth Pain Med 2001; 26:316–21
16. Nikolajsen L, Finnerup NB, Kramp S, Vimtrup AS, Keller J, Jensen TS: A randomized study of the effects of gabapentin on postamputation pain. ANESTHESIOLOGY 2006; 105: 1008–15
17. Wilson JA, Nimmo AF, Fleetwood-Walker SM, Colvin LA: A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. Pain 2008; 135:108–18
18. Borghi B, D'Addabbo M, White PF, Gallerani P, Toccaceli L, Raffaeli W, Tognù A, Fabbri N, Mercuri M: The use of prolonged peripheral neural blockade after lower extremity amputation: The effect on symptoms associated with phantom limb syndrome. Anesth Analg 2010; 111:1308–15