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ORIGINAL ARTICLE

Factors affecting phantom limb pain in patients undergoing amputation: retrospective study

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Abstract

Purpose The efficacy of preemptive analgesia for prevention of phantom limb pain has been controversial although pain management before amputation is empirically important. The aim of this study was to determine the associated factors with perioperative phantom limb pain.

Methods Following approval by the Medical Ethics Committee in our university, medical records of patients receiving limb amputation surgery in our hospital between April 1, 2013 and October 31, 2017 were retrospectively reviewed. To determine which pre-operative factors could affect the development of phantom limb pain, we performed univariate analysis to find candidate factors ($p < 0.05$), and then did multivariate regression analysis.

Results Incidence of phantom limb pain was 50% (22/44). There was no difference between the groups in types of anesthesia and post-operative pain levels. The multivariate logistic regression including possible confounders suggested that diabetes mellitus and uncontrollable preoperative pain with non-steroidal anti-inflammatory drugs (NSAIDs) were independently associated with the development of phantom limb pain (Adjusted odds ratio (OR) 0.238 [95% confidential interval (CI) 0.0643–0.883], $p = 0.032$, Adjusted OR 6.360 [95% CI 1.280–31.50], $p = 0.024$, respectively).

Conclusion The types of anesthesia and the degree of postoperative pain were not related to the development of phantom limb pain. The present data suggest that insufficient preoperative pain with NSAIDs and diabetes mellitus would give an impact on the development of phantom limb pain.

Keywords Phantom limb pain · Amputation · Preemptive analgesia · Diabetes mellitus

Background

The incidence of phantom limb pain was reported 50–80% of patients undergoing leg amputation, and prevention of phantom limb pain is important because of severe and uncontrollable pain [1, 2]. The mechanisms of phantom limb pain were explained as follows [3]; peripheral mechanism, changes at the level of spinal cord, changes at the level of the brain and psychogenic mechanism. It has also been suggested that phantom limb pain might be caused by multiple complicated mechanisms, but the mechanism remains unsolved.

The peri-operative mortality in patients undergoing leg amputation by peripheral vascular disease is 10–15% [4], and either emergency surgery or multiple organ dysfunctions could increase the mortality. Pre-amputation pain is considered as one of the phantom limb pain associated factors [2, 5, 6]. In some cases, amputations are performed with insufficient preoperative pain management and it may cause the phantom limb pain. Whereas two large clinical trials revealed that there was no relationship between the preoperative pain and postoperative phantom limb pain [7, 8]. Although pain management before amputation is empirically important, the efficacy of preemptive analgesia for prevention of phantom limb pain has been controversial. In addition, selection of anesthetic management either general are regional anesthesia often depends on the patient conditions.

In the present study, we retrospectively analyzed the data to determine perioperative phantom limb pain associated factors. Primary outcome of this study was the incidence of phantom limb pain due to the difference of perioperative management on the development of phantom limb pain, such

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as preoperative analgesia, type of anesthesia and postoperative analgesia.

Methods

Study subjects

Following approval by the Medical Ethics Committee of Hirosaki University Graduate School of Medicine (Approval Number 2017-1094), medical records of patients receiving limb amputation surgery in our hospital between April 1, 2013 and October 31, 2017 were retrospectively reviewed. There were 53 patients undergoing amputation during this period, and we excluded the patients undergoing only fingers or toe amputation because of minor surgery, 44 patients' records were finally used for the analysis.

Data collection and definitions

The following available data were collected from each patient's record: age, sex, emergency situation, American Society of Anesthesiologists-Physical Status (ASA-PS), comorbidity, reason for amputation, region and level of amputation, pre-operative analgesia, types of anesthesia, and numeric rating scale (NRS) for pain at the post-anesthesia care unit (PACU) and on post-operative day (POD) 1. Postoperative pain was assessed by nurses in the PACU and in the ward. They received pain assessment training. They always assessed degree of pain on NRS at rest. The postoperative pain during the stay in the PACU (about 45 min) was assessed just after tracheal extubation, at discharge from the PACU and also pain medications were required. After discharge from the PACU, the pain assessment was performed every 6 h using NRS by ward nurses. We recorded highest NRS on POD1.

Phantom limb pain was defined as follows: painful sensations referred to the absent limbs and diagnosed by surgeons or anesthesiologists within a month after amputation. In our hospital, almost patients discharged within 1 month and half of them were transferred to a rehabilitation hospital. We could not obtain the postdischage data of these patients in detail because of the retrospective study. Thus, we decided that the observation period would be during hospitalization (about 1 month). Patients with only phantom limb sensations which were non-painful sensations in the amputated part of limbs were excluded.

According to patient's condition, types of anesthesia were chosen by each anesthesiologist. In most cases, nonsteroidal anti-inflammatory drugs (NSAIDs) were used as a first-choice analgesic agent against pre-operative pain. If patients still complained of pain after NSAIDs medication, intravenous fentanyl, morphine, tramadol, pregabalin and their combinations were considered.

Outcome and statistical analyses

To evaluate factors related to phantom limb pain, univariate analyses between patients with and without the phantom limb pain were performed: Student's *t* test or Mann–Whitney test for continuous variables, and chi-squared test for categorical data. To determine which pre-operative factors could affect the development of phantom limb pain, we performed univariate analysis to find candidate factors ($p < 0.05$), and then did multivariate regression analysis. Statistical analysis was performed using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A $p < 0.05$ was considered statistically significant.

Results

Patient demographics are depicted in Table 1. Incidence of phantom limb pain was 50% (22/44). There was no difference in patient's demographics among the groups except diabetes mellitus that was found significantly higher in the non-phantom pain group than the phantom pain group.

Type of anesthesia and pre-operative analgesia are listed in Table 2. Patients with general anesthesia required mechanical ventilation while patients with monitored anesthesia care did not require mechanical ventilation. All patients were given intravenous anesthetics but not inhalational anesthetics. There was no difference between the groups in types of anesthesia. Patients in the phantom limb pain group complained of significantly stronger pre-operative pain which was not improved by NSAIDs. Post-operative pain levels did not differ between groups too (Table 3). No patients received duloxetine or other antidepressants during this observation periods.

After univariate analysis, diabetes mellitus and pre-operative pain which was not improved by NSAIDs were suggested to associate with phantom limb pain. The multivariate logistic regression was performed these two candidate factors, and the results suggested that both of them were independently associated with the development of phantom limb pain (Table 4).

Discussion

The incidence of phantom limb pain in the present study was 50%. As other studies showed almost all cases developed phantom limb pain within a few weeks [9, 10], so we believe that 1 month's observation was acceptable. On the

Table 1 Patient demographics

Variable	PLP (+) ($n=22$)	PLP (−) ($n=22$)	OR [95% CI]	p
Background factors				
Age (years)	62 ± 13	64 ± 13		0.649
Male	16 (72.7)	17 (77.3)	0.784 [0.199–3.085]	0.728
Emergency case	12 (54.5)	6 (27.3)	3.200 [0.909–11.27]	0.066
ASA-PS (III≦)	15 (68.2)	19 (86.4)	0.338 [0.075–1.536]	0.150
Hospital stay	27 ± 15	22 ± 16		0.261
Associated medical disorders				
DM	7 (31.8)	14 (63.6)	0.266 [0.076–0.930]	0.035*
PVD	4 (18.2)	4 (18.2)	1.000 [0.216–4.630]	1.000
Tumor	4 (18.2)	3 (13.6)	1.407 [0.276–7.185]	0.680
Trauma	5 (22.7)	2 (9.1)	2.941 [0.504–17.15]	0.216
Infection	3 (13.6)	2 (9.1)	1.579 [0.237–10.52]	0.635
Hemodialysis	6 (27.3)	7 (31.8)	0.804 [0.219–2.944]	0.741
Region of amputation				
Upper arm	1 (4.5)	1 (4.5)	1.000 [0.059–17.08]	1.000
Forearm	3 (13.6)	3 (13.6)	1.000 [0.179–5.598]	1.000
Femur	9 (40.9)	5 (22.7)	1.943 [0.518–7.293]	0.322
Lower leg	9 (40.9)	13 (59.1)	0.479 [0.014–1.595]	0.228

Data were shown as mean ± SD or n (%)

PLP phantom limb pain, *ASA-PS* American Society of Anesthesiologists physical status, *Hospital stay* post-surgical hospital stay, *DM* diabetes mellitus, *PVD* Peripheral vascular disease

*$p<0.05$

Table 2 Anesthetic management and pre- and post-operative analgesia

Variable	PLP (+) ($n=22$)	PLP (−) ($n=22$)	OR [95% CI]	p
Anesthetic management				
GA	8 (36.4)	7 (31.8)	0.571 [0.171–1.908]	0.361
GA + LA	0 (0)	4 (18.2)	0.098 [0.0045–2.140]	0.055
GA + EA	3 (13.6)	1 (4.5)	3.316 [0.317–34.67]	0.294
GA + PB	10 (45.5)	6 (27.3)	2.222 [0.631–7.827]	0.210
MAC + PB	1 (4.5)	3 (13.6)	0.302 [0.029–3.154]	0.294
SA	0 (0)	1 (4.5)	0.319 [0.123–8.260]	0.312
Pre-operative analgesia				
Insufficient pain with NSAIDs	10 (45.5)	3 (13.6)	5.280 [1.200–23.20]	0.028*
Opioid civ	4 (18.2)	1 (4.5)	4.667 [0.477–45.65]	0.154
Tramadol	4 (18.2)	2 (9.1)	2.222 [0.363–13.62]	0.380
Pregabalin	2 (9.1)	0 (0)	5.488 [0.248–121.3]	0.148

Data were shown as n (%)

PLP phantom limb pain, *GA* general anesthesia, *LA* local anesthesia by surgeons, *EA* epidural anesthesia, *PB* peripheral block, *MAC* monitored anesthesia care, *SA* spinal anesthesia, *NSAIDs* non-steroidal anti-inflammatory drug, *Opioid civ* continuous intravenous administration of Opioid (fentanyl or morphine)

*$p<0.05$

other hand, some previous studies reported the prevalence of phantom limb pain several months or years after amputation because the onset of phantom limb pain was variable [2]. Some patients might develop phantom limb pain after discharge in this study. This may be one of the reasons why the prevalence rate of phantom limb pain in this study was relatively low compared to the previous studies.

The multivariate regression analysis indicated that pre-operative pain which was not improved by NSAIDs would be the risk factor for the development of phantom limb pain.

Table 3 Numerical rating scale for post-operative pain

Variable	PLP (+) ($n=22$)	PLP (−) ($n=22$)	p
NRS at PACU	0 [0.0–1.0]	0 [0.0–2.0]	0.335
NRS on POD1	5 [2.8–6.3]	5 [3.8–7.0]	0.704

Data were shown as median [25% quartile − 75% quartile]

PLP phantom limb pain, *NRS* numerical rating scale, *PACU* post-anesthesia care unit, *POD* post-operative day

Table 4 Multivariate logistic regression

Variable	OR [95% CI]	p
Diabetes mellitus	0.222 [0.056–0.885]	0.032*
Insufficient pre-operative pain with NSAIDs	6.360 [1.280–31.50]	0.024*

NSAIDs non-steroidal anti-inflammatory drug

*$p<0.05$

In addition, patients with insufficient pain control using opioid or pregabalin before surgery were also more in phantom limb pain group. Ahmed and colleagues [10] showed the association between high prevalence of phantom limb pain and pre-amputation pain in patients receiving general anesthesia with postoperative opioid analgesia. Yin and colleagues [6] investigated the risk factors of phantom limb pain and found that the patients with the requirement of post-operative analgesia had almost five times higher prevalence of phantom limb pain than the patients without the requirement of post-operative analgesia. In the present study, any types of medication could not prevent the development of phantom limb pain. Two patients received pregabalin before amputation and they developed phantom limb pain. Indeed, univariate analyses clearly indicate that opioid, tramadol and pregabalin would not be associated with phantom limb pain. However, several reports [11–14] suggest that pregabalin and tramadol might be effective for treatment of phantom limb pain but the evidence level is low. Further studies are necessary to test our finding.

The multivariate analyses also revealed that patients with diabetes mellitus may have a low risk for development of phantom limb pain. There are only a few reports about the association between phantom limb pain and diabetes mellitus although diabetes mellitus was one of the major comorbidity of the patient undergoing leg amputation [15, 16]. Clark and colleagues [17] reported the incidence of phantom limb pain was not affected by the presence or absence of diabetes mellitus and suggested that there was no relationship between the development of phantom limb pain and duration of diabetes mellitus. In the present study, however, the patients with diabetes mellitus had low risk of phantom limb pain. According to the classification of diabetes neuropathy [18], loss of sensation with an abnormality of nerve conduction was defined as mild neuropathy. The incidence of amputation against foot ulcer in patients with diabetes mellitus in Japan was less than that in other countries [19]. In this study, thus, there might be few patients with painful diabetic neuropathy or severe neuropathy. This might cause the discrepancy between the present data and other studies.

There was no relationship between the development of phantom limb pain and types of anesthesia or the degree of pain immediately after operation in the present study. Some reports showed the efficacy of epidural anesthesia and peripheral nerve block for acute post-operative pain [10, 11, 20], however those authors also suggested no association between the degree of acute postoperative pain and the development of phantom limb pain. In addition, any types of anesthesia did not make difference in the incidence of phantom limb pain and morbidity and mortality after lower limb amputation [21]. Similarly, the present study shows that there was no difference in the degree of acute postoperative pain and types of anesthesia between the groups. Therefore, the types of anesthesia and analgesia may not strongly affect the development of phantom limb pain.

This study has some limitations. First, the major limitation is that this study was conducted retrospectively with small sample size in a single center. It was difficult to follow up the patients who have been discharged or transferred within 1 month in our institution and there was also possibility of mistakes in description or declaration of phantom limb pain. Therefore, some information bias could not exclude completely.

Second, the reason for amputation was so complex that it was difficult to identify the main reason. Tumor, trauma, and peripheral vascular disease seemed to be major reason for amputation, but we could not determine some of which had the impact on the incidence of phantom limb pain following the amputation. Finally, the patients with diabetes mellitus have low risk for development of phantom limb pain, but the relationship between the incidence of phantom limb pain and the severity and duration of diabetes mellitus could not be determined. Further prospective study will be required to determine why the patients with diabetes mellitus had low risk of phantom limb pain.

In conclusion, the types of anesthesia and the degree of post-operative pain were not related to the development of phantom limb pain. However, this study suggests that diabetes mellitus and uncontrollable preoperative pain with NSAIDs had impact on the incidence of the development of phantom limb pain. Further prospective studies will be required to confirm these factors affecting phantom limb pain.

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Author contributions SN designed the study, analyzed and interpreted the data, and drafted the manuscript. JS reviewed the analysis of the data and edited the manuscript. KN helped conduct the study. MK and KH made substantial contributions to the conception and design of the study, helped in writing the manuscript, and statistical analysis. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors do not have any conflict of interests regarding the content of the paper.

References

1. Nikolajsen L, Jensen TS. Phantom limb pain. Br J Anaesth. 2001;87:107–16.
2. Richardson C, Glenn S, Horgan M, Nurmikko T. A prospective study of factors associated with the presence of phantom limb pain six months after major lower limb amputation in patients with peripheral vascular disease. J Pain. 2007;8:793–801.
3. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. Pain Res Treat. 2011;2011:864605.
4. Stone PA, Flaherty SK, Aburahma AF, Hass SM, Jackson JM, Hayes JD, Hofeldt MJ, Hager CS, Elmore MS. Factors affecting perioperative mortality and wound-related complications following major lower extremity amputations. Ann Vasc Surg. 2006;20:209–16.
5. 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.
6. Yin Y, Zhang L, Xiao H, Wen CB, Dai YE, Yang G, Zuo YX, Liu J. The pre-amputation pain and the postoperative deafferentation are the risk factors of phantom limb pain: a clinical survey in a sample of Chinese population. BMC Anesthesiol. 2017;17:69.
7. 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.
8. 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.
9. Cadavid A, Mayungo T. Very early phantom limb pain following amputation of a lower extremity: case report. Rev Colomb Anestesiol. 2013;41:236–9.
10. Ahmed A, Bhatnagar S, Mishra S, Khurana D, Joshi S, Ahmad SM. Prevalence of phantom limb pain, stump pain, and phantom limb sensation among the amputated cancer patients in India: a prospective, observational study. Indian J Palliat Care. 2017;23:24–35.
11. Wolff A, Vanduynhoven E, van Kleef M, Huygen F, Pope JE, Mekhail N. 21. Phantom pain. Pain Pract. 2011;11:403–13.
12. Spiegel DR, Lappinen E, Gottlieb M. A presumed case of phantom limb pain treated successfully with duloxetine and pregabalin. Gen Hosp Psychiatry. 2010;32:228.e5-7.
13. McCormick Z, Chang-Chien G, Marshall B, Huang M, Harden RN. Phantom limb pain: a systematic neuroanatomical-based review of pharmacologic treatment. Pain Med. 2014;15:292–305.
14. Wössner S, Weber K, Steinbeck AC, Oberhauser M, Feuerecker M. Pregabalin as adjunct in a multimodal pain therapy after traumatic foot amputation—a case report of a 4-year-old girl. Scand J Pain. 2017;17:146–9.
15. Sahin SH, Colak A, Arar C, Tutunculer E, Sut N, Yılmaz B, Birtane M. A retrospective trial comparing the effects of different anesthetic techniques on phantom pain after lower limb amputation. Curr Ther Res Clin Exp. 2011;72:127–37.
16. Ong BY, Arneja A, Ong EW. Effects of anesthesia on pain after lower-limb amputation. J Clin Anesth. 2006;18:600–4.
17. Clark RL, Bowling FL, Jepson F, Rajbhandari S. Phantom limb pain after amputation in diabetic patients does not differ from that after amputation in nondiabetic patients. Pain. 2013;154:729–32.
18. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P, Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33:2285–93.
19. Iwase M, Fujii H, Nakamura U, Ohkuma T, Ide H, Jodai-Kitamura T, Sumi A, Komorita Y, Yoshinari M, Kitazono T. Incidence of diabetic foot ulcer in Japanese patients with type 2 diabetes mellitus: the Fukuoka diabetes registry. Diabetes Res Clin Pract. 2018;137:183–9.
20. 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.
21. Pisansky AJB, Brovman EY, Kuo C, Kaye AD, Urman RD. Perioperative outcomes after regional versus general anesthesia for above the knee amputations. Ann Vasc Surg. 2018;48:53–66.