The Effectiveness of Intravenous Morphine Infusion as Preemptive Analgesia in Preventing Phantom Limb Pain Following Lower Limb Amputation

KC Chong, M Med Ortho, **AR Sulaiman**, M Med Ortho, **MI Yusof**, M Med Ortho, **T Vishvanathan**, M Med Ortho, **M Anwar Hau***, M Med Ortho

Department of Orthopaedics, Universiti Sains Malaysia, 16150 Kota Bharu, Malaysia

*Department of Orthopaedics, Hospital Raja Perempuan Zainab II, Kota Bharu, Malaysia

ABSTRACT

Phantom limb pain may reduce ambulation and mobility in amputees, resulting in diminished quality of life. We conducted a prospective study to compare the perioperative analgesic use of intravenous morphine infusion in 27 patients (Group A) and intramuscular diclofenac sodium in 28 patients (Group B) in patients undergoing lower limb amputation. All patients underwent amputation under spinal anaesthesia and reported a Modified Verbal Numerical Pain Score of less than two prior to the procedure. Presence of phantom pain was assessed on the first, second, third and seventh day as well as at the third month and sixth month post-operatively. Twelve (44 %) patients from group A and 21 patients (75 %) from group B developed phantom limb pain following amputation, a statistically significant difference between groups ($p < 0.05$). We conclude that intravenous morphine infusion is more effective than intramuscular diclofenac sodium in preventing the occurrence of phantom limb pain following amputation.

Key Words:

Amputation, Phantom Pain, Intravenous Morphine, Preemptive Analgesia

INTRODUCTION

Phantom limb pain in amputees may reduce ambulation and mobility, and as a result may adversely quality of life¹. Clinical studies have suggested that phantom limb pain is more likely to occur in patients who had pain in the limb prior to amputation than in those who were pain free^{2,3}. Pain creates an imprint in the 'memorizing' structures of the central nervous system that cannot be erased⁴. Epidural opioid blockade, administered as pre-amputation pain relief, reduces the incidence of phantom limb pain⁵. Even though epidural anaesthesia provides good pain control, rarely it can cause devastating complications such as meningitis and epidural insertion site abscess⁶.

It has been reported that preoperative epidural morphine or intramuscular and oral morphine are effective in preventing phantom pain⁶. As the epidural or intramuscular routes have their own problems related to administration and risk, we designed this study to test the effectiveness of intravenous (IV) morphine as a preemptive analgesic in decreasing post-amputation phantom limb pain. We used intramuscular (IM) diclofenac sodium with IM tramadol as a rescue medication for the control group to ensure that all patients received comparable pain control. Our goal was to test whether perioperative IV morphine has an additive effect in controlling phantom pain.

MATERIALS AND METHODS

This prospective study was conducted at two institutions and involved patients undergoing amputation between May 2005 and May 2006. The amputation procedures included above knee amputation, below knee amputation and hind foot amputation. Before enrolling in the study, all subjects were informed about the entity of phantom limb pain and it was emphasized that the pain is a true phenomenon. This study was approved by the ethical committee of institutions participating in the project.

Pain assessment was performed using Modified Verbal Numerical Pain Score in which: 0=no pain, 1= slight pain, 2= tolerable pain, 3=bad pain and 4= worst pain imaginable⁷. All surgical patients in both groups had spinal anaesthesia. All patients had a Modified Verbal Numerical Pain Scores (MVNPS)⁷ of less than two prior to the procedure. Those patients who could not tolerate trial drugs due to allergies or previous adverse reactions were excluded from the study. The patient's respiratory rate, blood pressure, pulse rate and pulse oximetry were closely monitored. Adverse events including nausea, vomiting, gastritis and pruritus were recorded.

Study subjects were randomized into the morphine group (Group A) or the control group (Group B).

Table I: Characteristic of patients involved in the study

Characteristics of patients	Group A N=27	Group B N=28
Male/ female	17/10	15/13
Mean age (years)	60.3	55.8
Level of amputation		
- Syme	1	0
- Below knee	21	25
- Above knee	4	3
- Hip disarticulation	1	0

Table II: Occurrence of Phantom pain in both groups with its statistical test

Phantom pain / total number	Crude Odd ratio (95% CI)	Adjusted (95% CI)	Odd ratio	P value
Group A	12 /27(44%)	0.267	0.176	0.01
Group B	21/28 (75%)			

CI- confidence interval

Group A

All the patients in this group received an IV morphine infusion preoperatively from the time they agreed to participate in the study; postoperatively, the infusion was continued for 72 hours post-amputation. This part of the protocol, in addition to controlling pain, was intended to test whether perioperative IV morphine comes with the extra benefit of preventing future phantom pain. The dosage given was two to four mg/hour in those patients aged below 60 years old and one to two mg/hour for those above 60 years old. The infusion device was set to deliver a starting infusion rate at one to two mg/hour depending on the age of the patient and was titrated accordingly (with a maximum of two to 4 mg/hr depending on patient age) until the patient has good pain relief.

Group B

The patients in this group were given intramuscular (IM) Diclofenac sodium 50 mg pre-operatively only if their MVNPS was two or more to ensure that their pain was controlled prior to surgery. Post-operatively, 50 mg IM diclofenac sodium was given every 8 hours for 72 hours. A rescue dose of 50 mg IM tramadol hydrochloride was added for pain control if the pain score was persistently more than two, despite administration of the regular IM Diclofenac sodium doses. For those who developed gastric irritation, with or without upper gastrointestinal bleeding, Diclofenac sodium was stopped immediately and appropriate treatment started, either with intravenous (IV) ranitidine 50 mg three times daily or IV omeprazole 20 mg once a day (OD); these patients were then excluded from final analysis.

All patients were assessed for pain from the time they agreed to take part in the study until 72 hours after the operation. The presence of phantom pain was assessed on the first, second, third and seventh day postoperatively, and reassessed at the first, third and sixth postoperative month using a scoring system similar to the MVNPS. Phantom limb pain was considered as 'present' regardless of the time of

onset if it started within of the first six postoperative months. Results were analysed using SPSS version 11.0 (Chicago, IL, USA). Sample size was calculated using Pocok's formula with 95% confidence interval and 80 % power. Taking into account a 20% dropout rate, this study required 26 patients from each group. Data analyses include comparison of mean age while independent t-test was used to compare race and sex. The severity of pain between the two groups were analysed using ANOVA and ANCOVA methods. The difference in the number of patients with phantom limb pain between the two groups was analysed using logistic regression. A p value of < 0.05 was considered as statistically significant.

RESULTS

A total of 134 patients underwent lower limb amputation during the study period. There were 31 patients for group A and 35 patients for group B involved in the study. However 4 patients from group A refused to participate in the trial and participation of 7 patients from group B was discontinued due to onset of gastric irritation, leaving 27 patients in group A and 28 patients in group B. The patients' age ranged from 18 years to 84 years. The mean age of patients in group A was 60.3 years whereas group B it was 55.8 years (Table I). Twenty-three patients were female and 32 patients were male. Forty six (84%) of the patients were Malays, seven (12%) were Chinese and two were Indians. Forty-four patients were diabetic. There was no significant difference ($p>0.05$) in terms of age, race and sex between the two groups.

The indications for amputation were: diabetic foot complication in 41 patients (74%); traumatic injuries in seven patients (12.7%); lower extremity malignancy in five patients (9%); and peripheral vascular disease in two patients (4%). Below knee amputation (BKA) was performed in 46 patients (84%), above knee amputation in seven patients, Syme's amputation in one and hip disarticulation in one patient (Table I).

Two patients from group B required rescue doses of intramuscular tramadol. There was no significant difference in numerical pain scores before surgery or during the first 72 hours post-amputation between both groups. Thirty-three patients developed phantom limb pain following limb amputation, 12 patients (44%) from group A and 21 (75%) patients from group B (Table II). Logistic regression analysis revealed a crude odds ratio of 0.267 and an adjusted odds ratio of 0.176 with p value of 0.01 (Table II). An adjusted odds ratio was calculated to consider other factors such as age, sex and causes for amputation.

The duration of pre-operative morphine infusion in group A was between one to six days with a mean of 2.29 days. Twenty-one patients (64%) developed phantom pain within one week, 10 patients within three to four weeks, one patient within one to three months and one patient within four to six months.

DISCUSSION

Pre-amputation pain, noxious intraoperative inputs such as skin incision, and chronic stump pain due to neuroma may increase the likelihood of developing phantom limb pain^{8,9}. The benefit of epidural morphine administration as preemptive analgesia has been reported to be effective in decreasing phantom pain⁵. Epidural morphine is not superior to oral or IM morphine in preventing phantom pain⁶.

In this study we limited the objectives to comparison of intravenous morphine (which was given routinely without considering the amount of pain perceived by the patient) to the control group that received adequate pain control through IM diclofenac sodium with rescue doses of tramadol hydrochloride only as needed. This protocol was chosen as most of amputations in our population were necessary due to complications of diabetes and such patients are known to have neuropathy. Further study is needed to compare between routine morphine infusion and morphine infusion as needed for pain control.

In this study, phantom pain was considered to be 'present' regardless of the time it appeared. Results showed that even though diclofenac with tramadol rescue dosing may provide

comparable analgesic quality perioperatively in Group B as previously stated, it did not prevent phantom pain in a significant number of patients compared to those who received IV morphine. Patients who received morphine were less likely to develop phantom limb pain as compared to those in the control group. This finding supports the role of the 'mu' opiate receptor that prevents certain degree of central sensitization¹⁰. The incidence of phantom pain in the IV morphine group is comparable to the previously documented 52% incidence of phantom pain at one week postoperatively in a study using an epidural bupivacaine and morphine infusion⁶. Thus, considering the risk of meningitis and epidural abscess inherent in epidural infusions, intravenous morphine represents a viable alternative for preemptive analgesia in preventing phantom pain. One possible factor associated with phantom pain is chronic stump pain secondary to neuroma formation, which generates neural impulses after regional anaesthesia worn off^{8,9}. This factor may have influenced the results in this study.

Randomization of the sample in this study was conducted without consideration of the sex or indications for amputation, as the incidence of phantom limb pain is typically similar in females and male amputees^{2,3}. Similarly, indication for amputation was not exclusionary as the presence of coexisting diseases such as diabetes mellitus, cardiac disease, peripheral vascular disease, osteomyelitis and foot gangrene do not significantly influence phantom limb pain occurrence¹¹. Diabetic neuropathy is presumed to reduce tactile sensation, which in turn may reduce the incidence of phantom pain. However the incidence of phantom pain in the control group of the present study, with the majority being chronic diabetic patients, was almost identical to incidence of phantom pain in patients with peripheral vascular disease noted in previous studies².

From the results of this study, we conclude that the number of patients who developed phantom limb pain was significantly lower in the group that received IV morphine infusion as preemptive analgesia compared to results in the control group. Utilizing IV infusion as preemptive analgesia is an alternative to reduce the incidence of phantom pain following lower limb amputation.

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