PERIOPERATIVE ANALGESIA IN DECREASING THE INCIDENCE AND / OR SEVERITY OF PHANTOM PAIN– NON-RANDOMISED OBSERVATIONAL STUDY BETWEEN INTRAVENOUS MORPHINE VERSUS INTRAMUSCULAR DICLOFENATE

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ABSTRAK

PERANAN UBAT ANALGESIA SEBELUM DAN SELEPAS PEMBEDAHAN TERHADAP PENGURANGAN BILANGAN DAN TAHAP KESAKITAN PADA KAKI YANG SUDAH DIAMPUTASI "PHANTOM LIMB PAIN"(PERBANDINGAN ANTARA INFUSI INTRAVENA MORPHINE DENGAN INTRAOTOT DICLOFENATE)

TUJUAN KAJIAN

Perbandingan keberkesanan di antara ubat intravena morphine dan intraotot diclofenate terhadap kesakitan pada kaki tidak wujud lagi. Kajian ini cuba menghubungkaitkan kesakitan " phantom pain" terhadap tahap kesakitan dialami sebelum amputasi, jangka-masa kaki yang bermasalah dan jangka masa penyakit kencing manis dihidapi sebelum pembedahan.

KAEDAH

Dalam kajian prospektif secara tidak rawak, kami menilai 55 pesakit yang menjalani amputasi pada bahagian kakinya. 27 pesakit dari kumpulan intravena morphine diberikan ubat tersebut setelah mendapatkan kebenaran secara tertulis. Mereka dikehendaki memakai pulse oximeter untuk menyukat kandungan oksigen dalam darah dan peperiksaan dari segi kadar denyutan jantung, tekanan darah, kadar penafasan dan tahap pelalian dari masa ke semasa supaya mereka berkeadaan sempurna semasa rawatan ini. Manakala 28 pesakit dari kumpulan intraotot diclofenate diberikan ubat tersebut sekiranya pesakit mengalami tahap

kesakitan pada skala ke-dua atau melebihinya sebelum pembedahan and tiga kali sehari selepas amputasi. Intraotot tramadol diberikan sekiranya kesakitan yang dialami oleh pesakit tidak dapat dikawal oleh intraotot diclofenate. Kedua-dua ubat tersebut disambungkan sehingga hari ke tiga selepas pembedahan.

Tahap kesakitan dari segi kualiti, kuatiti dan lokasi sebelum kedua-dua ubat tersebut diberikan, selepas pengambilan ubat dan selepas amputasi dicatatkan dalam "numerical rating scale". Di samping itu, perasaan dan kesakitan terhadap kaki yang telah diamputasi dikenalpasti. Kesemua pesakit dalam kajian ini dihubungi pada minggu pertama, bulan pertama, ke-tiga dan ke-enam.

KEPUTUSAN

Kedua-dua kumpulan pesakit mengalami tahap kesakitan yang hampir sama antara satu sama lain semasa sebelum dan selepas operasi ($p > 0.05$). Tetapi dua pesakit yang menerima intraotot diclofenate terpaksa mengambil intraotot tramadol untuk mengurangkan kesakitan selepas operasi.

Terdapat 50 pesakit (90%) mengalami perasaan kaki yang telah diamputasi masih wujud lagi manakala 33 pesakit (60%) mengalami kesakitan terhadap kaki yang tidak wujud lagi"phantom pain". Kebanyakan kesakitan "phantom pain" adalah minima, hanya dua pesakit tersebut memerlukan rawatan terhadap "phantom pain" ini.

Perbandingan antara kedua-dua ubat menunjukkan bahawa pesakit menerima intravena morphine adalah 0.176 kali kurang mengalami kesakitan "phantom pain" berbanding intraotot diclofenate ($p<0.011$). Begitu juga purata tahap kesakitan phantom pain di antara kumpulan morphine dan diclofenate adalah 1.57 dan 2.37 ($p < 0.03$) setelah mengambil-kira faktor yang mungkin berkait-rapat dengan kesakitan phantom pain seperti umur, jantina, bangsa dan penyakit kencing manis.

Kajian ini juga menunjukkan bahawa kesakitan yang dialami oleh pesakit dan jangka-masa masalah yang dialami oleh pesakit sebelum operasi tidak ada hubung-kait dengan kesakitan phantom pain. Tetapi, jangka masa penyakit kencing manis ada hubung-kait dengan phantom pain ($p<0.03$).

KESIMPULAN

Kawalan kesakitan yang secukupnya sebelum dan selepas amputatsi oleh intravena morphine dapat mengurangkan bilangan dan tahap kesakitan 'phantom limb pain' ini.

ABSTRACT

THE ROLE OF PERIOPERATIVE ANALGESIA IN DECREASING THE INCIDENCE AND / OR SEVERITY OF PHANTOM LIMB PAIN (INTRAVENOUS MORPHINE VERSUS INTRAMUSCULAR DICLOFENATE).

PURPOSE OF THE STUDY

To evaluate the perioperative intravenous morphine and intramuscular diclofenate in reducing the incidence of phantom limb pain as well as the severity of phantom pain following lower limb amputation. In addition, to evaluate the association between phantom limb pain and the pain suffered before the amputation, the duration of diabetic mellitus and the duration of various feet or legs problems prior to amputation.

METHOD

This was a non-randomsed observational study involving a total 55 patients. 27 patients were selected for intravenous morphine infusion. The patients' blood pressure, heart rate, respiratory rate, sedation score, blood oxygen saturation were monitored closely. The other 28 patients were selected for intramuscular diclofenate. The drug was given to those patient who had pain score at 2 or more before operation and at regular dose after amputation. The rescue intramuscular tramadol was added if the pain was not adequately controlled in diclofenate group. Both medications were continued till day-3 post-amputation.

The characteristic, intensity and location of pain encountered before analgesia, after analgesia and after amputation was documented. The modified numerical pain score was

used to quantify the intensity of pain. The phantom sensation, phantom pain and stump pain following lower limb amputation was identified in both groups. The patients were followed up at one week, 1, 3 and 6 months after amputation via phone.

RESULTS

Patients in both groups experienced comparable pain intensity before and after the operation ($p > 0.05$). However, two patients in diclofenate group required rescue i/m tramadol 50 mg for post-amputation pain control.

Overall, 50 out of 55 patients (90%) experienced phantom limb sensation and 33 patients (60%) encountered phantom pain after amputation. Twenty one patients (75%) out of 28 in diclofenate group had phantom limb pain compared with 12 patients (44%) out of 27 in morphine group. The phantom sensation in diclofenate and morphine group was 89% and 92% respectively. In 16 patients with phantom limb pain (48%), the symptom subsided within 6 months. Most of the phantom pain encountered was low pain score and only 2 patients required medical treatment.

Patients in morphine group was 0.176 time (odd-ratio) less likely to develop phantom limb pain as compared to diclofenate group ($p < 0.05$). Intravenous morphine significantly reduced the severity of phantom limb pain after adjusting possible confounding factors like sex, age, race and presence or absence of diabetic mellitus ($p < 0.05$). The maximal phantom pain score in morphine and diclofenate groups was 1.57 and 2.37 respectively.

The severity of pre-analgesic pain and the duration of various leg and foot problem encountered prior to amputation did not significantly relate to phantom pain. However, the the longer history of diabetic mellitus had less risk or incidence of phantom pain ($p = 0.03$).

CONCLUSION

This study showed perioperative intravenous morphine infusion reduced the incidence and severity of phantom limb pain as compared to intramuscular diclofenate.

CHAPTER 1

INTRODUCTION

Phantom limb is the sensation perceived by the amputee where the amputated part is still present. The phantom limb pain is the uncomfortable sensation perceived over amputated body part. This type of pain is most commonly reported in relation to amputation of a limb, but it has been reported after tooth extraction, mastectomy, anorectal removal etc. Phantom limb pain has been given considerable attention in medical field for several reasons. First, it is difficult to comprehend that pain can be felt in a body part that is absent. Second, phantom limb pain may reduce ambulation and mobility, and as the result may reduce the quality of life of the amputee (Pieter U. Dijkstra, 2002).

Silas Weir Mitchell coined the term "phantom limb pain" in 1872 for this discomfort sensation as ghostly replicas of the lost limb. Ambroise Pare (1510-1590), French military surgeon who was the first to give medical description of post-amputation phantom pain.

The short term incidence of phantom pain was reported to occur in about 72% in the immediate postoperative period and 63% in 6 months after amputation. For phantom sensation, the short term incidence was 84% in the immediate postoperative period and 90% 6 months after amputation (T.S. Jensen, 1985). The pain generally believed to fade away and finally disappear. The differences in prevalence for phantom limb pain was reported for upper and lower limb amputees. A retrospective study showed that phantom

pain was present in 41% of upper limb amputees and in 80% of lower limb amputees (Carolien M. Kooijman, 2000).

This complex phantom limb pain showed episodic nature in term of frequency (number of pain per day), duration (average hour of pain per day) and variable intensity of pain (Anne S. Whyte BSc, 2001). 70% of patients suffered phantom pain more than one occasion per day ranging from 2-5 episodes daily. 80 % of the patients having phantom pain for average 6-10 hours each day.

Even though the phantom pain causing disability and bothersome is not that high which ranged between 10%-25% (Dawn M. Ehde, 2000), but this condition are difficult to treat. A maximum benefit of about 30 % has been reported from the treatments such as local anaesthesia, sympathectomy, dorsal root entry-zone lesion, cordotomy and rhizotomy, neurostimulation methods or pharmacological intervention such as anticonvulsion, barbiturates, antidepressants, neuroleptics and muscle relaxants (Flor, 2002). Controlled studies have been done in opioids (Ellena Huse, 2001), calcitonin and ketamine (Lone Nikolajsena, 1996) which effectively in reducing the phantom limb pain.

In modern times, traumatic amputation originating from World War 1 and 11, Vietnam, Israel as well as African nations wars and from landmine explosions all over the world were a tragic cause of phantom limb pain (Phillippe A. Lacoux, 2002, Richard A. Sherman, 1983). In western countries, the peripheral vascular disease and neoplasm are the other major reason for amputation (Dawn M. Ehde, 2000).

The scenario in Malaysia, especially Kelantan state is different. Most of our amputation of lower limbs were due to diabetic foot complication resulted from ischemia, ulceration, infection and Charcot's joint. The prevalence of diabetic mellitus was reported to have increase from 6.3% in 1986 to 14.6% in 1996. Fifteen percent of patients with diabetes mellitus will develop lower extremities ulcer during the course of their disease. The prevalence of foot ulceration in patients attending a diabetic outpatients clinic in Malaysia has been reported as 6 % (Clinical Practice Guideline In Management Of Diabetic Foot : 2004). Among the important factors contribute to high prevalence of diabetic foot complication are poor diabetic control secondary to lack of health conscious, local diet habit with high sugar content, ignorance and negligence about potential risk of diabetic foot, strongly believe in traditional management rather than scientific medical way of treatment in diabetic foot. Sadly, some of the unsalvageable diabetic feet have to be amputated. In certain cases amputation was the only way to control the sepsis and saving their life.

Even though exact mechanism of phantom limb pain is still not clear and many probable aetiologies have been discussed in detail in chapter 2 below. The development of phantom limb pain may be contributed by following three factors which inducing central sensitization at different times relative to surgery

a) pre-amputation pain

b) noxious intraoperative inputs brought about by cutting skin, muscle, nerve and bone

c) acute postoperative pain (including that due to pro-inflammatory process).

Preemptive analgesia prevent the nerve impulse arising from noxious intraoperative event from reaching and sensitizing neural structures involving the perception of pain. However, it is effective in short term, neural impulse that generate at an abnormal site like neuroma may induce state of central sensitization after short term effect of regional anaesthesia have worn off. By contrast, blockade of late intraoperative and postoperative noxious input does not seem to influence the development of persistent pain (Joelkatz, 1997; Soren Bach, 1988)

A few studies showed contrary results in term of reducing the number of phantom limb pain by using epidural opioid and anaesthesic medication amputation (Soren Bach, 1988. Troels S Jensen, 1983. Troels S Jensen, 1985. Lone Nikolajsen 1997). Even though epidural anaesthesia provide good pain control, it causes rare but devastating complications like meningitis and epidural insertion site abscess.

From the literature review, no study has been done on intravenous morphine as a preventive measure in phantom limb pain. In this study, intravenous morphine infusion was used instead of epidural morphine as perioperative analgesia. Intravenous morphine is comparatively easier as most of our medical staffs can do it. On the other hand, epidural analgesia requires only experienced anaesthetist to introduce the epidural catheter. In our center, intramuscular diclofenate was frequently given as perioperative analgesia especially those amputation related to diabetic mellitus as compared to other causes. The pain encountered in diabetic patients was presumed relatively lower and one of the reason could be due to diabetic peripheral polyneuropathy (Isselbacher, 1992). The intravenous

morphine effect was compared with intramuscular diclofenate in term of reducing the incidence and / or severity of phantom limb pain following lower limb amputation.

The other purpose of this study was to evaluate the association between phantom limb pain and the pre-analgesic pain encountered prior to amputation, the duration of diabetes mellitus as well as the duration of various leg or foot problem like ulcer, gangrene, tumour etc prior to amputation.

CHAPTER 2

LITERATURE REVIEW

2. 1) CLINICAL CHARACTERISTIC

Phantom limb pain is commonly classified as neuropathic pain, and it is assumed to be related to damage of central or peripheral neurons. Apart from surgical removal of body parts can produce such pain, lesions of the peripheral nerves or the central nervous system like brachial plexus alvusion or paraplegia can cause phantom limb pain as well. It seem to be more likely if individual had chronic pain before amputation and is less likely if the amputation was done when the individual very young. It is quite frequent that the patients in childhood and aldolescent group experienced phantom limb sensation and pain with overall incidence 100% and 92% respectively (Elliot, 1995).

The limb loss due to surgery dramatically increase in the likelihood of phantom phenomena compare those patients with congenital absence of limb. About 69.7% of surgical group had phantom sensation and 48.5% had phantom limb pain versus 7.4% and 3.7% of congenital amputees respectively (Krista L. Wilkinsa, 1998).

Commonly, the phantom limb pain experienced by amputees are similar to the pain felt in the limb before amputation (T. S. Jensen, 1985). The report ranged from 10% - 79%, depending on the type and time of assessment. As Nikolajsen and colleagues had pointed out, the type of assessment and potential errors in retrospective reports are important

determinants of the frequency of these " Pain Memories " (Lone Nikolajsena, 1997). There have been reported that phantom limb pain is more frequent in female than male amputees (Samuel A. Weiss, 1996) but other studies did not confirm the findings (Dawn M. Ehde, 2000).

2. 2) POSSIBLE MECHANISM OF PHANTOM SENSATION AND PAIN

2. 2. 1) PHANTOM SENSATION

Once the body part has been excised, either by trauma or surgery, the feeling persists that the body part is still present. In addition, phantom sensation is reported in the absence of amputation, for example, in patients with sensory loss due to spinal cord injury where normal sensation is absent (J. H. Frisbie, 1990). The same thing happen to those patient born with limb deficiencies, that is without all or part of a limb (Krista L. Wilkinsa, 1998).

Phantom sensation resembles the pre-amputation limb in shape, length and volume. Over the time, the proximal part of the phantom often fades. The remaining phantom is comprised of distal part which usually have greatest representation in the somatosensory cortex, eg. the thumb is experienced more vividly than the remaining part of the hand (Anne Hill BSc, 1999).

The length of the phantom may also change over time. In about one third of the patients, a process of telescoping occurs where the phantom is slowly felt to approach the residual limb. Gradually, the distal part of phantom will attach to the residual limb. The evidence suggested that only phantom sensation but not phantom limb pain is experienced in a telescoped phantom limb (Anne Hill BSc, 1999).

Evidence of the linked with cortical reorganization after amputation is demonstrated and experienced in a telescoped position. The cortical reorganization was showed in experimental studies with monkey. In a microelectrode study, the area of somatosensory cortex previously occupied by a digit was shown to be taken over by a cutaneous input from the stump and surrounding tissue following the amputation. These observation are consistent with studies comparing the sensory acuity of the stump and the intact contralateral limb in human amputee, eg : lower threshold have been observed at the stump for light touch, two point discrimination and point localization after amputation of an upper limb(M. M. Merzenich 1984; W. B. Haber, 1995).

Research done on amputee who have phantom pain by using ECAT Exact HR47 PET following intravenous bolus injection of 500 Mbq of H2150 to study the brain blood flow. Vibrotactile stimulation were given and the subject experiences strong phantom sensation, the scan showed increase regional blood flow of primary somatosensory and motor cortex. The strong activation of posterior parietal cortex may be responsible for phantom limb pain which can be suppressed with transcranial magnetic stimulation (Kupers, 2000).

The plasticity of the somatosensory cortex is related to the phantom limb pain rather than non-painful phantom limb. A strong relationship was found between cortical reorganization and the magnitude of phantom limb pain but not in phantom limb sensation (H. Flor, 1995).

The predominant description of the phantom sensation is that of mild tingling or tightness, other qualities noted are touch, temperature, pressure and itch. In some cases, the phantom is distorted in such a way that the position of the limb presented pre-amputation position. This common occur in traumatic lost and the limb was distorted by accident. However, there are numerous problems in evaluating the definition of phantom limb sensation as any sensation of the missing limb except pain. It is frequently confounded with phantom limb pain or pain in the residual limb (Anne Hill BSc, 1999).

2. 2. 2) PHANTOM PAIN

Several studies report that severe phantom limb pain occurs in only 0.5 to 5% of all amputees. In the other study on 2694 amputees reported that 51% of amputees have phantom pain which severe enough to hinder life style more than 6 days per month. Clearly difference in the definition of severe phantom limb pain account for the differences among studies (Richard A. Sherman, 1983).

Like phantom limb sensation, phantom limb pain is also primarily localized to the distal part of the missing limb. Given the similarity in location, it is possible that the changes in

receptive fields and cortical reorganization observed following limb amputation are related to both phantom limb pain and phantom sensation.

Many studies suggest that phantom limb pain either diminishes or disappears during the first 2 years post-amputation..A study showed small decline in pain prevalence from 72% 8 day post-operation to 67% at a 6 month follow up was accompanied by a significant reduction in intensity to 50% (T.S. Jensen, 1983). In contrast, other research has shown that phantom limb pain may be present in those who were operated more than 30 years (Richard A. Sherman, 1983).

Two most common descriptors applied to phantom limb pain are burning and cramping. The other description are numb, smarting, stinging, throbbing, piercing and tearing (T. S. Jensen, 1983; T. S. Jensen, 1985; Richard A. Sherman, 1985). Many patient report pain that resembles pre-amputation pain both in quality and location, eg: experienced as pre-amputation from surgical incision, wounds, bedsores, ingrown toenails, ulcer, arthritis, corns, and callus (Melzack, 1990)

Although some has examined the relationship between the patient characteristic like age, gender, duration of pain, reason for amputation, site of amputation and the level of pain, many yielded mixed results because of difference in the sample selection, sample size and the study method. Some studies said no difference in between male and female amputee with incidence of phantom limb pain (T. S. Jensen, 1983; T. S. Jensen, 1985). They also noted there was no difference between young and old amputee with phantom limb pain.

The evaluation of this studies is difficult because phantom limb pain often inferred rather than measured and when phantom limb is measured, different instruments are used.

A number of problems arise when making a distinction between phantom sensation, phantom limb pain and the pain in the residual limb. Examples, it is very difficult to see how phantom sensation can be compared across subjects or studies. Given the definition calls for amputee to decide which sensations are not painful. The pain perception is multifacet and therefore directly related to the individual unique history. While one amputee might report tingling sensation but other amputee might said that it was painful sensation. It is impossible to determine whether it is the amputee's interpretation of word or some difference in the quality of sensation that leads to difference classification. Similarly, amputees are not always able to differentiate between stump pain and phantom pain. The reported prevalence of residual pain ranged from 15 – 50% (Anne Hill BSc, 1999).

2. 2. 3) CAUSAL EXPLANATION OF PHANTOM PAIN

A) PERIPHERAL FACTORS

The recent research highlighted the role of peripheral nerve cut end that grow into nodules (neuroma) following amputation which generate abnormal impulse. This impulses activate central nervous system neurons and may result in perception of phantom limb pain. This hypothesis received support from the examination of the stump, which frequently reveal pathological change (skin pathology, circulatory disturbance, infection, bone spurs, or

neuroma). This has been proven by animal study on characteristic of ectopic discharges in a rat neuropathic pain model. These ectopic discharges from injured afferent neurons enter the spinal cord and alter central sensory processing by sensitizing the dorsal horn neurons. The data suggest that the amount of ectopic discharge is generally well correlated with the degree of pain behaviour. The surgical sympathectomy on neuropathic animal do lower the ectopic discharges along with neuropathic behavior (Hee Chul Han, 2000).

However , they are not the primary eliciting factor. Pain can also occur in absence of stump pathology and surgical revision of stump including removal of neuroma has limited success in alleviating phantom limb pain. Phantom limb can occur without nerve damage such as congenital absent limb and when information from periphery is blocked such as seen in complete transection of spinal cord (J. H. Frisbie, 1990). Moreover, some of phantom limb pain occur immediately after amputation before the neuroma formation.

Some researcher proposed that when the peripheral nerve are destroyed, thereby reducing input, inhibition is decreased and synchronous, self sustaining activities develops at all neural levels. This model has not been empirically tested (Anne Hill BSc, 1999).

B) PSYCHOLOGICAL EXPLANATION

There has been an assumption that phantom limbs and pain are related to unresolved grief over the loss of the limb and may be psychosomatic manifestation of a pre-morbid personality. Empirical studies on psychological characteristics of patients who have

phantom limb pain and controls show that these patients tend to have normal psychological profiles(Richard A. Sherman, 1987). However, episodics of phantom limb pain can be exacerbated by stress, anxiety and depression and insomnia, probably mediated by activity in sympathetic nervous system and increase in muscle tension. Many researchers based on their conclusion on unintentionally biased samples drawn from those amputees requesting treatment for phantom limb pain.

These problem are further exacerbated by the failure to differentiate clearly between adjustment reactions following amputation and chronic problems, for examples reaction of shock, grief, anger, frustration or denial in those who have recently undergone amputation (Richard A. Sherman, 1987). Cognition factors also play a part in the modulation of phantom limb pain, patients who lack coping strategies and fear the worst when confronted with episodes of pain are more affected by the pain and report more interference than patients who cope well with their problem (Anne Hill, 1995).

C) CENTRAL THEORIES

A study of somatosensory pain memories in phantom limb pain which are characterized by the quality of pain experienced in the intact limb prior to amputation. Eg. Phantom limb pain may be experienced as similar in quality and location to a painful wound being dressed, a painful foot ulcer, pain result from deep tissue injuries prior to amputation. Jensen et al., 1985 reported that 74% of the patients had pain in the similar location to pre-amputation pain. The characteristic of phantom pain was similar pre-amputation pain in

53% and 35% of patients after 8 days and 2 years respectively. When both location and quality of pain examined, phantom limb pain resembled pre-amputation pain in 36% of patients at 8 days and 10% after 2 years. Katz and Melzack reported that 42% of their sample had a somatosensory pain memory that resemble the quality and location of pre-amputation sensation. Recent finding suggested that the reason of for these somatosensory pain memory may lie in functional or structural change within the central nervous system in response to noxious somatosensory input (Melzack, 1990).

Given the diversity of phantom limb phenomena, no one causal mechanism can explain phantom limb pain. Melzack has proposed that this diversity can be better explained using the concept of a NEUROMATRIX. It is defined as a network of neurons that extends throughout widespread areas of the brain, composing the anatomical substrate of the physical self. The theory proposes that abnormal input to the neuromatrix following amputation alters the pattern generated by the neuromatrix and the results in output which is experienced as a painful phantom. Abnormal input can either result from lack of normal sensory input following amputation or from high level of input caused by excessive firing in the damaged nerves. The phantom itself appears to be felt because of the basic pattern of the neuromatrix, the NEUROSIGNITURE. The output from the neuromatrix then will include the basic neurosignature which has been modulated to include strong message for the limb to move even though neuromatrix no longer receives signal from the peripheral that the limb is moving after amputation. This not only result in pain but also associate EMG spike activity within the stump (Anne Hill BSc, 1999).

In the research on somatosensory pain memory, the experience can be shaped the pattern produced by the neuromatrix. It is suggested that a neural representation of the pre-amputation pain is formed subsequent to one very intense pain experience or is formed and gradually strengthened as a result of multiple occurence of pain. Therefore, it is reasonably assume that both these aspects of original experience have been encoded within neuromatrix. This is supported in a recent study by Hill et al., 1995.

Notably, neuromatrix theory implies that many facets of an amputee's experience might contribute to the quality and intensity of his or her phantom limb pain by initiating activity within the neuromatrix, this theory suggests that in addition to sensory input triggering the neuromatrix, psychological or social factors may also produce input that activates the matrix and result in the experience of phantom limb pain. For example: research show that episodes of phantom limb pain can be exacerbated by stress, fear or insomnia.

New insights into phantom limb pain have come from the studies that showed changes in the functional and structural architecture of primary somatosensory after amputation and deafferentation. Using non-invasive neuromagnetic study on the brain of amputees with arm amputation. It showed that the amputated hemisphere mouth representation invaded the hand region. Study showed that the larger the shift of mouth representation into the zone that formerly represented the amputated hand and arm, the greater the phantom limb pain. (H. Flor, 1995)

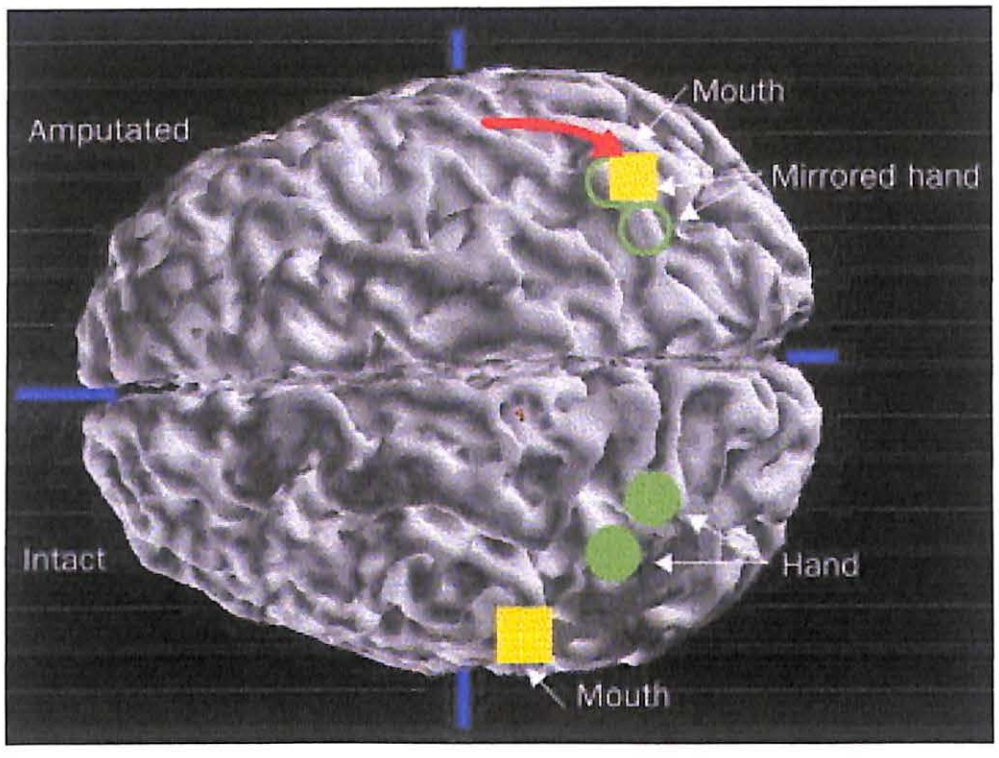

Figure 2.1. Assessment of reorganisation of the primary somatosensory cortex in an individual with amputation of the arm and phantom-limb pain. Neuromagnetic source imaging was used to define the localisation of the hand and mouth regions on the cortical hemisphere contralateral to the intact side and of the mouth region on the hemisphere contralateral to the amputation side. Magnetic fields evoked by pneumatic stimulation of the fingers of the intact side and the comer of the mouth on both sides were integrated with structural magnetic resonance images. The localisation of the intact hand was then transposed to the side contralateral to the amputation (with the assumption of a symmetrical localisation of the somatosensory homunculus) to assess where the former hand region was localised. The mouth representation on the amputated side has completely invaded the hand region. The amount of shift can be identified by calculating the Euclidean distance between the mouth and the hand region. The larger this distance (red arrow) the greater the cortical reorganization.

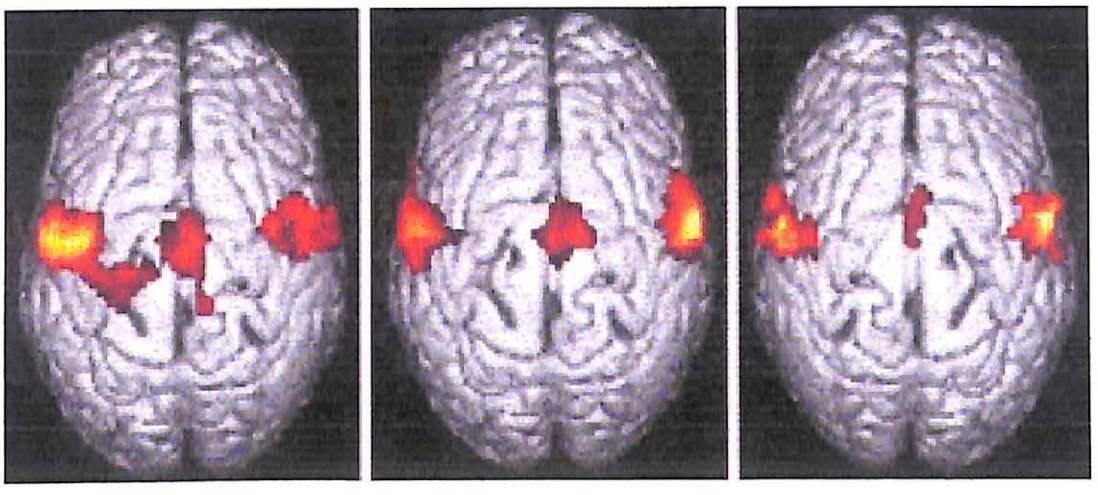

Figure 2. 2. Reorganisation in primary somatosensory and motor cortex in patients who had had unilateral arm amputation with phantom-limb pain (left) and without phantom-limb pain (middle), and in a healthy control. The participants had to pucker their lips at a metronome-paced speed while functional magnetic resonance images were taken. Only in amputees with phantom-limb pain did a shift of the mouth representation into the hand representation occur; those without pain and the healthy control do not display a similar shift.

Schematic diagram incorporating the main factors thought to be relevant for development of phantom limb pain

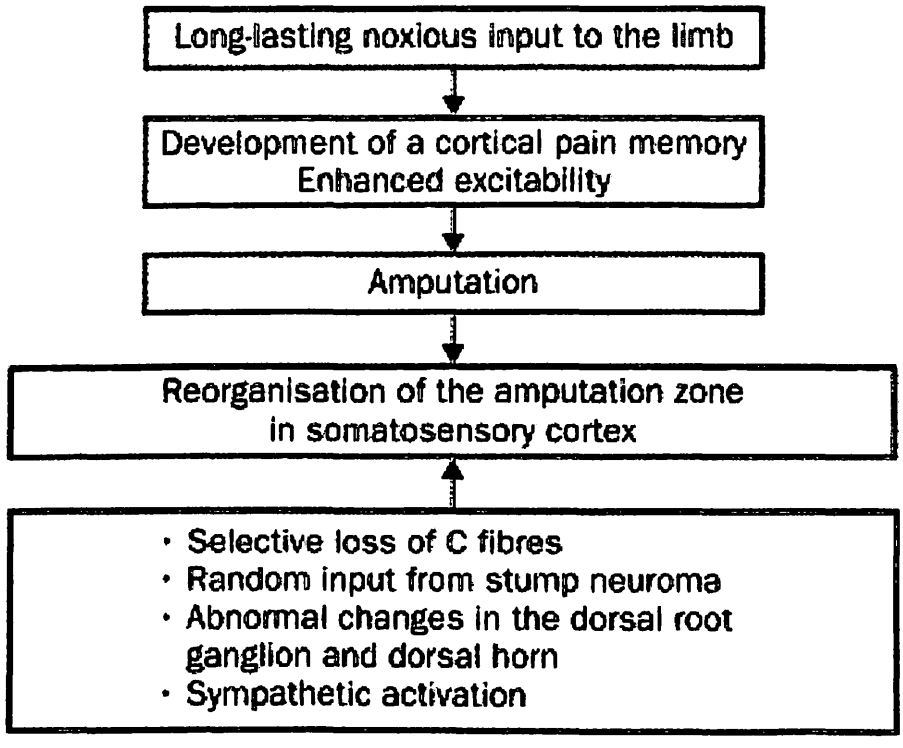

Figure 2. 3

2. 2. 4) RISK FACTORS

Many risk factors for phantom limb pain have been identified, including phantom sensation, stump pain, pain prior amputation, cause of amputation, prosthesis use, and years elapsed since amputation. The pre-amputation pain was found to be associated with immediate phantom pain but pain persist for 2 years after the amputation was less affected by pre-amputation. The most important risk factors for phantom limb pain found in the study by Pieter U. Dijkstra et al are vascular reason for amputation, lower limb amputation, proximal amputation, bilateral amputation, phantom sensation and the stump pain. Wherease the reason for amputation eg : vascular disease, trauma, cancer, or other reason did not contribute significantly (Dijkstra, 2002).

The risk factors for foot lesion and amputation were cigarrate smoking, being male, neuropathy, vascular impairement, duration of diabetic mellitus, presence of medial arterial calcification in the feet (Robert G. Nelson, 1988).

2. 2. 5) EFFECT OF PRE AND POST-AMPUTATION ANALGESIA

Few studies have been done to prevent or reduce the incidence of phantom limb by preamputation pain control which in hope that will reduce the somatosensory pain memory. Various method and different kind of analgesia have been used for the purpose. Their result claimed that it reduced the phantom pain but other did not.

Study done by Sore Bach et al using lumbar epidural blockade with bupivacain and morphine for 72 hours prior amputation which showed reduction of incidence of phantom limb pain in the first year of amputation (Soren Bach, 1988). The same author also found that those amputees with preoperative pain have significant more frequent phantom pain than those who did not have pre-amputation pain (Troels S Jensen, 1983). The similar result was obtained in the case study done by Robin L Fainsinger.

The prospective long term study designed by Troels S Jensen. It noted that the phantom limb was significantly more frequent in patient with long lasting pre-amputation limb pain and in patient with pain in the limb immediately prior to amputation (Troels S Jensen, 1985).

Neuraxial fentanyl acting on spinal opioid receptor alter the impulse pattern signaling pain in a way that was perceived as pleasant. The overall effect of intrathecal and extradural fentanyl as well as the inability of an identical intravenous dose to produce analgesia of either comparable quality or duration constitute evidence for spinal action of neuraxial fentanyl (Jacobson, 1989)

Other study done by Lone Nikolajsen et al, 1997 showed negative result. In his randomized trial of epidural bupivacaine and morphine in lower limb amputation, the perioperative epidural blockade begun about 18 hours before surgery and continued into the postoperative period did not prevent phantom limb pain as well as the stump pain.

Continuos post-operative regional analgesia by nerve sheath block by Allan Fisher, pilot study on eleven patients by inserting a catheter into the transected nerve sheath either sciatic nerve in above knee amputation or posterior tibial nerve for below knee amputation. The bupivacaine was continuously infused over a period of 72 hours. The 12 months follow up showed a total absence of phantom limb pain despite the presence of preoperative limb pain (Allan Fisher, 1991).

Above study later done by Micheal S. Pinzur et al, well design prospective, randomized clinical trial on those patients who underwent amputation lower limb because of ischemic necrosis secondary to peripheral vascular disease. One group was given continous bupivacaine infusion over transected nerve whereas the other group was given normal saline infusion. They concluded that it was effective method for the relief postoperative pain but it does not prevent phantom limb pain as well as the residual pain (Michael S. Pinzur, 1996).

Knowing that above preamputation epidural analgesia as well as the postoperative perineural analgesia infusion gave us different result in each respective group. Therefore, randomized prospective study by comparing preoperative epidural analgesia and

intraoperative perineural analgesia showed that did not significantly reduce the phantom limb pain in either way but obviously the epidural gives better relief of stump pain (A. W. Lambert, 2001)

Intraoperative and postoperative intravenous ketamine may prevent severe and clinically relevant phantom limb pain. From the observatory study done ketamine inhibits the NMDA (N-Methyl D-Aspartate receptor) which responsible for the neuroplastic reaction mediation via potentiation pattern of dorsal horn multiceptive neurones even after ceasation of nociceptive stimuli (Roman Dertwinkel MD, 2002).

2. 2. 6) PERIOPERATIVE PAIN

A number of factors may influence the intensity, quality, and duration of perioperative pain.

The most important of these are as follows :

1. The site, nature, and duration of surgery.
2. The type and extent of the incision and other surgical trauma.
3. The physiologic and psychologic make-up of the patient.
4. The preoperative psychologic, physiologic, and pharmacologic preparation of the patient.
5. The presence of complications related to the surgery.
6. The anaesthetic management before, during and after surgery.

7. The quality of perioperative care.
8. Preoperative treatment to eliminate painful stimuli prior to surgery.

By considering how each of these factors applies to individual patients, optimal care becomes more likely (Miller, R. D., 2000).

2. 2. 7) PAIN PATHWAY

Surgery produces local tissue damage with consequent release of analgesic substances (prostaglandins, histamine, serotonin, bradykinin, 5-hydroxytryptamine, substance P) and generation of noxious stimuli that are transduced by nociceptors and transmitted by A delta and C nerve fibres to the neuraxis.

Further transmission is further determined by complex modulating influences in the spinal cord. Some impulses pass to the anterior and anterolateral horns to provoke segmental reflex responses. Others are transmitted to higher centers via the spinothalamic and spinoreticular tracts, where they produce suprasegmental and cortical responses (Miller, R. D., 2000).

2. 3) OPIATES

2. 3 .1) HISTORY

Chronic pain and post-surgical pain can both be alleviated by the use of opiates. Opiates are a type of drug extracted from the pod of the Asian poppy. These drugs have been used medically and non-medically for centuries. Laudanum has been used since the 16th century to stop coughing and diarrhoea, and to calm nerves. In the 19th century morphine was extracted in its pure form and became an injectable solution with the use of the hypodermic needle. In 1898, heroin was introduced. At first heroin was thought to be a remedy for morphine addiction. It turned out to be not only a more potent pain killer, but also much more addictive than morphine. Heroin is the only opiate more liable to create dependence than morphine. Only two natural opium products are still used today for clinical use, morphine and codeine. The synthetic opium products are generally called opioids. These drugs were developed to produce the same type of analgesic uses, but with out the drug dependence (Addiction Research Foundation, 1995).

2. 3. 2) MORPHINE

Morphine is a prototype opioid agonist to which all other opioids are compared. It is a pure opioid agonist and tertiary amine being isolated from poppy plant in 1805 by Serturner. It acts on the mu and kappa receptor. Morphine is a weak base, water soluble in vitro but become poorly lipid soluble in vivo (Stoelting, R. K. 1999).