SAFE AND IMPROVED ANALGESIA FOLLOWING BUPIVACAINE WITH EPINEPHRINE INFILTRATION BEFORE SKIN GRAFT HARVESTING

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ABSTRACT

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Introduction: Skin grafting is the commonest surgical procedure performed to cover soft tissue defects. It has been known that the split skin graft donor site is more painful than the recipient site itself. Despite its frequent usage, the donor site preparation and postoperative protocol has not been standardized. Infiltration of lignocaine (or / in addition with bupivacaine) is consistently performed prior to harvesting of skin graft only if done under local anaesthesia. However it is not practiced routinely if skin harvesting was done under general anaesthesia. This prospective study determined the benefit and risk of bupivacaine with epinephrine infiltration before harvesting skin graft under general anaesthesia.

Method: Sixty patients admitted to University Malaya Medical Centre (UMMC) from July 2012 to April 2013 who required split skin graft from thigh as part of their management were randomized using online randomization tool into

either the infiltration group or no infiltration group. Post-operatively, all the patients were given patient-controlled analgesia (PCA) morphine for at least 24 hours to monitor morphine requirement. The Visual analog scale (VAS) assessment was started after 8 hours postoperatively then continued till 24 hours. Total consumption of patient-controlled analgesia morphine was charted every 4 hours to monitor consumption of opioid analgesia for breakthrough pain.

Results: Only 53 of the 60 (88.3%) recruited subjects participated in the research until completion (27 in the infiltration group while 26 in the no infiltration group). No statistical difference in the distribution between gender, age, ethnic group, indication for skin graft and estimated donor size among the two randomized groups. There was significant difference in pain intensity between the two groups from 8 to 20 hours post-operatively ($p < 0.05$). The difference between the two groups on cumulative usage of PCA morphine was also significant from 8 to 16 hours post-operatively. There was no neuro-cardiotoxicity detected in both group of patients. None of the donor sites was infected and all healed completely by one month review.

Conclusion: Subcutaneous infiltration of bupivacaine with epinephrine before harvesting of split skin graft under general anaesthesia improved postoperative analgesia and decreased opioid consumption. No sign of any toxicity or wound infection observed. It is a safe procedure in the selected group of patients. Therefore, this technique is strongly recommended to be routinely practised to improve postoperative care of skin graft patients.

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ABSTRAK

Graf kulit adalah prosedur pembedahan yang paling biasa dilakukan untuk menutup kecederaan tisu lembut. Telah diketahui bahawa kawasan penderma graf kulit adalah lebih sakit daripada tapak penerima itu sendiri. Walaupun penggunaan yang kerap, cara penyediaan tapak penderma dan protokol selepas pembedahan belum muktamatkan. Penyusupan lignocaine (atau / bersama dengan bupivacaine) secara konsisten dilakukan sebelum penuaian graf kulit hanya jika dilakukan di bawah bius setempat. Namun kaedah itu tidak dilakukan secara rutin jika penuaian kulit dilakukan di bawah bius am. Kajian ini bertujuan mengenalpasti faedah dan risiko penyusupan bupivacaine dengan epinephrine sebelum penuaian graf kulit di bawah bius am.

Enam puluh pesakit yang dimasukkan ke Pusat Perubatan Universiti Malaya (PPUM) dari julai 2012 hingga april 2013 yang memerlukan graf kulit dari bahagian paha sebagai rawatan diambil sebagai sampel. Mereka dirambangkan menggunakan alat rawak atas talian kepada sama ada kumpulan penyusupan atau kumpulan tanpa penyusupan . Selepas pembedahan, semua pesakit diberi pesakit-kendali-analgesia (PCA) morfin untuk sekurang-kurangnya 24 jam untuk memantau keperluan morfin. Soal selidik skala visual analog (VAS) dimulakan selepas 8 jam selepas itu kemudian berterusan sehingga 24 jam. Jumlah penggunaan bagi pesakit yang dikendalikan analgesia morfin dicatatkan setiap 4 jam untuk memantau penggunaan analgesia opioid.

Hanya 53 daripada 60 (88.3 %) pesakit yang dipilih melengkapkan kajian ini (27 dalam kumpulan penyusupan sedangkan 26 dalam kelompok tanpa penyusupan). Tiada perbezaan statistik yang signifikan dalam pengedaran antara jantina, umur, kumpulan etnik, indikasi untuk graf kulit dan anggaran saiz penderma di antara kedua-dua kumpulan. Terdapat perbezaan yang signifikan dalam tahap kesakitan antara kedua-dua kumpulan pada jam 8 sampai 20 jam selepas pembedahan ($p < 0.05$). Perbezaan di antara kedua-dua kumpulan pada penggunaan kumulatif PCA morfin juga signifikan 8-16 jam selepas pembedahan. Tidak ada kesan sampingan "neuro" atau "cardiotoxicity" dalam kedua-dua kumpulan pesakit kami. Tiada satu pun kulit penderma dijangkiti kuman dan semua sembuh sepenuhnya dalam satu bulan susulan.

Penyusupan "subcutaneous bupivacaine" dengan adrenalina sebelum penuaian "skin graft" di bawah anestesia am menurunkan tahap kesakitan selepas pembedahan dan pengurangkan penggunaan opioid. Tiada tanda-tanda kesan sampingan atau luka jangkitan ditemui. Kaedah ini adalah selamat dalam kumpulan pesakit kami. Oleh yang demikian, teknik ini dianjurkan untuk diamalkan secara rutin untuk menambah baik penjagaan pesakit susupan kulit selepas pembedahan.

ABSTRACT

Skin grafting is the commonest surgical procedure performed to cover soft tissue defects. It has been known that the split skin graft donor site is more painful than the recipient site itself. Despite its frequent usage, the donor site preparation and postoperative protocol has not been standardized. Infiltration of lignocaine (or / in addition with bupivacaine) is consistently performed prior to harvesting of skin graft only if done under local anaesthesia. However it is not practiced routinely if skin harvesting was done under general anaesthesia. This prospective study determined the benefit and risk of bupivacaine with epinephrine infiltration before harvesting skin graft under general anaesthesia.

Sixty patients admitted to University Malaya Medical Centre (UMMC) from July 2012 to April 2013 who required split skin graft from thigh as part of their management were randomized using online randomization tool into either the infiltration group or no infiltration group. Post-operatively, all the patients were given patient-controlled analgesia (PCA) morphine for at least 24 hours to monitor morphine requirement. The Visual analog scale (VAS) assessment was started after 8 hours postoperatively then continued till 24 hours. Total consumption of patient-controlled analgesia morphine was charted every 4 hours to monitor consumption of opioid analgesia for breakthrough pain.

Only 53 of the 60 (88.3%) recruited subjects participated in the research until completion (27 in the infiltration group while 26 in the no infiltration group). No

statistical difference in the distribution between gender, age, ethnic group, indication for skin graft and estimated donor size among the two randomized groups. There was significant difference in pain intensity between the two groups from 8 to 20 hours post-operatively ($p < 0.05$). The difference between the two groups on cumulative usage of PCA morphine was also significant from 8 to 16 hours post-operatively. There was no neuro-cardiotoxicity detected in both group of patients. None of the donor sites was infected and all healed completely by one month review.

Subcutaneous infiltration of bupivacaine with epinephrine before harvesting of split skin graft under general anaesthesia improved postoperative analgesia and decreased opioid consumption. No sign of any toxicity or wound infection observed. It is a safe procedure in the selected group of patients. Therefore, this technique is strongly recommended to be routinely practised to improve postoperative care of skin graft patients.

1. LITERATURE REVIEW

1.1 Introduction

For soft tissue coverage, split skin grafting is the commonest performed surgical procedure. It is done for wide range of indications, especially for trauma, burn, tumour reconstruction and soft tissue infections. Despite its frequent usage, skin graft donor site preparation and postoperative protocol has not been standardized (Voineskos S.H., 2009).

It has been known that the split skin graft donor site is more painful than the recipient site itself (Alvi R, 1998). Harvesting of skin graft fires up dermal pain receptors in direct relation to the donor size and the pain stimulus are carried to the central nervous system by afferent fibres in the cutaneous nerves (Lowrie AG, 2007).

If the split skin graft donor site is more painful postoperatively than the recipient site, then we can predict good graft take (Moriarty Sign) (Oluwatosin OM, 2000). Alleviation of this pain can achieve considerable reduction in postoperative distress of the patient and encourages early ambulation. Therefore, studies should be focused on techniques and materials to reduce post-operative donor site pain.

Opioid analgesics are the medication most commonly used to treat the postoperative pain. However, they are associated with significant undesirable

adverse effects such as nausea, vomiting, sedation and constipation. In their work to reduce the adverse consequences of opioids, Blades and Ford introduced the use of continuous local anaesthetic infusion in patients having thoracic surgery. They found that the supplement of slow, continuous local anaesthetic infusion at the surgery site in postoperative patients was associated with less opioids use, shorter length of hospital stay, reduced expenses, improved patient satisfaction, and earlier return to normal activity (Blades B, 1950).

Although various studies have found that the infiltration of local anaesthetic agent combined with epinephrine under donor skin decreases blood loss and pain, it is still not widely accepted practice. The hesitation to adapt this practice stems in part from the doubt that infiltrated local anaesthetic agent provides adequate pain relief and combined with a fear of its systemic and local side effects (Djurickovic S, 2001).

Some authors have used and shown that topical anaesthetic agents to be safe when delivered as a depot gel(Alvi R, 1998). It effectively produced an analgesic effect that reduced narcotic requirements compared with patients who received placebo(Scott, 1999). There is another research article by Mithat et al in Turkey who went all the way to introduce harvesting of split skin graft from insensate flap skin as a potential graft donor site for patients in whom reduction of donor site morbidity is of primary concern (Mithat Akan, 2002).

According to a study done by Trost et al in France, infiltration of split skin grafts donor site with ropivacaine after harvesting improves postoperative pain during 48 hours. It is a safe and efficient method to improve comfort in addition to a standardized occlusive dressing. This protocol has become a standard routine in the author's institution (Trost, 2005).

Other local anaesthetic agents including short as well as long acting have also been reported to reduce pain at split skin graft donor sites. Cenetoglu et al. used topical lignocaine gel at skin graft donor site and found significant pain relief. However, the effect was of shorter duration since lignocaine is a short acting anaesthetic agent though its onset of action is early (Cenetoglu S, 2000). Therefore, in our study, we chose bupivacaine over lignocaine because bupivacaine has a longer duration of action. The infiltration of the bupivacaine with epinephrine was done while patient was under the effect of general anaesthesia so that the local anaesthetic already taken effect before the patient has awakened postoperatively.

Another prospective double blind controlled trial done by Butler et al in Ireland studied the differences in post-op pain between sites dressed with a dry calcium alginate dressing (Kaltostat®), a saline moistened Kaltostat dressing and a bupivacaine (0.5%) moistened Kaltostat dressing. The study showed there was a significant reduction in post-operative pain in the Kaltostat and bupivacaine group ($p < 0.04$). There was no difference in ease of removal of dressings or the quality of wound healing on day 10 between the three groups (Butler, 1993).

A different method introduced to significantly minimize skin graft donor site pain is by ice packs directly applied to the donor sites. The main advantage is its low cost. However, this method complicated with leakages in 8 out of 36 of their patients (22.2%) requiring total replacement of the dressing (Akan M, 2003).

Some studies have shown bupivacaine to be safe when added to the subcutaneous infiltration solution for donor site harvesting. Fischer CG et al studied 14 patients in Cincinnati, Ohio with bupivacaine at a dose of slightly less than 1.9 mg/kg added to donor site infiltration. They concluded that the solution is safe, as demonstrated by low blood levels and the absence of clinical signs of toxicity (Fischer CG, 2003).

Both levobupivacaine and ropivacaine have a clinical profile similar to that of racemic bupivacaine as studied by Andrea Casati (Andrea Casati, 2005) in Italy. The minimal differences observed between the three agents are mainly related to the slightly different anaesthetic potency, with racemic bupivacaine > levobupivacaine > ropivacaine. Another consideration is the cost of the chosen dose of bupivacaine is about three times lower than the cost of ropivacaine (British Medical Association, 2011). This lower cost will have substantial impact on overall healthcare cost (Dhalwani, 2012).

Opioid administration is the dominant form of analgesic therapy for burn and post-operative patients (Ashburn, 1995). The pharmacokinetics of opioids are altered

especially in burn patients, both immediately after the event and for weeks to come because of changes in the volume of distribution, unbound drug fraction, clearance half-life, and sensitivity. In addition, opioid requirements may increase over time, reaching a ceiling effect, and may not be able to provide complete analgesia all the time (Silbert BS, 1991). Therefore, adjuvant treatments are sought to provide effective pain relief to such patients and to reduce opioid requirements

The use of lignocaine for tumescent technique liposuction has been commonly used for healthy non-burn adults. Burk RW measured that blood levels of lignocaine were below toxic threshold despite high doses (up to 35 mg/kg) in tumescent technique liposuction. (Burk RW, 1996) We would like to use a local anaesthetic agent which is widely available, long-acting and cost-effective. Because bupivacaine toxicity is a very serious complication, we did not feel the extrapolation of the lignocaine data to our patient population was appropriate without sufficient safety evidence. Therefore a prospective study was performed to assess the benefit and risk of bupivacaine infiltration for skin graft donor site.

To assess the most common dressing for skin graft donor site, a questionnaires survey was obtained from 279 British consultant plastic surgeons in 2006. The results showed alginates were the most popular dressings which were the first choice for 167 British consultant plastic surgeons (60%). On the basis of these results, the authors felt that any study of donor-site dressings should incorporate the most commonly used dressing (alginate) as a control (Geary PM, 2009).

1.2 Practice in standard literature

Infiltration of lignocaine (or/in addition with bupivacaine) is consistently performed prior to harvesting of split skin graft only if done under local anaesthesia. This is because the area of skin harvested was small area and it was carried out under local anaesthesia. Usually no routine infiltration if skin harvesting was done under general anaesthesia. Some surgeons do practice infiltrating the donor site with local anaesthetic agent after harvesting under general anaesthesia. Based on our anecdotal experience, we have found that those patients given local anaesthetic agent were much more comfortable postoperatively.

Although some studies have found that the infiltration of local anaesthetic agent and epinephrine under donor skin reduces post-operative pain as well as decreases blood loss, it is still not a widely accepted practice. The hesitation to adapt this practice stems in part from the belief that the infiltration will slow blood perfusion and, therefore, impairing the healing of these donor sites combined with a fear of systemic toxicity (Robertson RD, 2001). Therefore, this study was initiated to objectively assess the benefits of bupivacaine and epinephrine infiltration as well as its complications.

1.3 Bupivacaine

Bupivacaine is a local anaesthetic drug belonging to the amino amide group. It binds to sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. The duration of plain bupivacaine is long which is 180 minutes and it last even longer up to 420 minutes if combined with epinephrine.

The adverse reactions of bupivacaine due to systemic exposure can be divided into cardiovascular and central nervous system effects. The cardiovascular toxicities are hypotension, bradycardia, arrhythmias, and/or cardiac arrest. The central nervous system effects are nervousness, tinnitus, tremor, dizziness, blurred vision, seizures, drowsiness, loss of consciousness or respiratory depression (Thorne, 2007).

1.4 Epinephrine (Adrenaline)

Epinephrine is a hormone and a neurotransmitter. In the body, it is produced only by the adrenal glands from the amino acids phenylalanine and tyrosine. It is non-selective agonist of all adrenergic receptors. The local effect of epinephrine is it reduces cutaneous blood flow, thereby decreases bleeding and prolongs the local anaesthetic effects (Cartotto R, 2000). The systemic adverse reactions of epinephrine can also be divided into cardiovascular and central nervous systems. (Papp AA, 2009).

2. OBJECTIVES

2.1 Research Objectives

The general objective of this study is to assess the benefits and risk of bupivacaine and epinephrine infiltration when given before harvesting of skin graft during general anaesthesia

The specific aims of this study are:

(1) To assess the difference of pain score when bupivacaine with epinephrine infiltration were given pre harvesting of skin graft during general anaesthesia

(2) To evaluate the reduction of systemic analgesia given to control postoperative skin graft pain

(3) To determine the complication of bupivacaine and epinephrine infiltration

2.2 Research Hypothesis

(1) Infiltration of bupivacaine and epinephrine pre harvesting of split skin graft will result in significant pain relieve in the patient post-operatively

(2) Usage of systemic analgesia will be reduced following infiltration of bupivacaine and epinephrine pre harvesting of split skin graft

2.3 Hypothesized benefits of infiltration

(1) Reduced post-operative pain

(2) Reduced usage of systemic analgesia

(3) Reduced blood loss

2.4 Potential complications of infiltration

(1) Cardiac toxicity

(2) Central nervous system stimulation or depression

(3) Increasing risk of infection to donor site

3. METHODOLOGY

3.1 Patients and Setting

Subjects included in our prospective study were selected from patients admitted to the University Malaya Medical Centre (UMMC) from July 2012 to April 2013 who required split skin graft from thigh under general anaesthesia as part of their management. They were randomized using online randomization tool into either the infiltration group or no infiltration group (Randomizer).

The sample size calculation was based on detecting a difference of 0.9 pain score of the visual analog scale based on a similar study by Trost O et al using 30 patients (Trost, 2005). By using Power and Sample Size Calculations (Dupont and Plummer, Version 3.0), for standard deviation of 1 with 80% power and alpha 0.05, we needed 25 patients for each study group. Anticipated dropout rate was 10%. Therefore, total patients recruited were 60.

UMMC research committee has approved the research project (MEC Ref No 866.4). Research fund was obtained from UM "Bantuan Kecil Penyelidikan" (BK017-2011A). Written informed consent was obtained from all patients prior to surgery. Patient information sheet and consent forms available in 2 languages which are English and Malay languages.

The demographic information of the patients was collected, which include:

(1) Name

(2) Registration number/Identity card number

(3) Telephone number

(4) Gender

(5) Age

(6) Ethnic group

(7) Diagnosis

(8) Previous surger(ies)

(Appendix 1)

Inclusion criteria

- All adult patients (between 12 to 80 years old) undergoing split skin grafting
- Understanding the nature of the study and willing to complete frequent pain assessments via self-reported visual analogue scale score
- Donor site surface between 100 – 250 cm^2 from thigh region
- Only burn surgery or single procedure (SSG), not combined with other procedures
- Able to come back for follow-up reviews

Exclusion criteria

- Patients unable or refused to give consent

- Having an alternative source of severe, distracting pain that might down-score donor-site pain
- Patients on epidural anaesthesia after surgery
- Previous history of allergy to bupivacaine or epinephrine
- Presence of neurological or psychiatric pathology that is likely to affect the nociception
- Known history of cardiac pathology or liver failure
- Suffering from chronic pain requiring analgesia
- Uncontrolled diabetes or hypertension with evidence of end-organ damage (nephropathy, retinopathy, microvasculopathy)
- Immunosuppressive disorder

3.2. Statistical Analyses

Data analysis was performed using the Pearson Chi-Square test for gender, age, estimated donor size and indication for skin grafting. The Mann-Whitney U test was used to compare pain scores and dosage of patient-controlled analgesia morphine utilized. Statistical analysis was performed with Statistical Package for the Social Sciences Windows Version 22.0 (SPSS, Chicago, IL, USA). Significance value was taken at less than 0.05.

3.3. Materials and Methods

All of the donor sites were on the thigh. The area was planned preoperatively as shown in Plate 3.1. Area measured was estimated to be about 10-20% bigger than expected recipient site. All patients were given intravenous antibiotic prophylaxis during induction.

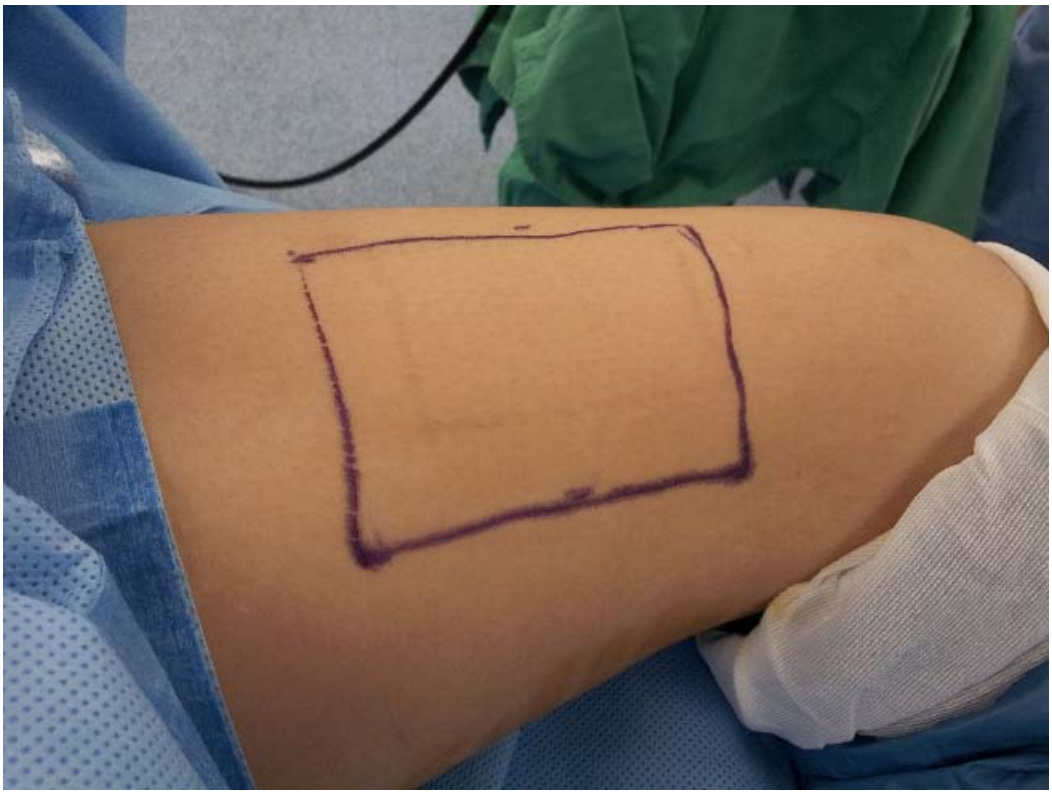

Plate 3.1: Marking of donor skin graft site on the thigh

Group 1 (study group) – 20ml 0.5% bupivacaine (with 1:200,000 epinephrine) diluted with 20ml 0.9% saline (total dose of 100mg bupivacaine and 0.1mg epinephrine). Infiltrated subcutaneously in a circular pattern (field block) underneath the pre-marked skin before harvesting the split skin graft as shown in Plate 3.2.

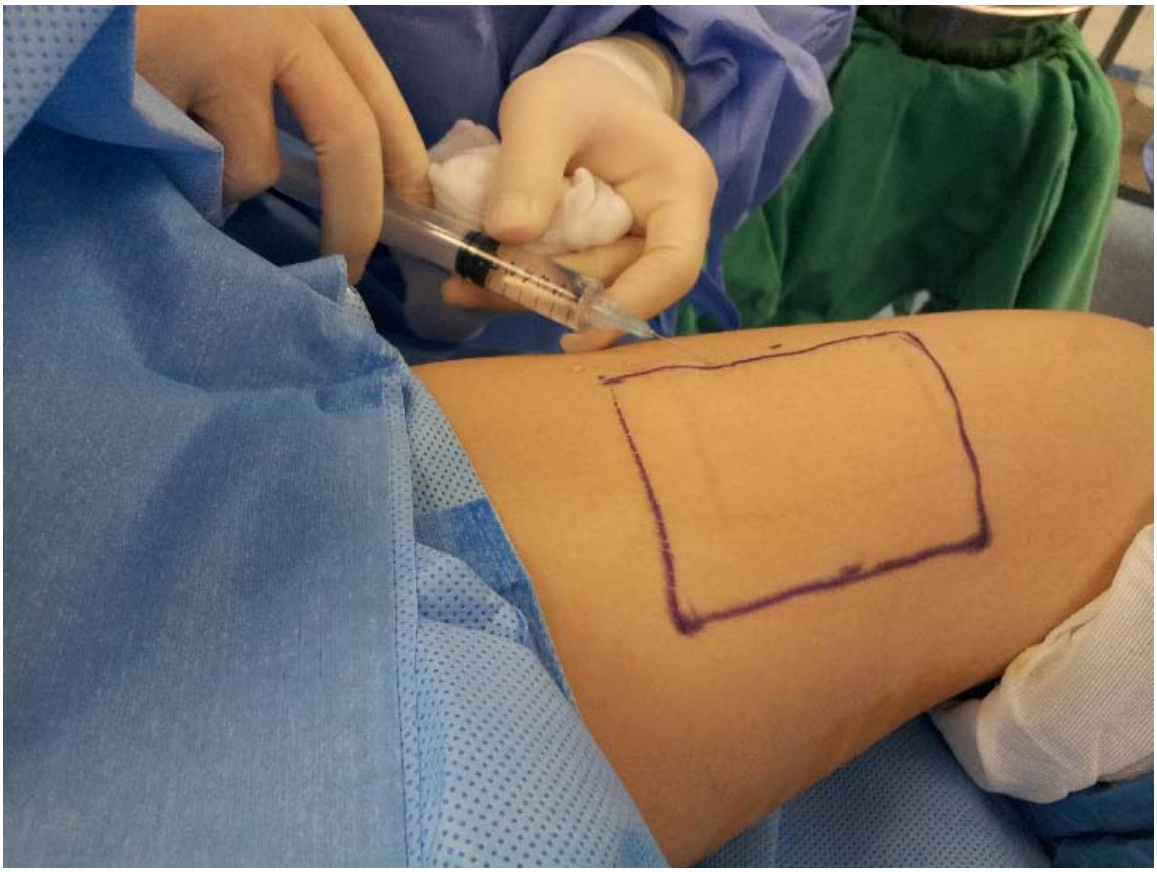

Plate 3.2: Subcutaneous infiltration of bupivacaine epinephrine

Group 2 (control group) – no infiltration

Senior residents performed all skin harvesting procedures. Skin graft was harvested with a Zimmer® Air dermatome at equal thickness on all donor sites (10/1000th an inch) and width 3 inch (Plate 3.3). Following skin harvesting, topical epinephrine solution soaked gauze (1:10,000) were applied for haemostasis.

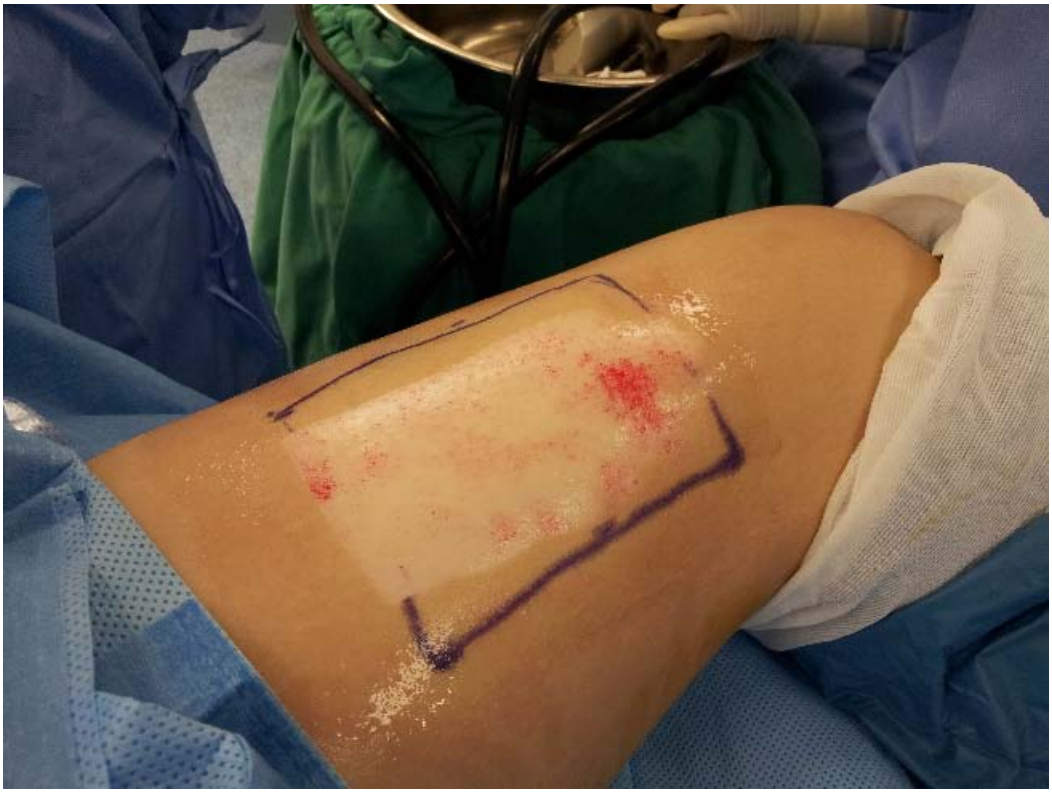

Plate 3.3: Harvesting of split skin graft

Donor skin graft site was then dressed with calcium alginate (Kaltostat®) (Plate 3.4) then dry gamzee and crepe bandage. The dressing was keep in situ for 10-14 days. Outer layer was changed when it was soaked or dirty.

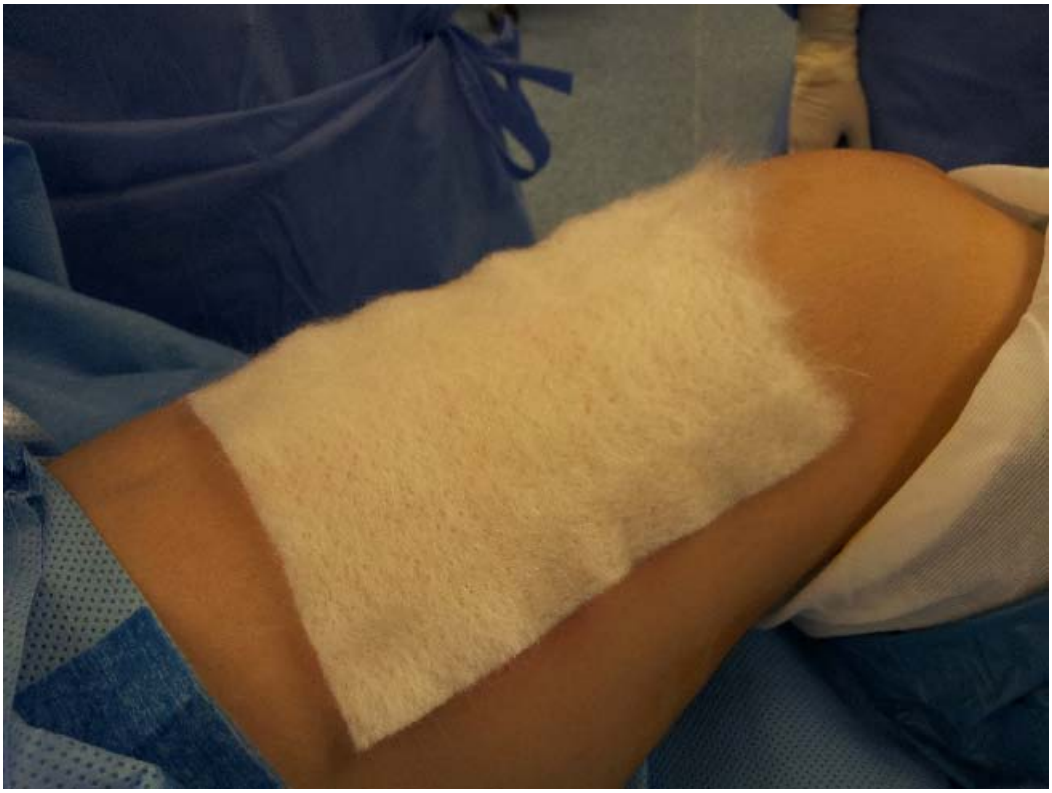

Plate 3.4: Dressing of donor site with calcium alginate (Kaltostat®)

Post-operatively, all the patients were given patient-controlled analgesia (PCA) morphine for at least 24 hours to monitor morphine requirement. The Visual analog scale (VAS) assessment was started after 8 hours postoperatively then continued 4 hourly till 24 hours (Appendix 2). This is a self-administered tool, well validated for research in the field (Lauren JD, 1998). The VAS pain scale were

10cm horizontal line anchored with "no pain" at left-most end and "worse possible pain" at right-most end. The patients were asked to mark the intensity of the pain at the donor site, rather than the pain in the recipient site. It is then converted to numerical scale measured from the left-most end.

Total consumption of patient-controlled analgesia morphine was charted every 4 hours to monitor consumption of opioid analgesia for breakthrough pain. Clinical symptoms or signs of postoperative cardiac or central nervous system toxicity were assessed during review.

The donor sites were inspected between days 10 – 14 postoperatively. If there were any signs of inflammation present on donor site, swabs were taken for microbiology culture. Patients were reviewed till complete healing of donor and recipient sites (Appendix 3).

4. RESULTS

4.1 Randomization

A total of 60 patients who underwent split skin graft in University Malaya Medical Centre (UMMC) were recruited. All of the patients were randomized using online randomization tool (Randomizer) into either the infiltration group or no infiltration group. Figure 4.1 show the randomization generated.

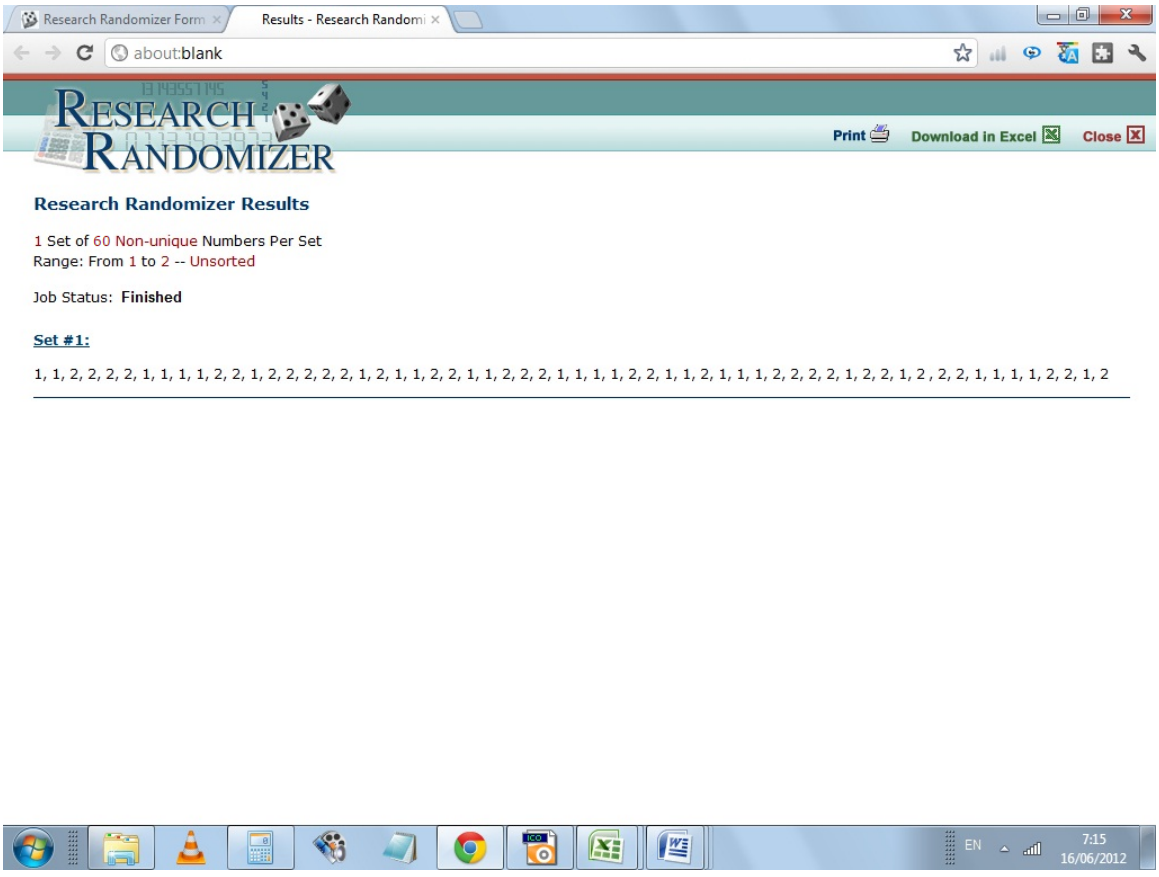

Figure 4.1: Online randomization generated

4.2 Study Population

Fifty three of the 60 (88.3%) recruited subjects completed the study (27 in the infiltration group while 26 in the no infiltration group). The remaining seven patients (11.7%) were excluded because they did not provide the assessments completely. The demographic data of the study population is displayed in Table 4.1. There were 13 males (n = 13/27) and 14 females (n = 14/27) in the infiltration group, and 14 males (n = 14/26) and 12 females (n = 12/26) in the no infiltration group. The difference between the two groups are not significant (p = 0.678) by Pearson Chi-Square test.

Table 4.1: Demographic data (p = 0.678)

Gender	**Infiltration** N (%)	**No infiltration** N (%)
Male	13 (48.1%)	14 (53.8%)
Female	14 (51.9%)	12 (46.2%)
Total	**27 (100%)**	**26 (100%)**

4.3 Patient Demography

Figure 4.2 shows the distribution of the patients according to their age groups. Peak age was in the 50-59 age group. The difference in age of patients recruited for the infiltration and no infiltration group was not significant (p = 0. 862).

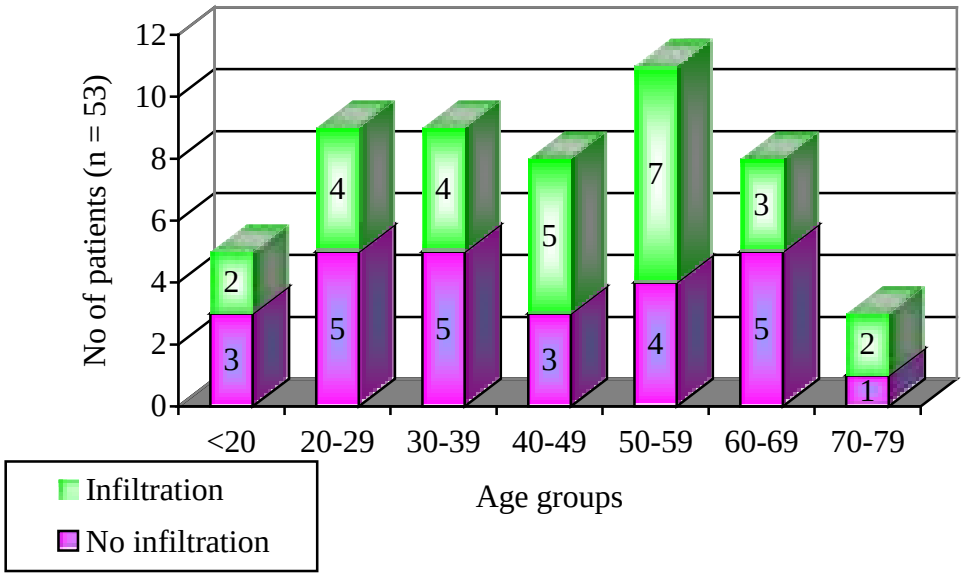

Figure 4.2: Age group of patients (p = 0. 862)

4.4 Ethnic Groups

Majority of our subjects are from ethnic Malay (49.1%), followed by Chinese (22.6%), Indian (22.6%) and Indonesian (5.7%). We have Indonesian patients because most of our foreign workers are from Indonesia. The ethnic distribution of our patient among the two groups was not significant (p = 0.458) as shown in Figure 4.3.

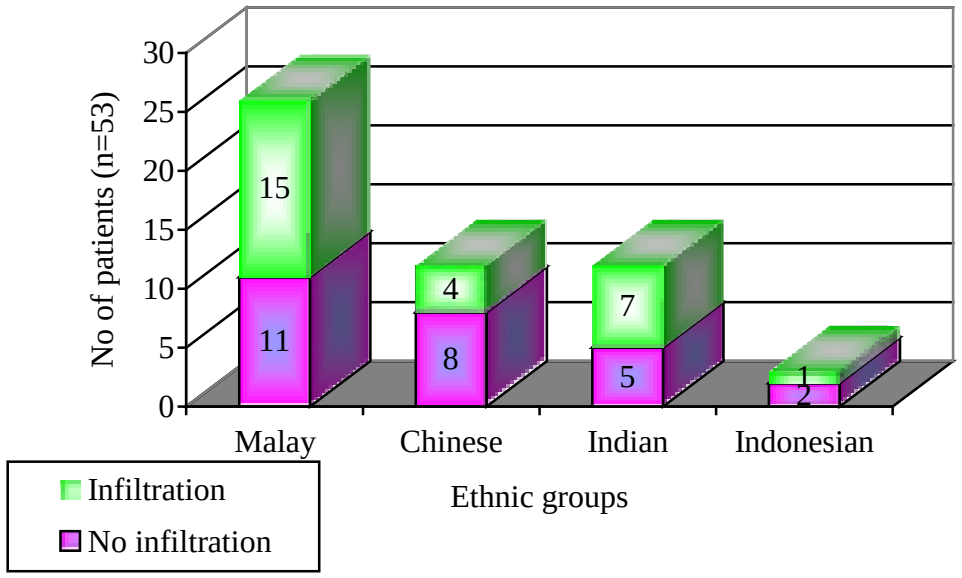

Fig 4.3: Ethnic group of patients (p = 0.458)

4.5 **Indications for skin graft**

Figure 4.4 illustrates that the majority or 35.8% of the skin grafting were done for patients who had burn injury (n = 19/53). The other patients had skin grafts for coverage of wounds secondary to trauma (24.5%), tumour (18.9%) or infection (20.8%). From T test analysis, there was no statistical difference in the distribution of indications between the groups (p = 0.796).

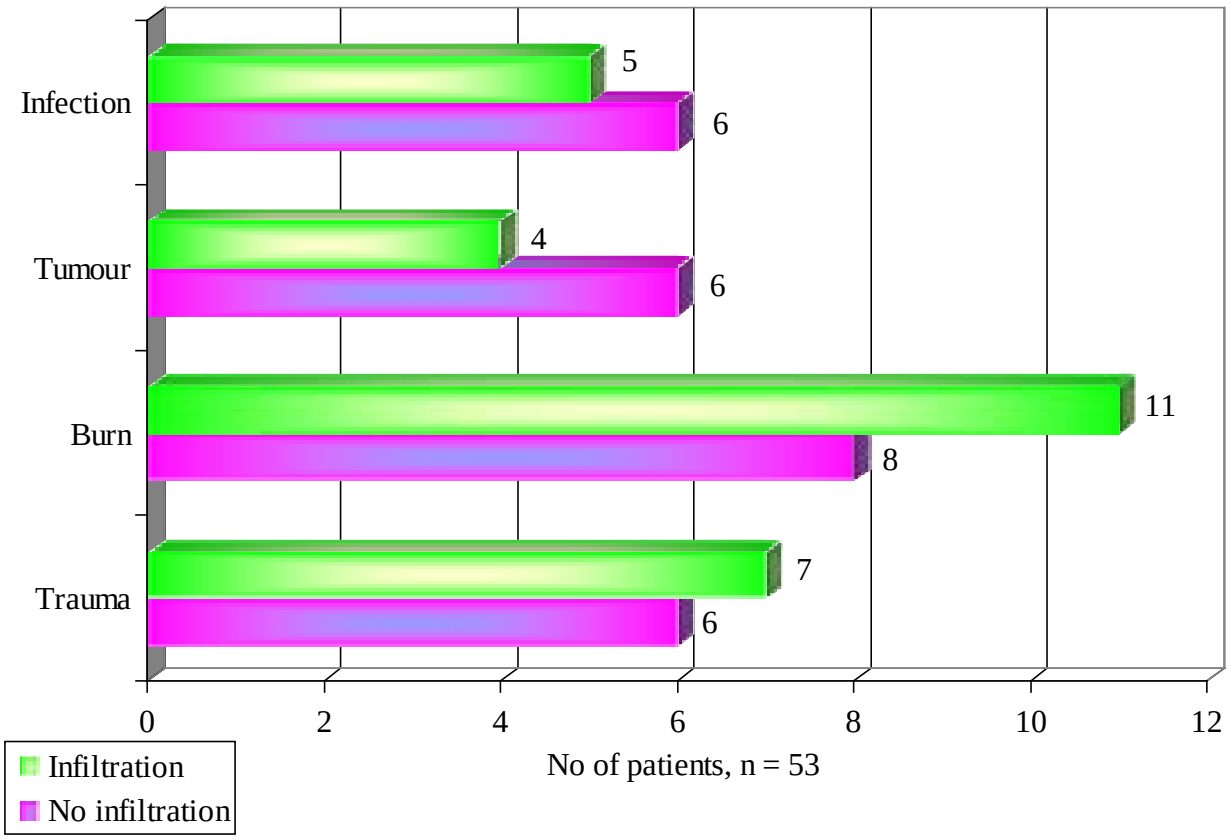

Fig 4.4: Indications for skin grafting (p = 0.796)

4.6 **Estimated Donor Size**

The donor size harvested was estimated between 116 – 232 cm^2. Majority or 22.6% of the patient (n = 12/53) had estimated donor size of about 174 cm^2 as shown in Figure 4.5. There was no statistical difference among the different estimated donor sizes between the groups (p = 0.559).

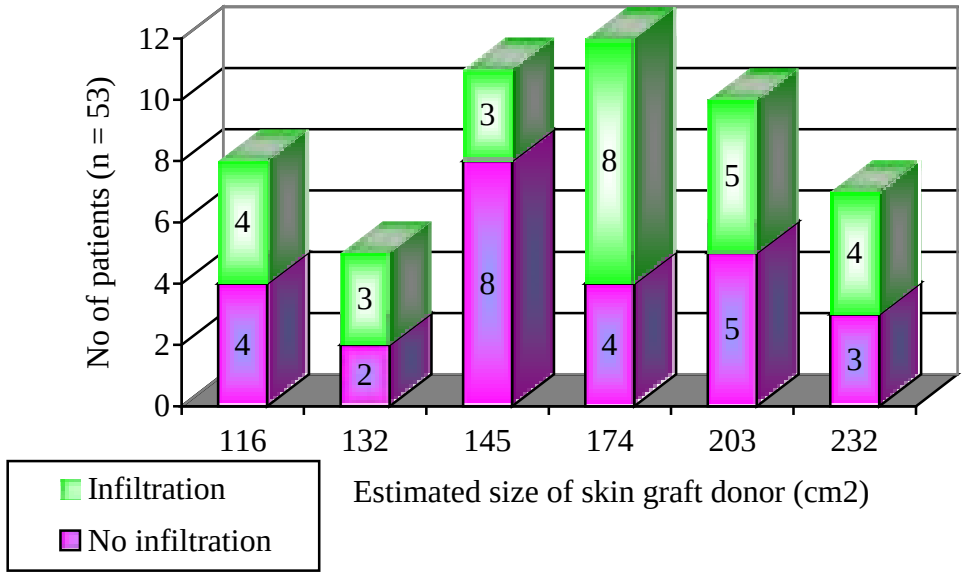

Fig 4.5: Estimated size of skin graft donor site (p = 0.559)

4.7 Pain score over 24 hours

The results of the visual analog score average postoperatively over 24 hours are shown in Figure 4.6. The first pain score assessment was done 8 hours postoperatively when patient has awakened from anaesthesia and able to provide pain assessment. The scores were compared by non-parametric independent samples Mann-Whitney U test. There was significant difference in pain intensity between the two groups from 8 to 20 hours post-operatively ($p < 0.05$). However, at hour 24, it was not significant with $p = 0.098$.

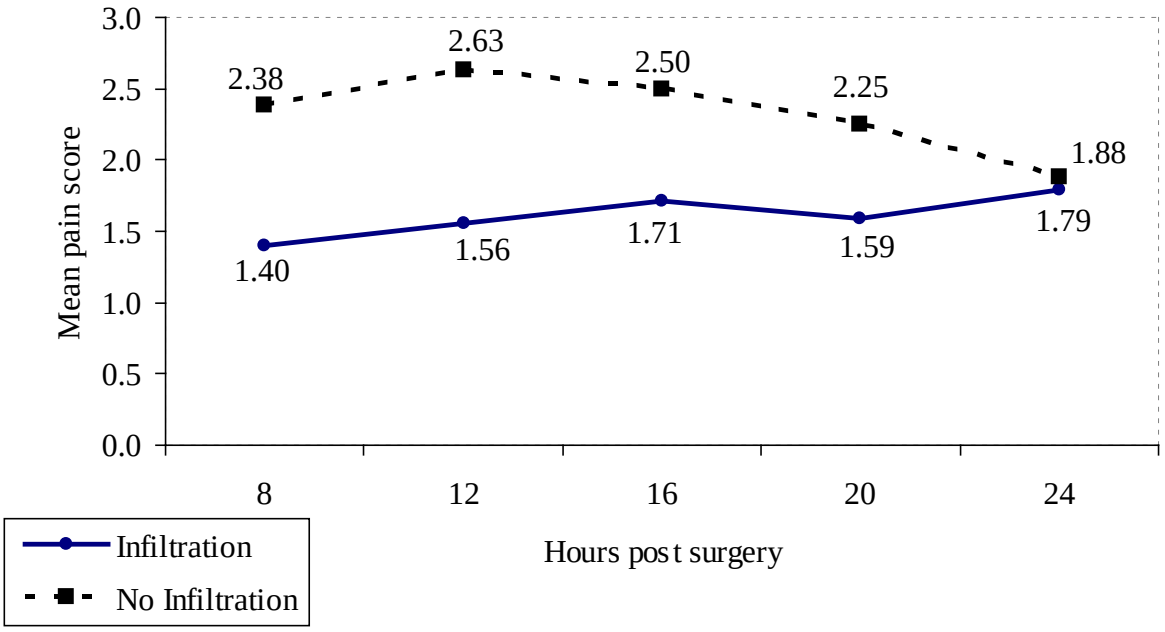

Fig 4.6: Pain score over 24 hours post-surgery