A SINGLE VERY LOW DOSE OF INTRATHECAL MORPHINE WITH FENTANYL AS A USEFUL ADJUNCT TO PATIENT CONTROLLED ANALGESIA IN PATIENTS UNDERGOING LUMBAR SPINE SURGERY : AN INTERVENTIONAL PILOT STUDY

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ABSTRACT

Background: There have been many studies addressing intrathecal morphine (ITM) use following spine surgery published attempting to identify the optimal dose of ITM as an effective adjuct to intravenous patient controlled analgesia (PCA) post lumbar surgery.

Primary aim: To determine whether administration of low dose morphine (0.1mg) plus fentanyl (25mcg) intrathecally (ITMF) is a useful adjunct to PCA for providing postoperative pain control following elective lumbar spine surgery in adult population.

Methods: A total of 18 patients were recruited for this trial. These patients were scheduled to undergo lumbar spine surgery under general anaesthesia. They were divided into Group I; receiving intrathecal morphine fentanyl prior to induction of general anaesthesia and group C; receiving intraoperative iv morphine at 0.1mg/kg (or at discretion of anaesthetist) upon skin closure. The patients were evaluated post operatively at 2,4, 6, 8, 12, 24 hours.

Results: The intervention group reported much lower mean VAS scores at rest and bending leg and the scores were largely maintained throughout postoperative periods. The mean scores for side effects such as motor block, nausea/ vomit, pruritis, and sedation were similar for both intervention and control groups. Total PCA morphine use was significantly lower in the ITMF group.

Conclusions: ITMF may be a useful adjunct to PCA morphine in post lumbar surgery with minimal opioid related complications.

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LIST OF ABBREVIATION

ITMF	intrathecal morphine with fentanyl
PCA	patient controlled analgesia
ASA	American Society of Anesthesiologist
Hr	hour
Min	minute
SS	sum square
Df	degree of freedom
P	p value
F	f-stat

1. BACKGROUND

Management of post operative pain has been an important concern not only for humanitarian reasons but also to alleviate nociception-induced responses, such as the endocrine metabolic response to surgery, autonomic reflexes with adverse effects on organ dysfunction and other undesirable consequences (12). Despite improvements and advancements in perioperative care, major surgeries are still followed by undesired sequelae such as pain, major organ dysfunction and prolonged immobility. It is common consensus that optimal pain relief is a criteria for early postoperative recovery (12).

A reduction in surgical stress responses is hypothesized to lead to reduction in post operative organ dysfunction and thus improve outcome. A major release mechanism of endocrine metabolic responses leading to various organ dysfunction is the afferent neural stimuli and activation of autonomic nervous system and other reflexes by pain. Pain relief may thus be an important technique in modifying surgical stress responses.

Patients undergoing lumbar spine surgery experience severe pain during the post operative period. Adequate post operative pain management has been seen to correlate well with improved functional outcome, early ambulation, early discharge, and the incidence of chronic back pain decreased (1).

Increased demand for spine surgery, and emphasis on patient-centred care and reduced length of stay in hospital, has lead to a search of better methods for post operative pain management. However, intense pain frequently accompanies spine surgery, delays discharge and prolongs recovery. Adequate post-operative pain management is also a directly modifiable risk of preventing chronic back pain post surgery.

2. LITERATURE REVIEW

There has been much improvement and advancement in perioperative care, however major surgeries are still followed by undesired consequences such as pain, major organ dysfunction and prolonged immobility. It is common consensus that optimal pain relief is a criteria for early postoperative recovery (12). At present, several techniques are available to treat post lower back surgery pain effectively. Sources of information include the Cochrane database and Google Scholar. Many studies have been done on the techniques used for post operative analgesia in lower back surgery. However for purposes of the research the review will focus only on the techniques commonly used for post operative analgesia in lower back surgery : PCA, NSAIDs, Paracetamol, epidural analgesia, intrathecal opioids.

Patient Controlled Analgesia (PCA)

PCA is a widely used modality for many surgeries post operatively. It has clear benefits as patient satisfaction is improved and nursing time is decreased. It has thus established superiority in terms of quality of analgesia and ease of use compared to intermittent opioid dosing. There have been studies demonstrating post operative morbidity (pulmonary, cardiac, thromboembolic events and hospital stay) is not improved with PCA compared with intermittent opioid therapy (3,4). PCA opioids are now used as post operative pain for lower back surgery, intravenous PCA provides better analgesia compared with opioids given intramuscularly. However, this method is expensive and subject to mechanical failure and human error. Patients using PCA opioids may also experience side-effects such as respiratory depression, nausea/vomiting, pruritis, urinary retention,drowsiness, especially when treating severe pain.

Non – Steroidal Anti-inflammatory Agents (NSAIDs)

NSAIDs have been widely used peri operatively for pain control. These drugs act by blocking COX enzyme and subsequent prostaglandin production and inflammatory pathways. It is well established that NSAIDs useful in reducing pain, inflammation, fever and improve post operative ambulation following spine surgeries. It also produces an opioid sparring effect of 20-30% (16). This is of clinically significant as the use of NSAIDs may then reduce the incidence of side-effects related to opioid use. However the use of NSAIDs have little effect on surgical stress responses and organ dysfunction (12). Exclusive use of NSAIDs for providing post operative pain relief is questionable. Evidence currently supports the concomitant use of NSAIDs along with opioids provides better analgesia as compared to either if the two classes of drugs used alone (14). Platelet dysfunction, risk of hemorrhage, gastric ulceration, and renal toxicity are known side effects of NSAID. Impaired bone healing occurs at high dose NSAID use has been reported (20). Additionally, all NSAIDs can increase risk of sodium and water absorption increasing the risk of exacerbating hypertension and heart failure

Paracetamol

acetaminophen

Intravenous paracetamol and its prodrug acitamenophen are a effective, safe and cheaper modality to treat post operative pain. It is helpful in providing pain relief in the immediate post operative period. Onset of action is between 5-10 minutes of intravenous administration. Exact mechanisms of action are still being studied but speculated mechanisms of action include involvement of central and peripheral sites of action (18), inhibition of prostaglandins, and inhibition of descending serotonergic pathways (24). Paracetamol as a sole analgesic agent may not be useful in alleviating post surgical pain, however is shown to decrease opioid use substantially when used in combination with opioids (7). There are some critiques to whether paracetamol has

questions are

opioid sparring effects. Hiller et al demonstrated the use of acetaminophen as an adjuvant provided enhanced pain relief, but it did not reduce the overall opioid consumption. (8).

Epidural Techniques

Epidural local anaesthetic techniques may lead to a substantial reduction in surgical stress response (12). They are also the most effective method at providing extended pain relief after major procedures, decreased incidences of respiratory and thromboembolic events. Thus substantial reduction in post operative morbidity may be expected (13). Local Anaesthetics, opioids, and steroids are the usual drugs used epidurally. Epidural analgesia has been shown to reduce pain scores and opioid consumption. Epidural administration of drugs can be via various techniques such as single and double catheters, intermittent boluses, PCA devices, or continuous infusions. Epidural catheters can be placed preoperatively by the anesthetist or intraoperatively by surgeons under direct vision. Local anaesthetics being used carries the risk of motor block and sympathectomy induced hypotension. Opioids can be administered exclusively or in combination with local anaesthetics. Epidural use of fentanyl boluses post lumbar decompression had been found to reduce VAS scores. Epidural administration of steroids is promising option as steroids reduce immediate and late pain due to peridural fibrosis. Joshi et al demonstrated using epidural opioids that neuraxial methods can provide better analgesia than systemic opioids if given in correct amount (11). The use of epidural analgesia however is not without potential complications. Technical complications like insertion difficulties and reinsertion rate and failure to achieve satisfactory block range between 2-5% (26). Incidence of catheter damage was 1 in 2200 (6). The risk of dural puncture is between 0-2.6% in obstetric anaesthesia where there is common use of epidural catheter analgesia, inversely linked to experience of the anaesthetist. Neurological complications are rare, Holdcroft et al identified 1 in 13000

patients with persistent traumatic mononeuropathy to be contributed by epidural technique in patients with post partum neurological dysfunction (9). Even in the obstetric population where epidural use of analgesia and anaesthesia are most frequent, incidence of epidural hematoma, abscess or paraplegia are exceptionally rare events (21). In patients on anticoagulant therapy and those receiving anti-platelet drugs we have to consider the risk of epidural hematoma formation

Intrathecal Opioids

Although there is less experience with neuraxial analgesia for spine surgery as compared to other surgical procedures, there is a growing literature demonstrating efficacy.

Intrathecal Morphine

Intrathecal morphine (ITM) use was first demonstrated by Wang in 1979 in patients with genitourinary malignancies. Since then, intrathecal opioids has become widely accepted as a technique for providing effective post operative pain relief. ITM use for spine surgery was reported by O' Neill in 1985 finding that that it was safe and effective (15). Urban et al found that a dose of 20 mcg.kg morphine (0.14mg for a 70kg adult) reduced the need for supplemental analgesia after lumbar fusion surgery for the first 12 hours (25). The occurance of side-effects like nausea and vomiting, urinary retention, pruritis, and respiratory depression are the limiting factors in ITM use. The potentially life-threatening complications was shown to be dose related (19). However, Boezaart and colleagues recommend using 0.002-0.004mg.kg (0.15-0.3mg for a 70kg adult) for lumbar surgery injected under direct vision at end of surgery. They concluded that such patients had effective analgesia with minimal side-effects and could be managed in the surgical ward (2).

Intrathecal Fentanyl

Fentanyl is a lipophilic opioid and when administered in single doses of 10-30mcg, has rapid onset (10-20mins) and short duration (4-6 hrs). It has minimal cephaled spread and is least likely among the intrathecal opioids to cause delayed respiratory depression. Chan and colleagues demonstrated that intrathecal fentanyl 15mcg bolus administered just before wound closure after lumbar surgery provided adequate pain control without adverse side effects (5).

In conclusion, a multimodal approach is recommended for management of post operative pain control. There is an increasing amount of literature demonstrating the effectiveness of intrathecal opioids as a means of early post lumbar surgery analgesia. To our knowledge, the use of low dose intrathecal morphine plus fentanyl as an adjunct to post operative analgesia in lumbar spine surgery has not yet been reported.

3. RATIONALE FOR STUDY

To our knowledge, the use of low dose intrathecal morphine combined with fentanyl as an adjunct to post operative analgesia in lumbar spine surgery has not yet been reported.

Current understanding of postoperative analgesia incorporates the use of regional aneasthetic techniques to minimize the potential side effects of systemic opioid administration such as pruritis, nausea and vomiting, urinary incontinence and respiratory depression. In spine surgery, an important limitation of spinal analgesia using local anaesthetics is the alteration of neurological function interfering with diagnosis and management of potential perioperative complications. Thus, only opioid analgesics are applicable for use in this circumstance (28).

ITM is established in the management of post operative pain in many surgical specialties. Its effectiveness in spine surgery has been well documented (15). Boezaart and colleagues demonstrated using 0.002-0.004mg.kg (0.15-0.3mg for a 70kg adult) for lumbar surgery that patients had effective analgesia with minimal side-effects and could be managed in the surgical ward (2). Chan and colleagues demonstrated that intrathecal fentanyl 15mcg bolus administered just before wound closure after lumbar surgery provided adequate pain control without adverse side effects (5). However, fentanyl is a lipophilic opioid and it has rapid onset of action and it short duration of action.

The use of fentanyl added to intrathecal morphine solution as part of neuraxial anaesthesia for various surgical procedures is well established. Silva-Moreno and colleagues have established that morphine and fentanyl when administered together have a synergistic effect for nociception (23).

We propose that the use of very low dose intrathecal morphine (0.1mg) plus fentanyl (25mcg) administered intrathecally would provide affective analgesia post operatively with nil or minimal side-effects.

4. OBJECTIVE AND OUTCOME MEASURES

Primary aim of this study is to determine whether administration of low dose morphine (0.1mg) plus fentanyl (25mcg) intrathecally is a useful adjunct to PCA for providing postoperative pain control following lumbar spine surgery in adult population.

Secondary goals are to determine whether intrathecal low dose morphine with fentanyl affected occurrences of side effects which are respiratory depression, nausea and vomiting, pruritis and urinary retention.

Outcome measures used for this study will be VAS for postoperative low back pain, time to first bolus of morphine PCA, and total dose of morphine PCA used. A 25mg decrease in mean total dose of morphine PCA between the two groups is considered to be significant. A 2 point change on VAS score is regarded as significant pain reduction.

5. SIGNIFICANCE AND PRATICAL IMPLICATIONS

Spinal procedures are generally associated with intense pain in the post operative period. Conventional spinal surgeries (non minimally invasive), often involve extensive dissection of subcutaneous tissues, bones, and ligaments resulting in a considerable degree of post operative pain. Adequate pain management in this period has been seen to correlate well with improved functional outcome, early ambulation, prevention of the development of chronic pain. We propose that the use of low dose intrathecal morphine (0.1mg) plus fentanyl (25mcg) administered intrathecally would provide effective analgesia post operatively with nil or minimal side-effects. This will reduce the incidence of potential complications commonly associated with systemic opioid use.

6. METHODOLOGY

6.1 Study Design

This will be a prospective pilot, randomized, parallel group, interventional controlled trial. This study design is referenced from the CONSORT guidelines. This study has been approved by the Medical Ethics Committee UMMC. It is a longitudinal, parallel study to assess the efficacy and safety of very low dose intrathecal morphine with fentanyl in the relief of postoperative pain in patients undergoing lumbar spinal surgery. Subjects fulfilling the inclusion and exclusion criteria will be recruited and randomized to two groups to receive either morphine 0.1mg with fentanyl 25 mcg prior to induction of anaesthesia or intravenous morphine 0.1mg/kg upon skin closure.

6.2 Study population

The study participants meeting the eligibility criteria will be offered enrollment in the study. Recruitment will be done during the preoperative assessment by the anesthetist running the orthopedic spine surgery list in UMMC. Recruitment period will be until fulfillment of sample size.

6.3 Eligibility criteria

Subjects must meet all inclusion criteria listed below to participate in the study

- Patients scheduled for lumbar spinal surgery with or without instrumentation
- Able to provide written informed consent for themselves
- Adult from age 18 years old and above
- ASA status I,II, or III

Individuals are excluded from participation in the study if they meet any of the following exclusion criteria:

- allergy to opioids or NSAIDs
- inability to complete the Visual Analogue Score (VAS) scale
- infection either systemically or locally at site of surgery
- current or past history of malignancy
- coagulopathy
- pregnant
- paresis of lower extremeties
- breastfeeding

6.4 Schedule of assessment and procedure

Schedule of assessment and procedure will be carried out from recruitment during pre op assessment until 24 hours post operatively. Details of activities involved are as follows:

(a) Screening

Pre-operative assessments by anesthetist will be done 24 to 48 hours prior to surgery. During this time eligible subjects will be given the informed consent form and explained regarding the study. Subject will have to sign the informed consent form prior to any study related procedure. Upon consent provided, subjects' medical history will be collected.

(b) Randomization and blinding

Patients who meet all study enrollment criteria will be randomized to the study. Prior to the start of the study, an electronic random number generator will be used to assign the required sample size number of patients equally to either the control (C) or intervention (T) group.

An independent member of staff (not involved in the surgery or the study) will place the assignments in opaque envelopes. The list will be kept by the independent member of staff until the last patient has been recruited. The envelopes be sealed and kept in the box.

When a patient has given consent and enrolled in the study, an envelope will be randomly drawn from the box and provided to the anesthetist. The envelope will only be opened before the induction of general anesthesia.

(c) Intervention

In the operating room, 2 peripheral intravenous lines will be established, and standard monitoring (continuous electrocardiography, pulse oximetry, and temperature, non-invasive blood pressure) will be applied.

Before induction of general anaesthesia, the patient's assigned enveloped will be opened by the anaesthetist. If they have been assigned to receive intrathecal morphine with fentanyl (ITMF), a 25 gauge pencan will be used to administer the ITMF.

After careful preoxygenation, patients will be given a standard general anaesthetic. This consists of induction with intravenous fentanyl and propofol. Maintenance of anaesthesia will be with continuous infusion of propofol and remifentanil according to clinical needs.

For the control group intraoperative morphine at 0.1mg/kg upon skin closure and further opioid requirement will be administered at the discretion of the anaesthetist. Surgery will be performed via the posterior approach with the patient in prone position. Intraooperative anti-emetic of intravenous dexamethasone and ondansetron was administered to all patients.

(d) Post-operative assessments

After surgery, every patient will receive an intravenous PCA pump containing morphine sulfate in the Recovery Bay programmed to administer 1mg bolus with a 5 minute lockout period. After a 2 hour period, patients will be assessed to ensure they can return to the general orthopedic ward.

Post operative back pain at 2, 4, 12 and 24 hours will be recorded using VAS. Total dose of morphine PCA will also be recorded. Any other side effects such as nausea/vomiting, or pruritus is recorded. In the orthopedic ward, respiratory rate is recorded each time vital signs are checked. The information required will be collected using a Post-Operative Assessment Form.

All patients were given regular supplemental analgesia of oral celecoxib and paracetamol once allowed orally.

6.5 Unblinding (unmasking)

All information pertaining to randomization and blinding of intervention group will be only be unblinded after the date of last-patient-out of the study. Drug identification information will be unmasked only if necessary for the welfare of the patient.

6.6 Withdrawal/termination from study

Subjects may withdraw from at any time or be terminated from the study at the discretion of the investigator if any untoward effects occur.

6.7 Patients' confidentiality

Upon signing the consent form to participate in this research, participants will be identified and referred to by a code to ensure anonymity throughout the research project and in any potential publication. Only the researchers involved in this study have access to the information recorded. Direct personal information (such as name, telephone number and address) will be kept confidential.

The researcher does not bear the responsibility for any information which a participant discloses during his or her doctor's visit. However, the information recorded on the Patient Assessment Form and Post-Operative Assessment Form will be the property of the researchers. Only if required by law or the ethics review board, authorized representatives will be permitted to review any information collected for this study.

6.8 Sample size and statistical analysis

The sample size determination was performed with support from UMMC Faculty of Medicine Research Management Centre. Power analysis was used to determine the sample size required for this study. This is to prove the sample size adequacy for our study and is a very useful and frequently used tool in medical research. This power analysis was performed using web based sample size calculator (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). Considering 90% power and 5% marginal error (type one error for α value=0.05), this study gives a minimum sample size of 22 per group (based on the median and IQR values obtained from references).

However, in practice, for a longitudinal study we may need to enrol more subjects to account for potential dropouts, using the following formula (Tushar, 2010) $n_I = n / (1-d)$, n= 137.63, d= 20%. The formula gives the sample size as 27.5 patients per group. We will use 28 patients per group for our study.

Data will be analyzed in line with objectives using the SPSS Statistics, a statistic analysing software. Descriptive statistics will be used to find the proportion/percentage for categorial variables. For continuous variables the mean/median (IQR) will be used. Independent sample t-test will be used to compare between 2 groups. If needed, analysis of variance (ANOVA) will be performed.

7. RESULTS

This study presented results based on a sample of 18 patients underwent lumbar spinal surgery. The sample excluded 3 patients who refused to participate or failed to meet eligibility criteria for the study. The full study would require a sample size of 60 patients to obtain a 95% chance of detecting a significant difference of preoperative ITMF (intrathecal morphine 0.1mg with fentanyl 25 mcg) between intervention and control groups (at two-tailed 5% significance level) in the mean score of pain VAS and side effects after surgery.

All patients were monitored for the first 24 hours postoperatively. In the Recovery Bay, each of them received an intravenous PCA pump containing morphine sulfate programmed to administer 1mg bolus with a 5-minute lockout period. In the general orthopedic ward, respiratory rate was also recorded each time vital signs were checked. The postoperative outcome measures that were evaluated and recorded were as follows. Back pain score at rest and bending leg, graded by patient subjectively on a 10-point scale from 1 (no pain) to 10 (worst possible pain). Total amount of PCA morphine used, measured in milligrams. Respiratory rate, measured in breathes per minute. Other known side effects of opioids after surgery such as motor block, nausea/ vomit, pruritis, sedation, and urine retention were measured on a 4-point scale from 1 (none) to 4 (severe).

7.1 Sample Demographic Data

The intervention group included 12 patients who received pre-operative ITMF while the control group included 6 patients who did not receive ITMF prior to induction of general anaesthesia. Table 1 summarized the demographic characteristics of patients recruited for this study.

Table 1: Sample Demographic

	Group 1: Intervention n = 12	Group 2: Control n = 6	p-value
Gender (Male/Female)	2/10	1/5	1.00 n.s.
Weight (kg)	65.5 ± 11.2	58.3 ± 9.0	0.19 n.s.
Height (cm)	161.3 ± 5.3	156.0 ± 4.7	0.06 n.s.
Age (year)	56.9 ± 18.8	74.5 ± 7.45	0.03 **
No. of Decompressed	1.08 ± 0.7	1.3 ± 0.5	0.44 n.s.
No. of Instrumented	4.17 ± 4.3	1.7 ± 2.3	0.21 n.s.
Pre-Op VAS Score (1-10):			
At Rest	2.9 ± 2.1	2.0 ± 0.6	0.32 n.s.
At Bending Leg	5.3 ± 2.3	5.7 ± 2.2	0.77 n.s.
Intra op IV Morphine (mg)	0 ± 0	6.2 ± 1.5	0.00 ***

Values are mean ± standard deviation (except gender).

Level of significance: n.s. p not significant, ** $p<0.05$, *** $p<0.01$

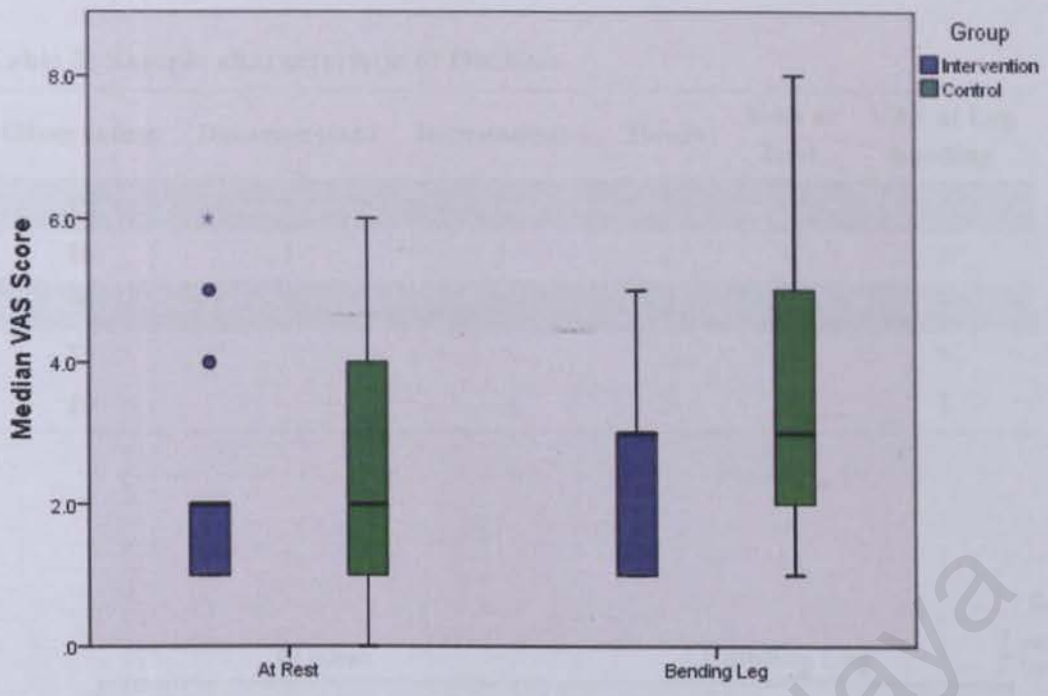
To compare mean difference between intervention and control groups, statistical analysis was performed using two-tailed independent-samples t-tests at 5% significance level for continuous variables (weight, height, age, decompressed, instrumented, pre-op VAS score at rest and bending leg, and post-op IV PCA morphine use). Group difference for nominal variable (gender) was tested using crosstabs statistics based on Phi and Cramer's V, chi-square based measures of association at 5% significant level. There was no statistically significant difference between the two groups with respect to gender, weight, height, number of decompressed and instrumented segments, and preoperative VAS scores (at rest and bending leg). However, the group differed in terms of age (significant at $p<0.05$) and intraoperative IV morphine required (significant at $p<0.01$). The full study would expect age difference to diminish as the sample size increases. The difference in postoperative total amount of IV morphine given intraoperatively was due to the methodological design of this study.

7.2 Pain VAS Scores

Early postoperative pain management was a key focus of the study. To compare between-group difference on pain VAS scores at rest and bending leg, the study employed several statistical methods as follows. *Boxplot* and *line with error bar plot* were presented to identify any outliers and visualize the distribution of VAS scores together with 95% confidence interval. Boxplot reported median VAS scores which were originally measured on a 10-point scale whereas line with error bar plot reported mean VAS scores which were converted during chart construction.

Student t test and *median test of two independent samples* were performed to examine whether the mean or median VAS scores were the same between intervention and control groups at each postoperative observation period (overall, 2, 4, 8, 12, and 24 hours, respectively). Student *t* test would be appropriate as each patient was randomly assigned to either intervention or control group and neither investigator nor patient knew which group each was assigned to. Median test would be meaningful in the event that the data was affected by outliers.

One-way ANOVA with repeated measures was performed to monitor within-patient change over time (from 2 to 24 hours) in the mean VAS score at rest and bending leg. But more importantly, *multivariate and univariate analysis of variance (MANOVA and ANOVA)* were performed to find out any between-group difference in the mean VAS scores at rest and bending leg, with least significant difference (LSD) post hoc test for multiple pairwise comparisons. MANOVA would be a more robust test than ANOVA in that the study could test mean differences of VAS score at rest and bending leg simultaneously between the two groups, whereas ANOVA tested each VAS score (at rest or bending leg) individually taking into account only the interdependence between intervention and control groups.



VAS Score is measured on a 10-point scale. Boxplot data are presented as median, first- and third-quartiles, minimum and maximum.

Figure 1: VAS score at Rest and Bending Leg over the observation period of 24 hours

Boxplot in Figure 1 showed that most patients reported VAS score of 2 at rest and 3 at bending leg. However, the intervention group had significantly smaller range of median VAS score at rest and bending leg compared to the control group. In fact, all patients in the intervention group reported a median VAS score of 2 or below at rest and 3 or below at bending leg. In contrast, about half of patients in the control group reported higher VAS score above the median. While the VAS score distribution of intervention group was skewed to the lower end, the VAS score distribution of control group was skewed to the upper end with upper quartile and top whisker being much longer than the bottom ones. The boxplot also identified some outliers in the VAS score at rest of intervention group. A closer examination on the data revealed that these outliers emerged from three patients namely observation I1, I6 and I9. The following Table 2 summarized some of their sample characteristics.

Table 2: Sample characteristic of Outliers

Observation	Decompressed	Instrumented	Hours	VAS at Rest	VAS at Leg bending
I1	1	6	2	4	5
I6	1	5	2	4	5
I9	0	15	2	4	5
I9			12	4	5
I9			24	4	5

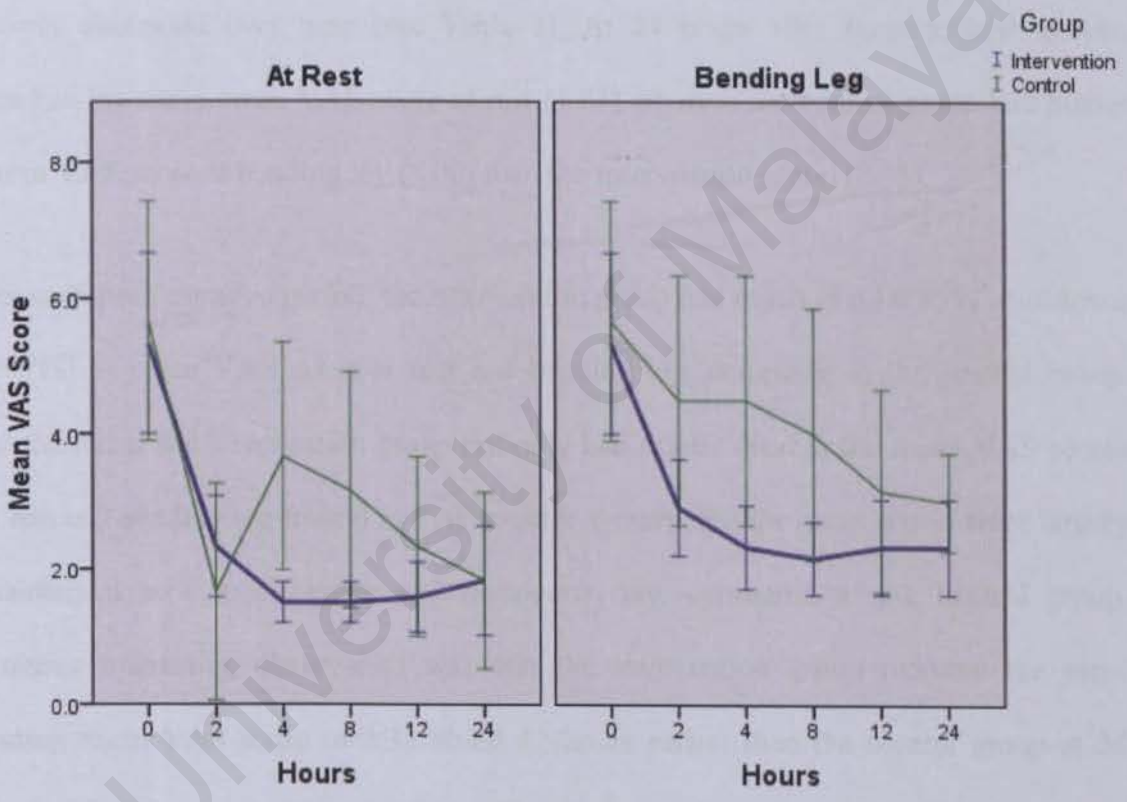


Figure 2: Pre- and Postoperative Mean VAS Scores with 95% Confidence Interval over the observation period of 24 Hours

Line with error bar plots in Figure 2 showed that mean VAS scores were similar before the start of surgery (at 0 hour). However, postoperative mean VAS scores were significantly different for both groups. At 2 hours after surgery, the control group had a lower mean VAS score at rest (1.67) but wider 95% confidence interval than the

intervention group (2.33). But for VAS at bending leg, the intervention group had a lower mean score (2.92) and smaller 95% confidence interval than the control group (4.50). At each 4, 8, 12 hours after surgery, both groups had significant contrast on mean VAS scores at rest and bending leg. The intervention group reported much lower mean VAS scores at rest and bending leg and the scores were largely maintained throughout postoperative periods. (see Table 3). Meanwhile for the control group, mean VAS scores at rest spiked from 1.67 at 2 hours to 3.67 at 4 hours while mean VAS scores at bending leg were maintained at 4.50 from 2 to 4 hours, before both scores slowly decreased over time (see Table 3). At 24 hours after surgery, both groups reached the same mean VAS score at rest (1.83) whereas the control group had higher mean VAS score at bending leg (3.00) than the intervention group (2.33).

For each postoperative period, the intervention group had much smaller 95% confidence interval of mean VAS score at rest and bending leg, compared to the control group. Furthermore, the intervention group not only had drastic drop in the mean VAS scores at rest and bending leg from 0 to 2 hours after surgery, but the mean scores were largely maintained at a much lower end postoperatively, compared to the control group. Another interesting observation was that the intervention group reported the same ending mean VAS score of 2.33 about 12 hours earlier than the control group at 24 hours after surgery. This implies effectiveness of preoperative ITMF on early postoperative pain management among the intervention group. Table 3 detailed the mean VAS scores over time. Overall, between-group mean VAS scores were significant at bending leg ($p = 0.04 < 0.05$) at 5% significance level. P-value for between-group mean VAS score differences at each postoperative hours were also presented in the table.

Table 3: Mean VAS Scores over the observation period of 24 Hours

Observation Period	Group 1: Intervention n = 12	Group 2: Control n = 6	T-Test p-value	Median Test p-value
At Rest: Overall	**1.75 ± 0.81**	**2.53 ± 1.47**	**# 0.16 n.s.**	**0.62 n.s.**
2 Hours	2.33 ± 1.30	1.67 ± 1.97	0.21 n.s.	1.00 n.s.
4 Hours	1.50 ± 0.52	3.67 ± 2.07	**0.00** ***	0.00 ***
8 Hours	1.50 ± 0.52	3.17 ± 2.14	**0.00** ***	0.03 **
12 Hours	1.58 ± 0.90	2.33 ± 1.63	**0.05** **	0.62 n.s.
24 Hours	1.83 ± 1.40	1.83 ± 1.60	0.46 n.s.	0.25 n.s.
At Bending Leg: Overall	**2.42 ± 1.05**	**3.83 ± 1.83**	**# 0.04** **	**1.00 n.s.**
2 Hours	2.92 ± 1.24	4.50 ± 2.26	0.52 n.s.	0.34 n.s.
4 Hours	2.33 ± 1.07	4.50 ± 2.26	**0.02** **	0.08 *
8 Hours	2.17 ± 0.94	4.00 ± 2.28	**0.06** *	0.03 **
12 Hours	2.33 ± 1.23	3.17 ± 1.84	0.18 n.s.	1.00 n.s.
24 Hours	2.33 ± 1.23	3.00 ± 0.89	0.30 n.s.	0.25 n.s.

Values are mean ± standard deviation. Level of significance: n.s. p not significant, * p<0.10, ** p<0.05, *** p<0.01

p-value on the overall between-group mean difference was obtained based on F-test from univariate ANOVA with repeated measures, taking into account the five temporal measures at 2, 4, 8, 12, 24 hours after surgery.

The study recognized the interdependency of VAS score at rest and VAS score at bending leg. As such, MANOVA was performed to further examine the between-group mean difference of VAS score at rest and bending leg simultaneously. Multivariate MANOVA results indicated no significant multivariate effect of group on mean VAS score at rest and bending leg (Wilk's Λ=.783, F=2.08, p<.160, partial η^2=.271) at 5% significance level. The results were tested at an adjusted significance level of 0.025 to protect the results against Type I error. The insignificant results may be preliminary as we did not remove outliers from statistical analysis and secondly due to the small sample size.

The assumption of variance homogeneity was not violated in MANOVA based on Box's M test of equality of covariance matrices of the mean VAS scores at rest and bending leg (Box's M=4.30, p=0.31 > 0.05). The Levene's test of equality in ANOVA also showed equality of error variances of mean VAS score at rest (F=5.10, p=0.038 > 0.01) and mean VAS score at bending leg (F=4.01, p=0.06 > 0.05). Hence, both the MANOVA and ANOVA results were statistically valid.

Subsequently, univariate ANOVA results in Table 4 showed that when tested individually, the between-group effect was statistically significant in the mean VAS score at bending leg (F=4.44, p=0.05, partial η^2=.22) but not significant in the mean VAS score at rest (F=2.16, p=0.16, partial η^2=.12. The ANOVA result was consistent with the results obtained in Table 3.

Table 4: Univariate ANOVA Tests of Between-Group Effect on Mean VAS Scores

	Between-Group Effect				
	SS	df	F	p	η^2
Mean VAS at Rest	2.45	1	2.16	0.16 $^{n.s.}$	0.81
Mean VAS at Bending Leg	8.03	1	4.44	**0.05** **	0.85

Level of significance: $^{n.s.}$ p not significant, ** p<0.05

Post-hoc test using least significant difference (LSD) for multiple pairwise comparisons were performed to further examine the between-group difference on mean VAS scores at rest and bending leg. Post-hoc results in Table 5 were similar with univariate ANOVA results as the mean differences were calculated based on two groups only, either intervention or control group. The mean difference and 95% confidence interval for mean difference were larger among patients at bending leg than patients at rest.

Table 5: Post Hoc Multiple Comparison Test for Mean VAS Scores

	Mean difference between group	SE	p	Lower bound	Upper bound
Mean VAS at Rest	0.78	0.53	0.16 n.s.	0	1.91
Mean VAS at Bending Leg	1.42	0.67	**0.05** **	0	2.84

Level of significance: n.s. p not significant, ** $p<0.05$
Mean difference based on estimated marginal means.
Adjustment for multiple comparisons: Least Square Difference (LSD).

7.3 Side Effect and Total PCA Morphine Use

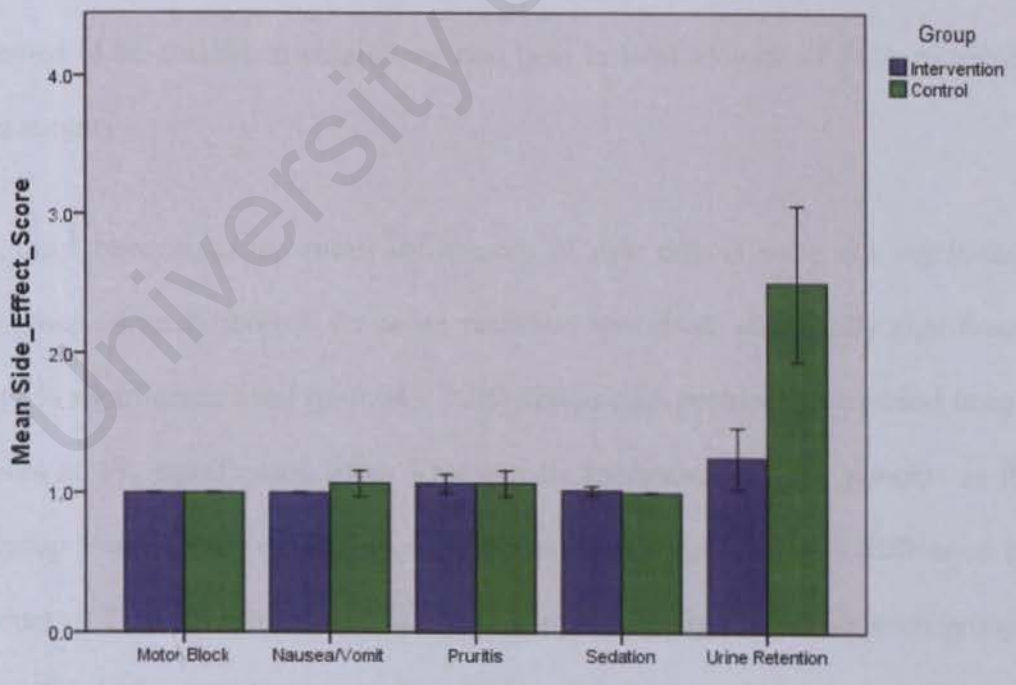
The study further examined the impact of preoperative ITMF on side effects after surgery and also total amount of intravenous morphine used with PCA. They were motor block, nausea/ vomit, pruritis intensity, sedation, urine retention, respiratory depression, and total amount of PCA morphine used after surgery. To compare mean score differences of these side effects between intervention and control groups, results were presented based on descriptive plots and statistical analysis using Student *t* test, median test, univariate and multivariate ANOVA.

Bar plot and *line with error bar plot* were presented to visualize the average mean scores for each type of side effects together with the 95% confidence interval. Bar plots depicted mean scores for motor block, nausea/ vomit, pruritis, sedation, and urine retention. Postoperative respiratory rate and total amount of PCA morphine used were shown in line with error bar plots.

Student t test and *median test of two independent samples* were performed to examine whether the mean or median scores of side effects were the same between intervention and control groups at each postoperative observation period (overall, 2, 4, 8, 12, and 24 hours, respectively). Student *t* test would be appropriate as each patient was randomly assigned to either intervention or control group and neither investigator nor patient

knew which group each was assigned to. Median test would be meaningful in the event that the data was affected by outliers.

One-way ANOVA with repeated measures was performed to monitor within-patient change over time (from 2 to 24 hours) in the mean score of pain VAS and side effects. But more importantly, *multivariate and univariate analysis of variance (MANOVA and ANOVA)* were performed to find out any between-group mean VAS scores difference with least significant difference (LSD) post hoc test for multiple pairwise comparisons. MANOVA would be a more robust test than ANOVA in that the study could test mean differences of VAS score at rest and bending leg simultaneously between the two groups, whereas ANOVA tested each VAS score (at rest or bending leg) individually taking into account only the interdependence between intervention and control groups.



Side effect score is measured on a 4-point Likert scale. Bars (and error bars) represent mean ± 2 SE.

Figure 3: Mean Side Effect Scores

Bar plot in Figure 3 showed that the mean scores for side effects such as motor block, nausea/ vomit, pruritis, and sedation were similar for both intervention and control groups. However, the mean score for urine retention was much higher in the control group than in the intervention group. Across all the mean scores for side effects, the 95% confidence intervals (mean ± SE) were smaller in the intervention group than in the control group.

Line with error bar plots in figure 4 and 5 showed that mean values for respiratory rate and total amount of PCA morphine used were similar for both groups at the start and end of postoperative observation period namely 2, 12, and 24 hours. The trend patterns of these two side effects were also similar over time. Both plots showed that the intervention group not only had stable and lower mean scores for respiratory rate and total amount of PCA morphine used but also smaller 95% confidence interval, compared to the control group. Overall, the between-group difference at 4 and 8 hours was observed to be smaller in respiratory rate than in total amount of PCA morphine used after surgery.

In short, most between-group mean differences of side effects were not significant. Between-group mean difference for urine retention was most statistically significant, overall at 5% significance level ($p=0.04 < 0.05$) and in each postoperative period from 2 to 24 hours at 1% significance level. This can be explained as three patients in the control group were already on urinary catheters prior to surgery. Mean difference for total amount of PCA morphine used was also statistically significant between groups, overall at 10% significance level ($p=0.08 < 0.10$) and from 4 to 12 hours after surgery at 1% and 5% significance level. Table 6 detailed the mean scores for each type of side effects over time.

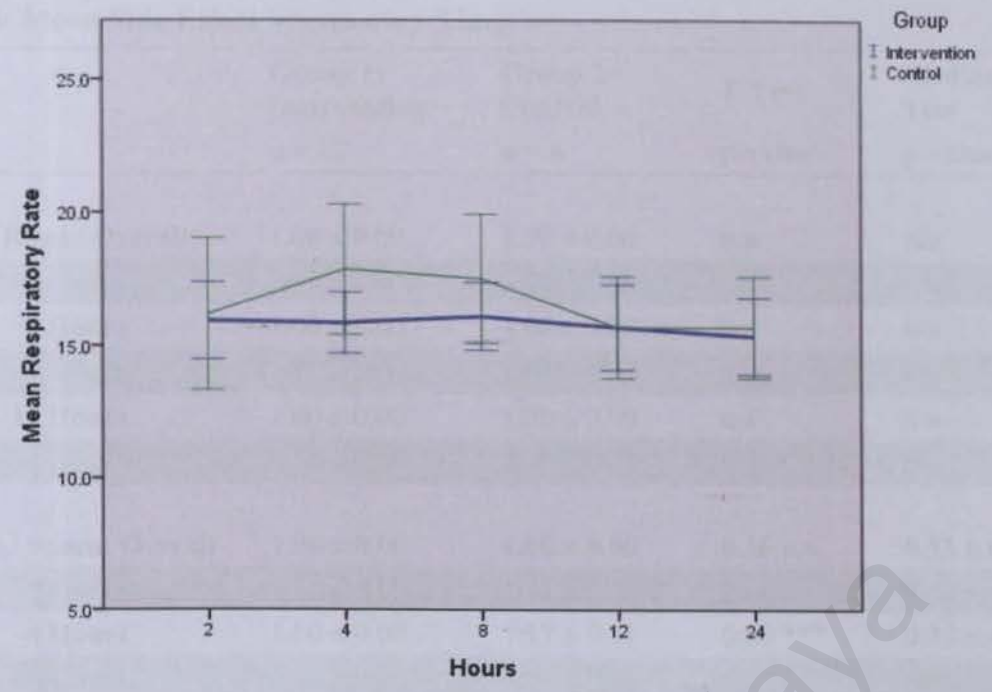


Figure 4: Mean Respiratory Rate

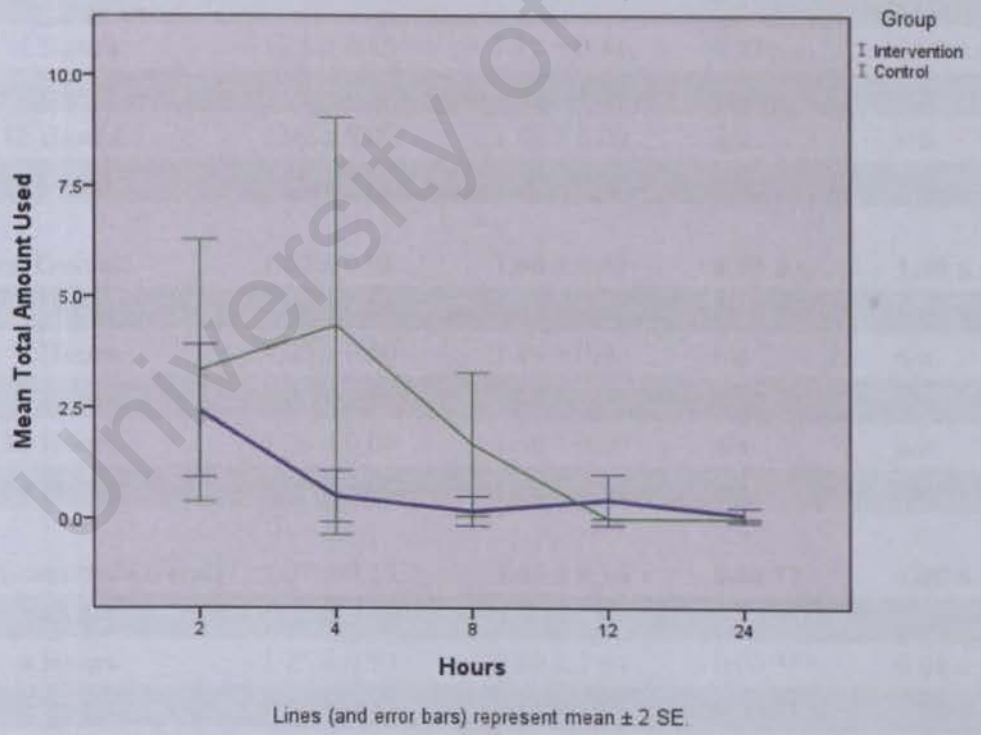


Figure 5: Mean Total Amount of PCA Morphine Used

Table 6: Mean Side Effect Scores over Time

	Group 1: Intervention n = 12	Group 2: Control n = 6	T-Test p-value	Median Test p-value
Motor Block: Overall	**1.00 ± 0.00**	**1.00 ± 0.00**	**n/a**	**n/a**
2 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
4 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
8 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
12 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
24 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
Nausea/ Vomit: Overall	**1.00 ± 0.00**	**1.00 ± 0.00**	**0.16 n.s.**	**0.33 n.s.**
2 Hours	1.00 ± 0.00	1.17 ± 0.41	0.00 ***	0.33 n.s.
4 Hours	1.00 ± 0.00	1.17 ± 0.41	0.00 ***	0.33 n.s.
8 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
12 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
24 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
Pruritis: Overall	**1.07 ± 0.13**	**1.07 ± 0.16**	**0.50 n.s.**	**1.00 n.s.**
2 Hours	1.25 ± 0.45	1.17 ± 0.41	0.43 n.s.	1.00 n.s.
4 Hours	1.25 ± 0.45	1.17 ± 0.41	0.33 n.s.	1.00 n.s.
8 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
12 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
24 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
Sedation: Overall	**1.02 ± 0.06**	**1.00 ± 0.00**	**0.50 n.s.**	**1.00 n.s.**
2 Hours	1.08 ± 0.29	1.00 ± 0.00	0.15	1.00 n.s.
4 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
8 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
12 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
24 Hours	1.00 ± 0.00	1.00 ± 0.00	n/a	n/a
Urine Retention: Overall	**1.07 ± 0.13**	**1.07 ± 0.16**	**0.04 ** **	**1.00 n.s.**
2 Hours	1.25 ± 0.87	2.50 ± 1.64	0.00 ***	0.08 n.s.
4 Hours	1.25 ± 0.87	2.50 ± 1.64	0.00 ***	0.08 n.s.
8 Hours	1.25 ± 0.87	2.50 ± 1.64	0.00 ***	0.08 n.s.
12 Hours	1.25 ± 0.87	2.50 ± 1.64	0.00 ***	0.08 n.s.
24 Hours	1.25 ± 0.87	2.50 ± 1.64	0.00 ***	0.08 n.s.
Total amount used: Overall	**0.72 ± 0.83**	**1.87 ± 1.84**	**0.08 ***	**0.63 n.s.**
2 Hours	2.42 ± 2.58	3.33 ± 3.62	0.23 n.s.	1.00 n.s.
4 Hours	0.50 ± 1.00	4.33 ± 5.75	0.00 ***	0.14 n.s.

8 Hours	0.17 ± 0.58	1.67 ± 1.97	0.00 ***	0.08 *
12 Hours	0.42 ± 0.99	0.00 ± 0.00	0.03 **	0.53 n.s.
24 Hours	0.08 ± 0.29	0.00 ± 0.00	0.15 n.s.	1.00 n.s.
Respiratory Rate: Overall	**15.77 ± 1.89**	**16.57 ± 2.28**	**0.44 n.s.**	**0.62 n.s.**
2 Hours	15.92 ± 2.50	16.17 ± 3.49	0.25	0.63 n.s.
4 Hours	15.83 ± 1.99	17.83 ± 2.99	0.33	0.14 n.s.
8 Hours	16.08 ± 2.19	17.50 ± 2.95	0.22	0.32 n.s.
12 Hours	15.67 ± 2.77	15.67 ± 2.34	0.65	1.00 n.s.
24 Hours	15.33 ± 2.50	15.67 ± 2.34	0.70	0.62 n.s.

Values are mean ± standard deviation. Level of significance: n.s. p not significant, * $p<0.10$, ** $p<0.05$, *** $p<0.01$.

p-value on the overall between-group mean difference was obtained based on F-test from univariate ANOVA with repeated measures, taking into account the five temporal measures at 2, 4, 8, 12, 24 hours after surgery.

The study recognized the interdependency of each side effects. As such, MANOVA was performed to further examine the between-group mean difference of mean scores for each type of side effects observed in the study. MANOVA results indicated no significant multivariate effect for mean side effect scores between intervention and control groups (Wilk's $\Lambda=.654$ $F=1.27$, $p<.339$, partial $\eta^2=.346$). The results were tested at an adjusted significance level of 0.025 to protect the results against Type I error. The insignificant results may be preliminary due to small sample size but desirable and unlikely to improve (as p-value is far from the significance level even at 10%). Thus, the study could safely conclude that the multivariate effect of groups on side effect was not statistically significant.

The assumption of variance homogeneity for MANOVA was not able to assessed adequately because there were fewer than two nonsingular cell covariance matrices due to small sample size in this pilot study. As for ANOVA, the Levene's test of equality showed that the assumption of error variance equality was not met for nausea/ vomit ($p=0.00 < 0.05$) and total amount of PCA morphine used after surgery ($p=0.00 < 0.05$),

thus ANOVA results for these side effects should be used with precaution. However, the error variances of the dependent variable were equal across groups for pruritis ($p=0.81 > 0.05$), sedation ($p=0.15 > 0.05$), urine retention ($p=0.81 > 0.05$), and respiratory rate ($p=0.42 > 0.05$). Hence, ANOVA results for these side effects were statistically valid.

Subsequently, univariate ANOVA results in Table 7 showed that when tested individually, the between-group effect was statistically significant only in the mean total amount of PCA morphine used after surgery ($F=0.63$, $p=0.08$, partial $\eta^2=.18$). All the other mean side effect scores were similarly between groups. The ANOVA result was consistent with the results obtained in Table 6.

Table 7: Univariate ANOVA Tests of Between-Group Effect on Mean Side Effect Scores

	Between-Group Effect				
Type of Side Effects:	**SS**	**df**	**F**	**P**	**η^2**
Motor Block	0.00	1	n/a	n/a	n/a
Nausea/ Vomit	0.02	1	2.13	0.16	0.12
Pruritis	0.00	1	0.00	1.00	0.00
Sedation	0.00	1	0.49	0.50	0.03
Urine Retention	0.00	1	0.00	1.00	0.00
Respiratory Rate	2.56	1	0.63	**0.08** *	0.18
Total Amount of PCA Morphine Used	5.29	1	3.45	0.44	0.04

Level of significance: n.s. p not significant, *** $p<0.05$

Post-hoc tests using least significant difference (LSD) for multiple pairwise comparisons were performed to further examine the between-group difference on mean VAS scores at rest and bending leg. Post-hoc results in Table 8 were similar with univariate ANOVA results as the mean differences were calculated based on two groups

only, either intervention or control group. The mean difference and 95% confidence interval for mean difference were larger in the total amount of PCA morphine used after surgery.

Table 8: Univariate MANOVA Tests of Between-Group Effect on Mean Side Effect Scores

Type of Side Effects:	Mean difference between group	SE	p	Lower bound	Upper bound
Motor Block	0.00	0.00	n/a	0	0.00
Nausea/ Vomit	0.07	0.05	0.16	0	0.16
Pruritis	0.00	0.07	1.00	0	0.15
Sedation	0.02	0.02	0.50	0	0.03
Urine Retention	0.00	0.07	1.00	0	0.15
Respiratory Rate	0.80	1.01	0.44	0	2.94
Total Amount of PCA Morphine Used	1.15	0.62	**0.08** *	0	2.46

Level of significance: n.s. p not significant, ** $p<0.05$
Mean difference based on estimated marginal means.
Adjustment for multiple comparisons: Least Square Difference (LSD).

8. DISCUSSION

A multimodal approach is recommended for management of post operative pain control. There is an increasing amount of literature demonstrating the effectiveness of intrathecal opioids as a means of early post lumbar surgery analgesia.

This study found PCA morphine use over the first 24 hours postoperatively was almost significantly lower in the ITMF group, although we used a very low dose of morphine rather than the low dose by Yen et al (27) and Boezarrt et al (2). This is due to the synergistic effect of morphine and fentanyl administered together on nociception as demonstrated by Silva-Moreno et al (23). Therefore very low dose morphine with fentanyl intrathecally is an effective early adjunct to PCA morphine in patients undergoing lumbar surgery.

Mean VAS scores were similar before the start of surgery (at 0 hour). However, postoperative mean VAS scores were almost significantly different for both groups.The intervention group not only had drastic drop in the mean VAS scores at rest and bending leg from 0 to 2 hours after surgery, but the mean scores were largely maintained at a much lower end postoperatively, compared to the control group. Another interesting observation was that the intervention group reported the same ending mean VAS score of 2.33 about 12 hours earlier than the control group at 24 hours after surgery. This implies effectiveness of preoperative ITMF on early postoperative pain management among the intervention group.

There were no differences in measurement of common opioid related complications which are respiratory depression, sedation, nausea and vomiting, and pruritis in both groups. In short, most between-group mean differences of side effects were not

significant. Between-group mean difference for urine retention was most statistically significant, overall at 5% significance level ($p=0.04 < 0.05$) and in each postoperative period from 2 to 24 hours at 1% significance level. This can be explained as three patients in the control group were already on urinary catheters prior to surgery.

9. LIMITATIONS

The number of patients in this study is small and inadequate to provide adequate power to the study. The duration of surgery was not included in the assessment. Long periods of surgery would possibly make a difference as the ITMF was administered prior to administration of general anaesthesia.

10. CONCLUSION

ITMF is an effective adjunct to PCA morphine allowing a decreased self-administered morphine use required by patients undergone lumbar surgery without increase in opioid related complications. Further studies, including larger sample sizes, are needed to show that a very low dose of intrathecal morphine with fentanyl provides superior efficacy in post lumbar surgery pain control with minimal opioid related complications.

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