

A randomised controlled trial comparing the effect of adjuvant intrathecal 2 mg midazolam to 20 micrograms fentanyl on postoperative pain for patients undergoing lower limb orthopaedic surgery under spinal anaesthesia.

Codero Francis, Mung'ayi Vitalis, Sharif Thikra

Department of Anaesthesia, Aga Khan University, East Africa

Abstract

Background: Intrathecal adjuvants are added to local anaesthetics to improve the quality of neuraxial blockade and prolong the duration of analgesia during spinal anaesthesia. Used intrathecally, fentanyl improves the quality of spinal blockade as compared to plain bupivacaine and confers a short duration of post-operative analgesia. Intrathecal midazolam as an adjuvant has been used and shown to improve the quality of spinal anaesthesia and prolong the duration of post-operative analgesia. No studies have been done comparing intrathecal fentanyl with bupivacaine and intrathecal 2 mg midazolam with bupivacaine.

Objective: To compare the effect of intrathecal 2mg midazolam to intrathecal 20 micrograms fentanyl when added to 2.6 ml of 0.5% hyperbaric bupivacaine, on post-operative pain, in patients undergoing lower limb orthopaedic surgery under spinal anaesthesia.

Methods: A total of 40 patients undergoing lower limb orthopaedic surgery under spinal anaesthesia were randomized to two groups.

Group 1: 2.6mls 0.5% hyperbaric bupivacaine with 0.4mls (20micrograms) fentanyl

Group 2: 2.6mls of 0.5% hyperbaric bupivacaine with 0.4mls (2mg) midazolam

Results: The duration of effective analgesia was longer in the midazolam group (384.05 minutes) as compared to the fentanyl group (342.6 minutes). There was no significant difference (P 0.4047). The time to onset was significantly longer in midazolam group 17.1 minutes as compared to the fentanyl group 13.2 minutes (P 0.023). The visual analogue score at rescue was significantly lower in the midazolam group (5.55) as compared to the fentanyl group 6.35 (P - 0.043).

Conclusion: On the basis of the results of this study, there was no significant difference in the duration of effective analgesia between adjuvant intrathecal 2 mg midazolam as compared to intrathecal 20 micrograms fentanyl for patients undergoing lower limb orthopaedic surgery.

Keywords: Midazolam fentanyl, lower limb, orthopaedic surgery, spinal anaesthesia

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Introduction

Acute postoperative pain is one of the most common postoperative problems, with an incidence up to 70% in certain categories of surgical patients¹. Apfelbaum et

al² conducted a national survey in the United States and concluded that, acute post-operative pain continues to be undermanaged with up to 60% of patients experiencing moderate to severe pain at hospital discharge. A recent study carried out at the Aga Khan University hospital investigated the incidence of post-operative pain after day care surgery and concluded, that 56% of patients suffer from moderate to severe pain after day care surgery³.

Acute post-operative pain is a complex physiological reaction to tissue injury which may result in unpleasant, unwanted sensory and emotional experiences⁴. It can result in delayed healing, delayed mobilization and increased

Corresponding author:

Mung'ayi Vitalis,
Department of Anaesthesia,
Aga Khan University, East Africa
Phone: +254 20 366 2157
Email: vitalis.mung'ayi@aku.edu

risk of myocardial infarction or ischemia, risk of tachycardia and dysrhythmia. Other published reports indicate that post-operative pain can lead to thromboembolic events, peripheral vasoconstriction, and metabolic acidosis^{5,6}. Controlling post-operative pain has the potential to allow for earlier hospital discharge and may improve the patient's ability to tolerate physical therapy.

In the past few years various pharmacological and non-pharmacological methods have been introduced to provide post-operative pain-relief. Systemic analgesics and conventional pain treatment modalities are effective in controlling post-operative pain for majority of patients. However, many other patients such as those with complex trauma, and extensive injuries, require more aggressive therapy to directly modulate pain transmission in the central nervous system; and a high dose of systemic analgesics may cause significant side effects such as alteration in mental processes, respiratory depression, and other cardiovascular instability.

The use of intrathecal opioids in controlling post-operative pain has developed from an understanding for the role of the spinal cord for modulating and processing nociceptive stimuli, and the discovery of opioid receptors in the spinal cord⁷. Several agents have been administered epidurally and intrathecally with and without local anaesthetic; such as opioids, benzodiazepines, neostigmine, clonidine, non-steroidal anti-inflammatory agents, vasoconstrictors. The objective of adding such agents is to provide more adequate analgesia, reduce the use of oral analgesics with unwanted side effects, and to prolong the duration of analgesia.

A vast number of researchers have demonstrated the efficacy of intrathecal administration of opioids such as fentanyl and other agents such as midazolam in controlling post-operative pain⁸⁻¹¹. Most of those studies have demonstrated benefits and side effects using different doses of fentanyl and midazolam in controlling post-operative-pain^{8,10-12}. Only one recent study by Talwar et al in 2008 has been done to compare fentanyl 20 micrograms with 1mg midazolam in which they investigated the net effect on post-operative pain and side effects²⁰.

Intrathecal opioids are associated with numerous complications including respiratory depression, urinary retention, pruritus, nausea and vomiting. The most feared

complication is respiratory depression. The mechanism is through the rostral spread immediately after injection and with fentanyl and sufentanyl occurs within 20-30 minutes after injection. Evidence from small controlled studies and large observational studies¹³ show an incidence of 0.07%-0.49% clinically significant, dose dependent, and non-drug specific respiratory depression. Pruritus is the most common complication with incidence of 30-100%^{14,15} and the management requires the administration of opioid antagonists naloxone and naltrexone^{16,17} which in larger doses may reverse the analgesic effect¹⁷. There has been much recent attention towards the use of benzodiazepine midazolam as an intrathecal drug in treatment of acute and chronic pain¹⁸.

A study conducted by Kim et al¹⁹ however compared various doses of intrathecal midazolam 1mg and 2 mg plain 0.5% hyperbaric bupivacaine, and found that time to first analgesia was significantly greater in the intrathecal group compared to plain bupivacaine and even more so for the 2 mg group.

Based on the above stated author's reviews it seems that 2 mg intrathecal midazolam has an obvious advantage over 1mg intrathecal midazolam as far as the density of the neural blockade and duration of postoperative analgesia. Shadangi et al²⁶ compared the effects of intrathecal bupivacaine with or without 2 mg midazolam and concluded that the addition of preservative-free midazolam to bupivacaine resulted in prolonged post-operative analgesia without increasing motor block.

The purpose of this study is to compare the effect of intrathecal bupivacaine with 2mg midazolam to intrathecal bupivacaine with 20 micrograms fentanyl on post-operative pain for patients undergoing lower limb orthopaedic surgery under spinal anaesthesia.

Methods

The study was performed following approval from the Department of Anaesthesia and the Research and Research Ethical Committees of the Aga Khan University. Eligible patients were recruited after having signed an informed consent, which clearly stated that it is a research study being conducted and that their information will be kept confidential and may be published. The patients were made to understand that they would receive health care as all other patients who came to theatre, and that they would not be denied care if they declined to participate

in the study. For those who did not understand English the above information on the pain scale and instructions were explained in Swahili by the principal investigator and further data collection by the research assistants were done in Swahili.

An explanation on the study procedure was given to the patient both verbally and using a written form. It was also made clear there shall be no direct benefit to the patient arising from participation in the study, but that the results could be used to change local practice in the future. There were no added expenses to the patient.

The patients voluntarily signed the consent form and were recruited in the pre-anaesthesia review before coming to the operating theatres.

This was a prospective single blinded randomized controlled trial. The study was conducted at Aga Khan University hospital, Nairobi; a tertiary not for profit hospital with a bed capacity of 250 beds and postgraduate medical education programs in various disciplines. Since Nairobi is a cosmopolitan city, the patients served by this hospital cut across most racial groups present within the country. Patients were recruited from the outpatient pre-anaesthesia clinics and as well inpatients from the wards.

The target population included all patients admitted for lower limb orthopaedic surgery at the Aga Khan University Hospital, Nairobi. The sample population included all ASA I, II and III patients scheduled for theatre for lower limb orthopaedic surgery between October 2012 and January 2013.

Sample size calculation was based on the expected difference in mean duration of analgesia between intrathecal midazolam and fentanyl effect. Sample size formula for comparing two means was used to determine the required sample size.

The reported mean duration of block for fentanyl is 296 (sd=73.64)²⁰ and for midazolam 2mg is 399 (sd=60)²¹. Using this information in the formula assuming 5% significance level and power of 90%, the required sample size was 20 patients in each group (total of 40 patients). A sample size of 40 patients was determined as sufficient to demonstrate a 103 minute mean difference in the duration of effective analgesia between patients undergoing spinal anaesthesia with adjuvant 2mg midazolam and those with adjuvant fentanyl at the Aga Khan University

hospital. The study was powered at 90%. Type 1 error was set at 0.05. The above formula was used since the aim of the study was to determine the mean difference in the duration of effective analgesia between the two intrathecal adjuvant medications.

Simple randomization was done using a computer program; the principal investigator generated a random sequence of numbers. Each of the random numbers was sequentially assigned to either;

Group 1; 2.6mls 0.5% hyperbaric bupivacaine with 0.4mls (20micrograms) fentanyl

Group 2; 2.6mls of 0.5% hyperbaric bupivacaine with 0.4mls (2mg) midazolam

At the pre-operative visit, an anaesthesiologist and /or trained research nurse familiarized the patients with the procedure of recording the post-operative pain scores using a Visual analogue scale (VAS) -chart, which consists of a 10cm line with 0 equalling "no pain" and 10 equaling "worst pain possible".

A flow diagram of patient distribution is shown in figure 1.

This study was undertaken at the Aga Khan University hospital, Nairobi operating theatres, ASA physical status I-III patients scheduled for lower limb orthopaedic surgery and were randomized to either receive 2.6mls of 0.5% hyperbaric bupivacaine with 0.4mls (20mcg) fentanyl or 2.6mls of 0.5% hyperbaric bupivacaine with 0.4mls (2mg) midazolam intrathecally at L3-S1 interspace. The anaesthesiologist conducting the procedure (principal investigator or research assistant) received together with the data entry form the randomization group and administered the study drugs as per randomization group.

On arrival to the operating theatres, standard monitoring was applied with automated non-invasive blood pressure measurement, electrocardiography and pulse oximetry, with the objective of obtaining the baseline cardiovascular parameters. Prior to performing the spinal anaesthesia the patient would receive 500mls of Ringers lactate solution intravenously

After a local infiltration of 2ml 2% lidocaine solution, a midline puncture with a 25 French gauge pencil point needle was performed at L3-L4, L4-L5 interspace, with the patient in the sitting or lateral decubitus position. After obtaining free flow of CSF, the study drugs previously prepared by anaesthesiologist as per randomization group were administered. Patients were then turned supine and

the sensory block level to both light touch and temperature were checked at 2.5 minute intervals until there was no change in 3 consecutive readings, the time of maximal block was documented as the time of onset of the block. After this, the anaesthesiologist assessed the modified Bromage motor score (1 - able to move hip, knee and ankle; 2 - unable to move hip, able to move knee and ankle; 3 - unable to move hip and knee, able to move ankle; 4 - unable to move hip, knee and ankle). Surgery was allowed to commence as soon as the sensory block height to light had been tested pre-incision and reached the desired level. Subsequently the sensory block height, the Bromage score, the vital signs (non-invasive blood pressure, heart rate and oxygen saturation) and VAS were determined and recorded every hour.

If pain or discomfort was felt, analgesia options of either GA or supplementary analgesia with IV adjuncts such as fentanyl 1-2mcg/Kg and IV paracetamol 1g was given. Hypotension (defined as a reduction in MAP of more than 20% from baseline determined just before the administration of regional anaesthesia) was treated with ephedrine boluses of 6 mg. Bradycardia (defined as heart rate less than 60bpm) was treated with atropine. The presence of intraoperative nausea, vomiting, pruritus, and shivering was also noted and treated appropriately; rescue antiemetic drugs using a combination of IV ondansetron 4mg or granisetron 1mg were administered at the discretion of the anaesthesiologist. Other complications that patients developed were noted (inadequate blocks, conversion to general anaesthesia, bradycardia, pruritus, hypotension, respiratory discomfort, ephedrine use, colloids use, and crystalloid use). All the complications that occurred were noted by the anaesthesiologist. At the end of surgery, the patient received IV paracetamol 1g and IM diclofenac 75mg.

The principal investigator together with the research assistants followed up the patients in the wards with hourly monitoring of the VAS, Bromage score, sensory block

height and vital signs (non-invasive blood pressure, heart rate and arterial oxygen saturation). The time of request first analgesia was taken as the first time the patient requested for analgesia or the VAS \geq 4.

Intraoperative data was collected by the principal investigator or trained research assistant using the data collection form.

Upon collection data was entered into the statistical software (SPSS version 15) on the same day in a coded form and saved, awaiting analysis. All data entered was verified by the principal investigator.

Data analysis was undertaken using the SPSS version 15 with the input of a statistician who had been involved since the beginning of the study.

Descriptive statistics were used to compare patients' characteristics in terms of age, sex, height, weight. Student's T test was used to compare if the 2 sample sizes were statistically different. The unpaired student's t test was used to compare the differences between duration of effective analgesia and VAS at administration of rescue analgesia. The Chi test was used to compare the proportions of various complications between the two groups. Survival time analysis (Kaplan Meir) was used to analyze the duration of effective analgesia. Log rank test was used to compare duration of effective analgesia.

A P value of < 0.05 was considered statically significant.

Results

Data collection was carried out over four months, October 2012 to January 2013. A total of 40 participants were recruited from the outpatient clinic and surgical wards and randomised for the study. All the participants recruited were followed up and included in the data analysis, twenty in each arm.

Age, weight, height, ASA status were similar in both groups. There was a significant difference in the number of males and females in either group (Table 1). There was no significant difference in age, weight, height and ASA status of the patients.

Table 1: Patient's baseline characteristics

	Midazolam	Fentanyl	'P'
Age	44.6 (18.1)	52.6(17.6)	0.164
Height	163.9(15.9)	158.3(19.6)	0.324
Weight	75.8(11)	76.1(12.7)	0.947
ASA status	2.1(0.9)	2(0.9)	0.713
Sex(Male)	7	15	0.002
Sex (Female)	13	5	0.004

Note: Mean age, height, weight and ASA are presented as Mean +/-_SD; t - test used for analysis

The majority of the procedures conducted were knee arthroscopy contributing to 32.5% of procedures conducted and the least was above knee amputation that contributed 2.5% of the total surgical procedures done. Table 2

shows the distribution of the procedures in each group. The duration of effective analgesia in the midazolam group 384.05minutes as compared to the fentanyl group 342.6 minutes; this was not significant ('P' -0.4047).

Table 2: Types of surgical procedures

Type of surgery	Midazolam group	Fentanyl group	Totals
Knee arthroscopy	8(40%)	5(25%)	13(32.5%)
Knee replacement	4(20%)	3(15%)	7(17.5%)
Hip replacement	0	3(15%)	3(7.5%)
ORIF femur	3(15%)	3(15%)	6(15%)
ORIF Tibia	1(5%)	1(5%)	2(5%)
ORIF ankle	3(15%)	5(25%)	8(20%)
Above knee amputation	1(5%)	0	5(2.5%)
Total	20	20	40(100%)

The time to onset was significantly longer in midazolam group 17.1 minutes as compared to the fentanyl group 13.2 minutes ('P - 0.023'). The visual analogue score at

rescue was significantly lower in the midazolam group 5.55 as compared to the fentanyl group 6.35 ('P - 0.043') (Table 3).

Table 3: Primary outcome

Variable	Midazolam Mean (sd) (CI)	Fentanyl Mean (sd) (CI)	Mean difference (CI)	'P'
Time to maximum block (minutes)	17.1(6.5) (14.08-20.12)	13.2(3.8) (13.8-14.9)	3.95(0.6-7.3)	0.023
VAS at rescue	5.55(1.099) (5.04-6.06)	6.35(1.31) (5.74-6.96)	0.8(0.02-1.57)	0.043
Duration of effective analgesia	384.05(158.99) (309-458)	342.6(152.04) (271-413)	41.45(0-141)	0.4047

Time to maximum block, VAS at rescue and duration of effective analgesia are presented as Mean +/-_SD and confidence intervals; t - test used for analysis

Intraoperatively there was a higher incidence of pruritus in the fentanyl group 57.9% as compared to none in the midazolam group ('p <0.001'). There was no significant

difference in the intraoperative incidences of nausea/vomiting and sedation in the midazolam group as compared to fentanyl group (table 4).

Table 4: incidence of intraoperative complications

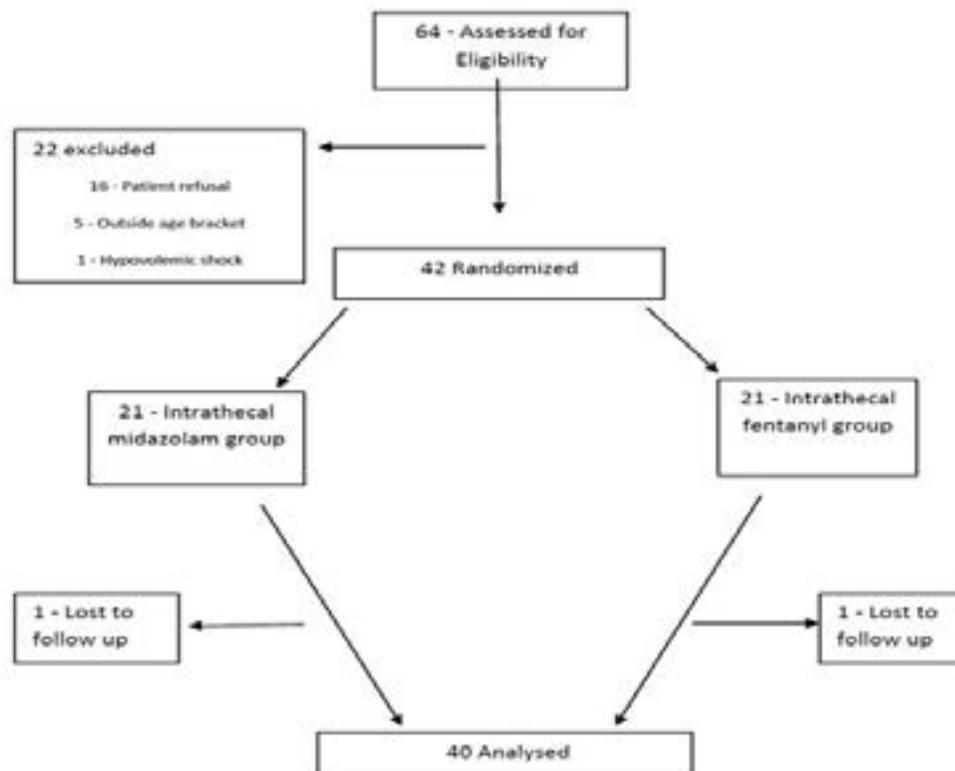
Complications	Midazolam	Fentanyl	'P'
Nausea / Vomiting	2(10%)	4(20%)	0.661
Hypotension	2(10%)	2(10%)	1.0
Pruritus	0	11(57.9%)	<0.001
Sedation	4(20%)	1(5%)	0.342
Respiratory depression	0	0	

Post operatively there was also no significant difference in the incidence of side effects (Table 5).

Table 5: Incidence of post-operative complications

Complications	Midazolam	Fentanyl	'P'
Urinary retention	1(5%)	3(15%)	0.605
Headache	5(25%)	5(25%)	1.0
Dizziness	4(20%)	4(20%)	1.0
Nausea / Vomiting	1(5%)	4(20%)	0.106
Respiratory depression	0	1(5%)	

Figure 1: Flow diagram of patient's



Discussion

In this single blind randomized control study of 40 patients undergoing lower limb orthopaedic surgery under spinal anaesthesia, there was no statistically significant difference between the duration of effective analgesia of adjuvant 2mg intrathecal midazolam as compared to 20mcg intrathecal fentanyl.

The rationale for the use of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pentameric-gamma-aminobutyric acid (GABA A) receptor. Agonist occupancy of the benzodiazepine binding site enhances the activity of GABA at the GABA A receptor. This receptor is a chloride ionophore that, when activated, typically stabilises the transmembrane potential at, or near, the resting potential. In neurons, this typically serves to decrease excitability. Intrathecal benzodiazepine-induced analgesia is spinally mediated. Binding sites are GABA receptors, abundantly present in the dorsal root nerve cells, with the maximum concentration found within lamina II of the dorsal nerve cells, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation²¹. The present cumulative experience with intrathecal midazolam across species broadly confirms the safety thereof, the analgesic activity of the molecule and its benzodiazepine pharmacology, and the lack of irreversible effects²².

In the present study it was observed, that there is no statistically significant difference in the duration of effective analgesia, this finding is different from that of a previous study comparing the two drugs²⁰. This relationship may be explained by another study comparing¹⁹ different doses of intrathecal midazolam that found that 2mg dose of adjuvant midazolam had a longer duration of effective analgesia as compared to the 1mg dose. The confidence intervals obtained for the primary outcome were very wide, since the study was powered for this outcome, the reason could have been due to equivalence but the study was not powered to determine this.

The 'P' obtained for the time to maximum block and VAS score showed there may be a difference but this was not statistically significant since there was an overlap of the confidence intervals in duration and pain score obtained between the two groups. In addition, the study was not

powered to measure this difference and assess its significance.

Safari et al while studying the effect of adjuvant 1 mg midazolam compared with 25 mcg fentanyl on the duration of spinal anaesthesia with 0.5% bupivacaine in opium abusers concluded midazolam is more effective than fentanyl in such cases. Our study further confirms their findings³⁰.

The incidence of nausea and vomiting noted in this study was determined to be 5% both intra-operatively and post-operatively and this was lower than that of intrathecal fentanyl; these findings are similar to one done²³ to compare fentanyl, midazolam and placebo and found the highest reduction in incidence of nausea was in the midazolam group. Our findings were comparable to those Ho et al²⁷ who in their meta-analysis of the use of intrathecal midazolam to improve postoperative analgesia concluded that it appeared to improve perioperative analgesia and reduce nausea and vomiting in caesarean delivery.

The incidence of respiratory depression in the present study was 5% of patients in the fentanyl group as compared to that of previous studies that found an incidence of up to 3.4%¹³. This may be explained by the fewer number of patients who were recruited in our study and the 5% incidence is attributable to one patient who developed respiratory depression both intra-operatively and post-operatively. The mechanism of intrathecal opioid induced respiratory depression is due to the rostral spread. Various studies have found different incidences of sedation following intrathecal midazolam. In the study conducted by Talwar and colleagues²⁰, the incidence of sedation was higher in the intrathecal fentanyl group than in the intrathecal midazolam group. Dureja et al while assessing the efficacy of intrathecal midazolam with or without methylprednisolone for management of post-herpetic neuralgia involving lumbosacral dermatomes found a mild degree of sedation in the midazolam group²⁸. In the present study, the incidence of sedation was higher in the midazolam group than in the fentanyl group. This difference may have occurred due the higher intrathecal dose of midazolam (2mg) that was used in the present study.

Niv and colleagues conducted neurotoxicologic studies in animals by studying histologic and vascular lesions in animal spinal cord samples, indicating the neurotoxic effects of intrathecal midazolam²⁴. Therefore, they advised

against the use of intrathecal midazolam in humans. Subsequent studies in humans^{9,25,29}, found no adverse neurological symptoms in those who had received intrathecal midazolam. In agreement with these studies, the present study observed no significant adverse neurological effects in any patient during the study period. Further current reports suggest that midazolam in a dose of 1-2mg at a concentration not exceeding 1mg/ml is not accompanied by an increase in adverse events²².

Limitations.

One of the limitations of this study was that despite randomization there was heterogeneity as concerns the nature of the procedures, these procedures varied from arthroscopy to total hip replacement. This therefore meant the difference in the extent of tissue damage and thereby the nociceptive input was large and may have had an effect on the duration of effective analgesia.

Another limitation is the lack of standardization as concerns the use of local anaesthetic infiltration at the surgical site. This may have resulted the longer duration of effective analgesia for certain procedures due to the routine use of local anaesthetic infiltration at the end of surgery by some surgeons.

Conclusion

On the basis of the results of this study, there was no difference in the duration of effective analgesia between adjuvant intrathecal 2mg midazolam as compared to intrathecal 20micrograms fentanyl for patients undergoing lower limb orthopaedic surgery.

References

1. Sommer M, De Rijke JM, Van Kleef M, Kessels AGH, Peters ML, Geurts JWJM. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *European Journal of Anaesthesiology*. 2008;25(4):267–74.
2. Apfelbaum JL, Chen C, Mehta SS, Gan and TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesthesia and Analgesia*. 2003;97(2):534–40.
3. G. Mwaka, S. Thikra, V. Mung'ayi. The prevalence of postoperative pain in the first 48 hours following day surgery at a tertiary hospital in Nairobi. *African Health Sciences* 2013; 13(3): 768-776
4. Merskey H BN. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. *Pain Supplement*. 1986;3:S1–S226.

5. Carr DB, Goudas LC. Acute pain. *Annual Review of Nursing Research*. 1999;35(2):107–32.
6. Breivik H. Postoperative pain management: why is it difficult to show that it improves outcome? *European Journal of Anaesthesiology*. 1998;15(6):748–51.
7. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. *Science*. 1973;179(77):1011–4.
8. Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal anesthesia. *Regional Anesthesia and Pain Medicine*. 1999;24(3):255–63.
9. Valentine JM, Lyons G, Bellamy MC. The effect of intrathecal midazolam on post-operative pain. *European Journal of Anaesthesiology*. 1996;13(6):589–93.
10. Sen A, Rudra A, Sarkar SK, Biswas B. Intrathecal midazolam for postoperative pain relief in caesarean section delivery. *Journal of the Indian Medical Association*. 2001;99(12):683–4, 686.
11. Borg PA, Krijnen HJ. Long-term intrathecal administration of midazolam and clonidine. *The Clinical Journal of Pain*. 1996;12(1):63–8.
12. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *The Journal of Pain*. 2002;3(3):159–80.
13. Gwartz KH, Young J V, Byers RS, Alley C, Levin K, Walker SG, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. *Anesthesia and Analgesia*. 1999;88(3):599–604.
14. Scott PV, Fischer HBJ. Spinal opiate analgesia and facial pruritus: a neural theory. *Postgraduate Medical Journal*. 1982;58(683):531–5.
15. Kyriakides K, Hussain SK, Hobbs GJ. Management of opioid-induced pruritus : a role for 5-HT 3 antagonists ? *British Journal of Anaesthesia*. 1999;82(3):439–41.
16. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *European Journal of Anaesthesiology*. 2001;18(6):346–57.
17. Wang JJ, Ho ST, Tzeng JI. Comparison of intravenous nalbuphine infusion versus naloxone in the prevention of epidural morphine-related side effects. *Regional Anesthesia and Pain Medicine*. 1998;23(5):479–84.
18. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. *Anesthesia and Analgesia*. 2005;101(5):S30–43.
19. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine

- in patients undergoing haemorrhoidectomy. *Clinical Journal of Pain*. 2001;86(1):77–9.
20. Talwar V, Rai A, Gandhi R, Gogia AR. Comparison of intrathecal midazolam and fentanyl added to bupivacaine for lower limb surgery. *Anesthesia and Analgesia*. 2008;24(4):447–50.
 21. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man--a pilot study. *British Journal of Clinical Pharmacology*. 1987;23(3):279–85.
 22. Yaksh TL, Allen JW. The use of intrathecal midazolam in humans: A case study of process. *Anesthesia and Analgesia*. 2004;98(6):1536–45.
 23. Rudra P, Rudra A. Comparison of intrathecal fentanyl and midazolam for prevention of nausea-vomiting. *Indian Journal of Anaesthesia*. 2004;48(6):461-464.
 24. Niv D, Whitwam JG, Loh L. Depression of nociceptive sympathetic reflexes by the intrathecal administration of midazolam. *British Journal of Anaesthesia*. 1983;55(6):541–7.
 25. Tucker AP, Mezzatesta J, Nadeson R, Goodchild CS. Intrathecal Midazolam II: Combination with Intrathecal fentanyl for labor pain. *Anesthesia and Analgesia*. 2004;(8):1521–7.
 26. Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study. *Singapore Med J*. 2011; 52(6):432-5
 27. Ho KM, Ismail H. Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. *Anaesth Intensive Care*. 2008; 36(3):365-73
 28. Dureja GP, Usmani H, Khan M, Tahseen M, Jamal A. Efficacy of intrathecal midazolam with or without epidural methylprednisolone for management of post-herpetic neuralgia involving lumbosacral dermatomes. *Pain Physician* 2010; 13(3):213-21
 29. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal midazolam I: a cohort study investigating safety. *Anesth Analg*. 2004;98(6):1512-20.
 30. Safari F, Dabbagh A, Sharifnia M. The effect of adjuvant midazolam compared with fentanyl on the duration of spinal anesthesia with 0.5% bupivacaine in opium abusers. *Korean J Anesthesiol*. 2012 ;63(6):521-6.