Original Article

Comparison of Single-Shot Intrathecal Morphine Injection and Continuous Epidural Bupivacaine for Post-Operative Analgaesia after Elective Abdominal Hysterectomy

Submitted: 16 Dec 2016
Accepted: 08 Oct 2017
Online: 29 Dec 2017

Wan Mohd Nazaruddin Wan Hassan[1], Anafairos Md Nayan[1], Azmi Abu Hassan[2], Rhendra Hardy Mohamad Zaini[1]

[1] *Department of Anaesthesiology, School of Medical Sciences, Jalan Sultanah Zainab II, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

[2] *Department of Anaesthesiology and Intensive Care, Hospital Sultanah Bahiyah, 05460 Alor Setar, Kedah, Malaysia*

To cite this article: Wan Hassan WMN, Md Nayan A, Abu Hassan A, Mohamad Zaini RH. Comparison of single-shot intrathecal morphine injection and continuous epidural bupivacaine for post-operative analgaesia after elective abdominal hysterectomy. *Malays J Med Sci.* 2017;**24(6)**:21–28. https://doi.org/10.21315/mjms2017.24.6.3

To link to this article: https://doi.org/10.21315/mjms2017.24.6.3

Abstract

***Background*: Abdominal hysterectomy (AH) is painful. The aim of this study was to compare intrathecal morphine (ITM) and epidural bupivacaine (EB) for their analgaesia effectiveness after this surgery.**

***Methods*: Thirty-two patients undergoing elective AH were randomised into Group ITM (ITM 0.2 mg + 2.5 mL 0.5% bupivacaine) (n = 16) and Group EB (0.25% bupivacaine bolus + continuous infusion of 0.1% bupivacaine-fentanyl 2 µg/mL) (n = 16).The procedure was performed before induction, and all patients subsequently received standard general anaesthesia. Both groups were provided patient-controlled analgaesia morphine (PCAM) as a backup. Visual analogue scale (VAS) scores, total morphine consumption, hospital stay duration, early mobilisation time and first PCAM demand time were recorded.**

***Results*: The median VAS score was lower for ITM than for EB after the 1st hour [1.0 (IqR 1.0) versus 3.0 (IqR 3.0), P < 0.001], 8th hour [1.0 (IqR 1.0) versus 2.0 (IqR 1.0), P = 0.018] and 16th hour [1.0 (IqR1.0) versus (1.0 (IqR 1.0), P = 0.006]. The mean VAS score at the 4th hour was also lower for ITM [1.8 (SD 1.2) versus 2.9 (SD 1.4), P = 0.027]. Total morphine consumption [11.3 (SD 6.6) versus 16.5 (SD 4.8) mg, P = 0.016] and early mobilisation time [2.1 (SD 0.3) versus 2.6 (SD 0.9) days, P = 0.025] were also less for ITM. No significant differences were noted for other assessments.**

***Conclusions*: The VAS score was better for ITM than for EB at earlier hours after surgery. However, in terms of acceptable analgaesia (VAS ≤ 3), both techniques were comparable over 24 hours.**

Keywords: *intrathecal, epidural, morphine, bupivacaine, abdominal hysterectomy, analgesics*

Introduction

Abdominal hysterectomy, or the surgical removal of the uterus, may also involve removal of the cervix, ovaries, fallopian tubes and other surrounding structures. The pain after this surgery can be considered moderate to severe if based on the assessment of the severity and experience of pain after surgery, as 40% of patients report moderate to severe pain during the first 24 hours (1). When compared to total laparoscopic hysterectomy, the mean pain scores for total abdominal hysterectomy were significantly higher even a week after surgery

(2.48 versus 1.62) and four weeks after surgery (0.89 versus 0.63) (2). Therefore, effective post-operative pain management is very important for patients' comfort and satisfaction, earlier mobilisation, fewer pulmonary and cardiac complications, reduced risk of deep vein thrombosis, faster recovery, and reduced cost of care (3).

Epidural analgaesia using a local anaesthetic agent is one of the common techniques and was previously considered the gold standard post-operative analgaesia for this surgery. A systematic review has shown that continuous epidural analgaesia is superior to patient controlled analgaesia (PCA) with opioid in relieving post-operative pain for up to 72 hours in patients undergoing intra-abdominal surgery (4). However, it is more invasive because requires a catheter placement in the epidural space up to 24 to 48 hours after surgery and this might also lead to delay in ambulation. Most of the adverse effects are related to the drugs used; for example, hypotension and dense motor blockade from local anaesthetics and nausea and pruritus from opioids (5).

Intrathecal morphine (ITM) is one of the potential alternatives to epidural analgaesia. It has the advantages of being a single injection procedure, easier to perform, a safer technique and more cost effective than epidural drugs. This technique has been proven to be a good option to epidural analgaesia in liver surgery as it significantly reduces total morphine consumption up to 48 hours, lowers the pain score at rest and with movement, provides superior haemodynamic stability, requires less total intravenous fluid and gives higher patient satisfaction (6). However, a comparison during caesarean section showed a contradictory result, where the epidural was more effective than ITM, with similar side effects between both groups (7). Nevertheless, the data comparing these two techniques are limited for gynaecological surgery.

The aim of our study was to compare the effectiveness of these two techniques based on the assessment of the visual analogue scale (VAS) scores, the time for the first PCA morphine demand, the total morphine consumption, the time to early mobilisation and the length of hospital stay.

Material and Methods

Study Design

This prospective, single-blinded, randomised controlled trial study was approved by Ministry of Health Ethics committee and was conducted in the operating theatre of Hospital Sultanah Bahiyah, Alor Setar, Kedah.

Study Population

A total of 32 patients undergoing elective abdominal hysterectomy for any gynaecological indications were recruited after obtaining written informed consent. The inclusion criteria were age 18 to 60 years and class I to II according to the American Society of Anaesthesiologists (ASA) classification. We excluded subjects who had known allergies to the study drugs, were on opioid treatment for chronic pain, were on anti-coagulant drugs, had a known history of coagulation disorder or were contraindicated for neuraxial anaesthesia techniques.

Randomisation and Allocation Concealment

The recruited patients were randomly allocated by a computer-generated table of numbers to two equal-sized groups, Group ITM and Group EB (epidural bupivacaine), followed by sealed opaque envelope assignment. The attending anaesthetist would break the seal to reveal the allocated group in the operating theatre.

Blinding

This was a single blinded study, where the patient and the primary investigator knew the type of intervention (either spinal or epidural techniques) because the procedures were commonly practised while the patient was still awake. Blinding of the set of equipment used in the procedure was also difficult because ITM required only a single injection whereas the epidural technique required placement of a catheter in situ throughout intervention. The technique was performed by single operator, who was the primary investigator. We could only blind the assessor, so assessments were done by a dedicated Acute Pain Services nurse who was not involved in the study and did not know the allocation group during the assessment.

Study Protocol

All patients were reviewed a day earlier for pre-operative assessment and were given premedication with oral midazolam (7.5 mg) on the night before and an hour before the surgery. Standard monitoring devices for non-invasive blood pressure (BP), pulse oximetry and electrocardiography were attached before performing the procedures and capnography was attached before induction. After gaining intravenous (IV) access, a preloading of 10 mL/kg of Ringer's lactate solution was given to all patients and baseline haemodynamic parameters were obtained before performing the procedures. Both procedures (either spinal or epidural) were done before induction, with the patient in a sitting position. The level of injection was at the lumbar level of L3/L4 or L4/L5.

Group ITM received a single injection of intrathecal morphine (0.2 mg) with 2.5 mL of 0.5% bupivacaine using a spinal needle (Spinocan® 25 G; B. Braun, United States), whereas, group EB received epidural analgaesia after the insertion of the epidural catheter, using the loss of resistance technique, with a Touhy needle (18 G, Perifix® epidural set; B. Braun, United States). Initially, a test dose of 3 mL lidocaine (2%) + adrenaline (1:200,000) was injected via the catheter to confirm placement and to exclude inadvertent intravascular or intrathecal placement. A total of 12 mL of 0.25% plain bupivacaine was given as an intermittent bolus over 15 min before induction of anaesthesia. The level of analgaesia was assessed and acceptable at least up to T6 dermatomes before starting general anaesthesia.

All patients were subsequently induced with IV fentanyl (2 μg/kg) and IV propofol (2 mg/kg). After loss of the eyelash reflex and verbal response, IV rocuronium (0.9 mg/kg) was given for muscle relaxation prior to intubation. After intubation, anaesthesia was then maintained with sevoflurane in a 30%–40% oxygen: air mixture, with minimal flow ventilation. Intra-operatively, analgaesia for group EB was continued with epidural infusion of 0.1% bupivacaine + fentanyl (2 μg/ mL) at flow rates of 6–12 mL/hr.

A decrease in blood pressure of more than 30% less than the pre-operative value in both groups was corrected with fluids, IV ephedrine, or both. All patients were observed in the recovery area after operation. In group EB, epidural analgaesia was continued with infusion at 6 mL/h. Rescue analgaesia was backed up with patient controlled analgesia morphine (PCAM) in both groups, with 1 mg of IV morphine delivered for each drug delivery. Lockout time was set at 5 minutes, dilution of morphine was 1 mg/mL and no background infusion was provided. Metoclopramide (10 mg) was given IV to patients who complained of post-operative nausea and vomiting.

Assessment

Pain was assessed in the ward on the first hour post-surgery and then every four hours, for up to 24 hours. The VAS with the scale of 0 (no pain) to 10 (worst pain) was used. The time for first PCA morphine demand, the total morphine consumption, the time to early mobilisation (the time from completion of surgery to first ambulation), the length of hospital stay and the side effects were also recorded. The potential complications related to ITM (such as itchiness, hypotension, etc.) and related to EB (such as hypotension) were also assessed.

Statistics

The sample size was calculated using 'PS-Power and sample size calculations' software version 3.0.10 (8), based on study by De Pietri et al. (9), which resulted in a significant difference in consumption of IV morphine with the PCA device in the ITM group compared to the EB group [12.0 (5.5) mg versus 3.1 (2.6) mg]. We used independent *t*-test method, α of 0.05, power of 0.9, mean difference of 8.9 and standard deviation of 5.5 for the calculation. After consideration of a 20% patient dropout, a total of 32 samples were finally evaluated.

SPSS software version 22 was used for all statistical analysis. Data were presented as medians (interquartile range) for the Mann-Whitney test, means (SD) for the independent *t*-test and percentages for the Chi-square test. $P < 0.05$ was considered to indicate statistical significance.

Results

The demographic data of the patients revealed no significant differences for any parameter (age, height, ASA) except for body mass index (BMI) and weight. The mean weight was significantly higher in Group ITM than in Group EB [73.9 (SD 14.0) versus 58.9 (SD 7.3); $P = 0.001$]. The BMI was significantly higher for Group ITM than for Group EB [30.5 (SD 7.1) versus 25.6 (SD 3.2); $P = 0.002$] (Table 1).

Comparison of the pain scores revealed a significantly lower median of the VAS scores for Group ITM than for Group EB after the 1st hour [1.0 (IqR 1.0) versus 3.0 (IqR 3.0), $P < 0.001$], 8th hour [1.0 (IqR 1.0) versus 2.0 (IqR 1.0), $P = 0.018$] and 16th hour [1.0 (IqR 1.0) versus (1.0 (IqR 1.0), $P = 0.006$] of surgery. The mean VAS at 4th hour was also significantly lower in Group ITM [1.8 (SD 1.2) versus 2.9 (SD 1.4), $P = 0.027$] (Table 2).

As shown in Table 3, the total morphine consumption was significantly less in Group ITM than in Group EB [11.3 (SD 6.6) versus 16.5 (SD 4.8) mg, $P = 0.016$] and the time for early mobilisation was also significantly shorter in Group ITM [2.1 (SD 0.3) versus 2.6 (SD 0.9) days, $P = 0.025$]. However, no significant differences were noted in the length of stay and the time of first PCA demand.

The two groups showed no significant differences in terms of side effects. However, group ITM showed higher percentage of nausea (18.8% versus 6.3%) and a higher percentage of pruritus (25% versus 0%) (Table 4).

Discussion

Our demographic data indicated significant differences in weight and BMI between the two groups. Group ITM showed a BMI of 30.46, which was categorised as obese, whereas group EB showed a BMI of 25.63, which was categorised as overweight. However, this difference did not generally affect our primary outcome assessment. Based on the data, only one patient had a body weight of 100 kg, while the others had weights ranges from 60 kg–80 kg.

Table 1. Demographic data of ITM ($n = 16$) and EB ($n = 16$) study groups.

Parameters	ITM Mean (SD)	EB Mean (SD)	*P*-value
Age (years)	47.5 (8.12)	48.63 (7.40)	0.685[b]
Height (m)	156.9 (5.5)	153.9 (3.6)	0.072[b]
Weight (kg)	73.9 (14.0)	58.9 (7.3)	0.001[b]
	Median (IQR)	**Median (IQR)**	
BMI (kg/m^2)	30.5 (7.05)	25.6 (3.2)	0.002[c]
	***n* (%)**	***n* (%)**	
ASA I	7 (41.2)	10 (58.8)	0.288[d]
ASA II	9 (60.0)	6 (40.0)	

[b]Independent t-test [c]Mann-Whitney [d]Chi-square
ITM = intrathecal morphine; EB = epidural bupivacaine

Table 2. Visual analog scale over 24 hours of ITM ($n = 16$) and EB ($n = 16$) study groups

Parameters	ITM Median (IQR)	EB Median (IQR)	*P*-value
VAS at 1 H	1.0 (1.0)	3.0 (3.0)	< 0.001[b]
	Mean (SD)	**Mean (SD)**	
VAS at 4 H	1.8 (1.2)[a]	2.9 (1.4)[a]	0.027[c]
	Median (IQR)	**Median (IQR)**	
VAS at 8 H	1.0 (1.0)	2.0 (1.0)	0.018[b]
VAS at 12 H	1.0 (1.0)	1.5 (1.0)	0.077[b]
VAS at 16 H	1.0 (1.0)	1.0 (1.0)	0.006[b]
VAS at 24H	0.0 (1.0)	0.0 (1.0)	0.301[b]

[b]Mann-Whitney [c]Independent *t*-test

Table 3. Comparison of the values of total morphine consumption, time to early mobilisation, length of stay and time for first PCA morphine demand of ITM (n = 16) and EB (n = 16) study groups

Parameters	ITM Mean (SD)	EB Mean (SD)	Mean difference (95% CI)	*P*-value
Total morphine consumption (mg)	11.3 (6.6)	16.5 (4.8)	-5.2 (-9.3, -1.0)	0.016[b]
Time to early mobilisation (days)	2.1 (0.3)	2.6 (0.9)	-0.6 (-1.1, -0.1)	0.025[b]
	Median (IQR)	**Median (IQR)**		
Length of stay (days)	4.0 (1.0)	4.0 (1.0)	-0.4 (-1.7, 0.8)	> 0.950[c]
	***n* (%)**	***n* (%)**		
Time for first PCA demand:				
Nil	2 (6.3)	0 (0.0)		0.107[d]
4th hour	2 (6.3)	1 (3.1)		
8th hour	11 (34.4)	9 (28.1)		
12th hour	1 (3.1)	6 (18.8)		

[b]Independent *t*-test [c]Mann-Whitney [d]Chi-Square

Table 4. The side effects of ITM (n = 16) and EB (n = 16) study groups

Parameters	ITM *n* (%)	EB *n* (%)	*P*-value
Hypotension:			
Yes	15 (46.9)	14 (43.8)	1.000[b]
No	1 (3.1)	2 (6.3)	
Side effects:			
Nausea	3 (9.4)	1 (3.1)	0.069[a]
Vomiting	0 (0.0)	1 (3.1)	
Pruritus	4 (12.5)	0 (0.0)	
Nil	9 (28.1)	14 (43.8)	

[a]Pearson Chi-square [b]Fisher Exact Test

Our results for pain assessment showed that Group ITM had lower pain scores when compared to Group EB at the 1st, 4th, 8th and 16th hours post-operation. This confirmed that ITM provided a better VAS score within 24 hours after surgery. Even though the difference was significant, the VAS was generally 3 or lower in both groups, which indicted only mild pain intensity, so both techniques generally managed to provide adequate analgaesia for abdominal hysterectomy surgery. In our study, the drugs given to the ITM group were supplied as a combination of intrathecal morphine (0.2 mg) with 2.5 mL of 0.5% bupivacaine (i.e. a combination of local anaesthetic and opioid), which might also provide spinal anaesthesia effects in the early hours after surgery, and this might have contributed to the lower VAS score in the ITM group than in the EB group. Even though we added fentanyl to the bupivacaine (0.1%) administered to the EB group (i.e. a combination of local anaesthetic and opioid), administration of intrathecal morphine (0.2 mg) alone in the ITM group and bupivacaine (0.1%) in the EB group might possibly be better in future research to remove confounders and allow direct comparison of the main drugs involved in each technique. Another study comparing ITM and a control group for total abdominal hysterectomy also concluded that ITM enhanced the quality of post-operative analgaesia, decreased morphine consumption and depressed systemic stress (10).

In pelvic surgery, a combination of high dose ITM with continuous IV naloxone infusion also provided excellent analgaesia when compared to IV opioid alone (11). The comparison between ITM and epidural analgaesia for post-operative analgaesia after liver resection showed that the VAS score remained less than 30 mm for 48 hours in both groups (9), in agreement with our results. A comparison of ITM and thoracic epidural analgaesia in patients undergoing abdominal cancer surgery also showed that both techniques produced the same level of analgaesia without relevant complications (12). However, another study showed that neither ITM (0.2 mg) nor 10 mL of 0.125% EB was effective in producing adequate pain relief during labour, but excellent analgaesia was produced by the combination of these two techniques (combined spinal epidural) (13). An investigation of thoracic epidural analgaesia versus a combination of ITM and PCA fentanyl in patients undergoing hepatic resection showed a lowering of pain scores to clinically significant levels at 12 hour post-operatively using thoracic epidural analgaesia, but no further differences were noted up to day five (6).

Our results also showed that the ITM group had a significantly lower total morphine consumption and required a shorter time to early mobilisation when compared to the EB group. Early mobilisation after surgery is important to reduce the risk of deep vein thrombosis, pressure sores, orthostatic pneumonia and other post-operative complications. The epidural technique for major surgery raises the possibility of delayed removal of the epidural catheter post-operatively because of the potential risk of post-operative coagulopathy. In this condition, a single bolus injection of ITM is better in terms of early facilitation of ambulation. One study conducted to compare morphine consumption with PCA between spinal anaesthesia (bupivacaine, morphine and fentanyl) and general anaesthesia for abdominal hysterectomy reported decreased post-operative pain and decreased morphine consumption by PCA in the ITM group (14). Another study compared the effects of addition of morphine (0, 100, 200 or 300 μg) to intrathecal bupivacaine on the PCA morphine consumption during the first post-operative 24 hours after abdominal hysterectomy under general anaesthesia. The ITM reduced the accumulated 24 hours post-operative morphine consumption, and morphine administered at 100 μg significantly reduced morphine consumption vs. placebo at 0–6 hours, 6–12 hours, and for the entire 0–24 hours time interval post operation. Morphine at 200 μg significantly reduced morphine consumption even further vs. morphine at 100 μg at 0–6 h and for the entire 0–24 hours post-operative period. The researchers concluded that ITM supplementation to bupivacaine reduces the PCA-morphine consumption during the first 24 hours after abdominal hysterectomy under general anaesthesia, and they found no benefit in increasing the dose over 200 mg (15).

We found no significant differences between Groups ITM and EB in the first PCA demand and the length of stay. These findings were similar to other data showing that the time to first demand of morphine was similar in the epidural (307.5 minutes) and intrathecal (310 minutes) groups (16). However, another study showed that the time to first pain drug requirement was longer in the epidural group than in the ITM group [25 (18.5) hours versus 12(10.3) hours] following liver resection surgery (9).

No significant side effects occurred in either of our two groups. However, the ITM group showed a higher percentage of nausea and pruritus. The side effects of nausea and pruritus are among the main ones associated with ITM and a significantly high incidence has been reported previously (13). Another study indicated an incidence of vomiting of 4% in both groups, whereas a more frequent incidence of pruritus (16% versus 0%) and nausea (16% versus 4%) was noted in the ITM group (9). No respiratory depression side effects occurred in either group.

The only limitation of the present study was inaccuracy in recording the time of early mobilisation because this information need to be tallied from the ward nurse documentation as well as the information from the patient. The other methods of assessment were actually not difficult and used assessment parameters that are commonly employed to assess the effects of post-operative analgaesia using PCA pumps. These assessments have also been typically used for clinical research using PCA pumps. The PCA pump is a special pump which is able to record the timing and number of demands for the drug whenever the patient presses the control button. The setup parameters include the safety setup of the amount of the drug that can be delivered within a certain duration despite a very high demand from the patient. The maximum dose

of 40 mg over 4 hours of morphine is normally set up to prevent any over-dosage. The pump will only deliver this total amount over 4 hours regardless of extra demands from the patient. The pump is also able to record the total amount of drug actually delivered to the patient. Therefore, the time for the first PCAM demand and the total amount of morphine consumption can be easily traced from the recorded data in the PCA pump.

The VAS assessment is also a common method for objective assessment of acute post-operative analgaesia. VAS scores are commonly used in daily routine practice and the VAS is a very familiar assessment tool for the APS nurse.

This study had some potential ethical issues that could be raised because the use of a combination of two anaesthetic techniques for surgery could expose the patients to unnecessary risks. A common practice when administering intra-operative as well as post-operative analgaesia for abdominal hysterectomy is to use an epidural, which is performed before induction of anaesthesia. However, the use of the spinal technique as an alternative technique for both intra-operative and post-operative analgaesia is becoming more popular in our centre following its successful use during hepatobiliary surgery. The ethics committee approved this study based on the reported safety practice of this combination technique in the literature and the concern that either spinal or epidural anaesthesia alone sometimes might not be sufficient for the extension of the surgical technique. Furthermore, the spinal technique was not a new technique; the only unfamiliar application in this study was its combination with general anaesthesia. The spinal technique is also only a single-shot technique and does not require placement of the catheter in the subarachnoid space. This single shot also has the potential to provide an intraoperative analgesic effect and reduce the consumption of intra-operative opioid.

A greater potential risk for hypotension also arises for the patient because of the spinal anaesthesia effect that is subsequently followed with induction of anaesthesia. However, we anticipated these effects early by preloading and by prompt vasopressor administration when the BP dropped more than 20% from the baseline. The epidural technique poses the same potential risk, but the effect is usually gradual because the epidural bolus dose is usually given in titration.

Conclusions

Our study showed that ITM provided better VAS scores at earlier hours after surgery, required less rescue analgaesia and resulted in a shorter time for early mobilisation when compared to EB. However, in terms of acceptable analgaesia (VAS score ≤ 3), both techniques were comparable over 24 hours. No significant occurrence of side effects was noted between the two groups, even though the occurrence of pruritus was lower in the epidural group. The ITM technique, being a single injection, is relatively safer, easier to perform, less invasive, less time consuming and more cost effective. Therefore, ITM is a potential alternative analgaesia to epidural analgaesia for elective abdominal hysterectomy.

Authors' Contributions

Conception and design: AMN, WMNWH, AAH, RHMZ
Analysis and interpretation of the data: AMN, WMNWH
Drafting of the article: AMN, WMNWH, AAH, RHMZ
Critical revision of the article for important intellectual content: AMN, WMNWH, AAH, RHMZ
Final approval of the article: AMN, WMNWH, AAH, RHMZ
Provision of study materials: AMN, AAH
Statistical expertise: AMN, WMNWH
Obtaining funding: WMNWH
Administrative, technical, or logistic support: WMNWH, AAH, RHMZ
Collection and assembly of data: AMN, AAH

Correspondence

Dr Wan Mohd Nazaruddin Wan Hassan
MD (Universiti Kebangsaan Malaysia),
MMed (Anaesth) (Universiti Sains Malaysia)
Department of Anaesthesiology, School of Medical Sciences, Jalan Sultanah Zainab II,
Universiti Sains Malaysia,
16150 Kubang Kerian, Kelantan, Malaysia.
Tel: +6012 8039500
Fax: +609 7653000
E-mail: drnaza_anaest@yahoo.co.uk

References

1. Beauregard L, Pomp A, Choinière M. Severity and impact of pain after day-surgery. *Can J Anaesth.* 1998;**45(4)**:304–311. https://doi.org/10.1007/BF03012019

2. Baker J, Janda M, Belavy D, Obermair A. Differences in epidural and analgesic use in patients with apparent stage I endometrial cancer treated by open versus laparoscopic surgery: Results from the randomised LACE trial. *Minim Invasive Surg*. 2013;**2013:764329**. https://doi.org/10.1155/2013/764329

3. Azari L, Santoso JT, Osborne SE. Optimal pain management in total abdominal hysterectomy. *Obstet Gynecol Surv*. 2013; **68(3)**:215–227. https://doi.org/10.1097/OGX.0b013e31827f5119

4. Werawatganon T, Charuluxananan S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane Database Syst Rev*. 2005;**1**:CD004088. https://doi.org/10.1002/14651858.CD004088.pub2

5. Rawal N. Epidural technique for postoperative pain: gold standard no more? *Reg Anesth Pain Med*. 2012;**37(3)**:310–317. https://doi.org/10.1097/AAP.0b013e31825735c6

6. Kasivisvanathan R, Abbassi-Ghadi N, Prout J, Clevenger B, Fusai GK, Mallett SV. A prospective cohort study of intrathecal versus epidural analgesia for patients undergoing hepatic resection. *HPB (Oxford)*. 2014; **16(8)**: 768–775. https://doi.org/10.1111/hpb.12222

7. Duale C, Frey C, Bolandard F, Barriere A, Schoeffler P. Epidural versus intrathecal morphine for postoperative analgesia after Caesarean section. *Br J Anaesth*. 2003;**91(5)**: 690–694. https://doi.org/10.1093/bja/aeg249

8. Dupont WD, Plummer WD, Jr. Power and sample size calculations for studies involving linear regression. *Control Clin Trials*. 1998 ;**19(6)**:589–601. https://doi.org/10.1016/S0197-2456(98)00037-3

9. De Pietri L, Siniscalchi A, Reggiani A, Masetti M, Begliomini B, Gazzi M, et al. The use of intrathecal morphine for postoperative pain relief after liver resection: a comparison with epidural analgesia. *Anesth Analgesia*. 2006 ;**102(4)**:1157–1163. https://doi.org/10.1213/01.ane.0000198567.85040.ce

10. Karaman S, Kocabas S, Uyar M, Zincircioglu C, Firat V. Intrathecal morphine: effects on perioperative hemodynamics, postoperative analgesia, and stress response for total abdominal hysterectomy. *Adv Ther*. 2006;**23(2)**:295–306. https://doi.org/10.1007/BF02850135

11. Rebel A, Sloan P, Andrykowski M. Retrospective analysis of high-dose intrathecal morphine for analgesia after pelvic surgery. *Pain Res Manag*. 2011;**16(1)**:19–26. https://doi.org/10.1155/2011/691712

12. Mercadante S, Villari P, Casuccio A, Marrazzo A. A randomized-controlled study of intrathecal versus epidural thoracic analgesia in patients undergoing abdominal cancer surgery. *J Clin Monit Comput*. 2008;**22(4)**:293–298. https://doi.org/10.1007/s10877-008-9132-1

13. Abouleish E, Rawal N, Shaw J, Lorenz T, Rashad MN. Intrathecal morphine 0.2 mg versus epidural bupivacaine 0.125% or their combination: effects on parturients. *Anesthesiology*. 1991;**74(4)**:711–716. https://doi.org/10.1097/00000542-199104000-00015

14. Massicotte L, Chalaoui K, Beaulieu D, Roy JD, Bissonnette F. Comparison of spinal anesthesia with general anesthesia on morphine requirement after abdominal hysterectomy. *Acta Anaesthesiol Scand*. 2009;**53(5)**:641–647. https://doi.org/10.1111/j.1399-6576.2009.01930.x

15. Hein A, Rösblad P, Gillis-Hargerstrand C, Schedvins K, Jakobsson J, Dahlgren G. Low dose intrathecal morphine effects on post-hysterectomy pain: a randomized placebo-controlled study. *Acta Anaesthesiol Scand*. 2012;**56(1)**:102–109. https://doi.org/10.1111/j.1399-6576.2011.02574.x

16. Duale C, Frey C, Bolandard F, Barriere A, Schoeffler P. Epidural versus intrathecal morphine for postoperative analgesia after Caesarean section. *Br J Anaesth*. 2003;**91(5)**: 690–694. https://doi.org/10.1093/bja/aeg249