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A Research Article entitled

Quality improvement of the postoperative recovery after abdominal surgery for gynecologic malignancy using intrathecal morphine. An open-label randomized trial.

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Abstract

Objectives: We aimed to determine whether regional analgesia with intrathecal morphine (ITM) in an enhanced recovery program (ERAS) gives a shorter hospital stay with equal health-related QoL to epidural analgesia (EDA) in women after midline laparotomy for proven or assumed gynecological malignancies.

Design: An open-label, randomized, single center study.

Setting: A tertiary referral Swedish university hospital.

Participants: Eighty women, 18-70 years of age, ASA I and II, admitted consecutively to the department of Obstetrics and Gynecology.

Interventions: The women were allocated (1:1) to either the standard analgesic method at the clinic (EDA) or the experimental treatment (ITM). An ERAS protocol with standardized perioperative routines and standardized general anesthesia were applied. The EDA or ITM started immediately preoperatively. The ITM group received morphine, clonidine and bupivacaine intrathecally; the EDA group had an epidural infusion of bupivacaine, adrenalin and fentanyl.

Primary and secondary outcome measures: Primary endpoints were length of hospital stay (LOS) and proportion of women discharged on postoperative day 3. Secondary endpoints were time to meet standardized discharge criteria, QoL, pain assessments and consumption of analgesics.

Results: Significantly more women allocated to ITM were discharged on day 3, 62.5% vs. 30% (adjusted OR 7.25, 95%CI 2.26 to 23.28; $p<0.001$). The LOS did not differ between the groups (median 3.3 vs. 4.3 days, adjusted $p=0.09$) but time to standardized discharge criteria was significantly shorter for the ITM group (3.0 vs. 4.0 days, adjusted $p<0.0001$). The ITM group used significantly less opioids. No differences were observed in pain assessment or QoL. No serious adverse events were attributed to ITM or EDA.

Conclusions: Compared with EDA, ITM is simpler to administer and manage, facilitates a short hospital stay and reduces opioid consumption postoperatively with an equally good QoL. ITM is effective as postoperative analgesia in gynecological cancer surgery.

Trial registration number: Clinical Trials NCT02026687

Keywords: Regional analgesia; Gynecological malignancy; Laparotomy; Opioid consumption; Quality improvement

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study evaluates quality improvement on postoperative recovery after gynecological cancer surgery in an enhanced recovery after surgery setting.
- The study is an open randomized controlled trial.
- The experimental treatment (intrathecal morphine) was compared with the standard care of postoperative analgesia (epidural analgesic) used in our setting.
- The objective was to compare the two analgesic methods in a clinical context, not to find the appropriate doses or types of analgesic agent for each method.

FUNDING STATEMENT

The study was supported financially by grants from the Swedish Society of Medicine (SLS-404711), the Medical Research Council of South-east Sweden (FORSS-8685), Linköping University and the Region Östergötland (LIO-356191, LIO-441781).

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

No additional data are available.

INTRODUCTION

Pain is an important component in the assessment of health-related quality of life (QoL). Besides the human suffering, insufficiently treated postoperative pain complicates mobilization, increases the risk for complications and might prolong hospitalization.

Regional analgesia with epidural analgesia (EDA) in abdominal surgery is recommended in most enhanced recovery after surgery (ERAS) protocols for use both during surgery and postoperatively.[1,2] Single-dose intrathecal morphine provide good analgesia during the first postoperative days after abdominal cancer surgery,[3-6] and improves the recovery after hysterectomy for benign conditions.[7,8] An additional analgesic effect can be obtained by adding the α-adrenergic agonist clonidine intrathecally.[4,9] In surgery for malignant gynecological diseases intrathecal morphine has been less described, although Kara et al. [10] in 2012 reported reduced morphine consumption and no increase in side effects. A few randomized studies have compared single-dose intrathecal morphine with continuous EDA after major abdominal surgery, showing disputed results concerning pain relief and hospital stay.[11-13]

Based on the potential benefits of intrathecal morphine as an effective and technically simple applied postoperative analgesic we designed this randomized study to compare the effects of a single-dose intrathecal combined morphine and clonidine (ITM) with the standard of care in the hospital using EDA in an ERAS program for abdominal surgery for proven or assumed gynecological malignant tumors.

The aim of the study was to determine whether ITM when compared with EDA in an ERAS program, shorten hospital stay with a similar patient experienced QoL. The primary endpoints were the proportion of women discharged from the hospital on the third day postoperatively and the *de facto* duration of hospital stay (LOS). Secondary outcome measurers were the time to meet standardized discharge criteria, QoL, pain assessment and analgesic consumption.

MATERIAL AND METHODS

We conducted an open-label, randomized, controlled, single center study in accordance with Good Clinical Practice guidelines.[14.9 From March 2014 to January 2016 all women who were admitted to the department of Obstetrics and Gynecology, University Hospital, Linköping, Sweden due to a proven or assumed gynecological abdominal malignancy were eligible for the study. Women 18 to 70 years, World Health Organization (WHO) performance status < 2, American Society of Anesthesiologists (ASA) score < 3 and speaking Swedish fluently were included. Exclusion criteria were contraindications against regional analgesia, physical or psychiatric disability and surgery where pain could not be expected to be controlled by the regional analgesia. Oral and written informed consent was obtained from all participants.

At the preoperative visit the women were allocated to ITM and EDA, 1:1, from a computer-generated randomization code,[15] using sealed opaque envelopes. The participant was informed about the allocation.

Surgery was conducted through a midline laparotomy with the preoperative intention to obtain macroscopically radical tumor resection. If this was not possible the tumor burden was either to be reduced to the minimal residual tumor (less than 1 cm in size) or samples were to be obtained, preferably by salpingo-oophorectomy, in order to establish the histopathological diagnosis. Board-certified gynecological oncologists performed the surgery. The surgical technique used was at the discretion of the surgeon.

All women received thrombosis prophylaxis (tinzaparin 4500 anti-Xa IE subcutaneously) once daily for 28 days beginning the evening before the surgery, and prophylactic antibiotics (1.5 gram cefuroxime and 1.0 gram metronidazole intravenously (iv.) as a single dose) before surgery start.

All women received a standardized premedication with paracetamol 1995 mg. The allocated intervention of regional analgesic was applied prior to commencing the general anesthesia. The experimental treatment group (the ITM) had an intrathecal combination of a single dose isobar bupivacaine 15 mg, morphine 0.2 mg and clonidine 75µg, preferably through a 25G spinal needle. The EDA group had the standard EDA regime used in the hospital. The EDA was performed by a low thoracic puncture. The epidural infusion was started after induction of the general anesthesia but before surgery by a bolus dose of fentanyl 50-100 µg and a bolus from a mixture of bupivacaine 2.4 mg/ml, adrenalin 2.4 µg/ml and fentanyl 1.8 µg/ml. The same mixture was used as a continuous infusion, typically 4-8 ml/h, throughout surgery.

General anesthesia was standardized in both groups: induction with fentanyl and propofol, intubation facilitated with rocuronium and maintenance with sevoflurane. Fentanyl and rocuronium was repeated if needed. All patients had a gastric tube and an indwelling urinary catheter. The

gastric tube was removed before waking the patient up. Local anesthetic (40 ml bupivacaine 2.5 mg/ml) was injected prefascially and subcutaneously in the abdominal wall in the area of the skin incision.

After the initial monitoring at the postoperative care unit, the postoperative pain management including surveillance of possible opioid side effects and neurological complications took place at the gynecological ward and followed the routines outlined by the Swedish Society of Anesthesiology and Intensive Care.[16]

The women in the ITM group received oral paracetamol 1330 mg and diclofenac 50 mg, both three times daily started on the day of surgery. Oxycodone 10-20 mg twice daily was added on the first postoperative day.

For the EDA group, a continuous epidural infusion of a mixture of bupivacain 1 mg/ml + adrenalin 2µg/ml + fentanyl 2 µg/ml including the possibility of additional patient-controlled bolus doses was started postoperatively at the postoperative care unit and continued until the morning of the third postoperative day. The infusion rate, normally 4-8 ml/h, and bolus doses, normally 2 ml, were decided on by the responsible physician. The patients also had oral paracetamol 1330 mg three times daily, starting on the day of surgery. Oral oxycodone 10-20 mg twice daily and diclofenac 50 mg three times daily were added in the morning of the third postoperative day before removal of the epidural catheter according to the guidelines.[16]

Rescue iv. morphine, 0.5-1 mg, iv. or oxycodone 5 mg orally was given if needed to women in both groups. In case of obvious pain relieving failure with the ITM or EDA iv. patient-controlled analgesia with morphine was started.

To quantify the amount of non-opioid analgesics given the defined daily dose (DDD) methodology was used.[17] All opioids, independent of administration route and including the ITM and the EDA, were converted to an equivalent iv. morphine dose.[18,19]

A numerical rating scale (NRS) 0-10 was used to assess the pain three times daily (8 am, 4 pm, 10 pm) at rest and at mobilization, i.e. when moving out of bed, raising both legs when in bed or when giving a strong cough.

The standardized criteria for discharge were: the patient was mobilized, tolerated a normal diet, had sufficient pain relief with oral analgesics (NRS ≤ 4), showed no signs of mechanical bowel obstruction and had voided spontaneously with less than 150 ml residual urine. If the last criterion was not met, the woman went home with the catheter, which was removed policlinically. The discharge criteria were checked twice daily. The decision on discharge was made according to the medical criteria but could be prolonged by social or other practical, personal conditions. Both the *de facto* hospital stay (LOS) and the length of the stay until the discharge criteria were met were calculated.

The research nurse had telephone contact with the participants the day after discharge and then once a week until six weeks postoperatively. Complications were registered and graded according to the Clavien-Dindo classification.[20] The study was completed after the six-week contact.

The QoL was assessed by two commonly used validated generic QoL forms. The EQ-5Dform was completed preoperatively, daily during the first week after surgery, then once weekly until the six-week postoperative visit. [21] The Short Form – 36 Health Survey (SF-36) form was completed preoperatively and six weeks postoperatively.[22]

Patient involvement

Patients were not involved in the study design or conduct of the study. By assessing QoL as part of the protocol, the patients reported a surrogate measure of the burden of the intervention.

Ethical approval

The study was approved by the Regional Ethics Board of Linköping University (D.nr. 2013/185-31, approval date 29 August 2013), the Swedish Medical Products Agency (Eu-nr. 2013-001873-25; D.nr. 5.1-2013-50334, approval date 1 August 2013) and monitored by an independent monitor.

Statistics

Power analysis was based on the primary outcome endpoints. Providing that the minimum clinical relevant difference in hospital stay between the groups was 0.5 days and the proportion of women discharged on the third postoperative day was 80% (ITM group) and 50% (EDA group), each group should consist of 40 women including a 10% dropout rate in order to show statistical significance at a 5% level with an 80% power.

Data are presented as median (range) or number (percent). χ^2 tests and Fisher's exact tests were used to analyze categorical data and Mann-Whitney U-tests for continuous data. Differences in continuous outcome measures between the two groups were analyzed by means of analysis of covariance (ANCOVA) and nominal effect measures by logistic regression. Adjustments were done simultaneously for age, body mass index (BMI), smoking habits, occurrence of complications during the hospital stay and final diagnosis malignant vs benign condition in the multivariate models. The results of the logistic regression models are given as odds ratios (ORs) or adjusted ORs (aORs) and 95% confidence intervals (CI).

A repeated measures analysis of variance (ANOVA) was used to analyze data measured on more occasions. Adjustments were made for the dichotomized final diagnosis of a malignant or benign disease. Fisher's protected least significant difference (PLSD) post hoc tests were used to analyze the pairwise associations between groups on each single occasion of measurement.

The significance level was set at $p<0.05$. The statistical tests were two-tailed. All analyses were carried out according to intention-to-treat principles using Statistica v13.2 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA).

RESULTS

The description of the selection and the randomization of the study population is presented in Figure 1. Forty women were chosen to receive EDA and 40 to receive ITM. One woman in each group did not receive any regional analgesia and one woman had ITM instead of EDA based on a mistake by the attending anesthesiologist.

The descriptive and demographic data are shown in Table 1. The clinical surgical and anesthesiological data are presented in Table 2.

In 20% the final diagnosis postoperatively was benign, most often showing a benign ovarian tumor or a large uterine fibroid. The benign diseases were evenly distributed between the two groups.

Significantly more women in the ITM group were discharged from the hospital on the third day (25 women (62.5%) in the ITM group vs. 12 (30%) in the EDA group, (OR 3.89, 95%CI; 1.53 to 9.87); p=0.004). When adjusting for age, BMI, smoking habits, complications during the hospital stay and malignant vs. benign condition, this association was even stronger (aOR 7.25, 95%CI; 2.26 to 23.28; p<0.001). The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (range) 3.3 (1.5-56.3) vs. 4.3 (2.2-43.2) days; p=0.01). However, when adjusted for the confounders the statistical significance disappeared (p=0.09). The time to meet standardized discharge criteria was significantly shorter in the ITM group compared with the EDA group (median (range) 3.0 (1.5-56.0) vs. 4.0 (1.5-7.5) days; p<0.001). This significant difference remained when adjusted for the confounders used previously (p<0.0001). Complications during the hospital stay was a strong independent risk factor for prolonged hospital stay (OR 9.53, 95%CI; 1.69 to 53.7).

The EDA group had a significantly higher total consumption of opioids than the ITM group whereas the use of non-opioids was similar in the two groups (Figure 2). Simultaneously, there was no significant difference in the overall assessment of pain (NRS) between the groups (Figure 3). The two groups showed different patterns in the NRS ratings as indicated by the significant interaction effects. The post hoc tests showed that the NRS ratings were significantly higher in the ITM group during the first two days at mobilization and on a few occasions at rest, whereas the EDA group scored significantly higher both at rest and at mobilization on day three when the EDA catheter was removed.

The QoL parameters as measured by the EQ-5D, day-by-day, presented no statistically significant difference in health index between the two groups (Figure 4). Neither did the SF-36 show any statistically significant difference in any of the subscales or summary scores between the groups (Table 3). The role physical and the physical component summary score had not recovered to baseline level in either of the two groups after six weeks whereas the mental health and the

mental component summary score showed a significant improvement after six weeks compared with the preoperative assessment.

The EDA failed in four women (10%) and ITM analgesia in one (2.5%). These women had either a new EDA in the post-anesthesia care or received patient-controlled morphine iv. One accidental dural puncture occurred in the EDA group. No post-dural puncture headache or serious adverse anesthesiological side effects were observed in either of the groups. The perioperative complications graded according to the Clavien-Dindo classification in the two groups did not differ significantly as shown in Table 4.

DISCUSSION

The study showed that a single-dose of intrathecal morphine used as postoperative analgesia compared with epidural analgesia gives advantages in abdominal gynecological cancer surgery in regard to the time to meet the standardized discharge criteria and lower consumption of opioids postoperatively. A substantially higher proportion of women with ITM was discharged on the third postoperative day with an evenly reported health-related QoL and assessment of pain as women with EDA. A key point of an ERAS protocol is simplicity and a single intrathecal injection is simpler that a continuous epidural requiring ongoing management and monitoring. We regard ITM as a quality improvement from the perspective of both the patients and the health care.

The strengths of this trial are the randomized design, the unanimous ERAS and postoperative surveillance of the patients in the gynecological ward, the assessment of pain at rest and during mobilization, and the active use of rescue analgesics on demand. For obvious reasons the interventions could not be blinded for the participants or the staff. A limitation for generalization of the results is the single center design. The ERAS concept is well established in daily clinical work and therefore the results can only be generalized to facilities with similar clinical standards and only to units that manage patients with regional analgesia. The two methods of regional analgesia may not be comparable in giving potentially equivalent analgesia with the dosage and preparation used. However, our objective was to compare the two analgesic methods in a clinical context, not to find the appropriate doses or types of analgesic agent for each method. Therefore, we selected conventional doses of the medications.

The use of intrathecal opioids requires close monitoring of sedation and respiratory rate for 12 hours. The nurses on the gynecological ward were educated regarding complications after ITM with special regard to late respiratory depression and the surveillance followed strict national recommendations. Intrathecal morphine is used in approximately two-thirds of Swedish gynecological units in connection with abdominal hysterectomy having a continued observation on the regular gynecological ward after an initial period of 2-6 hours in a postoperative care unit.[23] The intrathecal morphine dose 0.2 mg was chosen with the purpose of giving adequate analgesia at a risk of respiratory depression that equals systemic opioid analgesia.[24] Following abdominal hysterectomy there is no benefit from increasing the morphine dose over 0.2 mg.[25]

The *de facto* duration of hospital stay was shorter in the ITM group. A similar short length of stay has recently been reported from other ERAS programs for gynecological cancer.[26-28] Wijk et al.[28] used an analgesic regimen based on oral paracetamol and diclofenac and over 90% of the patients did not need systemic opioids from the day after surgery. Like our study, they used standardized discharge criteria. It is important to analyze when discharge criteria are fulfilled, as

they are robust and generalizable. The length of hospital stay is often influenced by context-specific social factors.

Multimodal analgesic regime minimizing opioid use has been shown to enhance recovery.[2,29] Despite the higher rating of NRS at mobilization during the first few days in the ITM group the consumption of opioids was nearly three times lower in the same time period compared with the EDA group, and the QoL index did not differ between the groups. This may imply that the women in the ITM group were as satisfied as the EDA group with their pain management, and the difference in NRS rating at mobilization was less clinically significant. The study included only ASA class I-II patients. For patients with more severe cardio-pulmonary comorbidity the EDA regimen may offer a better early analgesia that could be favorable. A study on abdominal hysterectomy for endometrial cancer showed that women without EDA ceased opioid analgesia earlier than those women who had an EDA,[30] indicating a possible overuse of opioids in EDA. An earlier removal of the EDA catheter, for example after 48 hours, is a possible development of the EDA regimen. Prior to this trial, the standard praxis in our department was removal of the EDA catheter on the third day. Consequently, we studied the ITM against this regime. The difference in DDD of non-opioids seen until the third postoperative day was due to the protocol demand and the clinical routine in the hospital that diclofenac was not allowed in the EDA group until the EDA catheter was removed. The uneven use of diclofenac in the groups during the first three postoperative days may be seen as a weakness of the study. However, the DDD of non-opioids raised from day 1 to day 3 in the EDA group by using diclofenac in some patients against the study protocol and the clinical routines in the department. It is therefore less likely that the difference in DDD of non-opioids can explain the significant difference in opioids. In spite of the addition of diclofenac and consequently an increased DDD on the third postoperative day, the women in the EDA group rated the NRS at rest and at mobilization higher than the ITM women.

In order to increase the patient-oriented focus on recovery we used two generic QoL forms to assess the patient's experience of the health status. The EQ-5D was used to determine the short-term recovery day-by-day, whereas the SF-36 was used for a longer-term assessment. We found no significant differences in QoL between the groups, indicating that ITM and EDA were equally effective in obtaining patient satisfaction.

Severe complications after EDA and ITM are rare but still the indication for the regional analgesia should always be considered individually. In this trial no severe complications attributed to the regional analgesia occurred and the surgical complications seemed to be equally distributed between the groups. However, the trial was not powered to detect a statistical difference in complications.

In conclusion, ITM given in an ERAS program seems to be safe, simple to administer and effective as postoperative analgesia and gives quality advantages concerning the postoperative recovery in gynecological abdominal cancer surgery.

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FIGURE LEGENDS

Figure 1. CONSORT flow chart of participants in the study. EDA, epidural analgesia. ITM, intrathecal morphine analgesia.

Figure 2. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and from Day 0 to Day 42 for DDD non-opioids are presented in the table below the diagram. Adjusted for malignant/benign condition. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Figure 3. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. Adjusted for malignant/benign condition. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Figure 4. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA and post hoc tests from Day 0 - 42 assessment is presented. Adjusted for malignant/benign condition. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

AUTHOR STATEMENT

AUTHOR´S CONTRIBUTION

PK, NBW and LN designed and conducted the study. PK performed the statistically analyses. PK, OB, NBW and LN undertook the initial interpretation of the data, which was followed by discussions with all the authors. PK, OB and LN drafted the initial version of the manuscript, followed by a critical revision process for intellectual content involving all authors. All authors agreed to the final version of the manuscript before submission. All authors agree to be accountable for the accuracy of any part of the work.

Table 1. Descriptive and demographic data of the study population.

	EDA group n = 40	ITM group n = 40
Age (years)	59.0 (30.0-70.0)	58.5 (35.0-68.0)
< 50 years	7 (17.5%)	6 (15%)
50 – 60 years	16 (40%)	20 (50%)
> 60 years	17 (42.5%)	14 (35%)
Body mass index (kg/m^2)	28.5 (18.2-38.1)	27.8 (20.3-43.5)
BMI < 25 kg/m^2	11 (27.5%)	13 (32.5%)
BMI 25-29.9 kg/m^2	15 (37.5%)	15 (37.5%)
BMI 30-34.9 kg/m^2	9 (22.5%)	7 (17.5%)
BMI ≥ 35 kg/m^2	5 (12.5%)	5 (12.5%)
Parity	2.0 (0-5)	2.0 (0-4)
Smokers	5 (12.5%)	4 (10%)
Previous laparotomy	17 (42.5%)	17 (42.5%)
ASA classification		
Class I	15 (37.5%)	15 (37.5%)
Class II	25 (62.5%)	25 (62.5%)
Comorbidity		
Diabetes mellitus	4 (10%)	4 (10%)
Cardiovascular disease	13 (32.5%)	12 (30%)
Pulmonary disease	4 (10%)	5 (12.5%)
Mild psychiatric disease	6 (12.5%)	4 (10%)
Previous malignancy	4 (10%)	2 (5%)
Current medication		
Antidepressant/sedative	8 (20%)	7 (17.5%)
Analgesics	7 (17.5%)	12 (30%)
Indication for surgery		
Proven/assumed gynecologic malignancy	16/24 (40%/60%)	18/22 (45%/55%)

Figures denote median and range or number and percent.
ASA, American Society of Anesthesiologists risk classification; BMI, body mass index. EDA, epidural analgesia. ITM, intrathecal morphine analgesia

Table 2. Clinical surgical and anesthesiological data.

	EDA group n = 40	ITM group n = 40	*p*-value*
Operation time (minutes)	116 (44-352)	139 (48-421)	0.10
Estimated per-operative blood loss (ml)	100 (20-800)	200 (20-2000)	0.28
Extent of skin incision from superior edge of symphysis pubis to:			
- umbilicus	6 (15%)	2 (5%)	
- between umbilicus and PX	17 (42.5%)	21 (52.5%)	0.30
- PX	17 (42.5%)	17 (42.5%)	
Extent of surgery (no. of women)			
- Category I	1 (2.5%)	1 (2.5%)	
- Category II	8 (20%)	2 (5%)	
- Category III	17 (42.5%)	18 (45%)	0.25
- Category IV	8 (20%)	14 (35%)	
- Category V	6 (15%)	5 (12.5%)	
Tumor status at end of surgery‡ (no. of women):			
- Macroscopically radical	17 (63%)	25 (76%)	
- Minimal disease	3 (11%)	5 (15%)	0.22
- Bulky disease	7 (26%)	3 (9%)	
Histopathological diagnosis			
- Ovarian/fallopian tube/peritoneal cancer	13 (32.5%)	18 (45%)	
- Ovarian borderline cancer	5 (12.5%)	0 (0%)	
- Uterus carcinoma or sarcoma	7 (17.5%)	13 (32.5%)	0.06
- Cervical cancer	1 (2.5%)	0 (0%)	
- Appendix or sigmoideum cancer	1 (2.5%)	2 (5%)	
- Benign ovarian or uterine tumor	13 (32.5%)	7 (17.5%)	
CAD at discharge (no. of women)	3 (7.7%)	4 (10.3%)	0.45†
Premedication			
Paracetamol (DDD)	0.67 (0-0.67))	0.67 (0-0.67)	0.99
Morphine § (mg)	0 (0-3.0)	0 (0-1.5)	0.30
Antiemetic, medication (no. of women)	16 (57%)	12 (43%)	0.35
Antiemetic, Acupressure band (no. of women)	22 (47%)	25 (53%)	0.50
Anesthetic drugs:			
Propofol (mg)	200 (120-2032)	200 (150-500)	0.62
Rokuroniumbromid (mg)	50 (15-80)	50 (30-110)	0.32
Equivalent morphine dose (mg)	30.5 (18.6-146.3)	45.0 (20.0-68.0)	<0.0001
Paracetamol (mg)	0 (0-1000)	0 (0-1000)	0.99
Vasoactive treatment during anesthesia			
Ephedrine (mg)	20 (0-100)	20 (0-80)	0.79
Phenylephrine (µg)	0 (0-4000)	0 (0-5200)	0.50
Norepinephrine (µg)	0 (0-2000)	0 (0-2698)	0.57
Atropine (mg)	0 (0-0.5)	0 (0-0.5)	0.24
Anesthesia time (minutes)	177.5 (110-465)	200 (98-475)	0.08
Lowest body temperature during surgery (°C)	35.7 (34.3-36.6)	35.6 (34.7-36.3)	0.16
Body temperature at end of surgery (°C)	36.1 (34.8-36.8)	36.1 (35.2-37.2)	0.68
Time in PACU (hours)	4.6 (2.9-27.2)	5.6 (3.4-18.4)	0.09

Figures denote number and (percent) or median and (range).

CAD, transurethral or supra pubic indwelling catheter. DDD, defined daily dose. EDA, epidural analgesia. ITM, intrathecal morphine analgesia. PACU, post anesthesia care unit. PX, processus xiphoideus.

Categories of extent of surgery: Category I, diagnostic surgery; Category II, resection of gynecologic organs only; Category III, resection of gynecologic organs, omentectomy and ± appendectomy; Category IV, as Category III + pelvic and/or paraaortic lymphadenectomy; Category V, as Category III ± pelvic and/or paraaortic lymphadenectomy + resection of abdominal visceral organs.

*Mann-Whitney U-test applied for continuous data and $\chi 2$- test (df 1-5) or †Fisher's exact test for categorical data. ‡ in women with malignant disease. § Equivalent dose morphine intravenously

Table 3. SF-36 subscales and summary scores. A high score represents a better health-related quality of life

	Time lapse						
	Baseline		Day 42		Repeated measures ANOVA*		
SF-36 subscales	EDA	ITM	EDA	ITM	Main effect between modes of analgesia	Main effect over time	Interaction effect
Physical functioning	76.6 (23.0)	74.9 (21.5)	76.4 (19.4)	76.1 (20.9)	*p*=0.90	*p*=0.96	*p*=0.80
Role physical	47.5 (45.6)	53.1 (44.3)	17.5 (35.0)	7.5 (24.8)	*p* =0.94	*p*<0.001	*p*=0.16
Bodily pain	59.5 (30.0)	65.1 (25.1)	58.5 (23.2)	65.5 (23.9)	*p*=0.20	*p*=0.78	*p*=0.74
General health	69.0 (21.3)	67.5 (16.8)	64.2 (22.4)	68.7 (16.9)	*p*=0.50	*p*=0.71	*p*=0.13
Vitality	54.0 (21.7)	54.4 (21.8)	48.5 (20.5)	54.6 (18.9)	*p*=0.37	*p*=0.97	*p*=0.12
Social functioning	70.0 (27.1)	69.4 (25.8)	65.6 (26.5)	70.9 (19.7)	*p*=0.37	*p*=0.88	*p*=0.20
Role emotional	62.5 (44.8)	63.3 (45.2)	58.3 (46.4)	73.3 (42.8)	*p*=0.14	*p*=0.15	*p*=0.14
Mental health	70.1 (19.4)	65.7 (19.8)	72.8 (19.8)	75.6 (15.3)	*p*=0.95	*p*=0.001	*p*=0.05
Physical component summary score	43.1 (12.0)	44.3 (11.6)	38.9 (8.1)	37.9 (7.4)	*p*=0.85	*p*<0.001	*p*=0.29
Mental component summary score	42.9 (13.5)	41.6 (13.2)	43.1 (12.8)	47.6 (10.2)	*p*=0.29	*p*<0.01	*p*=0.02

Figures indicate mean (1 SD). EDA = epidural analgesia. ITM = intrathecal morphine analgesia.

* Adjusted for malignant/benign condition.

No significant differences were observed in the subscales between the two groups at baseline (Mann-Whitney U-test).

Table 4. The Clavien-Dindo classification of surgical complications (contracted form) within the study period of six weeks.

	EDA group (n=40)	ITM group (n=40)	p-value*
No complications	19 (47.5)	19 (47.5)	
Grade I	13 (32.5)	8 (20.0)	
Grade II	6 (15.0)	6 (15.0)	0.313
Grade III	1 (2.5)	6 (15.0)	
Grade IV	1 (2.5)	1 (2.5)	

Figures denote number and (percent).
EDA = epidural analgesia. ITM = intrathecal morphine analgesia. * χ^2 for trends (df=4).

Insert Figure 2 A here	Insert Figure 2 B here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
Opioids (Equivalent morphine (mg))	*p*<0.001	*p*<0.001	*p*<0.001
DDD non-opioids	*p* = 0.70	*p* < 0.001	*p*<0.001

	Bonferroni post hoc tests, (p-value)						
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Opioids	<0.0001	<0.0001	<0.0001	1.00	1.00	1.00	1.00
DDD non-opioids	1.00	<0.001	1.00	1.00	1.00	1.00	0.10

Figure 2. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and from Day 0 to Day 42 for DDD non-opioids are presented in the table below the diagram. Adjusted for malignant/benign condition. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Insert Figure 3 A here	Insert Figure 3 B here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
NRS at rest	$p = 0.38$	$p < 0.001$	$p < 0.001$
NRS at mobilization	$p = 0.10$	$p < 0.001$	$p < 0.001$

	Bonferroni post hoc tests, (p-value)																		
	Day 0.3	Day 1.1	Day 1.2	Day 1.3	Day 2.1	Day 2.2	Day 2.3	Day 3.1	Day 3.2	Day 3.3	Day 4.1	Day 4.2	Day 4.3	Day 5.1	Day 5.2	Day 5.3	Day 6.1	Day 6.2	Day 6.3
NRS at rest	1.00	1.00	0.12	1.00	1.00	1.00	1.00	1.00	0.13	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
NRS at mobilization	0.01	0.06	0.01	0.46	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 3. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. Adjusted for malignant/benign condition. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Insert Figure 4 here

Repeated measures ANOVA		
Main effect between groups	Main effect over time	Interaction effect
$p = 0.32$	$p < 0.0001$	$p = 0.25$

Bonferroni post hoc tests. *p*-values

Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 4. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA and post hoc tests from Day 0 - 42 assessment is presented. Adjusted for malignant/benign condition. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

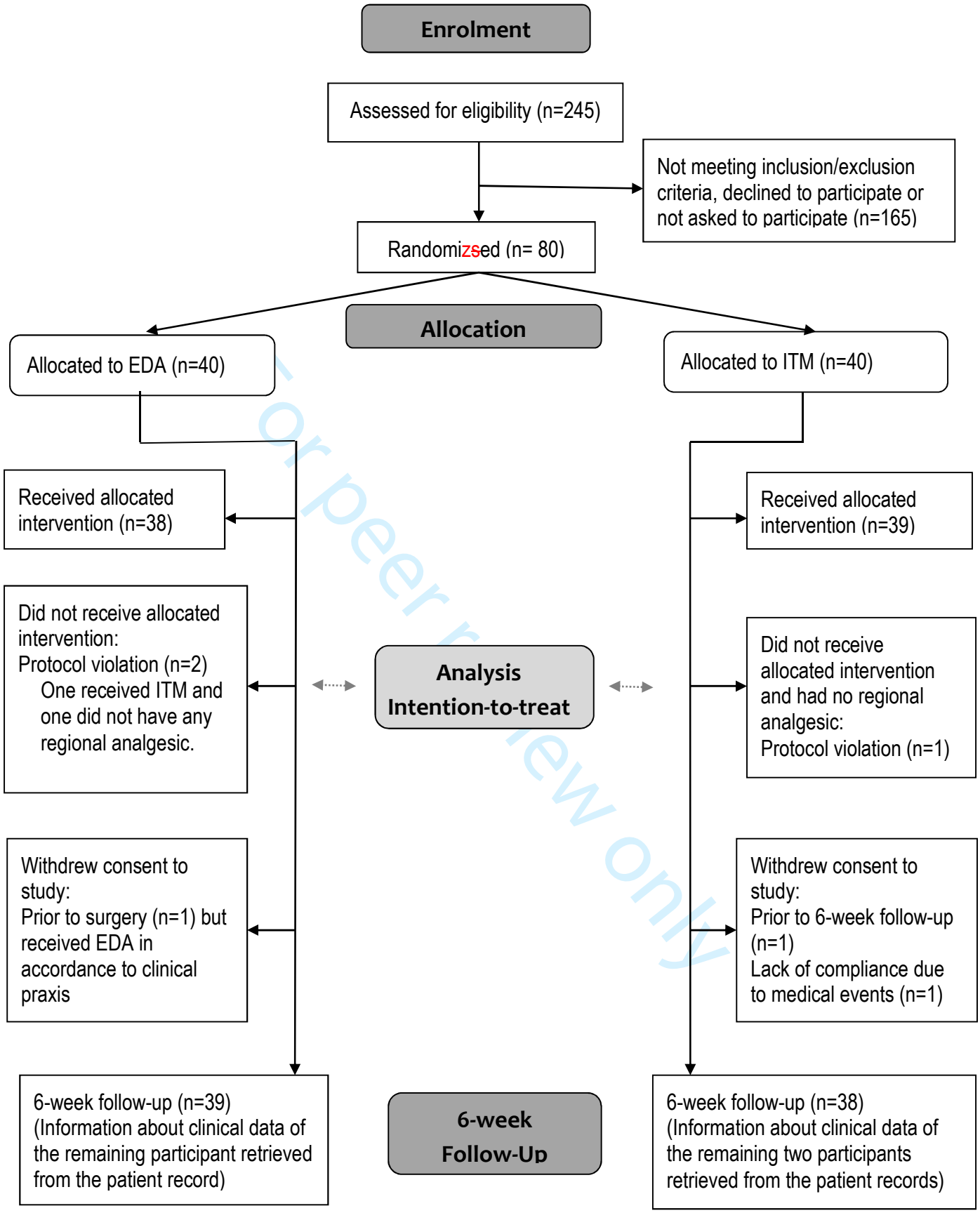

Figure 1.

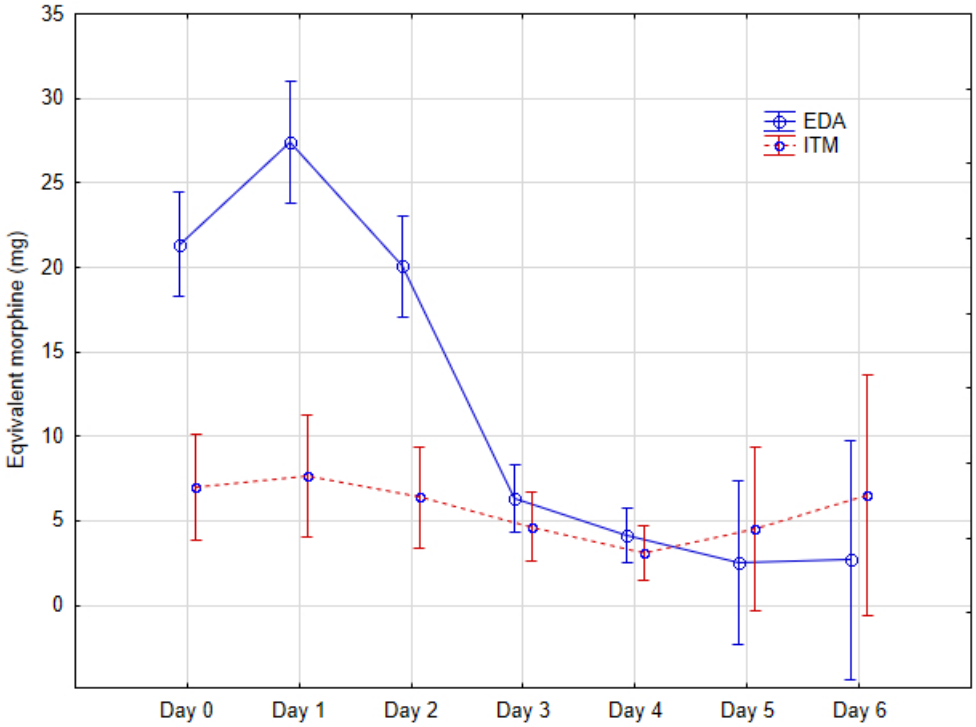

Figure 2A

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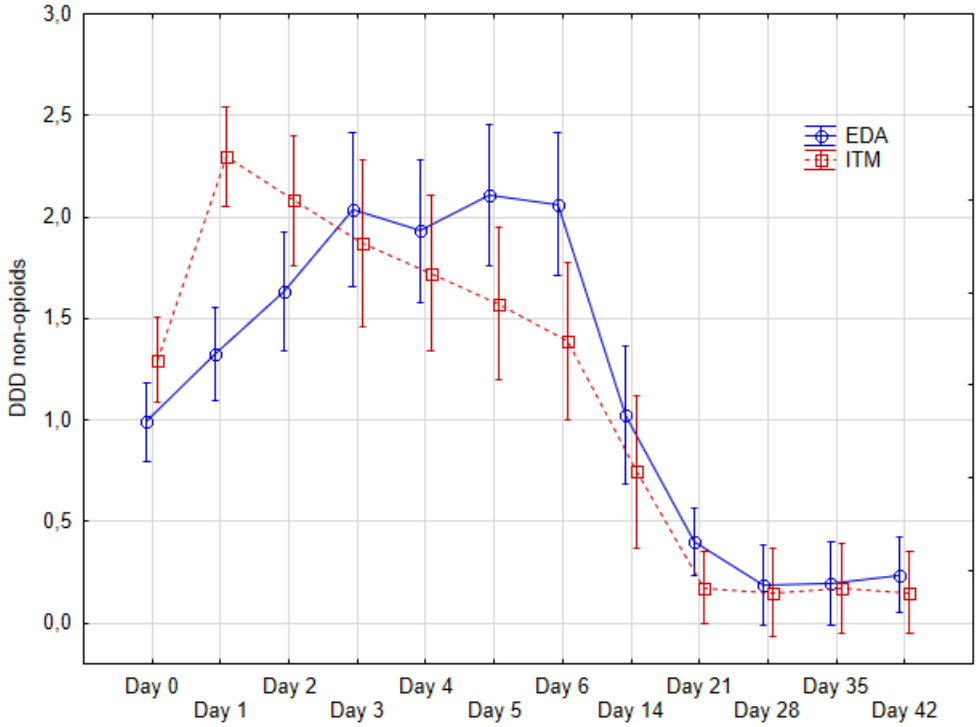

Figure 2B

165x123mm (96 x 96 DPI)

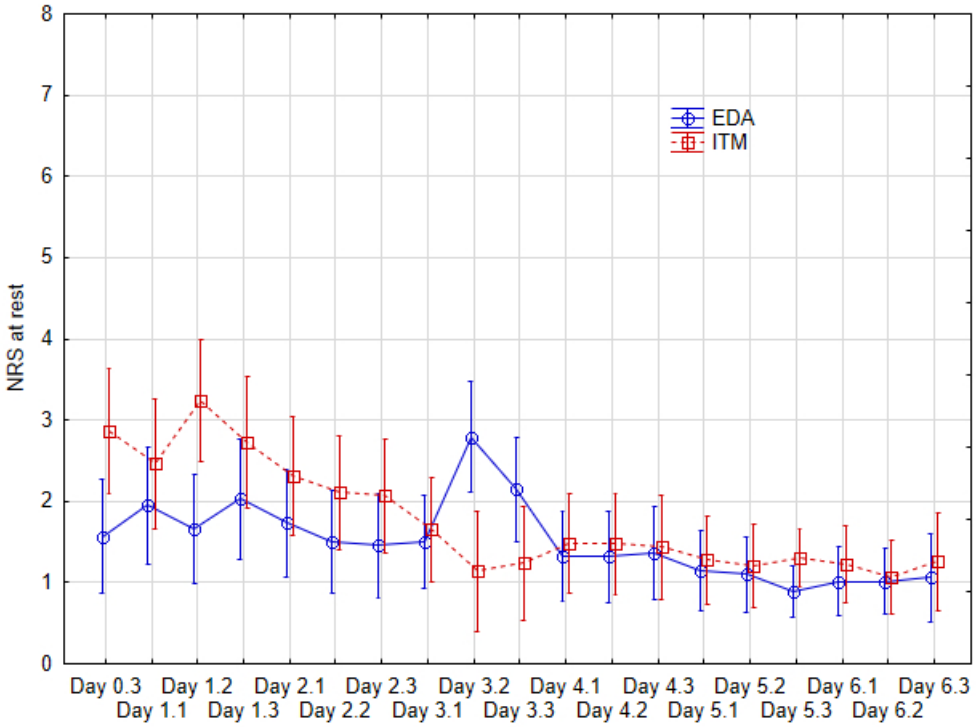

Figure 3A

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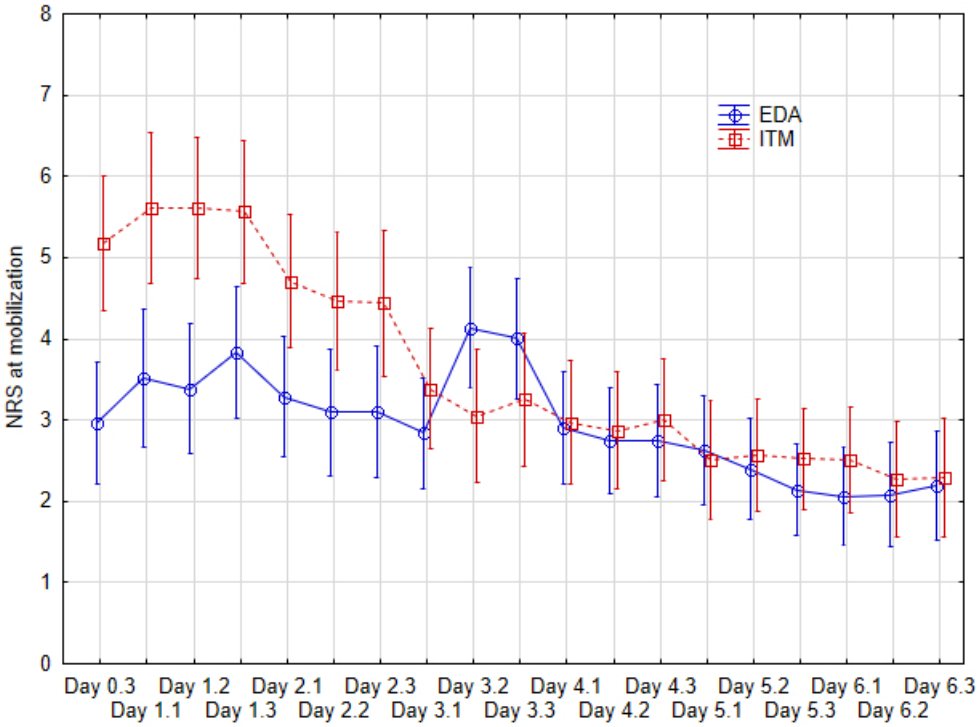

Figure 3B

165x123mm (96 x 96 DPI)

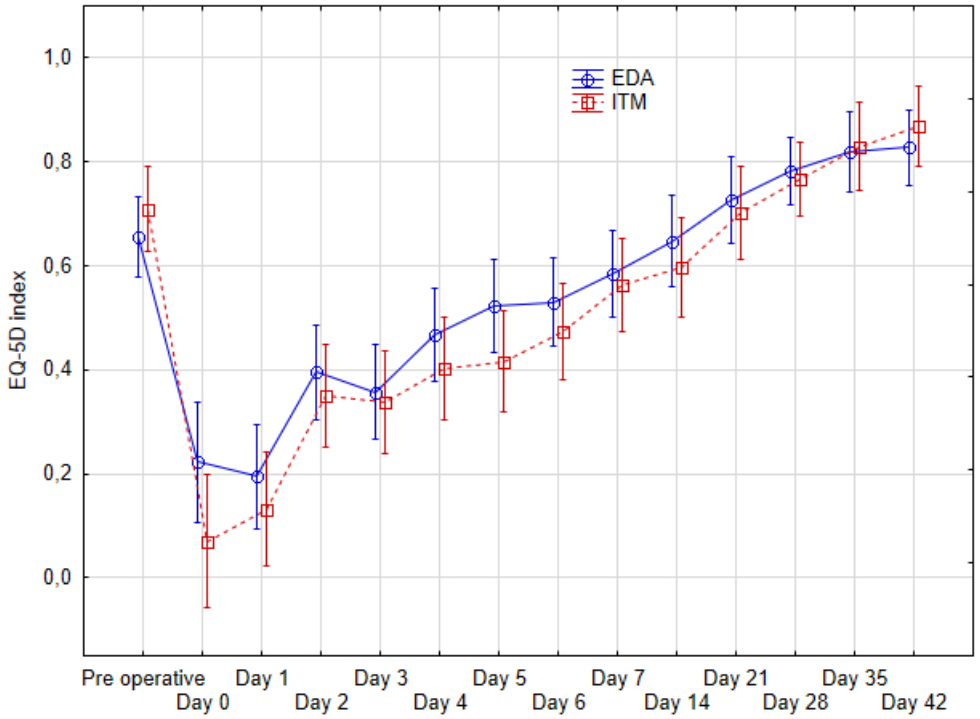

Figure 4

165x123mm (96 x 96 DPI)

Reporting checklist for randomized trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORT reporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Background and objectives	#2a	Scientific background and explanation of rationale	4
	#2b	Specific objectives or hypothesis	4
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	5
	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Na
Participants	#4a	Eligibility criteria for participants	5
	#4b	Settings and locations where the data were collected	5
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including	5-6

		how and when they were actually administered	
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	4-6
Sample size	#7a	How sample size was determined.	7
	#7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	5
	#8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	NA
	#11b	If relevant, description of the similarity of interventions	NA
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Participant flow diagram (strongly recommended)	#13a	A diagram is strongly recommended. For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1

Recruitment	#14a	Dates defining the periods of recruitment and follow-up	5
	#14b	Why the trial ended or was stopped	NA
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 1,2,4
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8, Figures 2-4
	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	10, Table 4
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	Se Cover letter
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	3

BMJ Open

The effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy. An open-label randomized trial.

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Keywords:	Gynaecological oncology < GYNAECOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult surgery < SURGERY, Anaesthesia in oncology < ANAESTHETICS

A Research Article entitled

The effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy. An open-label randomized trial.

Authors:

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Abstract

Objectives: We aimed to determine whether regional analgesia with intrathecal morphine (ITM) in an enhanced recovery program (ERAS) gives a shorter hospital stay with good pain relief and equal health-related quality of life (QoL) to epidural analgesia (EDA) in women after midline laparotomy for proven or assumed gynecological malignancies.

Design: An open-label, randomized, single center study.

Setting: A tertiary referral Swedish university hospital.

Participants: Eighty women, 18-70 years of age, ASA I and II, admitted consecutively to the department of Obstetrics and Gynecology.

Interventions: The women were allocated (1:1) to either the standard analgesic method at the clinic (EDA) or the experimental treatment (ITM). An ERAS protocol with standardized perioperative routines and standardized general anesthesia were applied. The EDA or ITM started immediately preoperatively. The ITM group received morphine, clonidine and bupivacaine intrathecally; the EDA group had an epidural infusion of bupivacaine, adrenalin and fentanyl.

Primary and secondary outcome measures: Primary endpoint was length of hospital stay (LOS). Secondary endpoints were QoL and pain assessments.

Results: The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (IQR) 3.3 (1.5-56.3) vs. 4.3 (2.2-43.2) days; p=0.01). No differences were observed in pain assessment or QoL. The ITM group used postoperatively the first week significantly less opioids than the EDA group, (median (IQR) 20 mg (14-35 mg) vs. 81 mg (67-101 mg; p<0.0001). No serious adverse events were attributed to ITM or EDA.

Conclusions: Compared with EDA, ITM is simpler to administer and manage, is associated with shorter hospital stay and reduces opioid consumption postoperatively with an equally good QoL. ITM is effective as postoperative analgesia in gynecological cancer surgery.

Trial registration number: Clinical Trials NCT02026687

Keywords: Regional analgesia; Gynecological malignancy; Laparotomy; Opioid consumption; Quality improvement

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study evaluates quality improvement on postoperative recovery after gynecological cancer surgery in an enhanced recovery after surgery setting.
- The study is an open randomized controlled trial.
- The experimental treatment (intrathecal morphine) was compared with the standard care of postoperative analgesia (epidural analgesic) used in our setting.
- The objective was to compare the two analgesic methods in a clinical relevant multimodal context, not to find the appropriate doses or types of analgesic agent for each method.

FUNDING STATEMENT

The study was supported financially by grants from the Swedish Society of Medicine (SLS-404711), the Medical Research Council of South-east Sweden (FORSS-8685), Linköping University and the Region Östergötland (LIO-356191, LIO-441781).

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

No additional data are available.

INTRODUCTION

Pain is an important component in the assessment of health-related quality of life (QoL). Besides the human suffering, insufficiently treated postoperative pain complicates mobilization, increases the risk for complications and might prolong hospitalization.

Regional analgesia with epidural analgesia (EDA) in abdominal surgery is recommended in most enhanced recovery after surgery (ERAS) protocols for use both during surgery and postoperatively.[1,2] Single-dose intrathecal morphine provide good analgesia during the first postoperative days after abdominal cancer surgery,[3-6] and improves the recovery after hysterectomy for benign conditions.[7,8] An additional analgesic effect can be obtained by adding the α-adrenergic agonist clonidine intrathecally.[4,9,10] In surgery for malignant gynecological diseases intrathecal morphine has been less described, although Kara et al. [11] in 2012 reported reduced morphine consumption and no increase in side effects. A few randomized studies have compared single-dose intrathecal morphine with continuous EDA after major abdominal surgery, showing disputed results concerning pain relief and hospital stay.[12-14]

Based on the potential benefits of intrathecal morphine as an effective and technically simple applied postoperative analgesic we designed this randomized study to compare the effects of a single-dose intrathecal combined morphine and clonidine (ITM) with the standard of care in the hospital using EDA in an ERAS program for abdominal surgery for proven or assumed gynecological malignant tumors.

The aim of the study was to determine whether ITM when compared with EDA in an ERAS program, shorten hospital stay with a similar patient experienced QoL.

MATERIAL AND METHODS

We conducted an open-label, randomized, controlled, single center study in accordance with Good Clinical Practice guidelines.[15] From March 2014 to January 2016 all women who were admitted to the department of Obstetrics and Gynecology, University Hospital, Linköping, Sweden due to a proven or assumed gynecological abdominal malignancy were eligible for the study. Women 18 to 70 years, World Health Organization (WHO) performance status < 2, American Society of Anesthesiologists (ASA) score < 3 and speaking Swedish fluently were included. Exclusion criteria were contraindications against regional analgesia, physical or psychiatric disability and surgery where pain could not be expected to be controlled by the regional analgesia. Oral and written informed consent was obtained from all participants.

At the preoperative visit the women were allocated to ITM and EDA, 1:1, from a computer-generated randomization code,[16] using sealed opaque envelopes. The participant was informed about the allocation.

Surgery was conducted through a midline laparotomy with the preoperative intention to obtain macroscopically radical tumor resection. If this was not possible the tumor burden was either to be reduced to the minimal residual tumor (less than 1 cm in size) or samples were to be obtained, preferably by salpingo-oophorectomy, in order to establish the histopathological diagnosis. Board-certified gynecological oncologists performed the surgery. The surgical technique used was at the discretion of the surgeon.

All women received thrombosis prophylaxis (tinzaparin 4500 anti-Xa IE subcutaneously) once daily for 28 days beginning the evening before the surgery, and prophylactic antibiotics (1.5 gram cefuroxime and 1.0 gram metronidazole intravenously (iv.) as a single dose) before surgery start.

All women received a standardized premedication with paracetamol 1995 mg. The allocated intervention of regional analgesic was applied prior to commencing the general anesthesia. The experimental treatment group (the ITM) had an intrathecal combination of a single dose isobar bupivacaine 15 mg, morphine 0.2 mg and clonidine 75µg, preferably through a 25G spinal needle. The EDA group had the standard EDA regime used in the hospital. The EDA was performed by a low thoracic puncture. The epidural infusion was started after induction of the general anesthesia but before surgery by a bolus dose of fentanyl 50-100 µg and a bolus from a mixture of bupivacaine 2.4 mg/ml, adrenalin 2.4 µg/ml and fentanyl 1.8 µg/ml. The same mixture was used as a continuous infusion, typically 4-8 ml/h, throughout surgery.

General anesthesia was standardized in both groups: induction with fentanyl and propofol, intubation facilitated with rocuronium and maintenance with sevoflurane. Fentanyl and rocuronium was repeated if needed. All patients had a gastric tube and an indwelling urinary catheter. The

gastric tube was removed before waking the patient up. Local anesthetic (40 ml bupivacaine 2.5 mg/ml) was injected prefascially and subcutaneously in the abdominal wall in the area of the skin incision.

After the initial monitoring at the postoperative care unit, the postoperative pain management including surveillance of possible opioid side effects and neurological complications took place at the gynecological ward and followed the routines outlined by the Swedish Society of Anesthesiology and Intensive Care.[17]

The women in the ITM group received oral paracetamol 1330 mg and diclofenac 50 mg, both three times daily started on the day of surgery. Oxycodone 10-20 mg twice daily was added on the first postoperative day.

For the EDA group, a continuous epidural infusion of a mixture of bupivacain 1 mg/ml + adrenalin 2µg/ml + fentanyl 2 µg/ml including the possibility of additional patient-controlled bolus doses was started postoperatively at the postoperative care unit and continued until the morning of the third postoperative day. The infusion rate, normally 4-8 ml/h, and bolus doses, normally 2 ml, were decided on by the responsible physician. The patients also had oral paracetamol 1330 mg three times daily, starting on the day of surgery. Oral oxycodone 10-20 mg twice daily and diclofenac 50 mg three times daily were added in the morning of the third postoperative day before removal of the epidural catheter according to the guidelines.[17]

Rescue opioids were the same for both groups; iv. morphine, 0.5-1 mg, iv. or oxycodone 5 mg orally was given if needed. In case of obvious pain relieving failure with the ITM or EDA iv. patient-controlled analgesia with morphine was started.

To quantify the amount of non-opioid analgesics given the defined daily dose (DDD) methodology was used.[18] All opioids, independent of administration route and including the ITM and the EDA, were converted to an equivalent iv. morphine dose.[19,20]

A numerical rating scale (NRS) 0-10 was used to assess the pain three times daily (8 am, 4 pm, 10 pm) at rest and at mobilization, i.e. when moving out of bed, raising both legs when in bed or when giving a strong cough.

The standardized criteria for discharge were: the patient was mobilized, tolerated a normal diet, had sufficient pain relief with oral analgesics (NRS ≤ 4), showed no signs of mechanical bowel obstruction and had voided spontaneously with less than 150 ml residual urine. If the last criterion was not met, the woman went home with the catheter, which was removed policlinically. The discharge criteria were checked twice daily. The decision on discharge was made according to the medical criteria but could be prolonged by social or other practical, personal conditions. Both the *de facto* hospital stay (LOS) and the length of the stay until the discharge criteria were met were calculated.

The research nurse had telephone contact with the participants the day after discharge and then once a week until six weeks postoperatively. Adverse events were registered and graded according to the Clavien-Dindo classification.[21] The study was completed after the six-week contact.

The QoL was assessed by two commonly used validated generic QoL forms. The EQ-5Dform was completed preoperatively, daily during the first week after surgery, then once weekly until the six-week postoperative visit. [22] The Short Form – 36 Health Survey (SF-36) form was completed preoperatively (baseline) and six weeks postoperatively.[23]

Trial outcomes

The primary endpoint was the de facto duration of hospital stay (LOS). Secondary outcome measurers were QoL and pain assessments. As secondary post hoc outcomes we also registered the analgesic consumption, time to meet standardized discharge criteria, proportion of women discharged on the third postoperative day and adverse events.

Patient involvement

Patients were not involved in the study design or conduct of the study. By assessing QoL as part of the protocol, the patients reported a surrogate measure of the burden of the intervention.

Ethical approval

The study was approved by the Regional Ethics Board of Linköping University (D.nr. 2013/185-31, approval date 29 August 2013), the Swedish Medical Products Agency (Eu-nr. 2013-001873-25; D.nr. 5.1-2013-50334, approval date 1 August 2013) and monitored by an independent monitor.

Statistics

Sample size calculation was based on the primary outcome endpoint. From our earlier studies on abdominal hysterectomy using ITM in an ERAS setting [7] the standard deviation for LOS was 0.75 days. Providing that the minimum clinical relevant difference in hospital stay between the groups was 0.5 days, each group should consist of 40 women including a 10% dropout rate in order to show statistical significance at a 5% level with an 80% power.

Data are presented as median (inter quartile range), mean and (95% confidence interval) or number (percent). χ^2 tests and Fisher's exact tests were used to analyze categorical data and Mann-Whitney U-tests and Wilcoxon matched pair tests for continuous data.

A repeated measures analysis of variance (ANOVA) was used to analyze data measured on more occasions. When $p \leq 0.10$ in the analysis of the main effect between groups in the repeated measures ANOVA, the pairwise associations between groups on each single occasion of measurement were analyzed using the Bonferroni post hoc test.

The significance level was set at $p<0.05$. The statistical tests were two-tailed. All analyses were carried out according to intention-to-treat principles using Statistica v13.2 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA).

RESULTS

The description of the selection and the randomization of the study population is presented in Figure 1. Forty women were chosen to receive EDA and 40 to receive ITM. One woman in each group did not receive any regional analgesia and one woman had ITM instead of EDA based on a mistake by the attending anesthesiologist.

The descriptive and demographic data are shown in Table 1. The clinical surgical and anesthesiological data are presented in Table 2.

In 20% the final diagnosis postoperatively was benign, most often showing a benign ovarian tumor or a large uterine fibroid. The benign diseases were evenly distributed between the two groups.

The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (IQR) 3.3 (3.1-4.8) vs. 4.3 (3.4-5.2) days; p=0.01). The time to meet standardized discharge criteria was significantly shorter in the ITM group compared with the EDA group (median (IQR) 3.0 (2.5-3.5) vs. 4.0 (3.5-4.5) days; p<0.001). Significantly more women in the ITM group were discharged from the hospital on the third day (25 women (62.5%) in the ITM group vs. 12 (30%) in the EDA group, (p=0.004).

The ITM group had a significantly lower total consumption of opioids than the EDA group whereas the use of non-opioids was similar in the two groups (Figure 2 and 3). Postoperatively, during day 0 to day 6 the total consumption of opioids were median (IQR) 20 mg (14-35 mg) in the ITM group compared with 81 mg (67-101 mg) in the EDA group (p<0.0001). Simultaneously, there was no significant difference in the overall assessment of pain (NRS) between the groups (Figure 4 and 5). The two groups showed different patterns in the NRS ratings as indicated by the significant interaction effects. The post hoc tests showed that the NRS ratings were significantly higher in the ITM group during the first two days at mobilization, whereas the EDA group scored significantly higher both at rest and at mobilization on day three when the EDA catheter was removed.

The QoL parameters as measured by the EQ-5D, day-by-day, presented no statistically significant difference in health index between the two groups (Figure 6). Neither did the SF-36 show any statistically significant differences in the difference of baseline and 42-days assessments in any of the subscales or summary scores between the groups (Table 3). The role physical and the physical component summary score had not recovered to baseline level in either of the two groups after six weeks whereas the mental health and the mental component summary score showed a significant improvement after six weeks compared with the baseline assessment in the ITM group.

The EDA failed in four women (10%) and ITM analgesia in one (2.5%). These women had either a new EDA in the post-anesthesia care or received patient-controlled morphine iv. One accidental dural puncture occurred in the EDA group. No post-dural puncture headache or

anesthesiological adverse effects were observed in either of the groups. The perioperative adverse events graded according to the Clavien-Dindo classification in the two groups did not differ significantly (p=0.31) as shown in Table 4.

DISCUSSION

The study showed that a single-dose of intrathecal morphine used as postoperative analgesia compared with epidural analgesia gives advantages in abdominal gynecological cancer surgery in regard to the length of hospital stay, the time to meet the standardized discharge criteria and lower consumption of opioids postoperatively. A substantially higher proportion of women with ITM was discharged on the third postoperative day with an evenly reported health-related QoL and assessment of pain as women with EDA. A key point of an ERAS protocol is simplicity and a single intrathecal injection is simpler that a continuous epidural requiring ongoing management and monitoring. We regard ITM as a quality improvement from the perspective of both the patients and the health care.

The strengths of this trial are the randomized design, the unanimous ERAS and postoperative surveillance of the patients in the gynecological ward, the assessment of pain at rest and during mobilization, and the active use of rescue analgesics on demand. For obvious reasons the interventions could not be blinded for the participants or the staff. This might be a source of bias, but we believe that the potential influence of such bias will be limited and unavoidable in the study design used. A limitation for generalization of the results is the single center design. The ERAS concept is well established in daily clinical work and therefore the results can only be generalized to facilities with similar clinical standards and only to units that manage patients with regional analgesia. The two methods of regional analgesia may not be comparable in giving potentially equivalent analgesia with the dosage and preparation used. However, our objective was to compare the two analgesic methods in a clinical context, not to find the appropriate doses or types of analgesic agent for each method. Therefore, we selected conventional doses of the medications.

The use of intrathecal opioids requires close monitoring of sedation and respiratory rate for 12 hours. The nurses on the gynecological ward were educated regarding complications after ITM with special regard to late respiratory depression and the surveillance followed strict national recommendations. Intrathecal morphine is used in approximately two-thirds of Swedish gynecological units in connection with abdominal hysterectomy having a continued observation on the regular gynecological ward after an initial period of 2-6 hours in a postoperative care unit.[24] The intrathecal morphine dose 0.2 mg was chosen with the purpose of giving adequate analgesia at a risk of respiratory depression that equals systemic opioid analgesia.[25] Following abdominal hysterectomy there is no benefit from increasing the morphine dose over 0.2 mg.[26] The α-agonist clonidine possesses an anti nociceptive effect from receptors located in the central nervous system. The addition of clonidine to intrathecal opioids further prolongs postoperative analgesia.[10]

The *de facto* duration of hospital stay was shorter in the ITM group. A reduction of hospital stay with one day has clinical relevance for both the patient and the health care system. A similar

short length of stay has recently been reported from other ERAS programs for gynecological cancer.[27-29] Wijk et al.[27] used an analgesic regimen based on oral paracetamol and diclofenac and over 90% of the patients did not need systemic opioids from the day after surgery. Like our study, they used standardized discharge criteria. It is important to analyze when discharge criteria are fulfilled, as they are robust and generalizable. The length of hospital stay is often influenced by context-specific social factors.

In this study, we compared two multimodal analgesic regimens considered clinically relevant. For that reason, we aimed to make each regimen as optimal as possible. As a consequence, there were differences in non-opioids as well as opioid regimens until the epidural catheter was removed. Only rescue opioids were equal for both groups. Thus, the aim was not to compare the intrathecal and the epidural routes per se.

Multimodal analgesic regime minimizing opioid use has been shown to enhance recovery.[2,30] ITM has become a well-documented component in several ERAS protocols [29, 31-34] and a protocol for a systematic review of ITM in abdominal and thoracic surgery patients has recently been published.[35] Despite the higher rating of NRS at mobilization during the first few days in the ITM group the consumption of opioids was nearly three times lower in the same time period compared with the EDA group, and the QoL index did not differ between the groups. This may imply that the women in the ITM group were as satisfied as the EDA group with their pain management, and the difference in NRS rating at mobilization was less clinically significant. The study included only ASA class I-II patients. For patients with more severe comorbidity the EDA regimen could be favorable as it offers a better early analgesia that especially patients at risk for complications could benefit from. A study on abdominal hysterectomy for endometrial cancer showed that women without EDA ceased opioid analgesia earlier than those women who had an EDA,[36] indicating a possible overuse of opioids in EDA. An earlier removal of the EDA catheter, for example after 48 hours, is a possible development of the EDA regimen. Prior to this trial, the standard praxis in our department was removal of the EDA catheter on the third day. Consequently, we studied the ITM against this regime. The difference in DDD of non-opioids seen until the third postoperative day was due to the protocol demand and the clinical routine in the hospital that diclofenac was not allowed in the EDA group until the EDA catheter was removed. The uneven use of diclofenac in the groups during the first three postoperative days may be seen as a weakness of the study. However, the DDD of non-opioids raised from day 1 to day 3 in the EDA group by using diclofenac in some patients against the study protocol and the clinical routines in the department. It is therefore less likely that the difference in DDD of non-opioids can explain the significant difference in opioids. In spite of the addition of diclofenac and consequently an increased DDD on the third postoperative day, the women in the EDA group rated the NRS at rest and at mobilization

higher than the ITM women. Our EDA regimen including complementary analgesics was obviously not optimal in preventing breakthrough pain in connection with terminating the epidural infusion. The opioid sparing effect of ITM has been demonstrated in a study analyzing the first 48 postoperative hours.[37] Our study might indicate an even longer benefit.

In order to increase the patient-oriented focus on recovery we used two generic QoL forms to assess the patient-reported outcome of the health status. The EQ-5D was used to determine the short-term recovery day-by-day, whereas the SF-36 was used for a longer-term assessment. The short-term recovery in QoL did not seem to differ between the two regimes but at the longer term, the ITM seemed to give more pronounced advantages than EDA in the recovery of the mental health. The clinical importance of this remains unclear and merits further exploration. To the best of our knowledge, there is no condition-specific patient-reported outcome form for our patient group. Although there is no evidence of content validity for the EQ-5D or SF-36 for the specific patient group in this study, they are widely used and allow comparisons with population norms. A new form of the EQ-5D, EQ-5D-5L, has been developed with the aim to better capture smaller health changes.[38] At the time of the study there was no Swedish value set available for EQ-5D-5L.

Severe complications after EDA and ITM are rare but still the indication for the regional analgesia should always be considered individually. In this trial no severe complications attributed to the regional analgesia occurred and the adverse events seemed to be equally distributed between the groups. However, the trial was not powered to detect a statistical difference in adverse events.

In conclusion, ITM given in an ERAS program seems to be safe, simple to administer and effective as postoperative analgesia and gives quality advantages concerning the postoperative recovery in gynecological abdominal cancer surgery.

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FIGURE LEGENDS

Figure 1. CONSORT flow chart of participants in the study. EDA, epidural analgesia. ITM, intrathecal morphine analgesia.

Figure 2 and 3. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and from Day 0 to Day 42 for DDD non-opioids are presented in the table below the diagrams. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Figure 4 and 5. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 are shown in the table below the diagrams. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Figure 6. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA and post hoc tests from Day 0 - 42 assessment is presented. EDA = epidural analgesia; ITM = intrathecal morphine analgesia. No significant differences were observed in the EQ-5D health index between the two groups preoperatively.

AUTHOR STATEMENT

AUTHOR´S CONTRIBUTION

PK, NBW and LN designed and conducted the study. PK performed the statistically analyses. PK, OB, NBW and LN undertook the initial interpretation of the data, which was followed by discussions with all the authors. PK, OB and LN drafted the initial version of the manuscript, followed by a critical revision process for intellectual content involving all authors. All authors agreed to the final version of the manuscript before submission. All authors agree to be accountable for the accuracy of any part of the work.

Table 1. Descriptive and demographic data of the study population.

	EDA group n = 40	ITM group n = 40
Age (years)	59.0 (51.5-66.0)	58.5 (54.0-62.5)
< 50 years	7 (17.5%)	6 (15%)
50 – 60 years	16 (40%)	20 (50%)
> 60 years	17 (42.5%)	14 (35%)
Body mass index (kg/m^2)	28.5 (24.7-31.2)	27.8 (23.4-31.2)
BMI < 25 kg/m^2	11 (27.5%)	13 (32.5%)
BMI 25-29.9 kg/m^2	15 (37.5%)	15 (37.5%)
BMI 30-34.9 kg/m^2	9 (22.5%)	7 (17.5%)
BMI ≥ 35 kg/m^2	5 (12.5%)	5 (12.5%)
Parity	2.0 (0-5)	2.0 (0-4)
Smokers	5 (12.5%)	4 (10%)
Previous laparotomy	17 (42.5%)	17 (42.5%)
ASA classification		
Class I	15 (37.5%)	15 (37.5%)
Class II	25 (62.5%)	25 (62.5%)
Comorbidity		
Diabetes mellitus	4 (10%)	4 (10%)
Cardiovascular disease	13 (32.5%)	12 (30%)
Pulmonary disease	4 (10%)	5 (12.5%)
Mild psychiatric disease	6 (12.5%)	4 (10%)
Previous malignancy	4 (10%)	2 (5%)
Current medication		
Antidepressant/sedative	8 (20%)	7 (17.5%)
Analgesics	7 (17.5%)	12 (30%)
Indication for surgery		
Proven/assumed gynecologic malignancy	16/24 (40%/60%)	18/22 (45%/55%)

Figures denote median and (inter quartile range) or number and (percent).
ASA, American Society of Anesthesiologists risk classification; BMI, body mass index. EDA, epidural analgesia. ITM, intrathecal morphine analgesia

Table 2. Clinical surgical and anesthesiological data.

	EDA group n = 40	ITM group n = 40	*p*-value*
Operation time (minutes)	116 (80-151.5)	139 (99.5-169)	0.10
Estimated per-operative blood loss (ml)	100 (50-275)	200 (50-250)	0.28
Extent of skin incision from superior edge of symphysis pubis to:			
- umbilicus	6 (15%)	2 (5%)	
- between umbilicus and PX	17 (42.5%)	21 (52.5%)	0.30
- PX	17 (42.5%)	17 (42.5%)	
Extent of surgery (no. of women)			
- Category I	1 (2.5%)	1 (2.5%)	
- Category II	8 (20%)	2 (5%)	
- Category III	17 (42.5%)	18 (45%)	0.25
- Category IV	8 (20%)	14 (35%)	
- Category V	6 (15%)	5 (12.5%)	
Tumor status at end of surgery‡ (no. of women):			
- Macroscopically radical	17 (63%)	25 (76%)	
- Minimal disease	3 (11%)	5 (15%)	0.22
- Bulky disease	7 (26%)	3 (9%)	
Histopathological diagnosis: malignant /benign	27/13 (67.5/32.5%)	33/7 (82.5/17.5%)	0.12
- Ovarian/fallopian tube/peritoneal cancer	13 (32.5%)	18 (45%)	
- Ovarian borderline cancer	5 (12.5%)	0 (0%)	
- Uterus carcinoma or sarcoma	7 (17.5%)	13 (32.5%)	
- Cervical cancer	1 (2.5%)	0 (0%)	
- Appendix or sigmoideum cancer	1 (2.5%)	2 (5%)	
- Benign ovarian or uterine tumor	13 (32.5%)	7 (17.5%)	
CAD at discharge (no. of women)	3 (7.7%)	4 (10.3%)	0.45†
Premedication			
Paracetamol (DDD)	0.67 (0.44-0.67))	0.67 (0.67-0.67)	0.99
Morphine § (mg)	0 (0-0.75)	0 (0-0)	0.30
Antiemetic, medication (no. of women)	16 (57%)	12 (43%)	0.35
Antiemetic, Acupressure band (no. of women)	22 (47%)	25 (53%)	0.50
Anesthetic drugs:			
Propofol (mg)	200 (160-240)	200 (160-260)	0.62
Rokuroniumbromid (mg)	50 (40-60)	50 (40-62.5)	0.32
Equivalent morphine dose (mg)	30.5 (27.3-41.3)	45.0 (40.0-50.0)	<0.0001
Paracetamol (mg)	0 (0-0)	0 (0-0)	0.99
Vasoactive treatment during anesthesia			
Ephedrine (mg)	20 (7.5-25)	20 (15-25)	0.79
Phenylephrine (µg)	0 (0-1062)	0 (0-1440)	0.50
Norepinephrine (µg)	0 (0-21)	0 (0-130)	0.57
Atropine (mg)	0 (0-0)	0 (0-0.5)	0.24
Anesthesia time (minutes)	177.5 (142.5-202.5)	200 (155-240)	0.08
Lowest body temperature during surgery (°C)	35.7 (35.5-36.1)	35.6 (35.4-35.9)	0.16
Body temperature at end of surgery (°C)	36.1 (35.9-36.4)	36.1 (35.7-36.3)	0.68
Time in PACU (hours)	4.6 (4.2-5.6)	5.7 (4.0-8.1)	0.09

Figures denote number and (percent) or median and (inter quartile range).

CAD, transurethral or supra pubic indwelling catheter. DDD, defined daily dose. EDA, epidural analgesia. ITM, intrathecal morphine analgesia. PACU, post anesthesia care unit. PX, processus xiphoideus.

Categories of extent of surgery: Category I, diagnostic surgery; Category II, resection of gynecologic organs only; Category III, resection of gynecologic organs, omentectomy and ± appendectomy; Category IV, as Category III + pelvic and/or paraaortic lymphadenectomy; Category V, as Category III ± pelvic and/or paraaortic lymphadenectomy + resection of abdominal visceral organs.

*Mann-Whitney U-test applied for continuous data and $\chi 2$- test (df 1-4) or †Fisher's exact test for categorical data. ‡ in women with malignant disease. § Equivalent dose morphine intravenously

Table 3. SF-36 subscales and summary scores. A high score represents a better health-related quality of life

	Time lapse				Day 42 - Baseline		
	Baseline		Day 42		EDA	ITM	EDA vs. ITM
SF-36 subscales	EDA	ITM	EDA	ITM	p-value *	p-value *	p-value **
Physical functioning	85 (63-95)	80 (65-95)	80 (65-95)	83 (68-90)	0.91	0.95	0.69
Role physical	38 (0-100)	63 (0-100)	0 (0-13)	0 (0-0)	<0.001	<0.0001	0.16
Bodily pain	51 (37-100)	62 47-84)	58 (42-74)	74 (52-84)	0.96	0.92	0.95
General health	75 (57-85)	72 (55-81)	70(47-87)	72 (59-81)	0.10	0.65	0.10
Vitality	53 (40-75)	53 (43-70)	45 (33-68)	55 (43-70)	0.08	0.90	0.20
Social functioning	75 (50-100)	75 (56-81)	75 (50-88)	75 (50-75)	0.15	0.70	0.09
Role emotional	100 (0-100)	100 (0-100)	83 (0-100)	100 (33-100)	0.65	0.25	0.30
Mental health	76 (60-84)	70 (60-80)	78 (66-84)	80 (66-86)	0.54	<0.01	0.13
Physical component summary score	44 (34-53)	45 (34-53)	39 (3444)	38 (35-42)	0.03	<0.01	0.41
Mental component summary score	46 (35-52)	46 (35-51)	49 (34-53)	51 (39-55)	0.69	0.01	0.05

Figures indicate median (inter quartile range). EDA = epidural analgesia. ITM = intrathecal morphine analgesia.

* Wilcoxon matched pair tests. ** Mann-Whitney U test.

No significant differences were observed in the subscales between the two groups at baseline (Mann-Whitney U-test).

Table 4. The Clavien-Dindo classification of adverse events (contracted form) within the study period of six weeks.

	EDA group (n=40)	ITM group (n=40)
No complications	19 (47.5)	19 (47.5)
Grade I	13 (32.5)	8 (20.0)
Grade II	6 (15.0)	6 (15.0)
Grade III	1 (2.5)	6 (15.0)
Grade IV	1 (2.5)	1 (2.5)

Figures denote number and (percent).

EDA = epidural analgesia. ITM = intrathecal morphine analgesia. p= 0.31; χ^2 for trends (df=4).

Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic or radiological intervention

Grade IV: Life-threatening complication requiring intermediate care/intensive care unit management

Insert Figure 2 here

Insert Figure 3 here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
Opioids (Equivalent morphine (mg))	$p<0.001$	$p<0.0001$	$p<0.0001$
DDD non-opioids	$p = 0.75$	$p < 0.0001$	$p<0.0001$

	Bonferroni post hoc tests, (p-value)						
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Opioids	<0.0001	<0.0001	<0.001	1.00	1.00	1.00	1.00

Figure 2 and 3. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given are presented in the table below the diagram. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

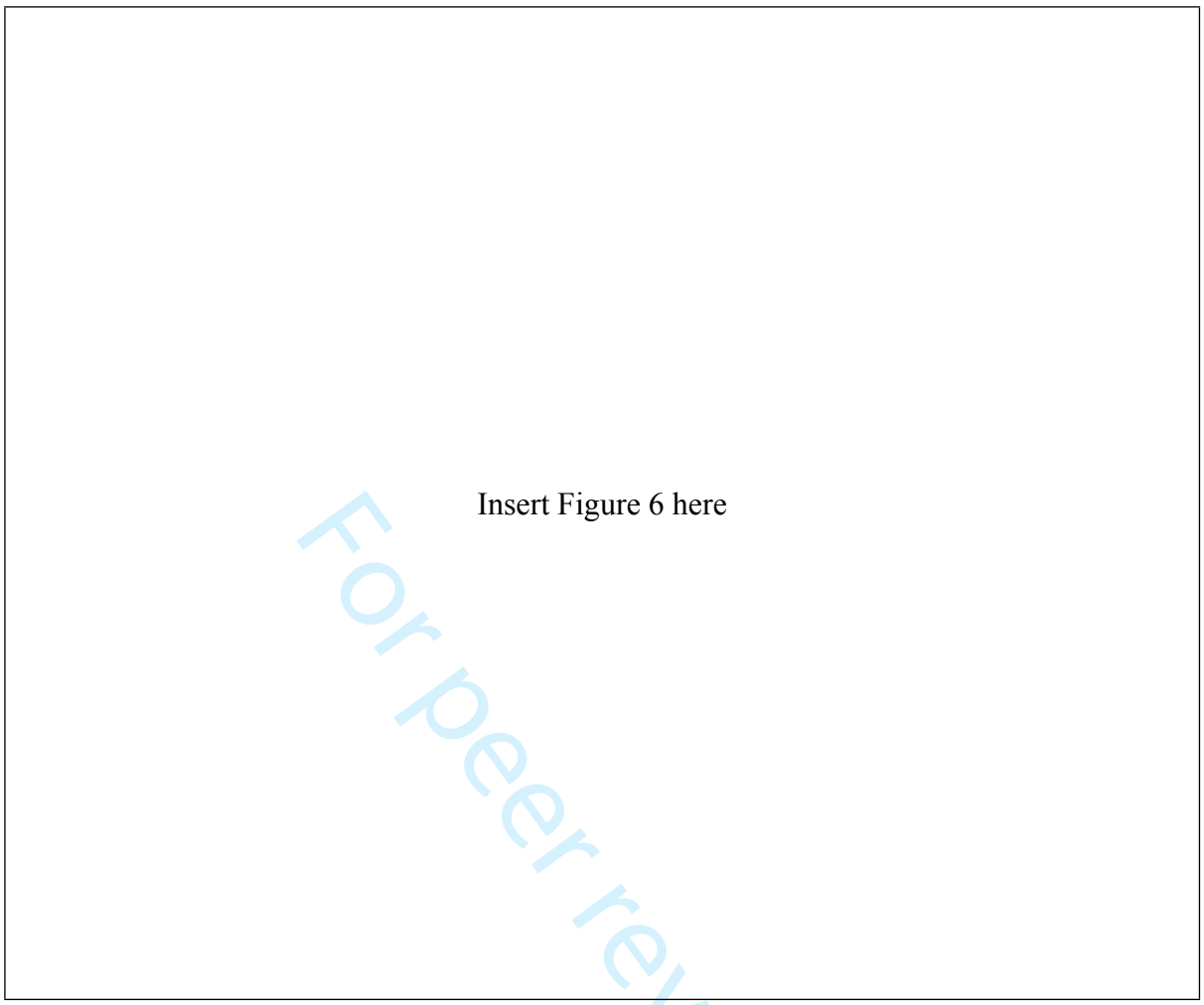
Insert Figure 4 here

Insert Figure 5 here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
NRS at rest	$p = 0.34$	$p < 0.001$	$p < 0.0001$
NRS at mobilization	$p = 0.08$	$p < 0.0001$	$p < 0.0001$

	Bonferroni post hoc tests, (p-value)																		
	Day 0.3	Day 1.1	Day 1.2	Day 1.3	Day 2.1	Day 2.2	Day 2.3	Day 3.1	Day 3.2	Day 3.3	Day 4.1	Day 4.2	Day 4.3	Day 5.1	Day 5.2	Day 5.3	Day 6.1	Day 6.2	Day 6.3
NRS at mobilization	0.01	0.06	0.01	0.44	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 4 and 5. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 are shown in the table below the diagrams. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.



Repeated measures ANOVA		
Main effect between groups	Main effect over time	Interaction effect
$p = 0.22$	$p < 0.0001$	$p = 0.33$

Figure 6. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA from Day 0 - 42 assessment is presented. EDA = epidural analgesia; ITM = intrathecal morphine analgesia. No significant differences were observed in the EQ-5D health index between the two groups preoperatively.

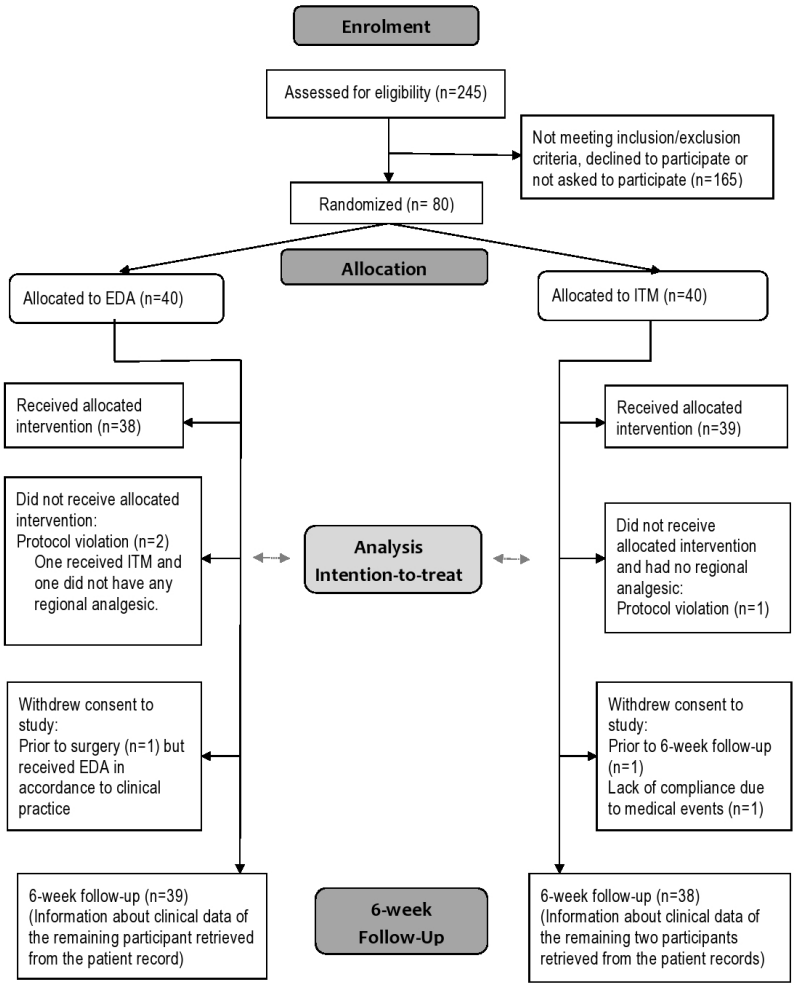


Figure 1.

Figure 1

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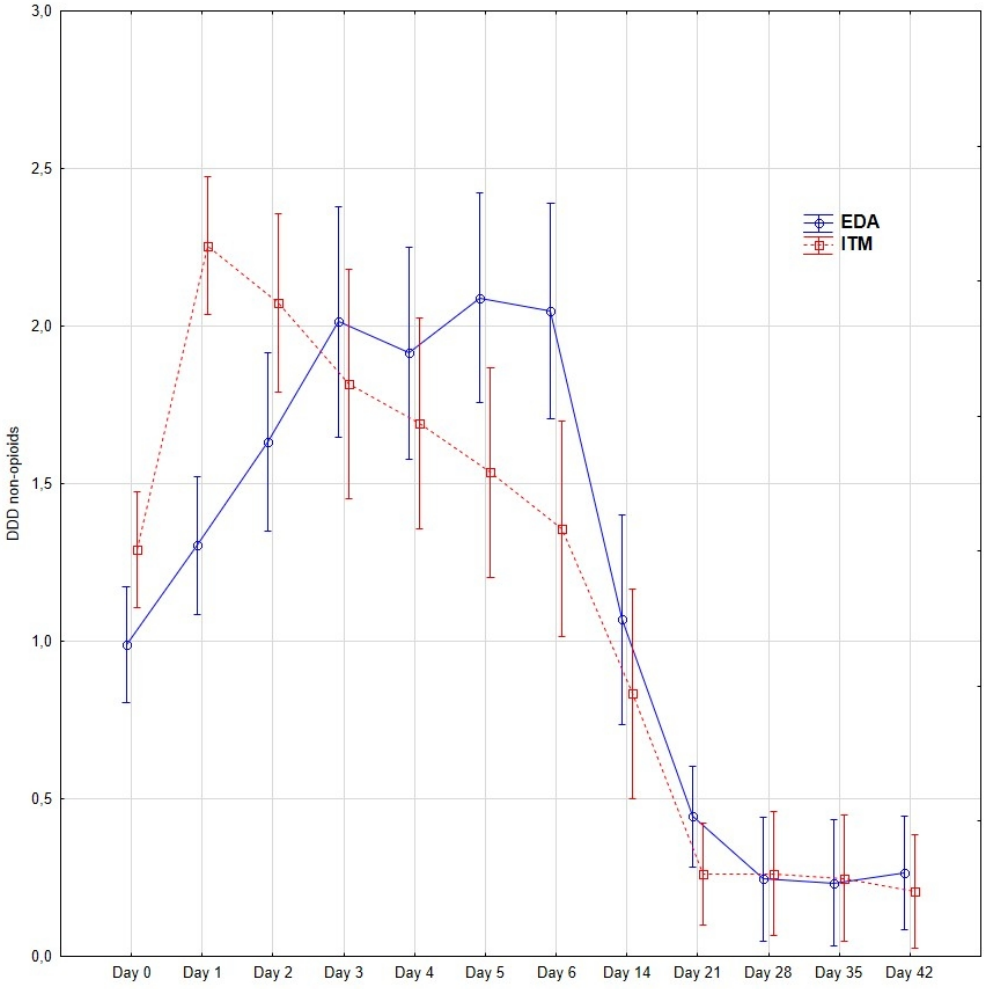

Figure 2 and 3

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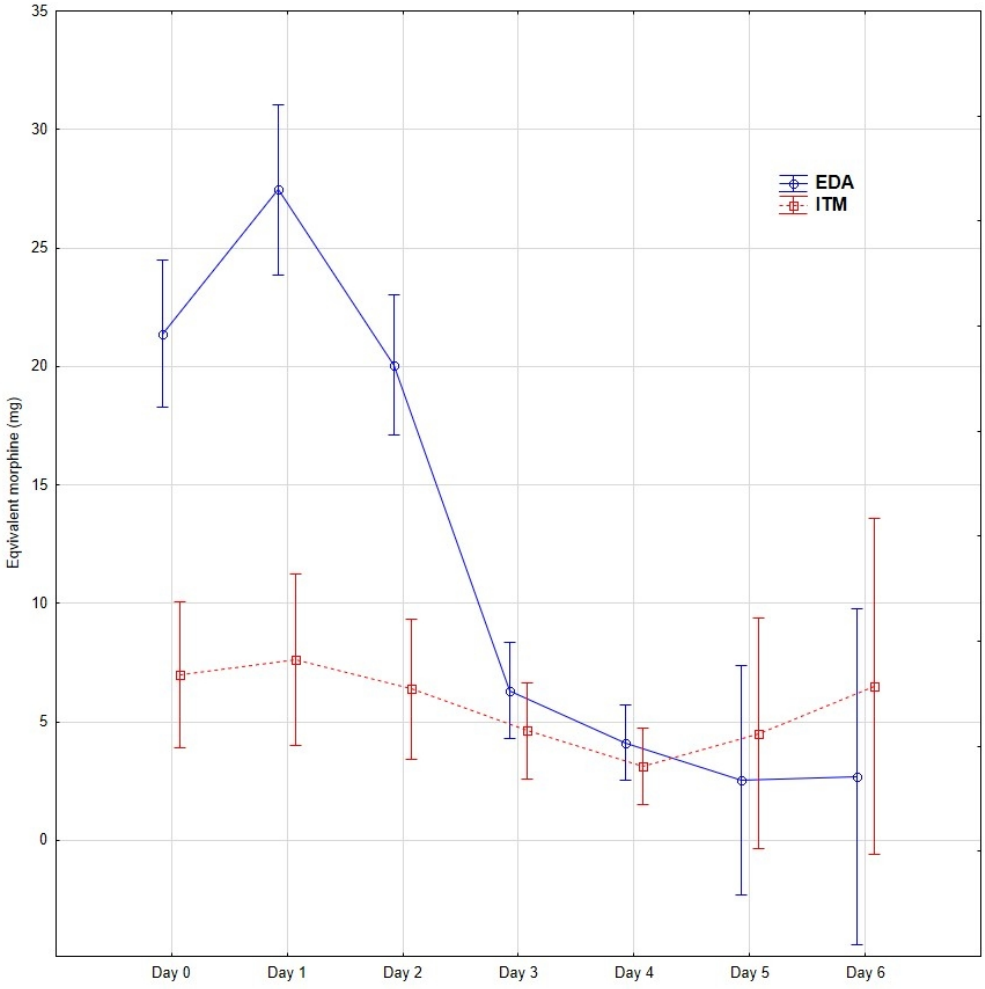

Figure 2 and 3

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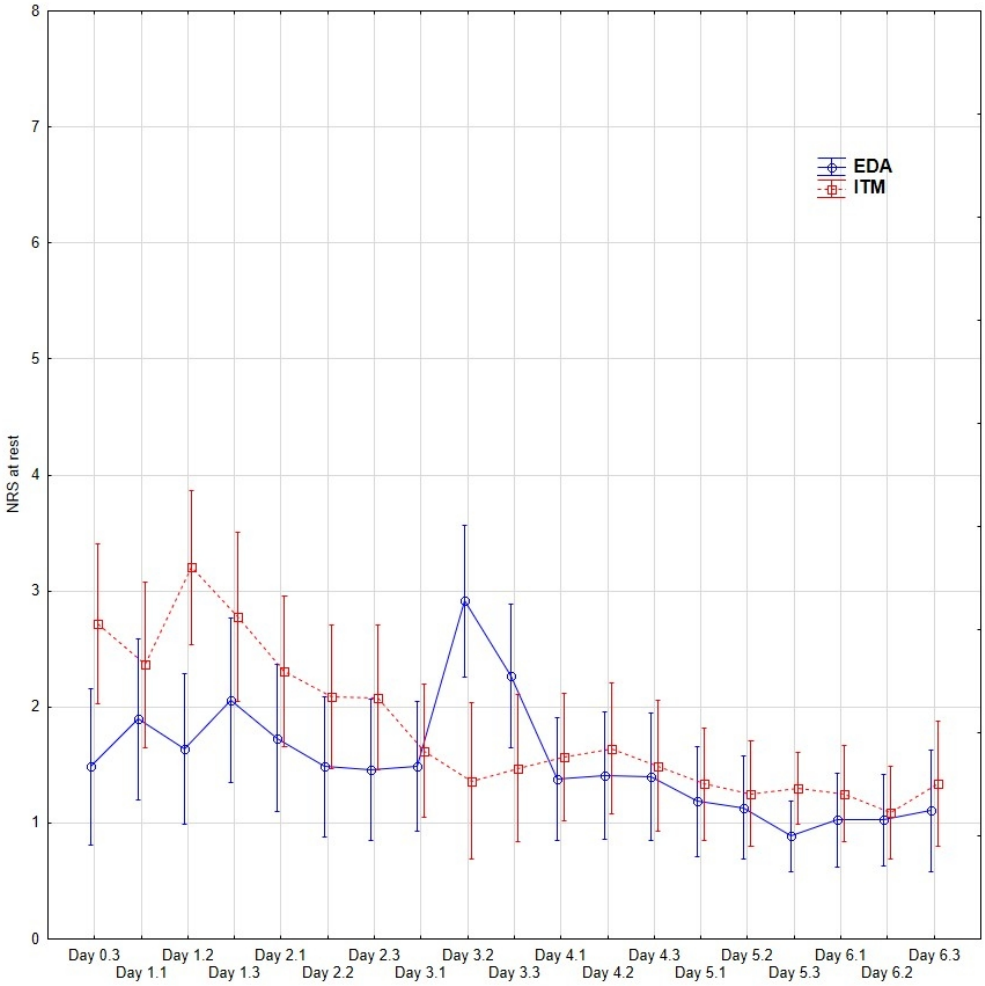

Figure 4 and 5

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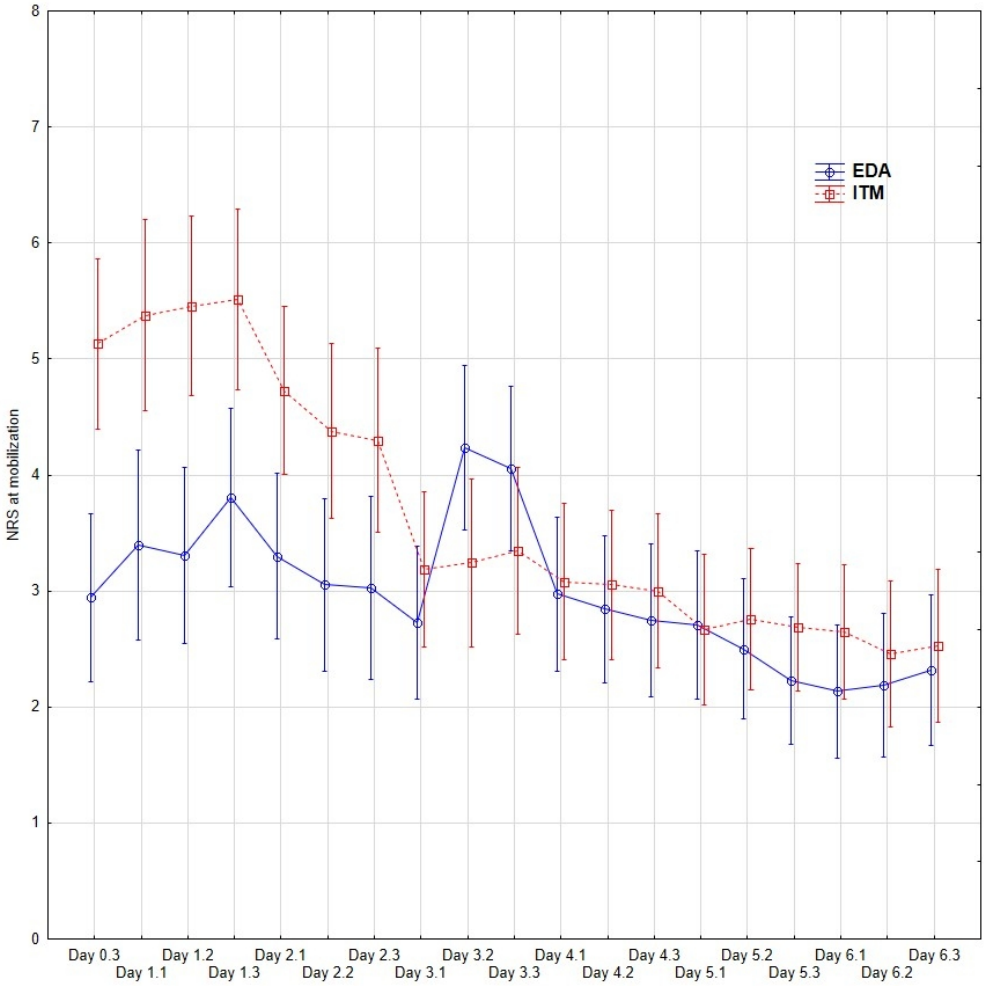

Figure 4 and 5

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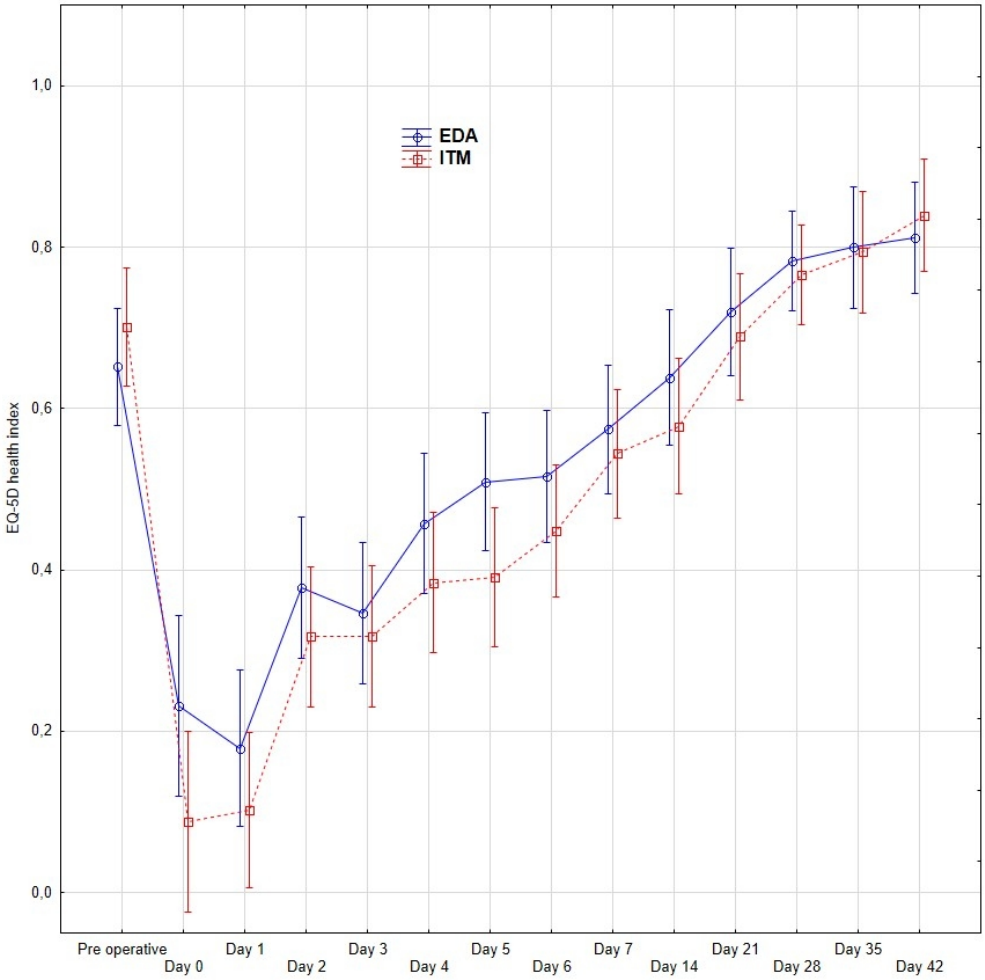

Figure 6

228x228mm (96 x 96 DPI)

Reporting checklist for randomized trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORT reporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Background and objectives	#2a	Scientific background and explanation of rationale	4
	#2b	Specific objectives or hypothesis	4
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	5
	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Na
Participants	#4a	Eligibility criteria for participants	5
	#4b	Settings and locations where the data were collected	5
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including	5-6

		how and when they were actually administered	
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	4-6
Sample size	#7a	How sample size was determined.	7
	#7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	5
	#8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	NA
	#11b	If relevant, description of the similarity of interventions	NA
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Participant flow diagram (strongly recommended)	#13a	A diagram is strongly recommended. For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1

Recruitment	#14a	Dates defining the periods of recruitment and follow-up	5
	#14b	Why the trial ended or was stopped	NA
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 1,2,4
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8, Figures 2-4
	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	10, Table 4
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	Se Cover letter
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	3

BMJ Open

The effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy. An open-label randomized trial.

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A Research Article entitled

The effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy. An open-label randomized trial.

Authors:

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Abstract

Objectives: We aimed to determine whether regional analgesia with intrathecal morphine (ITM) in an enhanced recovery program (ERAS) gives a shorter hospital stay with good pain relief and equal health-related quality of life (QoL) to epidural analgesia (EDA) in women after midline laparotomy for proven or assumed gynecological malignancies.

Design: An open-label, randomized, single center study.

Setting: A tertiary referral Swedish university hospital.

Participants: Eighty women, 18-70 years of age, ASA I and II, admitted consecutively to the department of Obstetrics and Gynecology.

Interventions: The women were allocated (1:1) to either the standard analgesic method at the clinic (EDA) or the experimental treatment (ITM). An ERAS protocol with standardized perioperative routines and standardized general anesthesia were applied. The EDA or ITM started immediately preoperatively. The ITM group received morphine, clonidine and bupivacaine intrathecally; the EDA group had an epidural infusion of bupivacaine, adrenalin and fentanyl.

Primary and secondary outcome measures: Primary endpoint was length of hospital stay (LOS). Secondary endpoints were QoL and pain assessments.

Results: The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (IQR) 3.3 (1.5-56.3) vs. 4.3 (2.2-43.2) days; p=0.01). No differences were observed in pain assessment or QoL. The ITM group used postoperatively the first week significantly less opioids than the EDA group, (median (IQR) 20 mg (14-35 mg) vs. 81 mg (67-101 mg; p<0.0001). No serious adverse events were attributed to ITM or EDA.

Conclusions: Compared with EDA, ITM is simpler to administer and manage, is associated with shorter hospital stay and reduces opioid consumption postoperatively with an equally good QoL. ITM is effective as postoperative analgesia in gynecological cancer surgery.

Trial registration number: Clinical Trials NCT02026687

Keywords: Regional analgesia; Gynecological malignancy; Laparotomy; Opioid consumption; Quality improvement

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study evaluates quality improvement on postoperative recovery after gynecological cancer surgery in an enhanced recovery after surgery setting.
- The study is an open randomized controlled trial.
- The experimental treatment (intrathecal morphine) was compared with the standard care of postoperative analgesia (epidural analgesic) used in our setting.
- The objective was to compare the two analgesic methods in a clinical relevant multimodal context, not to find the appropriate doses or types of analgesic agent for each method.

FUNDING STATEMENT

The study was supported financially by grants from the Swedish Society of Medicine (SLS-404711), the Medical Research Council of South-east Sweden (FORSS-8685), Linköping University and the Region Östergötland (LIO-356191, LIO-441781).

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

No additional data are available.

INTRODUCTION

Pain is an important component in the assessment of health-related quality of life (QoL). Besides the human suffering, insufficiently treated postoperative pain complicates mobilization, increases the risk for complications and might prolong hospitalization.

Regional analgesia with epidural analgesia (EDA) in abdominal surgery is recommended in most enhanced recovery after surgery (ERAS) protocols for use both during surgery and postoperatively.[1,2] Single-dose intrathecal morphine provide good analgesia during the first postoperative days after abdominal cancer surgery,[3-6] and improves the recovery after hysterectomy for benign conditions.[7,8] An additional analgesic effect can be obtained by adding the α-adrenergic agonist clonidine intrathecally.[4,9,10] In surgery for malignant gynecological diseases intrathecal morphine has been less described, although Kara et al. [11] in 2012 reported reduced morphine consumption and no increase in side effects. A few randomized studies have compared single-dose intrathecal morphine with continuous EDA after major abdominal surgery, showing disputed results concerning pain relief and hospital stay.[12-14]

Based on the potential benefits of intrathecal morphine as an effective and technically simple applied postoperative analgesic we designed this randomized study to compare the effects of a single-dose intrathecal combined morphine and clonidine (ITM) with the standard of care in the hospital using EDA in an ERAS program for abdominal surgery for proven or assumed gynecological malignant tumors.

The aim of the study was to determine whether ITM when compared with EDA in an ERAS program, shorten hospital stay with a similar patient experienced QoL.

MATERIAL AND METHODS

We conducted an open-label, randomized, controlled, single center study in accordance with Good Clinical Practice guidelines.[15] From March 2014 to January 2016 all women who were admitted to the department of Obstetrics and Gynecology, University Hospital, Linköping, Sweden due to a proven or assumed gynecological abdominal malignancy were eligible for the study. Women 18 to 70 years, World Health Organization (WHO) performance status < 2, American Society of Anesthesiologists (ASA) score < 3 and speaking Swedish fluently were included. Exclusion criteria were contraindications against regional analgesia, physical or psychiatric disability and surgery where pain could not be expected to be controlled by the regional analgesia. Oral and written informed consent was obtained from all participants.

At the preoperative visit the women were allocated to ITM and EDA, 1:1, from a computer-generated randomization code,[16] using sealed opaque envelopes. The participant was informed about the allocation.

Surgery was conducted through a midline laparotomy with the preoperative intention to obtain macroscopically radical tumor resection. If this was not possible the tumor burden was either to be reduced to the minimal residual tumor (less than 1 cm in size) or samples were to be obtained, preferably by salpingo-oophorectomy, in order to establish the histopathological diagnosis. Board-certified gynecological oncologists performed the surgery. The surgical technique used was at the discretion of the surgeon.

All women received thrombosis prophylaxis (tinzaparin 4500 anti-Xa IE subcutaneously) once daily for 28 days beginning the evening before the surgery, and prophylactic antibiotics (1.5 gram cefuroxime and 1.0 gram metronidazole intravenously (iv.) as a single dose) before surgery start.

All women received a standardized premedication with paracetamol 1995 mg. The allocated intervention of regional analgesic was applied prior to commencing the general anesthesia. The experimental treatment group (the ITM) had an intrathecal combination of a single dose isobar bupivacaine 15 mg, morphine 0.2 mg and clonidine 75µg, preferably through a 25G spinal needle. The EDA group had the standard EDA regime used in the hospital. The EDA was performed by a low thoracic puncture. The epidural infusion was started after induction of the general anesthesia but before surgery by a bolus dose of fentanyl 50-100 µg and a bolus from a mixture of bupivacaine 2.4 mg/ml, adrenalin 2.4 µg/ml and fentanyl 1.8 µg/ml. The same mixture was used as a continuous infusion, typically 4-8 ml/h, throughout surgery.

General anesthesia was standardized in both groups: induction with fentanyl and propofol, intubation facilitated with rocuronium and maintenance with sevoflurane. Fentanyl and rocuronium was repeated if needed. All patients had a gastric tube and an indwelling urinary catheter. The

gastric tube was removed before waking the patient up. Local anesthetic (40 ml bupivacaine 2.5 mg/ml) was injected prefascially and subcutaneously in the abdominal wall in the area of the skin incision.

After the initial monitoring at the postoperative care unit, the postoperative pain management including surveillance of possible opioid side effects and neurological complications took place at the gynecological ward and followed the routines outlined by the Swedish Society of Anesthesiology and Intensive Care.[17]

The women in the ITM group received oral paracetamol 1330 mg and diclofenac 50 mg, both three times daily started on the day of surgery. Oxycodone 10-20 mg twice daily was added on the first postoperative day.

For the EDA group, a continuous epidural infusion of a mixture of bupivacain 1 mg/ml + adrenalin 2µg/ml + fentanyl 2 µg/ml including the possibility of additional patient-controlled bolus doses was started postoperatively at the postoperative care unit and continued until the morning of the third postoperative day. The infusion rate, normally 4-8 ml/h, and bolus doses, normally 2 ml, were decided on by the responsible physician. The patients also had oral paracetamol 1330 mg three times daily, starting on the day of surgery. Oral oxycodone 10-20 mg twice daily and diclofenac 50 mg three times daily were added in the morning of the third postoperative day before removal of the epidural catheter according to the guidelines.[17]

Rescue opioids were the same for both groups; iv. morphine, 0.5-1 mg, iv. or oxycodone 5 mg orally was given if needed. In case of obvious pain relieving failure with the ITM or EDA iv. patient-controlled analgesia with morphine was started.

To quantify the amount of non-opioid analgesics given the defined daily dose (DDD) methodology was used.[18] All opioids, independent of administration route and including the ITM and the EDA, were converted to an equivalent iv. morphine dose.[19,20]

A numerical rating scale (NRS) 0-10 was used to assess the pain three times daily (8 am, 4 pm, 10 pm) at rest and at mobilization, i.e. when moving out of bed, raising both legs when in bed or when giving a strong cough.

The standardized criteria for discharge were: the patient was mobilized, tolerated a normal diet, had sufficient pain relief with oral analgesics (NRS ≤ 4), showed no signs of mechanical bowel obstruction and had voided spontaneously with less than 150 ml residual urine. If the last criterion was not met, the woman went home with the catheter, which was removed policlinically. The discharge criteria were checked twice daily. The decision on discharge was made according to the medical criteria but could be prolonged by social or other practical, personal conditions. Both the *de facto* hospital stay (LOS) and the length of the stay until the discharge criteria were met were calculated.

The research nurse had telephone contact with the participants the day after discharge and then once a week until six weeks postoperatively. Adverse events were registered and graded according to the Clavien-Dindo classification.[21] The study was completed after the six-week contact.

The QoL was assessed by two commonly used validated generic QoL forms. The EQ-5Dform was completed preoperatively, daily during the first week after surgery, then once weekly until the six-week postoperative visit. [22] The Short Form – 36 Health Survey (SF-36) form was completed preoperatively (baseline) and six weeks postoperatively.[23]

Trial outcomes

The primary endpoint was the de facto duration of hospital stay (LOS). Secondary outcome measurers were QoL and pain assessments. As secondary post hoc outcomes we also registered the analgesic consumption, time to meet standardized discharge criteria, proportion of women discharged on the third postoperative day and adverse events.

Patient involvement

Patients were not involved in the study design or conduct of the study. By assessing QoL as part of the protocol, the patients reported a surrogate measure of the burden of the intervention.

Ethical approval

The study was approved by the Regional Ethics Board of Linköping University (D.nr. 2013/185-31, approval date 29 August 2013), the Swedish Medical Products Agency (Eu-nr. 2013-001873-25; D.nr. 5.1-2013-50334, approval date 1 August 2013) and monitored by an independent monitor.

Statistics

Sample size calculation was based on the primary outcome endpoint. From our earlier studies on abdominal hysterectomy using ITM in an ERAS setting [7] the standard deviation for LOS was 0.75 days. Providing that the minimum clinical relevant difference in hospital stay between the groups was 0.5 days, each group should consist of 40 women including a 10% dropout rate in order to show statistical significance at a 5% level (two-sided test) with an 80% power.

Data are presented as median (inter quartile range), mean and (95% confidence interval) or number (percent). χ^2 tests and Fisher's exact tests were used to analyze categorical data and Mann-Whitney U-tests and Wilcoxon matched pair tests for continuous data.

A repeated measures analysis of variance (ANOVA) was used to analyze data measured on more occasions. When $p \leq 0.10$ in the analysis of the main effect between groups in the repeated measures ANOVA, the pairwise associations between groups on each single occasion of measurement were analyzed using the Bonferroni post hoc test.

The significance level was set at $p<0.05$. The statistical tests were two-tailed. All analyses were carried out according to intention-to-treat principles using Statistica v13.2 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA).

RESULTS

The description of the selection and the randomization of the study population is presented in Figure 1. Forty women were chosen to receive EDA and 40 to receive ITM. One woman in each group did not receive any regional analgesia and one woman had ITM instead of EDA based on a mistake by the attending anesthesiologist.

The descriptive and demographic data are shown in Table 1. The clinical surgical and anesthesiological data are presented descriptively in Table 2. None of the differences between the two treatment groups were considered to be of clinical significance.

In 20% the final diagnosis postoperatively was benign, most often showing a benign ovarian tumor or a large uterine fibroid. The benign diseases were evenly distributed between the two groups.

The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (IQR) 3.3 (3.1-4.8) vs. 4.3 (3.4-5.2) days; p=0.01). The time to meet standardized discharge criteria was significantly shorter in the ITM group compared with the EDA group (median (IQR) 3.0 (2.5-3.5) vs. 4.0 (3.5-4.5) days; p<0.001). Significantly more women in the ITM group were discharged from the hospital on the third day (25 women (62.5%) in the ITM group vs. 12 (30%) in the EDA group, (p=0.004).

The QoL parameters as measured by the EQ-5D, day-by-day, presented no statistically significant difference in health index between the two groups (Figure 2). Neither did the SF-36 show any statistically significant differences in the difference of baseline and 42-days assessments in any of the subscales or summary scores between the groups (Table 3). The role physical and the physical component summary score had not recovered to baseline level in either of the two groups after six weeks whereas the mental health and the mental component summary score showed a significant improvement after six weeks compared with the baseline assessment in the ITM group.

There was no significant difference in the overall assessment of pain (NRS) between the groups (Figure 3 and 4). The two groups showed different patterns in the NRS ratings as indicated by the significant interaction effects. The post hoc tests showed that the NRS ratings were significantly higher in the ITM group during the first two days at mobilization, whereas the EDA group scored significantly higher both at rest and at mobilization on day three when the EDA catheter was removed. The ITM group had a significantly lower total consumption of opioids than the EDA group whereas the use of non-opioids was similar in the two groups (Figure 5 and 6). The comparison of the non-opioids first started on Day 3 when the protocol allowed equal administration of per oral analgesics for the EDA and ITM groups. Postoperatively, during day 0 to day 6 the total consumption of opioids were median (IQR) 20 mg (14-35 mg) in the ITM group compared with 81 mg (67-101 mg) in the EDA group (p<0.0001).

The EDA failed in four women (10%) and ITM analgesia in one (2.5%). These women had either a new EDA in the post-anesthesia care or received patient-controlled morphine iv. One accidental dural puncture occurred in the EDA group. No post-dural puncture headache or anesthesiological adverse effects were observed in either of the groups. The perioperative adverse events graded according to the Clavien-Dindo classification in the two groups did not differ significantly (p=0.31) as shown in Table 4.

DISCUSSION

The study showed that a single-dose of intrathecal morphine used as postoperative analgesia compared with epidural analgesia gives advantages in abdominal gynecological cancer surgery in regard to the length of hospital stay, the time to meet the standardized discharge criteria and lower consumption of opioids postoperatively. A substantially higher proportion of women with ITM was discharged on the third postoperative day with an evenly reported health-related QoL and assessment of pain as women with EDA. A key point of an ERAS protocol is simplicity and a single intrathecal injection is simpler that a continuous epidural requiring ongoing management and monitoring. We regard ITM as a quality improvement from the perspective of both the patients and the health care.

The strengths of this trial are the randomized design, the unanimous ERAS and postoperative surveillance of the patients in the gynecological ward, the assessment of pain at rest and during mobilization, and the active use of rescue analgesics on demand. For obvious reasons the interventions could not be blinded for the participants or the staff. This might be a source of bias, but we believe that the potential influence of such bias will be limited and unavoidable in the study design used. A limitation for generalization of the results is the single center design. The ERAS concept is well established in daily clinical work and therefore the results can only be generalized to facilities with similar clinical standards and only to units that manage patients with regional analgesia. The two methods of regional analgesia may not be comparable in giving potentially equivalent analgesia with the dosage and preparation used. However, our objective was to compare the two analgesic methods in a clinical context, not to find the appropriate doses or types of analgesic agent for each method. Therefore, we selected conventional doses of the medications.

The use of intrathecal opioids requires close monitoring of sedation and respiratory rate for 12 hours. The nurses on the gynecological ward were educated regarding complications after ITM with special regard to late respiratory depression and the surveillance followed strict national recommendations. Intrathecal morphine is used in approximately two-thirds of Swedish gynecological units in connection with abdominal hysterectomy having a continued observation on the regular gynecological ward after an initial period of 2-6 hours in a postoperative care unit.[24] The intrathecal morphine dose 0.2 mg was chosen with the purpose of giving adequate analgesia at a risk of respiratory depression that equals systemic opioid analgesia.[25] Following abdominal hysterectomy there is no benefit from increasing the morphine dose over 0.2 mg.[26] The α-agonist clonidine possesses an anti nociceptive effect from receptors located in the central nervous system. The addition of clonidine to intrathecal opioids further prolongs postoperative analgesia.[10]

The *de facto* duration of hospital stay was shorter in the ITM group. A reduction of hospital stay with one day has clinical relevance for both the patient and the health care system. A similar

short length of stay has recently been reported from other ERAS programs for gynecological cancer.[27-29] Wijk et al.[27] used an analgesic regimen based on oral paracetamol and diclofenac and over 90% of the patients did not need systemic opioids from the day after surgery. Like our study, they used standardized discharge criteria. It is important to analyze when discharge criteria are fulfilled, as they are robust and generalizable. The length of hospital stay is often influenced by context-specific social factors.

In this study, we compared two multimodal analgesic regimens considered clinically relevant. For that reason, we aimed to make each regimen as optimal as possible. As a consequence, there were differences in non-opioids as well as opioid regimens until the epidural catheter was removed. Only rescue opioids were equal for both groups. Thus, the aim was not to compare the intrathecal and the epidural routes per se.

Multimodal analgesic regime minimizing opioid use has been shown to enhance recovery.[2,30] ITM has become a well-documented component in several ERAS protocols [29, 31-34] and a protocol for a systematic review of ITM in abdominal and thoracic surgery patients has recently been published.[35] Despite the higher rating of NRS at mobilization during the first few days in the ITM group the consumption of opioids was nearly three times lower in the same time period compared with the EDA group, and the QoL index did not differ between the groups. This may imply that the women in the ITM group were as satisfied as the EDA group with their pain management, and the difference in NRS rating at mobilization was less clinically significant. The study included only ASA class I-II patients. For patients with more severe comorbidity the EDA regimen could be favorable as it offers a better early analgesia that especially patients at risk for complications could benefit from. A study on abdominal hysterectomy for endometrial cancer showed that women without EDA ceased opioid analgesia earlier than those women who had an EDA,[36] indicating a possible overuse of opioids in EDA. An earlier removal of the EDA catheter, for example after 48 hours, is a possible development of the EDA regimen. Prior to this trial, the standard praxis in our department was removal of the EDA catheter on the third day. Consequently, we studied the ITM against this regime. The difference in DDD of non-opioids seen until the third postoperative day was due to the protocol demand and the clinical routine in the hospital that diclofenac was not allowed in the EDA group until the EDA catheter was removed. The uneven use of diclofenac in the groups during the first three postoperative days may be seen as a weakness of the study. However, the DDD of non-opioids raised from day 1 to day 3 in the EDA group by using diclofenac in some patients against the study protocol and the clinical routines in the department. It is therefore less likely that the difference in DDD of non-opioids can explain the significant difference in opioids. In spite of the addition of diclofenac and consequently an increased DDD on the third postoperative day, the women in the EDA group rated the NRS at rest and at mobilization

higher than the ITM women. Our EDA regimen including complementary analgesics was obviously not optimal in preventing breakthrough pain in connection with terminating the epidural infusion. The opioid sparing effect of ITM has been demonstrated in a study analyzing the first 48 postoperative hours.[37] Our study might indicate an even longer benefit.

In order to increase the patient-oriented focus on recovery we used two generic QoL forms to assess the patient-reported outcome of the health status. The EQ-5D was used to determine the short-term recovery day-by-day, whereas the SF-36 was used for a longer-term assessment. The short-term recovery in QoL did not seem to differ between the two regimes but at the longer term, the ITM seemed to give more pronounced advantages than EDA in the recovery of the mental health. The clinical importance of this remains unclear and merits further exploration. To the best of our knowledge, there is no condition-specific patient-reported outcome form for our patient group. Although there is no evidence of content validity for the EQ-5D or SF-36 for the specific patient group in this study, they are widely used and allow comparisons with population norms. A new form of the EQ-5D, EQ-5D-5L, has been developed with the aim to better capture smaller health changes.[38] At the time of the study there was no Swedish value set available for EQ-5D-5L.

Severe complications after EDA and ITM are rare but still the indication for the regional analgesia should always be considered individually. In this trial no severe complications attributed to the regional analgesia occurred and the adverse events seemed to be equally distributed between the groups. However, the trial was not powered to detect a statistical difference in adverse events.

In conclusion, ITM given in an ERAS program seems to be safe, simple to administer and effective as postoperative analgesia and gives quality advantages concerning the postoperative recovery in gynecological abdominal cancer surgery.

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FIGURE LEGENDS

Figure 1. CONSORT flow chart of participants in the study. EDA, epidural analgesia. ITM, intrathecal morphine analgesia.

Figure 2. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA and post hoc tests from Day 0 - 42 assessment is presented. EDA = epidural analgesia; ITM = intrathecal morphine analgesia. No significant differences were observed in the EQ-5D health index between the two groups preoperatively.

Figure 3 and 4. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 are shown in the table below the diagrams. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Figure 5 and 6. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and from Day 3 to Day 42 for DDD non-opioids are presented in the table below the diagrams. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

AUTHOR STATEMENT

AUTHOR´S CONTRIBUTION

PK, NBW and LN designed and conducted the study. PK performed the statistically analyses. PK, OB, NBW and LN undertook the initial interpretation of the data, which was followed by discussions with all the authors. PK, OB and LN drafted the initial version of the manuscript, followed by a critical revision process for intellectual content involving all authors. All authors agreed to the final version of the manuscript before submission. All authors agree to be accountable for the accuracy of any part of the work.

Table 1. Descriptive and demographic data of the study population.

	EDA group n = 40	ITM group n = 40
Age (years)	59.0 (51.5-66.0)	58.5 (54.0-62.5)
< 50 years	7 (17.5%)	6 (15%)
50 – 60 years	16 (40%)	20 (50%)
> 60 years	17 (42.5%)	14 (35%)
Body mass index (kg/m^2)	28.5 (24.7-31.2)	27.8 (23.4-31.2)
BMI < 25 kg/m^2	11 (27.5%)	13 (32.5%)
BMI 25-29.9 kg/m^2	15 (37.5%)	15 (37.5%)
BMI 30-34.9 kg/m^2	9 (22.5%)	7 (17.5%)
BMI ≥ 35 kg/m^2	5 (12.5%)	5 (12.5%)
Parity	2.0 (0-5)	2.0 (0-4)
Smokers	5 (12.5%)	4 (10%)
Previous laparotomy	17 (42.5%)	17 (42.5%)
ASA classification		
Class I	15 (37.5%)	15 (37.5%)
Class II	25 (62.5%)	25 (62.5%)
Comorbidity		
Diabetes mellitus	4 (10%)	4 (10%)
Cardiovascular disease	13 (32.5%)	12 (30%)
Pulmonary disease	4 (10%)	5 (12.5%)
Mild psychiatric disease	6 (12.5%)	4 (10%)
Previous malignancy	4 (10%)	2 (5%)
Current medication		
Antidepressant/sedative	8 (20%)	7 (17.5%)
Analgesics	7 (17.5%)	12 (30%)
Indication for surgery		
Proven/assumed gynecologic malignancy	16/24 (40%/60%)	18/22 (45%/55%)

Figures denote median and (inter quartile range) or number and (percent).
ASA, American Society of Anesthesiologists risk classification; BMI, body mass index. EDA, epidural analgesia. ITM, intrathecal morphine analgesia

Table 2. Clinical surgical and anesthesiological data.

	EDA group n = 40	ITM group n = 40
Operation time (minutes)	116 (80-151.5)	139 (99.5-169)
Estimated per-operative blood loss (ml)	100 (50-275)	200 (50-250)
Extent of skin incision from superior edge of symphysis pubis to:		
- umbilicus	6 (15%)	2 (5%)
- between umbilicus and processus xiphoideus	17 (42.5%)	21 (52.5%)
- processus xiphoideus	17 (42.5%)	17 (42.5%)
Extent of surgery (no. of women)		
- Category I	1 (2.5%)	1 (2.5%)
- Category II	8 (20%)	2 (5%)
- Category III	17 (42.5%)	18 (45%)
- Category IV	8 (20%)	14 (35%)
- Category V	6 (15%)	5 (12.5%)
Tumor status at end of surgery‡ (no. of women):		
- Macroscopically radical	17 (63%)	25 (76%)
- Minimal disease	3 (11%)	5 (15%)
- Bulky disease	7 (26%)	3 (9%)
Histopathological diagnosis: malignant /benign	27/13 (67.5/32.5%)	33/7 (82.5/17.5%)
- Ovarian/fallopian tube/peritoneal cancer	13 (32.5%)	18 (45%)
- Ovarian borderline cancer	5 (12.5%)	0 (0%)
- Uterus carcinoma or sarcoma	7 (17.5%)	13 (32.5%)
- Cervical cancer	1 (2.5%)	0 (0%)
- Appendix or sigmoideum cancer	1 (2.5%)	2 (5%)
- Benign ovarian or uterine tumor	13 (32.5%)	7 (17.5%)
CAD at discharge (no. of women)	3 (7.7%)	4 (10.3%)
Premedication		
Paracetamol (DDD)	0.67 (0.44-0.67))	0.67 (0.67-0.67)
Morphine § (mg)	0 (0-0.75)	0 (0-0)
Antiemetic, medication (no. of women)	16 (57%)	12 (43%)
Antiemetic, Acupressure band (no. of women)	22 (47%)	25 (53%)
Anesthetic drugs:		
Propofol (mg)	200 (160-240)	200 (160-260)
Rocuronium bromid (mg)	50 (40-60)	50 (40-62.5)
Equivalent morphine dose (mg)	30.5 (27.3-41.3)	45.0 (40.0-50.0)
Paracetamol (mg)	0 (0-0)	0 (0-0)
Vasoactive treatment during anesthesia		
Ephedrine (mg)	20 (7.5-25)	20 (15-25)
Phenylephrine (µg)	0 (0-1062)	0 (0-1440)
Norepinephrine (µg)	0 (0-21)	0 (0-130)
Atropine (mg)	0 (0-0)	0 (0-0.5)
Anesthesia time (minutes)	177.5 (142.5-202.5)	200 (155-240)
Lowest body temperature during surgery (°C)	35.7 (35.5-36.1)	35.6 (35.4-35.9)
Body temperature at end of surgery (°C)	36.1 (35.9-36.4)	36.1 (35.7-36.3)
Time in PACU (hours)	4.6 (4.2-5.6)	5.7 (4.0-8.1)

Figures denote number and (percent) or median and (inter quartile range).
CAD, transurethral or supra pubic indwelling catheter. DDD, defined daily dose. EDA, epidural analgesia. ITM, intrathecal morphine analgesia. PACU, post anesthesia care unit.

Categories of extent of surgery: Category I, diagnostic surgery; Category II, resection of gynecologic organs only; Category III, resection of gynecologic organs, omentectomy and ± appendectomy; Category IV, as Category III + pelvic and/or paraaortic lymphadenectomy; Category V, as Category III ± pelvic and/or paraaortic lymphadenectomy + resection of abdominal visceral organs.

Table 3. SF-36 subscales and summary scores. A high score represents a better health-related quality of life

	Time lapse				Day 42 - Baseline		
	Baseline		Day 42		EDA	ITM	EDA vs. ITM
SF-36 subscales	EDA	ITM	EDA	ITM	p-value *	p-value *	p-value **
Physical functioning	85 (63-95)	80 (65-95)	80 (65-95)	83 (68-90)	0.91	0.95	0.69
Role physical	38 (0-100)	63 (0-100)	0 (0-13)	0 (0-0)	<0.001	<0.0001	0.16
Bodily pain	51 (37-100)	62 47-84)	58 (42-74)	74 (52-84)	0.96	0.92	0.95
General health	75 (57-85)	72 (55-81)	70(47-87)	72 (59-81)	0.10	0.65	0.10
Vitality	53 (40-75)	53 (43-70)	45 (33-68)	55 (43-70)	0.08	0.90	0.20
Social functioning	75 (50-100)	75 (56-81)	75 (50-88)	75 (50-75)	0.15	0.70	0.09
Role emotional	100 (0-100)	100 (0-100)	83 (0-100)	100 (33-100)	0.65	0.25	0.30
Mental health	76 (60-84)	70 (60-80)	78 (66-84)	80 (66-86)	0.54	<0.01	0.13
Physical component summary score	44 (34-53)	45 (34-53)	39 (3444)	38 (35-42)	0.03	<0.01	0.41
Mental component summary score	46 (35-52)	46 (35-51)	49 (34-53)	51 (39-55)	0.69	0.01	0.05

Figures indicate median (inter quartile range). EDA = epidural analgesia. ITM = intrathecal morphine analgesia.

* Wilcoxon matched pair tests. ** Mann-Whitney U test.

No significant differences were observed in the subscales between the two groups at baseline (Mann-Whitney U-test).

Table 4. The Clavien-Dindo classification of adverse events (contracted form) within the study period of six weeks.

	EDA group (n=40)	ITM group (n=40)
No complications	19 (47.5)	19 (47.5)
Grade I	13 (32.5)	8 (20.0)
Grade II	6 (15.0)	6 (15.0)
Grade III	1 (2.5)	6 (15.0)
Grade IV	1 (2.5)	1 (2.5)

Figures denote number and (percent).

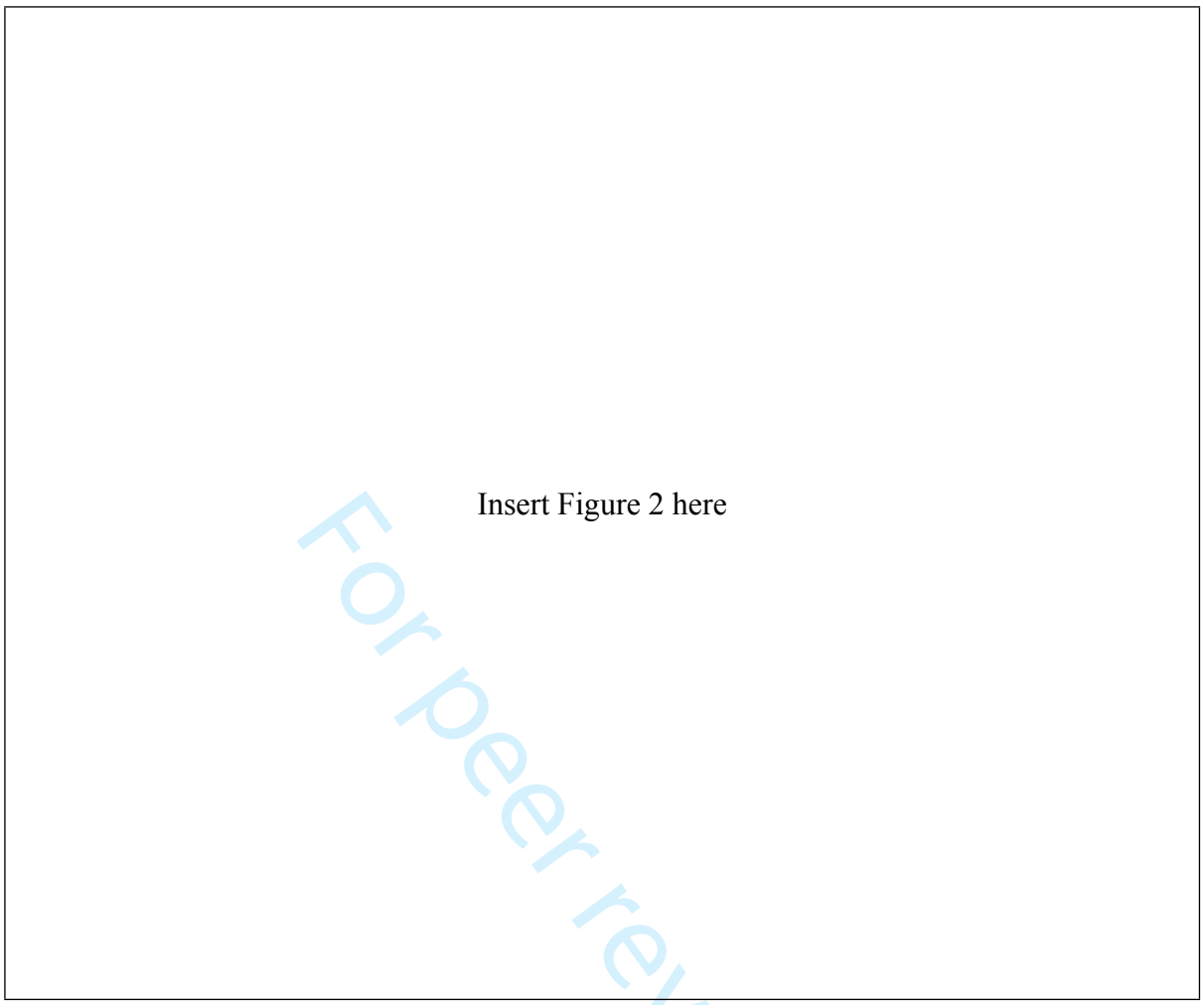
EDA = epidural analgesia. ITM = intrathecal morphine analgesia. p= 0.31; χ^2 for trends (df=4).

Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic or radiological intervention

Grade IV: Life-threatening complication requiring intermediate care/intensive care unit management



Repeated measures ANOVA		
Main effect between groups	Main effect over time	Interaction effect
$p = 0.22$	$p < 0.0001$	$p = 0.34$

Figure 2. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA from Day 0 - 42 assessment is presented. EDA = epidural analgesia; ITM = intrathecal morphine analgesia. No significant differences were observed in the EQ-5D health index between the two groups preoperatively.

Insert Figure 3 here

Insert Figure 4 here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
NRS at rest	$p = 0.34$	$p < 0.001$	$p < 0.0001$
NRS at mobilization	$p = 0.08$	$p < 0.0001$	$p < 0.0001$

	Bonferroni post hoc tests, (p-value)																		
	Day 0.3	Day 1.1	Day 1.2	Day 1.3	Day 2.1	Day 2.2	Day 2.3	Day 3.1	Day 3.2	Day 3.3	Day 4.1	Day 4.2	Day 4.3	Day 5.1	Day 5.2	Day 5.3	Day 6.1	Day 6.2	Day 6.3
NRS at mobilization	0.01	0.06	0.01	0.44	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 3 and 4. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 are shown in the table below the diagrams. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Insert Figure 5 here	Insert Figure 6 here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
Opioids (Equivalent morphine (mg))	*p*<0.001	*p*<0.0001	*p*<0.0001
DDD non-opioids	*p* = 0.06	*p* < 0.0001	*p*=0.08

	Bonferroni post hoc tests, (p-value)						
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Opioids	<0.0001	<0.0001	<0.001	1.00	1.00	1.00	1.00
DDD non-opioids				1.00	1.00	0.93	0.10

Figure 5 and 6. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and for Day 3 to Day 42 for DDD non-opioids are presented in the table below the diagram. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

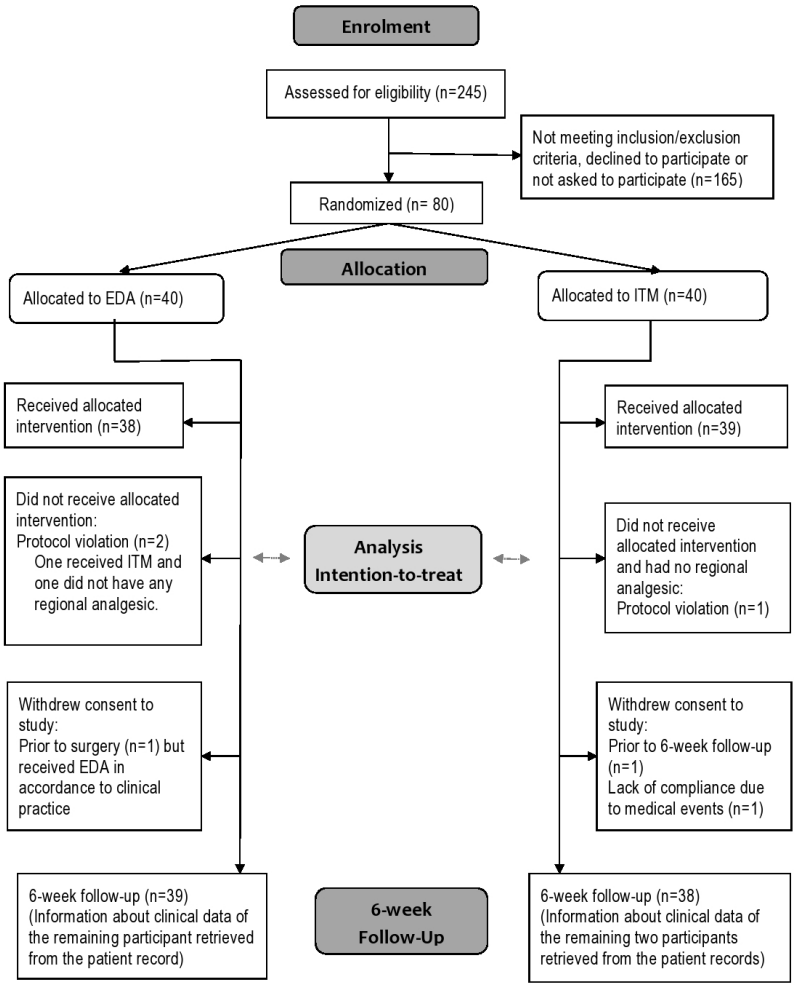


Figure 1.

Figure 1

449x582mm (72 x 72 DPI)

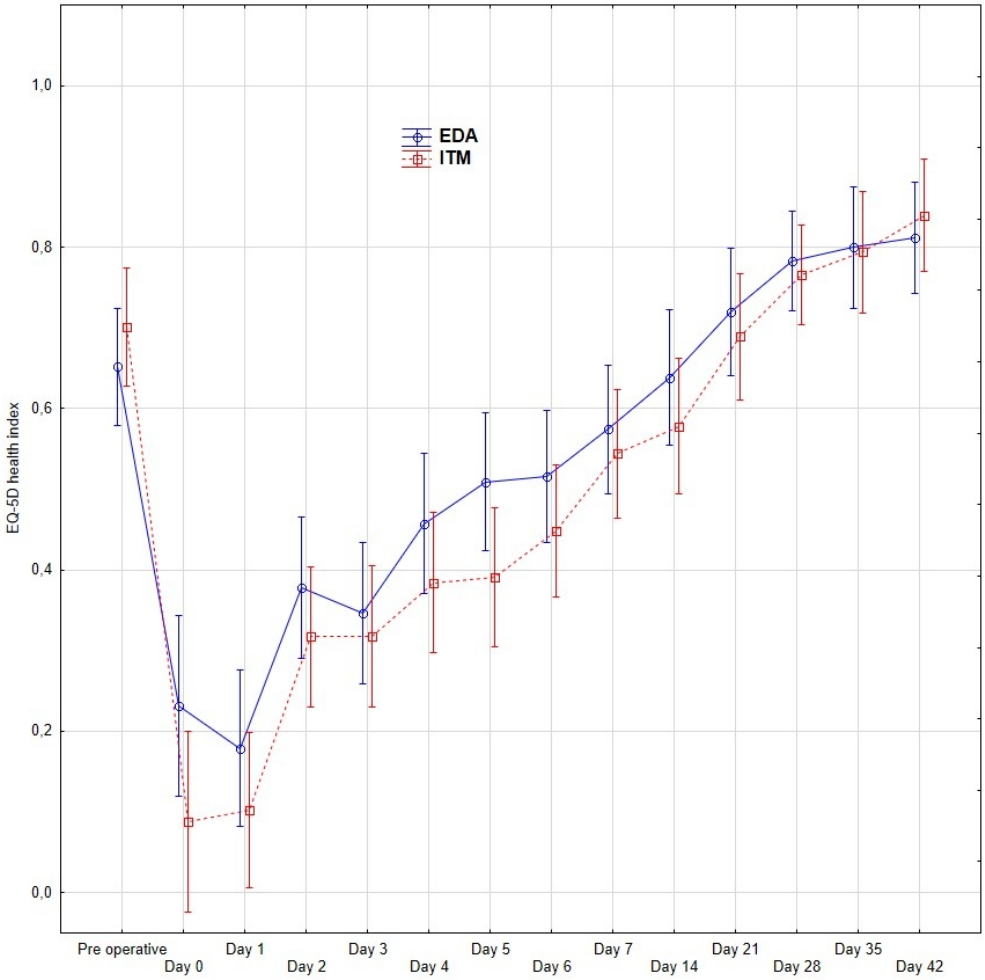


Figure 2

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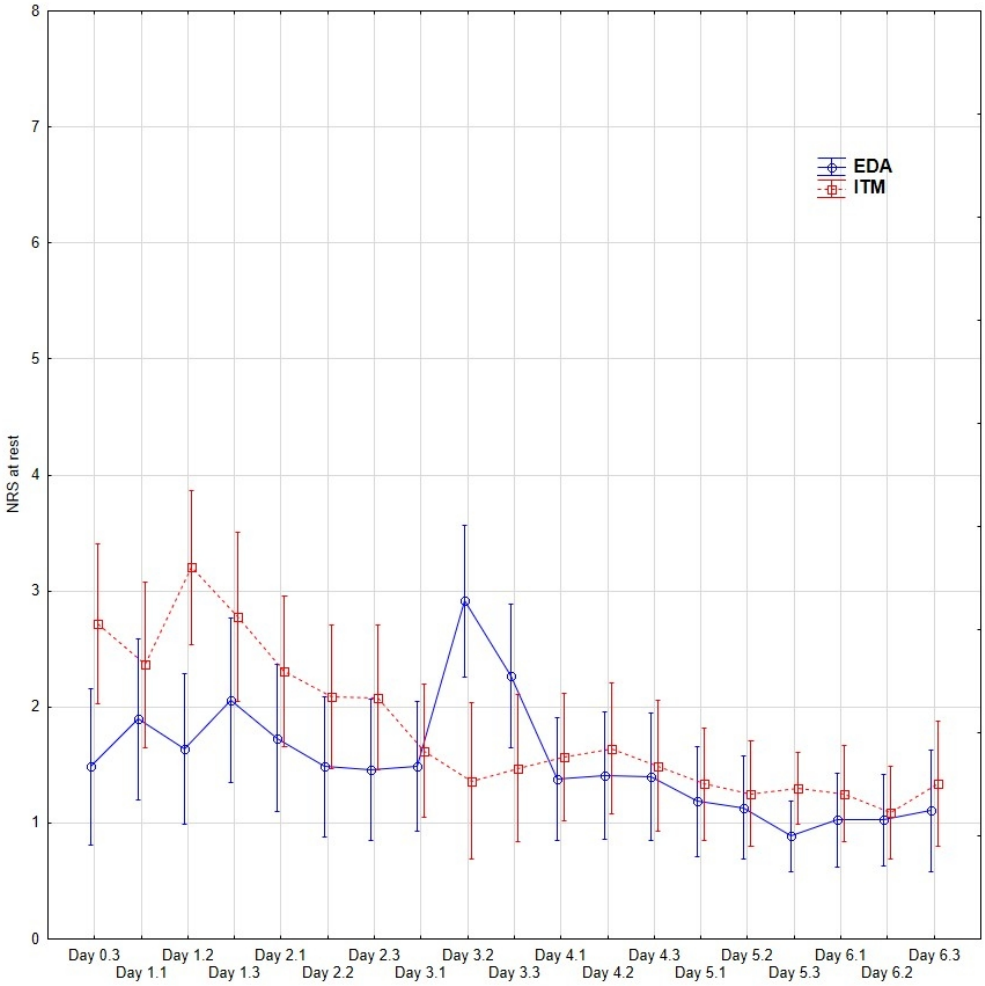

Figure 3

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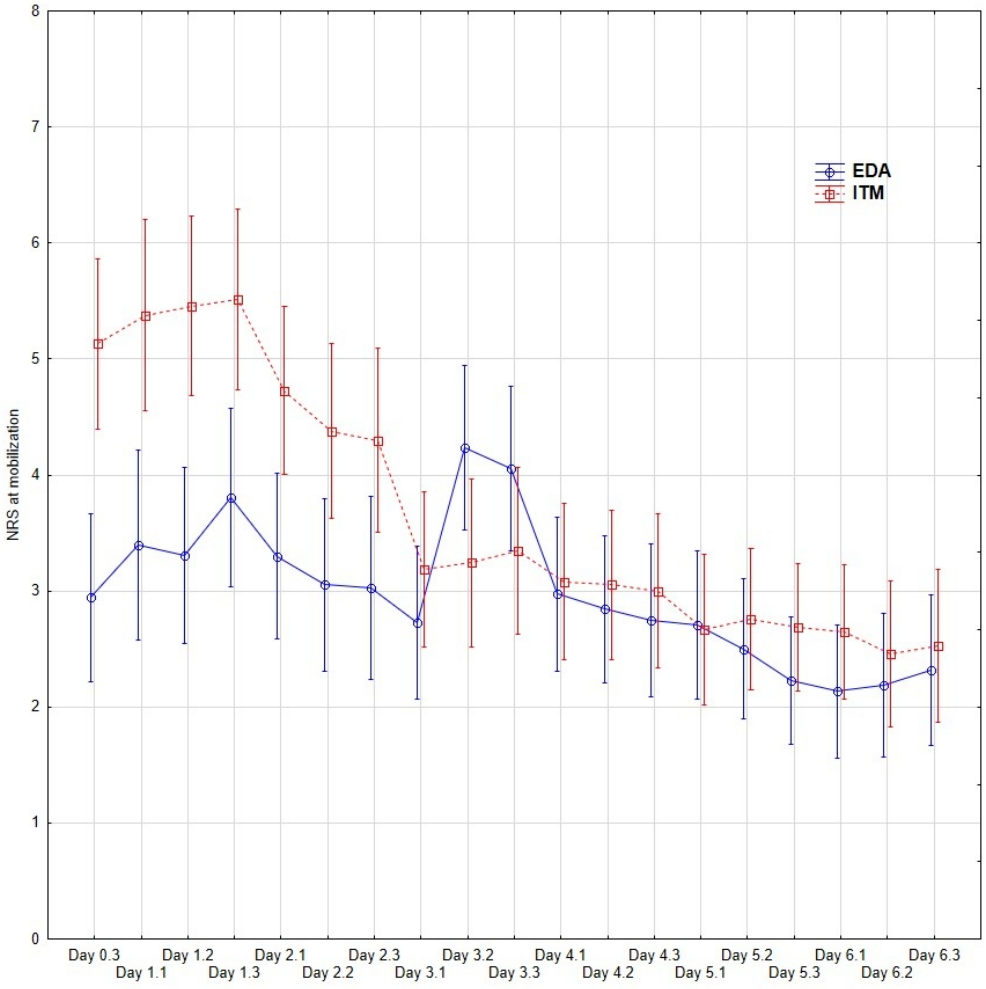

Figure 4

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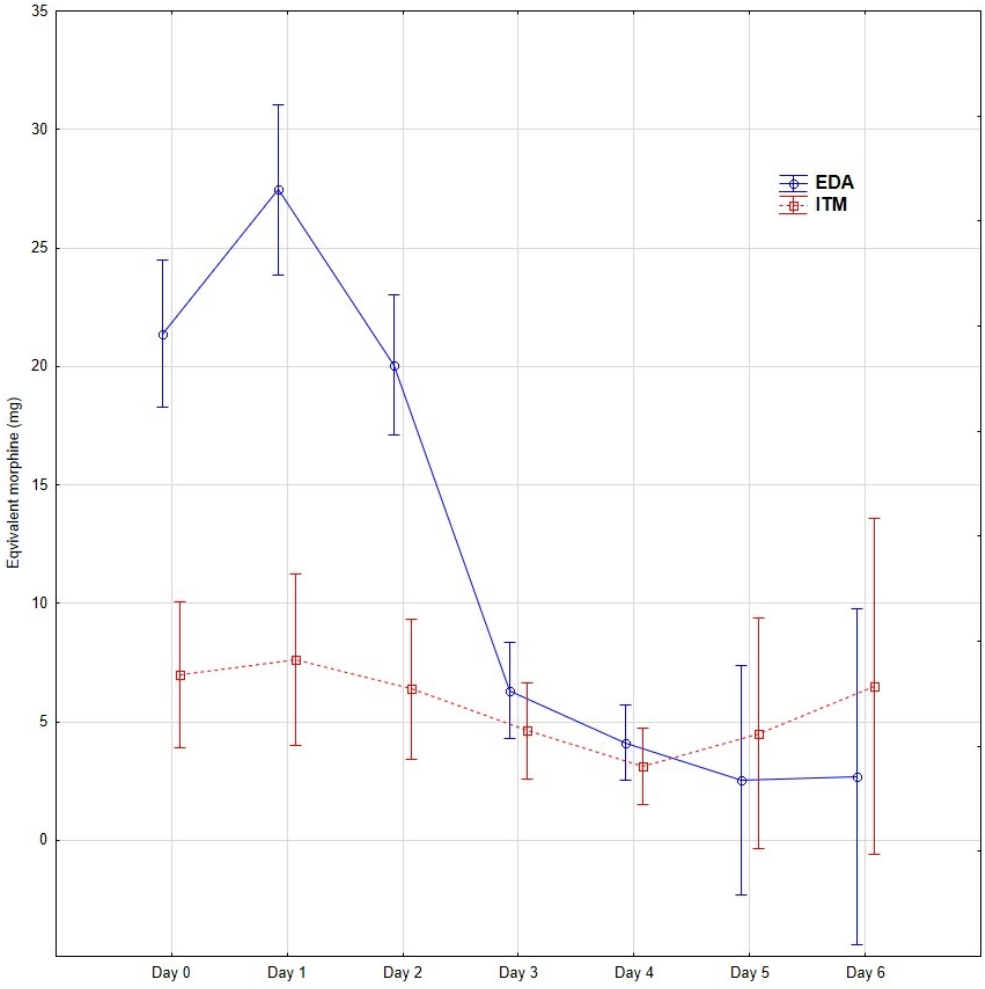

Figure 5

228x228mm (96 x 96 DPI)

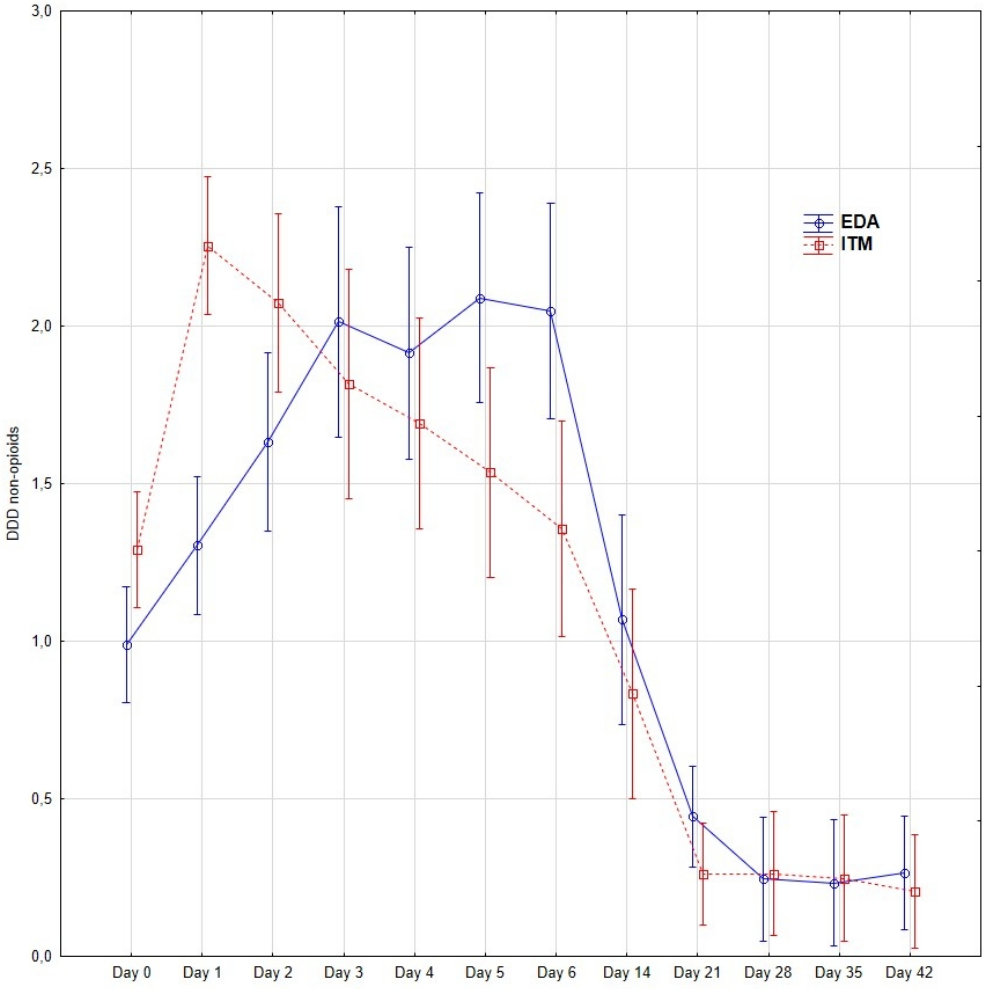

Figure 6

228x228mm (96 x 96 DPI)

Reporting checklist for randomized trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORT reporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Background and objectives	#2a	Scientific background and explanation of rationale	4
	#2b	Specific objectives or hypothesis	4
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	5
	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Na
Participants	#4a	Eligibility criteria for participants	5
	#4b	Settings and locations where the data were collected	5
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including	5-6

		how and when they were actually administered	
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	4-6
Sample size	#7a	How sample size was determined.	7
	#7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	5
	#8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	NA
	#11b	If relevant, description of the similarity of interventions	NA
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Participant flow diagram (strongly recommended)	#13a	A diagram is strongly recommended. For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1

Recruitment	#14a	Dates defining the periods of recruitment and follow-up	5
	#14b	Why the trial ended or was stopped	NA
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 1,2,4
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8, Figures 2-4
	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	10, Table 4
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	Se Cover letter
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	3

BMJ Open

The effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy. An open-label randomized trial.

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A Research Article entitled

The effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy. An open-label randomized trial.

Authors:

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Abstract

Objectives: We aimed to determine whether regional analgesia with intrathecal morphine (ITM) in an enhanced recovery program (ERAS) gives a shorter hospital stay with good pain relief and equal health-related quality of life (QoL) to epidural analgesia (EDA) in women after midline laparotomy for proven or assumed gynecological malignancies.

Design: An open-label, randomized, single center study.

Setting: A tertiary referral Swedish university hospital.

Participants: Eighty women, 18-70 years of age, ASA I and II, admitted consecutively to the department of Obstetrics and Gynecology.

Interventions: The women were allocated (1:1) to either the standard analgesic method at the clinic (EDA) or the experimental treatment (ITM). An ERAS protocol with standardized perioperative routines and standardized general anesthesia were applied. The EDA or ITM started immediately preoperatively. The ITM group received morphine, clonidine and bupivacaine intrathecally; the EDA group had an epidural infusion of bupivacaine, adrenalin and fentanyl.

Primary and secondary outcome measures: Primary endpoint was length of hospital stay (LOS). Secondary endpoints were QoL and pain assessments.

Results: The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (IQR) 3.3 (1.5-56.3) vs. 4.3 (2.2-43.2) days; p=0.01). No differences were observed in pain assessment or QoL. The ITM group used postoperatively the first week significantly less opioids than the EDA group, (median (IQR) 20 mg (14-35 mg) vs. 81 mg (67-101 mg; p<0.0001). No serious adverse events were attributed to ITM or EDA.

Conclusions: Compared with EDA, ITM is simpler to administer and manage, is associated with shorter hospital stay and reduces opioid consumption postoperatively with an equally good QoL. ITM is effective as postoperative analgesia in gynecological cancer surgery.

Trial registration number: Clinical Trials NCT02026687

Keywords: Regional analgesia; Gynecological malignancy; Laparotomy; Opioid consumption; Quality improvement

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study evaluates quality improvement on postoperative recovery after gynecological cancer surgery in an enhanced recovery after surgery setting.
- The study is an open randomized controlled trial.
- The experimental treatment (intrathecal morphine) was compared with the standard care of postoperative analgesia (epidural analgesic) used in our setting.
- The objective was to compare the two analgesic methods in a clinical relevant multimodal context, not to find the appropriate doses or types of analgesic agent for each method.

FUNDING STATEMENT

The study was supported financially by grants from the Swedish Society of Medicine (SLS-404711), the Medical Research Council of South-east Sweden (FORSS-8685), Linköping University and the Region Östergötland (LIO-356191, LIO-441781).

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

No additional data are available.

INTRODUCTION

Pain is an important component in the assessment of health-related quality of life (QoL). Besides the human suffering, insufficiently treated postoperative pain complicates mobilization, increases the risk for complications and might prolong hospitalization.

Regional analgesia with epidural analgesia (EDA) in abdominal surgery is recommended in most enhanced recovery after surgery (ERAS) protocols for use both during surgery and postoperatively.[1,2] Single-dose intrathecal morphine provide good analgesia during the first postoperative days after abdominal cancer surgery,[3-6] and improves the recovery after hysterectomy for benign conditions.[7,8] An additional analgesic effect can be obtained by adding the α-adrenergic agonist clonidine intrathecally.[4,9,10] In surgery for malignant gynecological diseases intrathecal morphine has been less described, although Kara et al. [11] in 2012 reported reduced morphine consumption and no increase in side effects. A few randomized studies have compared single-dose intrathecal morphine with continuous EDA after major abdominal surgery, showing disputed results concerning pain relief and hospital stay.[12-14]

Based on the potential benefits of intrathecal morphine as an effective and technically simple applied postoperative analgesic we designed this randomized study to compare the effects of a single-dose intrathecal combined morphine and clonidine (ITM) with the standard of care in the hospital using EDA in an ERAS program for abdominal surgery for proven or assumed gynecological malignant tumors.

The aim of the study was to determine whether ITM when compared with EDA in an ERAS program, shorten hospital stay with a similar patient experienced QoL.

MATERIAL AND METHODS

We conducted an open-label, randomized, controlled, single center study in accordance with Good Clinical Practice guidelines.[15] From March 2014 to January 2016 all women who were admitted to the department of Obstetrics and Gynecology, University Hospital, Linköping, Sweden due to a proven or assumed gynecological abdominal malignancy were eligible for the study. Women 18 to 70 years, World Health Organization (WHO) performance status < 2, American Society of Anesthesiologists (ASA) score < 3 and speaking Swedish fluently were included. Exclusion criteria were contraindications against regional analgesia, physical or psychiatric disability and surgery where pain could not be expected to be controlled by the regional analgesia. Oral and written informed consent was obtained from all participants.

At the preoperative visit the women were allocated to ITM and EDA, 1:1, from a computer-generated randomization code,[16] using sealed opaque envelopes. The participant was informed about the allocation.

Surgery was conducted through a midline laparotomy with the preoperative intention to obtain macroscopically radical tumor resection. If this was not possible the tumor burden was either to be reduced to the minimal residual tumor (less than 1 cm in size) or samples were to be obtained, preferably by salpingo-oophorectomy, in order to establish the histopathological diagnosis. Board-certified gynecological oncologists performed the surgery. The surgical technique used was at the discretion of the surgeon.

All women received thrombosis prophylaxis (tinzaparin 4500 anti-Xa IE subcutaneously) once daily for 28 days beginning the evening before the surgery, and prophylactic antibiotics (1.5 gram cefuroxime and 1.0 gram metronidazole intravenously (iv.) as a single dose) before surgery start.

All women received a standardized premedication with paracetamol 1995 mg. The allocated intervention of regional analgesic was applied prior to commencing the general anesthesia. The experimental treatment group (the ITM) had an intrathecal combination of a single dose isobar bupivacaine 15 mg, morphine 0.2 mg and clonidine 75µg, preferably through a 25G spinal needle. The EDA group had the standard EDA regime used in the hospital. The EDA was performed by a low thoracic puncture. The epidural infusion was started after induction of the general anesthesia but before surgery by a bolus dose of fentanyl 50-100 µg and a bolus from a mixture of bupivacaine 2.4 mg/ml, adrenalin 2.4 µg/ml and fentanyl 1.8 µg/ml. The same mixture was used as a continuous infusion, typically 4-8 ml/h, throughout surgery.

General anesthesia was standardized in both groups: induction with fentanyl and propofol, intubation facilitated with rocuronium and maintenance with sevoflurane. Fentanyl and rocuronium was repeated if needed. All patients had a gastric tube and an indwelling urinary catheter. The

gastric tube was removed before waking the patient up. Local anesthetic (40 ml bupivacaine 2.5 mg/ml) was injected prefascially and subcutaneously in the abdominal wall in the area of the skin incision.

After the initial monitoring at the postoperative care unit, the postoperative pain management including surveillance of possible opioid side effects and neurological complications took place at the gynecological ward and followed the routines outlined by the Swedish Society of Anesthesiology and Intensive Care.[17]

The women in the ITM group received oral paracetamol 1330 mg and diclofenac 50 mg, both three times daily started on the day of surgery. Oxycodone 10-20 mg twice daily was added on the first postoperative day.

For the EDA group, a continuous epidural infusion of a mixture of bupivacain 1 mg/ml + adrenalin 2µg/ml + fentanyl 2 µg/ml including the possibility of additional patient-controlled bolus doses was started postoperatively at the postoperative care unit and continued until the morning of the third postoperative day. The infusion rate, normally 4-8 ml/h, and bolus doses, normally 2 ml, were decided on by the responsible physician. The patients also had oral paracetamol 1330 mg three times daily, starting on the day of surgery. Oral oxycodone 10-20 mg twice daily and diclofenac 50 mg three times daily were added in the morning of the third postoperative day before removal of the epidural catheter according to the guidelines.[17]

Rescue opioids were the same for both groups; iv. morphine, 0.5-1 mg, iv. or oxycodone 5 mg orally was given if needed. In case of obvious pain relieving failure with the ITM or EDA iv. patient-controlled analgesia with morphine was started.

To quantify the amount of non-opioid analgesics given the defined daily dose (DDD) methodology was used.[18] All opioids, independent of administration route and including the ITM and the EDA, were converted to an equivalent iv. morphine dose.[19,20]

A numerical rating scale (NRS) 0-10 was used to assess the pain three times daily (8 am, 4 pm, 10 pm) at rest and at mobilization, i.e. when moving out of bed, raising both legs when in bed or when giving a strong cough.

The standardized criteria for discharge were: the patient was mobilized, tolerated a normal diet, had sufficient pain relief with oral analgesics (NRS ≤ 4), showed no signs of mechanical bowel obstruction and had voided spontaneously with less than 150 ml residual urine. If the last criterion was not met, the woman went home with the catheter, which was removed policlinically. The discharge criteria were checked twice daily. The decision on discharge was made according to the medical criteria but could be prolonged by social or other practical, personal conditions. Both the *de facto* hospital stay (LOS) and the length of the stay until the discharge criteria were met were calculated.

The research nurse had telephone contact with the participants the day after discharge and then once a week until six weeks postoperatively. Adverse events were registered and graded according to the Clavien-Dindo classification.[21] The study was completed after the six-week contact.

The QoL was assessed by two commonly used validated generic QoL forms. The EQ-5Dform was completed preoperatively, daily during the first week after surgery, then once weekly until the six-week postoperative visit. [22] The Short Form – 36 Health Survey (SF-36) form was completed preoperatively (baseline) and six weeks postoperatively.[23]

Trial outcomes

The primary endpoint was the de facto duration of hospital stay (LOS). Secondary outcome measurers were QoL and pain assessments. As secondary post hoc outcomes we also registered the analgesic consumption, time to meet standardized discharge criteria, proportion of women discharged on the third postoperative day and adverse events.

Patient involvement

Patients were not involved in the study design or conduct of the study. By assessing QoL as part of the protocol, the patients reported a surrogate measure of the burden of the intervention.

Ethical approval

The study was approved by the Regional Ethics Board of Linköping University (D.nr. 2013/185-31, approval date 29 August 2013), the Swedish Medical Products Agency (Eu-nr. 2013-001873-25; D.nr. 5.1-2013-50334, approval date 1 August 2013) and monitored by an independent monitor.

Statistics

Sample size calculation was based on the primary outcome endpoint. From our earlier studies on abdominal hysterectomy using ITM in an ERAS setting [7] the standard deviation for LOS was 0.75 days. Providing that the minimum clinical relevant difference in hospital stay between the groups was 0.5 days, each group should consist of 40 women including a 10% dropout rate in order to show statistical significance at a 5% level (two-sided test) with an 80% power.

Data are presented as median (inter quartile range), mean and (95% confidence interval) or number (percent). χ^2 tests and Fisher's exact tests were used to analyze categorical data and Mann-Whitney U-tests and Wilcoxon matched pair tests for continuous data.

A repeated measures analysis of variance (ANOVA) was used to analyze data measured on more occasions. When $p \leq 0.10$ in the analysis of the main effect between groups in the repeated measures ANOVA, the pairwise associations between groups on each single occasion of measurement were analyzed using the Bonferroni post hoc test.

The significance level was set at $p<0.05$. The statistical tests were two-tailed. All analyses were carried out according to intention-to-treat principles using Statistica v13.2 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA).

RESULTS

The description of the selection and the randomization of the study population is presented in Figure 1. Forty women were chosen to receive EDA and 40 to receive ITM. One woman in each group did not receive any regional analgesia and one woman had ITM instead of EDA based on a mistake by the attending anesthesiologist.

The descriptive and demographic data are shown in Table 1. The clinical surgical and anesthesiological data are presented descriptively in Table 2. None of the differences between the two treatment groups were considered to be of clinical significance.

In 20% the final diagnosis postoperatively was benign, most often showing a benign ovarian tumor or a large uterine fibroid. The benign diseases were evenly distributed between the two groups.

The LOS was statistically significantly shorter for the ITM group compared with the EDA group (median (IQR) 3.3 (3.1-4.8) vs. 4.3 (3.4-5.2) days; p=0.01). The time to meet standardized discharge criteria was significantly shorter in the ITM group compared with the EDA group (median (IQR) 3.0 (2.5-3.5) vs. 4.0 (3.5-4.5) days; p<0.001). Significantly more women in the ITM group were discharged from the hospital on the third day (25 women (62.5%) in the ITM group vs. 12 (30%) in the EDA group, (p=0.004).

The QoL parameters as measured by the EQ-5D, day-by-day, presented no statistically significant difference in health index between the two groups (Figure 2). Neither did the SF-36 show any statistically significant differences in the difference of baseline and 42-days assessments in any of the subscales or summary scores between the groups (Table 3). The role physical and the physical component summary score had not recovered to baseline level in either of the two groups after six weeks whereas the mental health and the mental component summary score showed a significant improvement after six weeks compared with the baseline assessment in the ITM group.

There was no significant difference in the overall assessment of pain (NRS) between the groups (Figure 3 and 4). The two groups showed different patterns in the NRS ratings as indicated by the significant interaction effects. The post hoc tests showed that the NRS ratings were significantly higher in the ITM group during the first two days at mobilization, whereas the EDA group scored significantly higher both at rest and at mobilization on day three when the EDA catheter was removed. The ITM group had a significantly lower total consumption of opioids than the EDA group whereas the use of non-opioids was similar in the two groups (Figure 5 and 6). The comparison of the non-opioids first started on Day 3 when the protocol allowed equal administration of per oral analgesics for the EDA and ITM groups. Postoperatively, during day 0 to day 6 the total consumption of opioids were median (IQR) 20 mg (14-35 mg) in the ITM group compared with 81 mg (67-101 mg) in the EDA group (p<0.0001).

The EDA failed in four women (10%) and ITM analgesia in one (2.5%). These women had either a new EDA in the post-anesthesia care or received patient-controlled morphine iv. One accidental dural puncture occurred in the EDA group. No post-dural puncture headache or anesthesiological adverse effects were observed in either of the groups. The perioperative adverse events graded according to the Clavien-Dindo classification in the two groups did not differ significantly (p=0.31) as shown in Table 4.

DISCUSSION

The study showed that a single-dose of intrathecal morphine used as postoperative analgesia compared with epidural analgesia gives advantages in abdominal gynecological cancer surgery in regard to the length of hospital stay, the time to meet the standardized discharge criteria and lower consumption of opioids postoperatively. A substantially higher proportion of women with ITM was discharged on the third postoperative day with an evenly reported health-related QoL and assessment of pain as women with EDA. A key point of an ERAS protocol is simplicity and a single intrathecal injection is simpler that a continuous epidural requiring ongoing management and monitoring. We regard ITM as a quality improvement from the perspective of both the patients and the health care.

The strengths of this trial are the randomized design, the unanimous ERAS and postoperative surveillance of the patients in the gynecological ward, the assessment of pain at rest and during mobilization, and the active use of rescue analgesics on demand. For obvious reasons the interventions could not be blinded for the participants or the staff. This might be a source of bias, but we believe that the potential influence of such bias will be limited and unavoidable in the study design used. A limitation for generalization of the results is the single center design. The ERAS concept is well established in daily clinical work and therefore the results can only be generalized to facilities with similar clinical standards and only to units that manage patients with regional analgesia. The two methods of regional analgesia may not be comparable in giving potentially equivalent analgesia with the dosage and preparation used. However, our objective was to compare the two analgesic methods in a clinical context, not to find the appropriate doses or types of analgesic agent for each method. Therefore, we selected conventional doses of the medications.

The use of intrathecal opioids requires close monitoring of sedation and respiratory rate for 12 hours. The nurses on the gynecological ward were educated regarding complications after ITM with special regard to late respiratory depression and the surveillance followed strict national recommendations. Intrathecal morphine is used in approximately two-thirds of Swedish gynecological units in connection with abdominal hysterectomy having a continued observation on the regular gynecological ward after an initial period of 2-6 hours in a postoperative care unit.[24] The intrathecal morphine dose 0.2 mg was chosen with the purpose of giving adequate analgesia at a risk of respiratory depression that equals systemic opioid analgesia.[25] Following abdominal hysterectomy there is no benefit from increasing the morphine dose over 0.2 mg.[26] The α-agonist clonidine possesses an anti nociceptive effect from receptors located in the central nervous system. The addition of clonidine to intrathecal opioids further prolongs postoperative analgesia.[10]

The *de facto* duration of hospital stay was shorter in the ITM group. A reduction of hospital stay with one day has clinical relevance for both the patient and the health care system. A similar

short length of stay has recently been reported from other ERAS programs for gynecological cancer.[27-29] Wijk et al.[27] used an analgesic regimen based on oral paracetamol and diclofenac and over 90% of the patients did not need systemic opioids from the day after surgery. Like our study, they used standardized discharge criteria. It is important to analyze when discharge criteria are fulfilled, as they are robust and generalizable. The length of hospital stay is often influenced by context-specific social factors.

In this study, we compared two multimodal analgesic regimens considered clinically relevant. For that reason, we aimed to make each regimen as optimal as possible. As a consequence, there were differences in non-opioids as well as opioid regimens until the epidural catheter was removed. Only rescue opioids were equal for both groups. Thus, the aim was not to compare the intrathecal and the epidural routes per se.

Multimodal analgesic regime minimizing opioid use has been shown to enhance recovery.[2,30] ITM has become a well-documented component in several ERAS protocols [29, 31-34] and a protocol for a systematic review of ITM in abdominal and thoracic surgery patients has recently been published.[35] Despite the higher rating of NRS at mobilization during the first few days in the ITM group the consumption of opioids was nearly three times lower in the same time period compared with the EDA group, and the QoL index did not differ between the groups. This may imply that the women in the ITM group were as satisfied as the EDA group with their pain management, and the difference in NRS rating at mobilization was less clinically significant. The study included only ASA class I-II patients. For patients with more severe comorbidity the EDA regimen could be favorable as it offers a better early analgesia that especially patients at risk for complications could benefit from. A study on abdominal hysterectomy for endometrial cancer showed that women without EDA ceased opioid analgesia earlier than those women who had an EDA,[36] indicating a possible overuse of opioids in EDA. An earlier removal of the EDA catheter, for example after 48 hours, is a possible development of the EDA regimen. Prior to this trial, the standard praxis in our department was removal of the EDA catheter on the third day. Consequently, we studied the ITM against this regime. The difference in DDD of non-opioids seen until the third postoperative day was due to the protocol demand and the clinical routine in the hospital that diclofenac was not allowed in the EDA group until the EDA catheter was removed. The uneven use of diclofenac in the groups during the first three postoperative days may be seen as a weakness of the study. However, the DDD of non-opioids raised from day 1 to day 3 in the EDA group by using diclofenac in some patients against the study protocol and the clinical routines in the department. It is therefore less likely that the difference in DDD of non-opioids can explain the significant difference in opioids. In spite of the addition of diclofenac and consequently an increased DDD on the third postoperative day, the women in the EDA group rated the NRS at rest and at mobilization

higher than the ITM women. Our EDA regimen including complementary analgesics was obviously not optimal in preventing breakthrough pain in connection with terminating the epidural infusion. The opioid sparing effect of ITM has been demonstrated in a study analyzing the first 48 postoperative hours.[37] Our study might indicate an even longer benefit.

In order to increase the patient-oriented focus on recovery we used two generic QoL forms to assess the patient-reported outcome of the health status. The EQ-5D was used to determine the short-term recovery day-by-day, whereas the SF-36 was used for a longer-term assessment. The short-term recovery in QoL did not seem to differ between the two regimes but at the longer term, the ITM seemed to give more pronounced advantages than EDA in the recovery of the mental health. The clinical importance of this remains unclear and merits further exploration. To the best of our knowledge, there is no condition-specific patient-reported outcome form for our patient group. Although there is no evidence of content validity for the EQ-5D or SF-36 for the specific patient group in this study, they are widely used and allow comparisons with population norms. A new form of the EQ-5D, EQ-5D-5L, has been developed with the aim to better capture smaller health changes.[38] At the time of the study there was no Swedish value set available for EQ-5D-5L.

Severe complications after EDA and ITM are rare but still the indication for the regional analgesia should always be considered individually. In this trial no severe complications attributed to the regional analgesia occurred and the adverse events seemed to be equally distributed between the groups. However, the trial was not powered to detect a statistical difference in adverse events.

In conclusion, ITM given in an ERAS program seems to be safe, simple to administer and effective as postoperative analgesia and gives quality advantages concerning the postoperative recovery in gynecological abdominal cancer surgery.

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FIGURE LEGENDS

Figure 1. CONSORT flow chart of participants in the study. EDA, epidural analgesia. ITM, intrathecal morphine analgesia.

Figure 2. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA and post hoc tests from Day 0 - 42 assessment is presented. EDA = epidural analgesia; ITM = intrathecal morphine analgesia. No significant differences were observed in the EQ-5D health index between the two groups preoperatively.

Figure 3 and 4. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 are shown in the table below the diagrams. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Figure 5 and 6. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and from Day 3 to Day 42 for DDD non-opioids are presented in the table below the diagrams. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

AUTHOR STATEMENT

AUTHOR´S CONTRIBUTION

PK, NBW and LN designed and conducted the study. PK performed the statistically analyses. PK, OB, NBW and LN undertook the initial interpretation of the data, which was followed by discussions with all the authors. PK, OB and LN drafted the initial version of the manuscript, followed by a critical revision process for intellectual content involving all authors. All authors agreed to the final version of the manuscript before submission. All authors agree to be accountable for the accuracy of any part of the work.

Table 1. Descriptive and demographic data of the study population.

	EDA group n = 40	ITM group n = 40
Age (years)	59.0 (51.5-66.0)	58.5 (54.0-62.5)
< 50 years	7 (17.5%)	6 (15%)
50 – 60 years	16 (40%)	20 (50%)
> 60 years	17 (42.5%)	14 (35%)
Body mass index (kg/m^2)	28.5 (24.7-31.2)	27.8 (23.4-31.2)
BMI < 25 kg/m^2	11 (27.5%)	13 (32.5%)
BMI 25-29.9 kg/m^2	15 (37.5%)	15 (37.5%)
BMI 30-34.9 kg/m^2	9 (22.5%)	7 (17.5%)
BMI ≥ 35 kg/m^2	5 (12.5%)	5 (12.5%)
Parity	2.0 (0-5)	2.0 (0-4)
Smokers	5 (12.5%)	4 (10%)
Previous laparotomy	17 (42.5%)	17 (42.5%)
ASA classification		
Class I	15 (37.5%)	15 (37.5%)
Class II	25 (62.5%)	25 (62.5%)
Comorbidity		
Diabetes mellitus	4 (10%)	4 (10%)
Cardiovascular disease	13 (32.5%)	12 (30%)
Pulmonary disease	4 (10%)	5 (12.5%)
Mild psychiatric disease	6 (12.5%)	4 (10%)
Previous malignancy	4 (10%)	2 (5%)
Current medication		
Antidepressant/sedative	8 (20%)	7 (17.5%)
Analgesics	7 (17.5%)	12 (30%)
Indication for surgery		
Proven/assumed gynecologic malignancy	16/24 (40%/60%)	18/22 (45%/55%)

Figures denote median and (inter quartile range) or number and (percent).
ASA, American Society of Anesthesiologists risk classification; BMI, body mass index. EDA, epidural analgesia. ITM, intrathecal morphine analgesia

Table 2. Clinical surgical and anesthesiological data.

	EDA group n = 40	ITM group n = 40
Operation time (minutes)	116 (80-151.5)	139 (99.5-169)
Estimated per-operative blood loss (ml)	100 (50-275)	200 (50-250)
Extent of skin incision from superior edge of symphysis pubis to:		
- umbilicus	6 (15%)	2 (5%)
- between umbilicus and processus xiphoideus	17 (42.5%)	21 (52.5%)
- processus xiphoideus	17 (42.5%)	17 (42.5%)
Extent of surgery (no. of women)		
- Category I	1 (2.5%)	1 (2.5%)
- Category II	8 (20%)	2 (5%)
- Category III	17 (42.5%)	18 (45%)
- Category IV	8 (20%)	14 (35%)
- Category V	6 (15%)	5 (12.5%)
Tumor status at end of surgery‡ (no. of women):		
- Macroscopically radical	17 (63%)	25 (76%)
- Minimal disease	3 (11%)	5 (15%)
- Bulky disease	7 (26%)	3 (9%)
Histopathological diagnosis: malignant /benign	27/13 (67.5/32.5%)	33/7 (82.5/17.5%)
- Ovarian/fallopian tube/peritoneal cancer	13 (32.5%)	18 (45%)
- Ovarian borderline cancer	5 (12.5%)	0 (0%)
- Uterus carcinoma or sarcoma	7 (17.5%)	13 (32.5%)
- Cervical cancer	1 (2.5%)	0 (0%)
- Appendix or sigmoideum cancer	1 (2.5%)	2 (5%)
- Benign ovarian or uterine tumor	13 (32.5%)	7 (17.5%)
CAD at discharge (no. of women)	3 (7.7%)	4 (10.3%)
Premedication		
Paracetamol (DDD)	0.67 (0.44-0.67))	0.67 (0.67-0.67)
Morphine § (mg)	0 (0-0.75)	0 (0-0)
Antiemetic, medication (no. of women)	16 (57%)	12 (43%)
Antiemetic, Acupressure band (no. of women)	22 (47%)	25 (53%)
Anesthetic drugs:		
Propofol (mg)	200 (160-240)	200 (160-260)
Rocuronium bromid (mg)	50 (40-60)	50 (40-62.5)
Equivalent morphine dose (mg)	30.5 (27.3-41.3)	45.0 (40.0-50.0)
Paracetamol (mg)	0 (0-0)	0 (0-0)
Vasoactive treatment during anesthesia		
Ephedrine (mg)	20 (7.5-25)	20 (15-25)
Phenylephrine (µg)	0 (0-1062)	0 (0-1440)
Norepinephrine (µg)	0 (0-21)	0 (0-130)
Atropine (mg)	0 (0-0)	0 (0-0.5)
Anesthesia time (minutes)	177.5 (142.5-202.5)	200 (155-240)
Lowest body temperature during surgery (°C)	35.7 (35.5-36.1)	35.6 (35.4-35.9)
Body temperature at end of surgery (°C)	36.1 (35.9-36.4)	36.1 (35.7-36.3)
Time in PACU (hours)	4.6 (4.2-5.6)	5.7 (4.0-8.1)

Figures denote number and (percent) or median and (inter quartile range).
CAD, transurethral or supra pubic indwelling catheter. DDD, defined daily dose. EDA, epidural analgesia. ITM, intrathecal morphine analgesia. PACU, post anesthesia care unit.

Categories of extent of surgery: Category I, diagnostic surgery; Category II, resection of gynecologic organs only; Category III, resection of gynecologic organs, omentectomy and ± appendectomy; Category IV, as Category III + pelvic and/or paraaortic lymphadenectomy; Category V, as Category III ± pelvic and/or paraaortic lymphadenectomy + resection of abdominal visceral organs.

Table 3. SF-36 subscales and summary scores. A high score represents a better health-related quality of life

	Time lapse				Day 42 - Baseline		
	Baseline		Day 42		EDA	ITM	EDA vs. ITM
SF-36 subscales	EDA	ITM	EDA	ITM	p-value *	p-value *	p-value **
Physical functioning	85 (63-95)	80 (65-95)	80 (65-95)	83 (68-90)	0.91	0.95	0.69
Role physical	38 (0-100)	63 (0-100)	0 (0-13)	0 (0-0)	<0.001	<0.0001	0.16
Bodily pain	51 (37-100)	62 47-84)	58 (42-74)	74 (52-84)	0.96	0.92	0.95
General health	75 (57-85)	72 (55-81)	70(47-87)	72 (59-81)	0.10	0.65	0.10
Vitality	53 (40-75)	53 (43-70)	45 (33-68)	55 (43-70)	0.08	0.90	0.20
Social functioning	75 (50-100)	75 (56-81)	75 (50-88)	75 (50-75)	0.15	0.70	0.09
Role emotional	100 (0-100)	100 (0-100)	83 (0-100)	100 (33-100)	0.65	0.25	0.30
Mental health	76 (60-84)	70 (60-80)	78 (66-84)	80 (66-86)	0.54	<0.01	0.13
Physical component summary score	44 (34-53)	45 (34-53)	39 (3444)	38 (35-42)	0.03	<0.01	0.41
Mental component summary score	46 (35-52)	46 (35-51)	49 (34-53)	51 (39-55)	0.69	0.01	0.05

Figures indicate median (inter quartile range). EDA = epidural analgesia. ITM = intrathecal morphine analgesia.

* Wilcoxon matched pair tests. ** Mann-Whitney U test.

No significant differences were observed in the subscales between the two groups at baseline (Mann-Whitney U-test).

Table 4. The Clavien-Dindo classification of adverse events (contracted form) within the study period of six weeks.

	EDA group (n=40)	ITM group (n=40)
No complications	19 (47.5)	19 (47.5)
Grade I	13 (32.5)	8 (20.0)
Grade II	6 (15.0)	6 (15.0)
Grade III	1 (2.5)	6 (15.0)
Grade IV	1 (2.5)	1 (2.5)

Figures denote number and (percent).

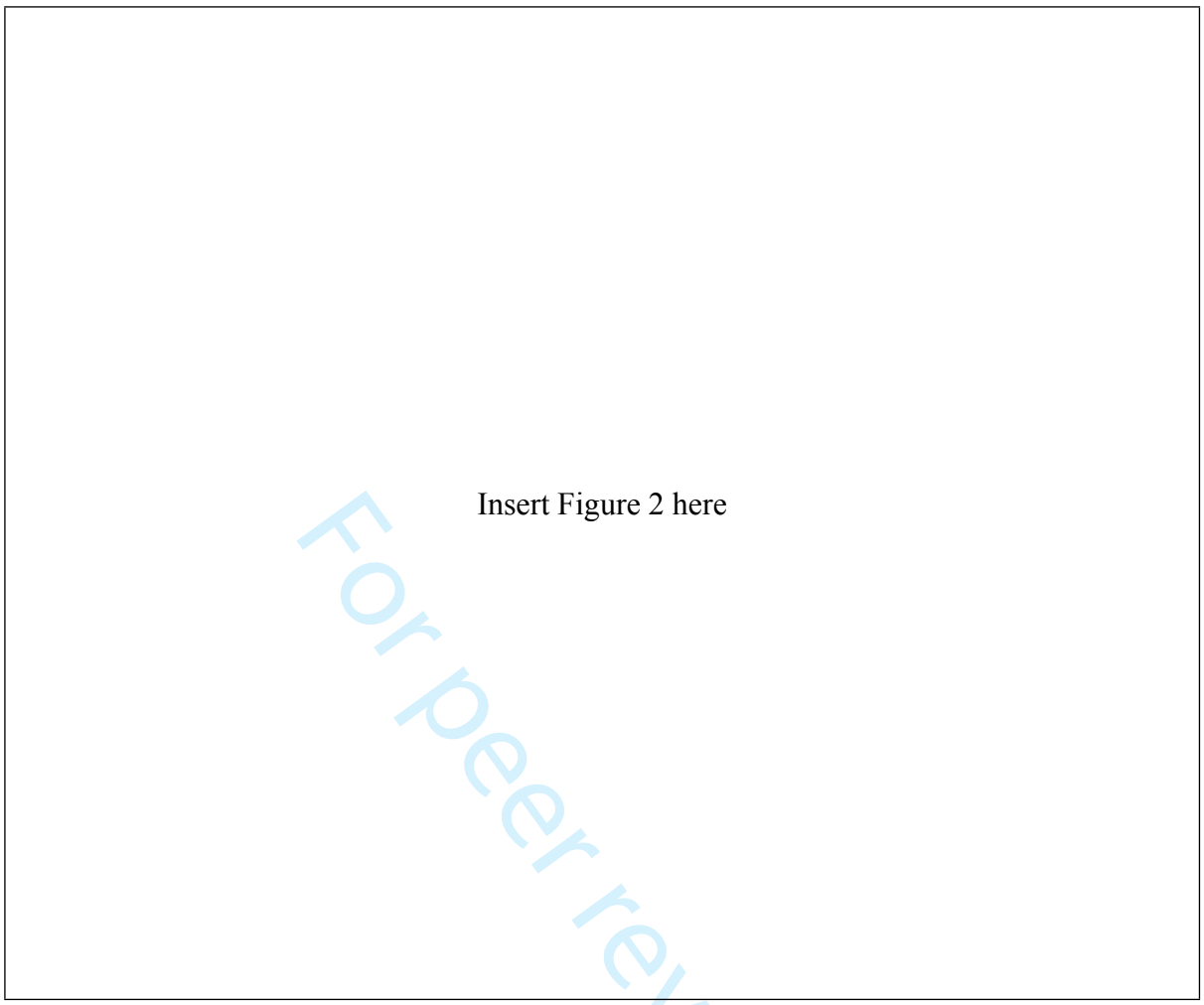
EDA = epidural analgesia. ITM = intrathecal morphine analgesia. p= 0.31; χ^2 for trends (df=4).

Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic or radiological intervention

Grade IV: Life-threatening complication requiring intermediate care/intensive care unit management



Repeated measures ANOVA		
Main effect between groups	Main effect over time	Interaction effect
$p = 0.22$	$p < 0.0001$	$p = 0.34$

Figure 2. Illustration of EQ-5D weighted health state index in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Result of the repeated measures ANOVA from Day 0 - 42 assessment is presented. EDA = epidural analgesia; ITM = intrathecal morphine analgesia. No significant differences were observed in the EQ-5D health index between the two groups preoperatively.

Insert Figure 3 here

Insert Figure 4 here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
NRS at rest	$p = 0.34$	$p < 0.001$	$p < 0.0001$
NRS at mobilization	$p = 0.08$	$p < 0.0001$	$p < 0.0001$

	Bonferroni post hoc tests, (p-value)																		
	Day 0.3	Day 1.1	Day 1.2	Day 1.3	Day 2.1	Day 2.2	Day 2.3	Day 3.1	Day 3.2	Day 3.3	Day 4.1	Day 4.2	Day 4.3	Day 5.1	Day 5.2	Day 5.3	Day 6.1	Day 6.2	Day 6.3
NRS at mobilization	0.01	0.06	0.01	0.44	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure 3 and 4. Assessment of pain by means of a 10 graded numeric rating scale (NRS) at rest and at mobilization. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 are shown in the table below the diagrams. Assessments done from the evening of surgery and three times daily. Day 1.1, 1.2 and 1.3, respectively, represent the measurements performed in the morning, the afternoon and the evening on Day 1. EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

Insert Figure 5 here	Insert Figure 6 here

	Repeated measures ANOVA		
	Main effect between groups	Main effect over time	Interaction effect
Opioids (Equivalent morphine (mg))	*p*<0.001	*p*<0.0001	*p*<0.0001
DDD non-opioids	*p* = 0.06	*p* < 0.0001	*p*=0.08

	Bonferroni post hoc tests, (p-value)						
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Opioids	<0.0001	<0.0001	<0.001	1.00	1.00	1.00	1.00
DDD non-opioids				1.00	1.00	0.93	0.10

Figure 5 and 6. Consumption of analgesics after surgery in relation to occasion of measurement. Plots represent means and bars represent 95% confidence interval. Results of the repeated measures ANOVA and post hoc tests from Day 0 to the Day 6 assessment for equivalent morphine given and for Day 3 to Day 42 for DDD non-opioids are presented in the table below the diagram. DDD = defined daily dose; EDA = epidural analgesia; ITM = intrathecal morphine analgesia.

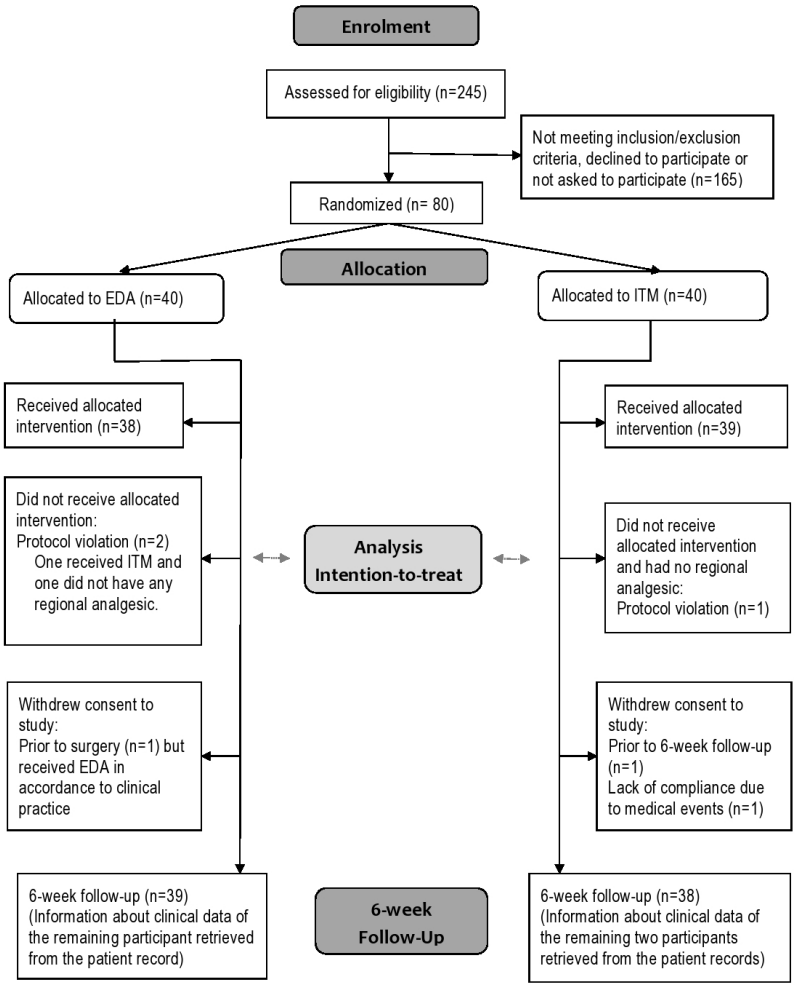


Figure 1.

Figure 1

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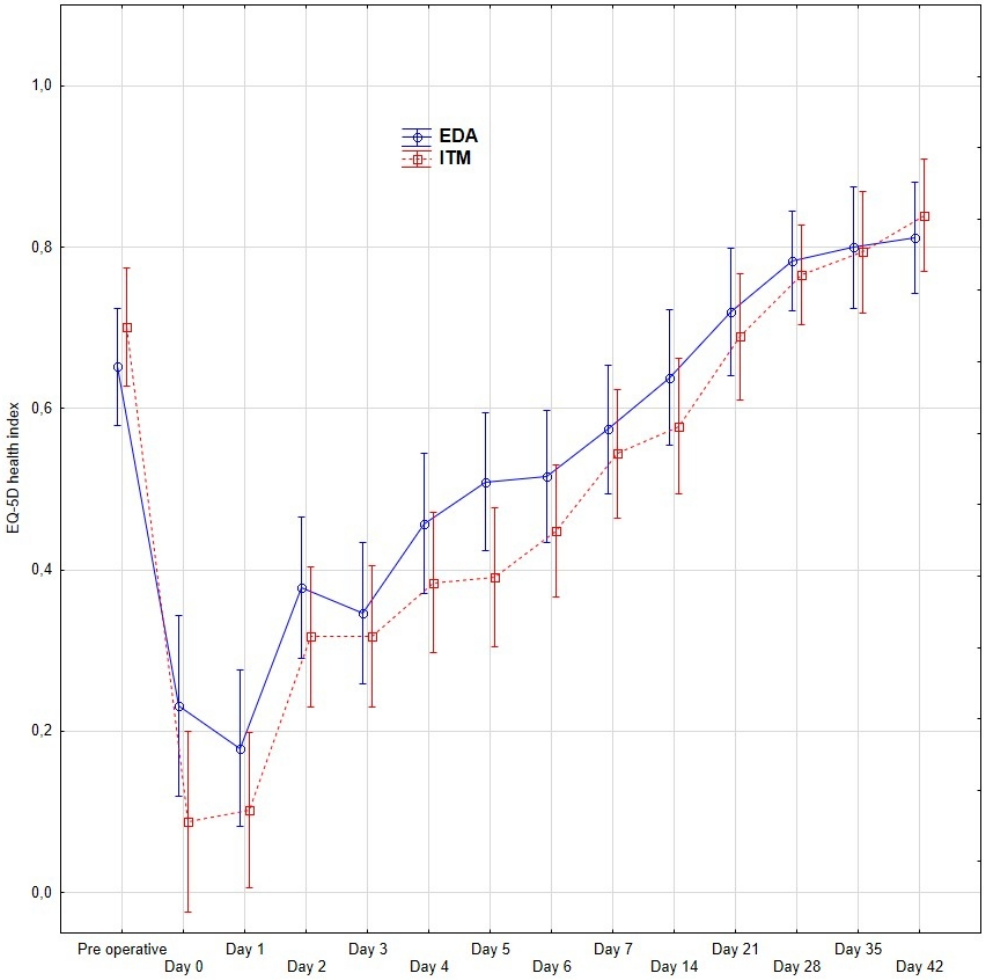

Figure 2

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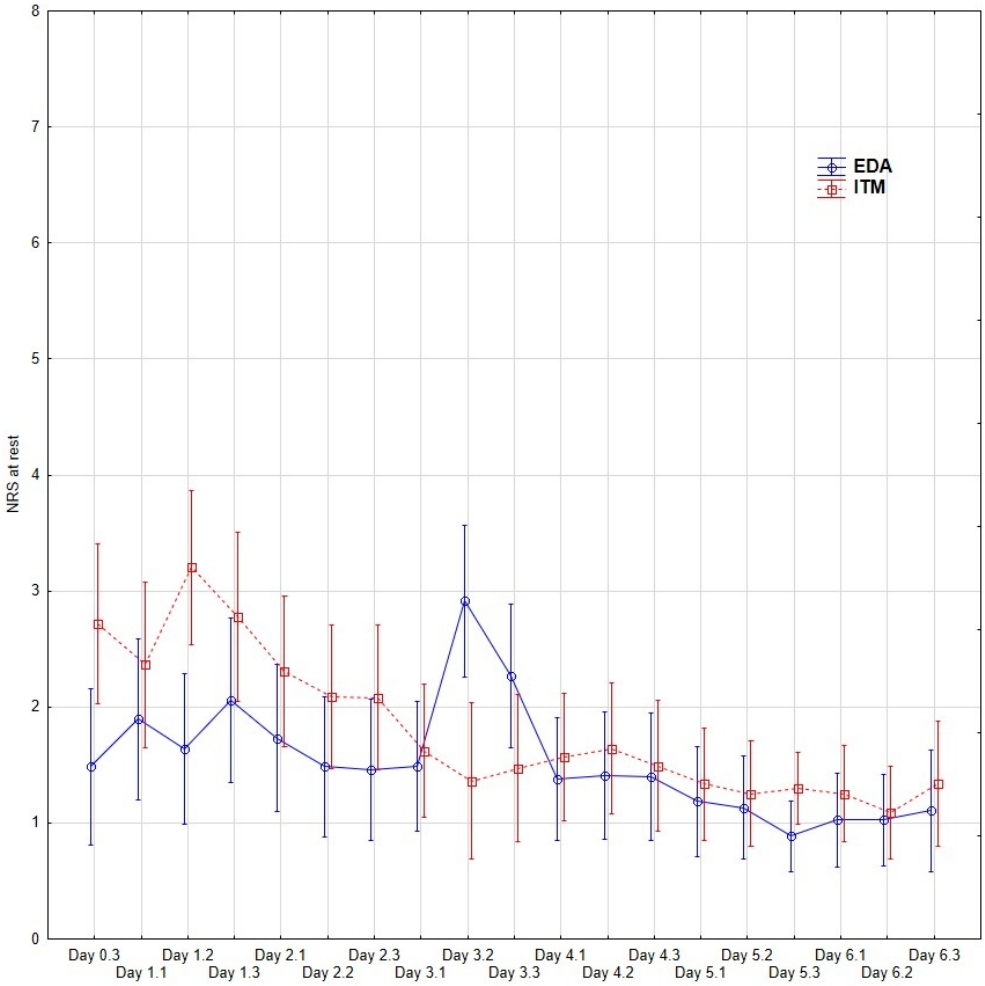

Figure 3

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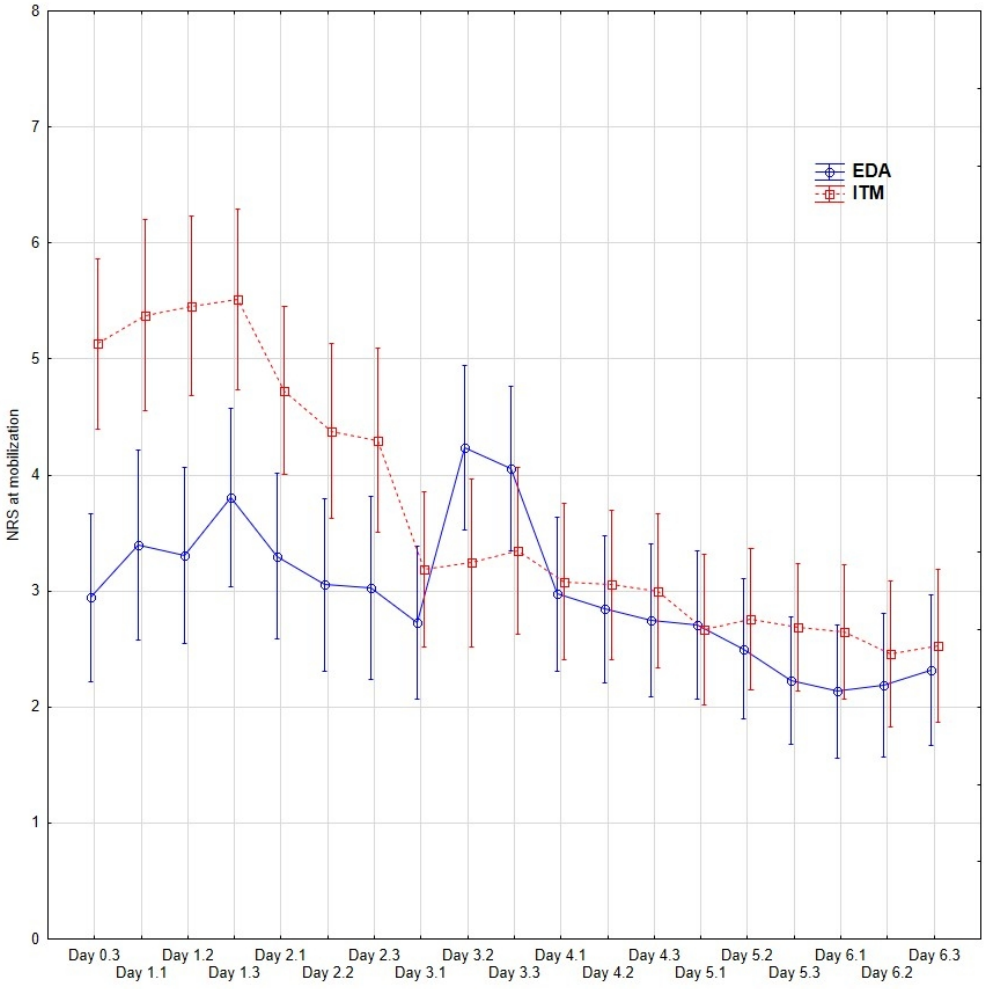

Figure 4

228x228mm (96 x 96 DPI)

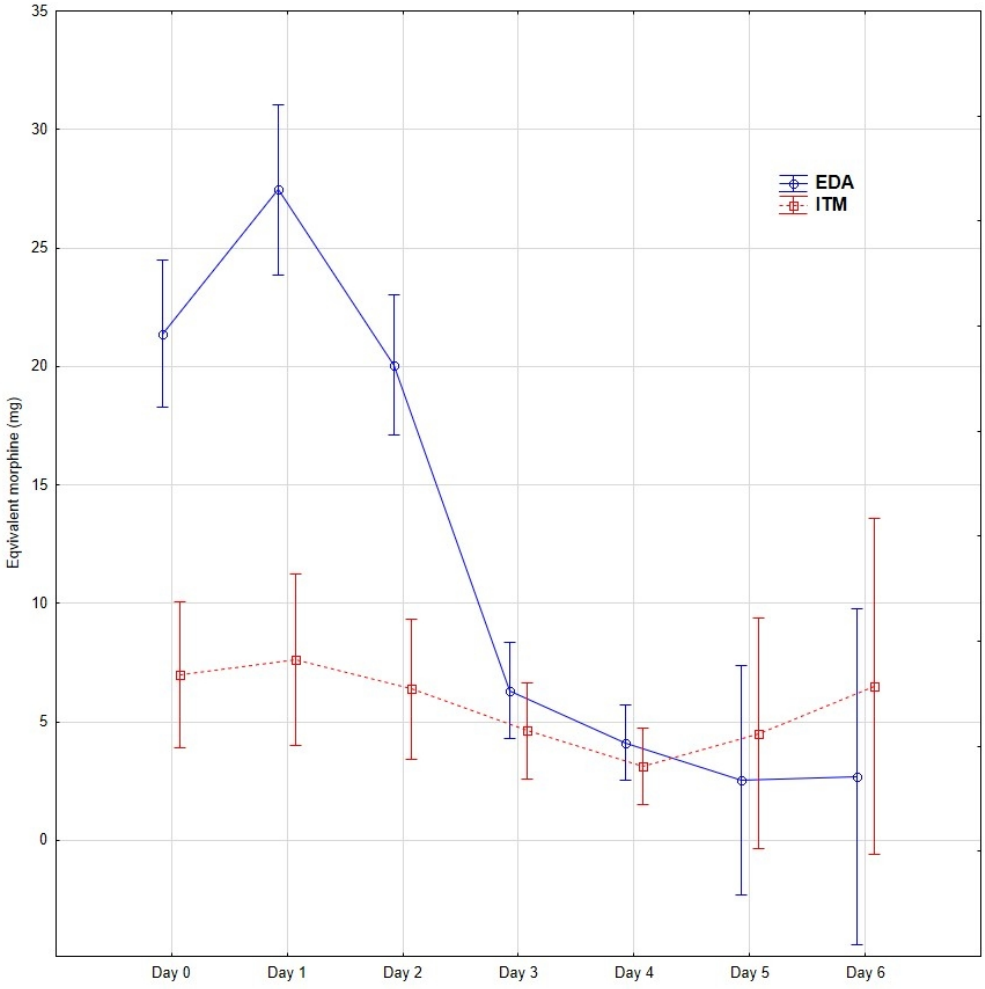

Figure 5

228x228mm (96 x 96 DPI)

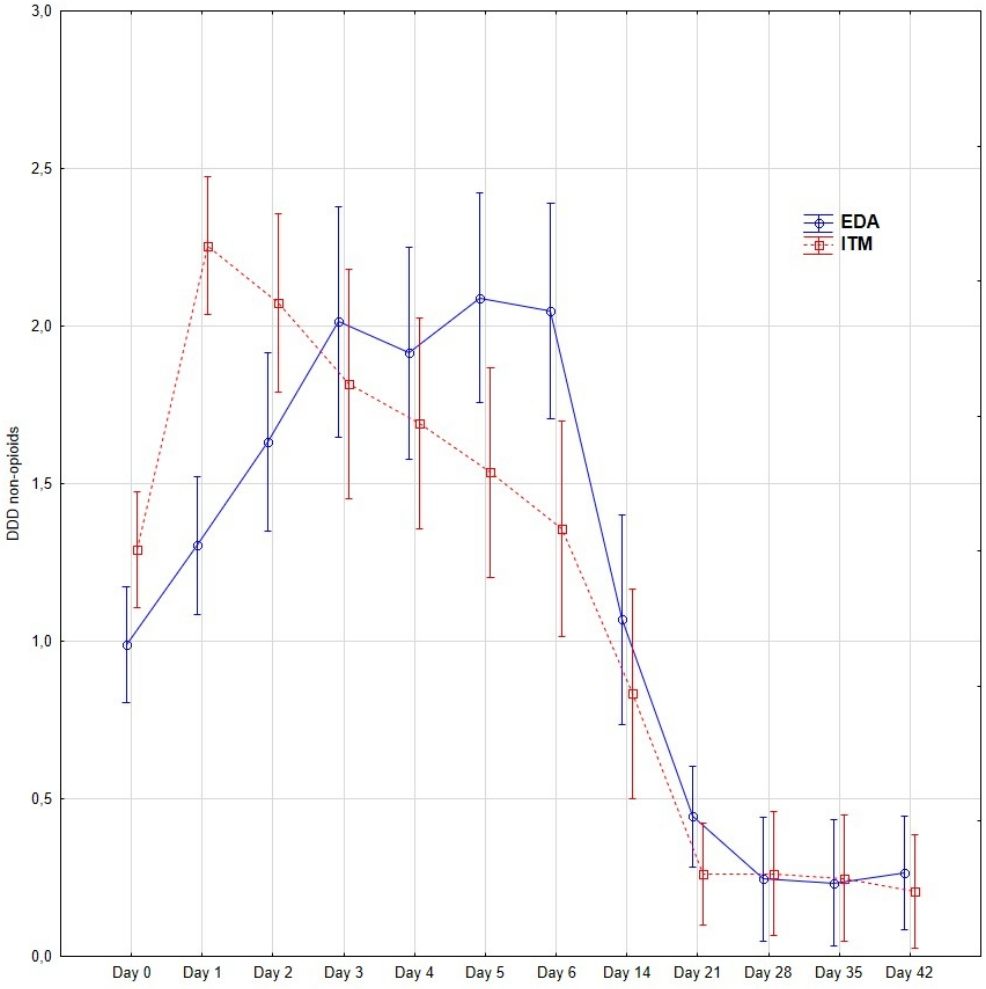

Figure 6

228x228mm (96 x 96 DPI)

Reporting checklist for randomized trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORT reporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Background and objectives	#2a	Scientific background and explanation of rationale	4
	#2b	Specific objectives or hypothesis	4
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	5
	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Na
Participants	#4a	Eligibility criteria for participants	5
	#4b	Settings and locations where the data were collected	5
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including	5-6

		how and when they were actually administered	
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	4-6
Sample size	#7a	How sample size was determined.	7
	#7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	5
	#8b	Type of randomization; details of any restriction (such as blocking and block size)	5
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	NA
	#11b	If relevant, description of the similarity of interventions	NA
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Participant flow diagram (strongly recommended)	#13a	A diagram is strongly recommended. For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1

Recruitment	#14a	Dates defining the periods of recruitment and follow-up	5
	#14b	Why the trial ended or was stopped	NA
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 1,2,4
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8, Figures 2-4
	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	10, Table 4
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	Se Cover letter
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	3