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N.B.: When citing this work, cite the original article.

Original Publication:

Ninnie Borendal Wodlin, Lena Nilsson, Kristofer Arestedt and Preben Kjölhede, Mode of anesthesia and postoperative symptoms following abdominal hysterectomy in a fast-track setting, 2011, ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA, (90), 4, 369-379. http://dx.doi.org/10.1111/j.1600-0412.2010.01059.x

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Postprint available at: Linköping University Electronic Press http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-67978

Mode of anesthesia and postoperative symptoms following abdominal hysterectomy in a fast track setting.

Running title: Postoperative symptoms after fast track hysterectomy

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Abstract

Objective: To determine whether postoperative symptoms differ between women who undergo abdominal benign hysterectomy in a fast track model under general anesthesia or spinal anesthesia with intrathecal morphine.

Design: Secondary analysis from a randomized, open, multicentre study *Setting*: Five hospitals in south-east Sweden

Population: One-hundred and eighty women scheduled for benign hysterectomy were randomized; 162 completed the study, 82 were allocated to spinal and 80 to general anesthesia.

Methods: The Swedish Postoperative Symptoms Questionnaire, completed daily during one week and thereafter once a week until five weeks postoperatively.

Main outcome measures: Occurrence, intensity and duration of postoperative symptoms. *Results*: Women who had hysterectomy under spinal anesthesia with intrathecal morphine experienced significantly less discomfort postoperatively compared with those who had the operation under general anesthesia. Spinal anesthesia reduced the need for opioids postoperatively. The most common symptoms were pain, nausea and vomiting, itching, drowsiness and fatigue. Abdominal pain, drowsiness and fatigue occurred significantly less often and with lower intensity among the spinal anesthesia group. Although postoperative nausea and vomiting was reported equally in the two groups, vomiting episodes were reported significantly more often during the first day after surgery in the spinal anesthesia group. Spinal anesthesia was associated with a higher prevalence of postoperative itching. *Conclusions*: Spinal anesthesia with intrathecal morphine carries advantages regarding postoperative symptoms and recovery following fast track abdominal hysterectomy.

Keywords:

Abdominal hysterectomy; Anesthesia; Fast track; Postoperative symptoms; Randomized study.

Abbreviations:

ANOVA	analysis of variance
GA	general anesthesia
PONV	postoperative nausea and vomiting
SA	spinal anesthesia with intrathecal morphine
SPSQ	Swedish Postoperative Symptoms Questionnaire

Introduction

Minimizing postoperative symptoms is crucial for faster recovery (1,2). Above all, reducing pain has a high priority among patients undergoing surgery (3,4). Gastrointestinal paralysis and postoperative nausea and vomiting (PONV) are other common symptoms following abdominal surgery. The occurrence, intensity and duration of postoperative symptoms related to benign abdominal gynecological surgery have not been sufficiently described (5–7) and seldom in connection with a fast track concept (8,9).

The fast track concept includes strategies to reduce postoperative symptoms by means of pain treatment with minimal use of emetogenic opioids, pre-emptive antiemetics, i.v. fluid restriction, early enteral nutrition and mobilization (10,11). The physiological stress response and organ dysfunction are claimed to be reduced by this, diminishing postoperative symptoms and accelerating recovery. For optimal pain management after surgery, regional anesthesia provides prolonged analgesic effects. Positive effects on stress response and pain seem most pronounced in procedures carried out in the lower part of the abdomen including the pelvis, due to a nearly total afferent neural blockade accomplished by the regional anesthesia (10). Spinal anesthesia is often used in obstetrical and gynecological surgery and adding opioids intrathecally prolongs the analgesia postoperatively (12,13).

A positive impact of spinal anesthesia with morphine intrathecally in a fast track regimen has only recently been reported in relation to abdominal hysterectomy (14). This could reduce postoperative symptoms, enhance recovery and increase patient satisfaction during, but equally importantly, after the hospital stay. It could contribute to making abdominal hysterectomy a day surgery procedure.

In this study, which emanates from the prospective, randomized multicentre trial, the "GASPI study" (15), we aimed to describe postoperative symptoms and determine whether the occurrence and intensity of postoperative symptoms for up to five weeks postoperatively differed between women who had abdominal hysterectomy in a fast track model under general anesthesia compared with spinal anesthesia with intrathecal morphine.

Material and Methods

The Departments of Obstetrics and Gynecology at five hospitals in the southeast health region of Sweden participated in this open, prospective, randomized, controlled multicentre study of women undergoing abdominal hysterectomy for benign gynecological diseases. Women who were admitted for elective hysterectomy between March 2007 and June 2009 were asked to participate. Details about the study design, flow chart, inclusion and exclusion criteria, material and methods have previously been described (15).

After giving verbal and written informed consent, the enrolled women were randomized to receive either general anesthesia or spinal anesthesia including intrathecal morphine. Of the 180 women randomized, 162 completed the study. The women received similar information about care and advice for the perioperative period according to the fast track program shown in Figure 1 The program specified that there would be no use of sedatives for premedication, i.v. fluid restriction, analgesics based on non-opioids, pre-emptive antiemetic therapy using acupressure wrist bands, early start of enteral nutrition and mobilization postoperatively and standardized criteria for discharge.

Premedication and summary of the modes of anesthesia are presented in Figure 1. If the spinal anesthesia was insufficient the patient received GA as described in Figure 1

The surgeon decided on mode of skin incision and abdominal hysterectomy prior to randomization. The hysterectomy was to be carried out by the "routine procedure" of the department but surgical technique was otherwise left to the surgeon's discretion.

Swedish Postoperative Symptoms Questionnaire

Postoperative symptoms were measured by the Swedish Postoperative Symptoms Questionnaire (SPSQ) (7). The patient completed the form on a daily basis, preferably in the evening (starting on the day of surgery (Day 0)) and at the same time of the day during the first seven days and thereafter once weekly until the 5-week clinic visit.

Questions in the SPSQ were both open- and closed-ended. The latter could be answered by choosing an answer from a set given on a Likert-type scale. The open-ended questions required written responses. The patient was initially asked if she at *the moment of completing the form* experienced any of the following symptoms commonly reported after surgery (pain in the area of surgery, nausea, retching, headache, abdominal pain, tiredness, drowsiness and blurred vision) and how she rated the intensity of each of these symptoms. The answers were rated on a 4-point scale: "none" (0), "yes, a little" (1), "yes, somewhat" (2), and "yes, a lot"

Preoperatively Information	Information repeated, concerning pre-, per- and postoperative care, management of pain and PONV, early postoperative mobilization, enteral nutrition and discharge.
Premedication	Two gram paracetamol orally one hour before surgery. Clear fluids orally until two hours before surgery. Acupressure wrist bands applied and maintained through hospital stay.
<u>Peroperatively</u> Spinal anesthesia (SA)	Hyperbaric bupivacaine 20 milligrams (5mg/ml) and morphine 0.2 milligrams (0.4mg/ml) intrathecally. Sedation with iv infusion of propofol. In case of insufficient effect of spinal anesthesia conversion to general anesthesia according to protocol.
General anesthesia (GA)	Induced with propofol and fentanyl. Tracheal intubation facilitated by rocuronium. Anesthesia maintained with propofol and oxygen in air. Rocuronium and fentanyl repeated when needed. Twenty minutes before ending the operation 5 mg morphine applied iv. Orogastric tube during surgery, removed before end of anesthesia.
Parenteral fluids	A restricted regimen used in both groups. The total amount aimed at 25 ml/kg and day. Fenylephrine given if systolic blood pressure decreased > 30% from the baseline.
Local anesthesia	100 mg bupivacaine (2.5 mg/ml) injected subcutaneously and pre-fascially in abdominal wound at conclusion of surgery.
Bladder catheter	Transurethral catheter inserted before start of surgery. Catheter left until next morning.
Postoperatively	
Post anesthetic care unit (PACU)	Pain management initiated orally with paracetamol and diclofenac. Additional pain management with morphine offered if VAS (visual analog scale) score > 3. Patient permitted to drink. Mobilization actively encouraged. Rescue antiemetic treatment when needed with droperidol and/or 5-HT3 receptor antagonist. Patient discharged to the gynecological ward when vital signs were stable.
Gynecological ward.	Monitoring of hemodynamic and respiratory stability, sedation, pain, nausea and itching once every hour during first 12 hours postoperatively, then once every third hour for another 12 hours. Pain management orally continued with 1,330 mg paracetamol and 50 mg diclofenac three times daily. Additional pain relief offered if VAS score >3. Opioids avoided if possible. Rescue antiemetic treatment as in PACU. Patient was encouraged to drink and eat as soon as possible. Mobilization actively encouraged.
After discharge from hospital	Standardized criteria of discharge: patient mobilized; tolerating normal diet; sufficient pain control with oral analgesia (VAS \leq 4); no signs of mechanical bowel obstruction; preferable spontaneous voiding with residual urine \leq 150 ml; otherwise transurethral catheter at discharge. Pain management orally continued with 1,330 mg paracetamol and 50 mg diclofenac three times daily. If NSAID were contraindicated tramadol 50 mg four times daily were given. A package of 6 tablets of oxycodone (10 mg twice daily) was given to the patient if necessary. Duration of treatment with analgesics decided by the patient. Patient contacted by research nurse by telephone the day after discharge, then once weekly until

Figure 1. Fast track protocol with standardized regimes. NSAID = non-steroidal anti-inflammatory drugs. PONV = postoperative nausea and vomiting.

(3). To estimate overall discomfort from the symptoms at the moment of completing the form a sum score was calculated. The minimum sum score was 0 and maximum 24. The higher the sum score, the more discomfort was experienced.

Thereafter the patient was asked to report the intensity of pain in the surgical area *a*) when it was *at its worst* and *b*) how it was felt *on average* on the particular day. The answers to these questions were rated on a 7-point scale as: "none" (0), "very mild" (1), "mild" (2), "moderate" (3), "bad" (4), "severe" (5), and "very severe" (6).

The patient was also asked to state if she experienced other symptoms that she found troublesome in addition to pain in the surgical area. If so, she was asked to specify these (could be more than one). There were nine possible alternative answers: ("none"; "nausea/vomiting"; "headache"; "abdominal pain"; "drowsiness"; "fatigue"; "blurred vision"; "itching" and "others"). The patient was further required to specify the alternative "others" in detail. Assessments similar to those for intensity of pain were made. For practical reasons the self-reported "other" troublesome symptoms were categorized according to organ system of origin in the analysis as gastro-intestinal (bloating, constipation, difficulty emptying the bowels, diarrhea, stomach cramps, gastritis), urinary tract (stranguria, urinary retention, urgency, dysuria, frequency), musculoskeletal system (feeling of weakness in the lower limbs, feeling of reduced mobility in general, back, hip and shoulder pain), and wound-related symptoms (smarting pain, leakage of seroma or hematoma, superficial wound infection). Thus the number of troublesome symptoms made up 11 at most. The patient also recorded any experience of vomiting with answers: "no vomiting", "once daily", or "several times daily".

At discharge the patient was instructed to complete a diary once a day for 35 days concerning self-reported consumption of analgesics, giving information on the trade name of the drug, dosage and quantity. A research nurse contacted the patient by telephone on the day after discharge and then once weekly until the 5-week visit. The purpose of the frequent contacts was to support and provide a reminder to fill in the diary and the SPSQ.

Data analysis

The study was approved by the Regional Ethical Board at Linköping University and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The trial underwent quality control by independent monitoring during the study period. Data from the case report forms and the questionnaires were manually entered into the data base that likewise was checked up by the monitor. The study was registered in ClinicalTrial.gov Protocol Registration System (NCT00527332) with initial release September 7, 2007. (http://clinicaltrials.gov/show/NCT00527332)

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Power calculation and estimation of the sample size were based on the primary outcome measure, duration of hospital stay and have been described in detail (15). No power calculations were done *a priori* for the end-points of this study.

Continuous data are presented as medians (range) and nominal data as numbers and percentages. Comparison of nominal data was by means of Yates' corrected χ^2 test or Fishers' exact test, when appropriate. For univariate comparative analysis of continuous data non-parametric tests were used (Mann-Whitney U-test). For analysis of continuous variables repeatedly measured in a single group, Friedman's test was applied. To compare repeated measures analysis of variance (ANOVA) was used. Statistical significance was set at *p* < 0.05. All analyses were on an *intention-to-treat* basis. In addition, *per protocol* analyses were performed and reported as appropriate.

To validate the sum score in the SPSQ, factor analyses (principal component factoring with orthogonal/varimax rotation) were performed to reveal the dimensionality of the scale. In the first step, the Kaiser criteria (communality >1.0) were used to identify the number of factors. In the second step, a predetermined factor solution with one factor was tested. Factor loadings \geq 0.4 were regarded as significant. The internal consistency reliability was estimated by means of Cronbach's alpha. All validation analyses were performed on data in the SPSQ derived at the third occasion of measurement i.e. in the evening on the second day after surgery.

The software StatView for Windows, SAS Institute Incorp Copyright© 1992 - 1998, Version 5.0.1 was used for the statistical analyses except for the factor analyses which were performed with STATA 11.0 for Windows (StataCorp LP).

Due to the requirement of data for every moment of measurement in the repeated measures analysis of variance (ANOVA) missing data in the SPSQ with repeated measures were managed as follows: if an answer to a question in a questionnaire was missing, the cell was substituted by the mean value of the score for the group on that occasion.

Overall the number of missing data was equally distributed between the treatment groups. Missing data in the SPSQ made up 1.4%. A complete SPSQ form was missing on 13 occasions (0.7%).

Results

Demographic and clinical data has been reported (15). As shown in Table 1 the first factor analysis of the SPSQ sum score revealed a three factor solution. The first factor consisted of the items headache, tiredness, drowsiness and blurred vision. The second factor included the items nausea and retching and the third factor included pain in the area of surgery and abdominal pain. The second factor analysis with one predetermined factor resulted in factor loadings between 0.50 and 0.75 across the eight items. The reliability of these items was 0.73. Given these constraints the sum score of the eight items seemed to be a useful and valid measure to demonstrate comprehensive expression of symptoms.

The women in the SA group experienced significantly less discomfort postoperatively as measured by the SPSQ sum score than the GA group (Figure 2). The self-reported intensity of pain in the surgical area when it was at its worst and on average day-by-day is illustrated in Figure 3. The day-by-day consumption of analgesics postoperatively is shown in Table 2. The use of opioids was significantly higher in the GA group than among the women in the SA group. The women in the GA group estimated pain intensity as significantly higher than the SA group women. After postoperative Day 2 no significant difference was observed in pain intensity for neither peak nor average estimates. The estimates of pain intensity differed significantly from Day 0 to Day 2 within the GA group (p<0.0001, Friedman's test, df =2) from "bad–severe" to "mild–moderate" for pain at peak and from "moderate–bad" to "mild–moderate". In contrast, no such differences were observed within the SA group where the pain intensity estimates at peak as on average were unaffected at a relatively low level Day 0 to Day 2 ("mild–moderate" pain).

The number of troublesome symptoms and the comprehensive estimated average intensity of these are shown in Figure 4. Overall, no significant differences were revealed between women who had GA or those who had SA, neither in number nor average intensity of the symptoms. However, considering the first three days only (Day 0 to Day 2), intensity was significantly higher in the GA than in the SA group (p=0.0004 for the main effect between groups; repeated measures ANOVA). On average the estimated intensity of the symptoms in the GA group decreased from "moderate–bad" on Day 0 to "mild–moderate" on Day 2 whereas it was almost unchanged within the range "mild–moderate" over this time among the SA group.



Figure 2. Illustration of the SPSQ sum score in relation to day after surgery. Day 0 is the day of surgery. Boxes represent mean sum score and error bars represent SD. GA =general anesthesia. SA = spinal anesthesia with intrathecal morphine.

The day-by-day prevalence of the symptoms is illustrated in Figure 5. Only those symptoms that exceeded a prevalence of 10% on any occasion of measurement are presented. The occurrence of difficulty with blurred vision, urinary tract symptoms and musculoskeletal system symptoms did not reach 10% on any occasion. Abdominal pain, besides surgical site related pain, was reported more often by women in the GA than the SA group on Day 0 and Day 1 (p<0.0001 and p=0.0006, respectively; Yates' corrected $\chi^2_{df=1}$ test). Likewise, drowsiness was more prevalent in the GA than the SA group on the same days (p=0.0016 and p=0.0443, respectively; Yates' corrected $\chi^2_{df=1}$ test). Although the prevalence of PONV was initially high it did not differ between the groups on any occasion except for day 3 (p=0.0443; Yates' corrected $\chi^2_{df=1}$ test). More women in the GA group experienced PONV on that occasion than did the women in the SA group. In contrast, itching was more prevalent in the SA than the GA group during the first two days (p<0.0001 and p=0.0007, respectively;

Fishers' exact test). Prevalence of symptoms on all other occasions was similar in the two groups.



Figure 3. Illustration of self reported intensity of pain in surgical area (at peak and on average) over time in relation to mode of anesthesia. GA = general anesthesia. SA = spinal anesthesia with intrathecal morphine. Boxes indicate mean values of pain intensity and error bars indicate 1 SD. Grading of the pain intensity was done on a 7-points scale. 0=no pain; 1=very mild; 2=mild; 3=moderate; 4=bad; 5=severe, and 6=very severe pain. The results of the ANOVA for repeated measures are shown in the table below each diagram.



Figure 4. Number of troublesome symptoms and comprehensive on average intensity of these, day-by-day, in relation to mode of anesthesia. GA = general anesthesia. SA = spinal anesthesia with intrathecal morphine. Boxes indicate mean values of comprehensive symptom intensity and error bars indicate 1 SD. Grading of the comprehensive symptom intensity was done on a 7-points scale. 0=no trouble; 1=very mild; 2=mild; 3=moderate; 4=bad; 5=severe, and 6=very severe trouble. The results of the ANOVA for repeated measures are shown in the table below each diagram.



Figure 5. Frequency of symptoms in relation to time postoperatively after fast track abdominal hysterectomy conducted under general anesthesia (GA) (n = 80) or spinal anesthesia with intrathecal morphine (SA) (n = 82). PONV = postoperative nausea and vomiting.

Vomiting occurred significantly more often and more frequently in the SA than the GA group only during Day 0 (Table 3). Until the 5-week follow-up only a very few women experienced vomiting on single occasions. The use of pre-emptive antiemetics and the need of rescue antiemetics did not differ between the groups on any occasion (data not shown).

Analyzing data using *per protocol* principles did not change the results of all above mentioned analyses.

Discussion

Spinal anesthesia with intrathecal morphine in fast track abdominal hysterectomy for benign disease provided significant advantages over general anesthesia with regard to occurrence of postoperative symptoms during recovery. Drawbacks with SA were a higher prevalence of itching and a more frequent vomiting in the immediate postoperative period.

The study was not blinded for obvious reasons. This may be considered a weakness and a source of bias. However, it was clearly emphasized in the study protocol that the groups should be treated and attended to in the same way with the exception of the peroperative anesthesia in order to reduce possible bias. Since we wanted to reflect daily clinical routine for common major gynecological operations (16), the study was done in a multicenter setting with several participating surgeons and anesthesiologists. The surgical technique was not standardized except for recommendations to perform the hysterectomy with the extrafascial technique and avoid peritonealization of the pelvis and anchoring of the round ligaments to the vaginal cuff or cervical stump. Abdominal hysterectomy is a routine procedure often performed rather similarly with minor variations by different surgeons.

To our knowledge no validated standardized form exists to measure symptoms specifically after hysterectomy. The SPSQ was developed to address and assess postoperative symptoms comprehensively, based on the patient's own assessment of recovery and has the advantage of measuring the symptoms in three ways: at the moment, and at peak and on average during a given time period (17). SPSQ has previously been validated (7) concerning content validity. However, important aspects of summated scales such as construct validity and reliability have not been tested previously. The results of the factor analyses (one aspect of construct validity) as well as the satisfactory level of internal consistency reliability supported the use of the sum score in order to reflect the overall level of postoperative discomfort. The women participating were repeatedly faced with questions concerning experience and intensity of several postoperative symptoms. This might have brought to their attention even symptoms that they otherwise might not have paid specific attention to and this may therefore have created an overestimation of perceived symptoms.

All participating women were thoroughly informed about the importance of notifying staff of pain and to immediately address the nursing staff when necessary in order to receive additional analgesics. The SA group reported significantly less pain in the surgical area compared with the GA group, in spite of a significantly lower amount of opioids given day-by-day. This indicates that SA supplied a superior and prolonged analgesia postoperatively,

which also have been reported in previous studies (12,13). Interestingly, in a recently published Danish study of risk factors for chronic pelvic pain after hysterectomy, spinal anesthesia was associated with a lower frequency of chronic pelvic pain (18). Although this issue has not been addressed in our study, this speaks in favor of using spinal anesthesia for hysterectomy. The pathophysiological mechanism behind this effect is not clearly understood and needs further investigation. Intrathecally applied opioids have been shown to prevent the hormonal stress response associated with surgery (13,19), which might explain the significant difference in overall postoperative discomfort as measured by SPSQ sum score, favoring SA.

Fatigue was reported by a substantial proportion of the women. The etiology of postoperative fatigue is considered to be multifactorial with interactions between biological, psychological, and possibly social factors. The biological aspect of postoperative fatigue can be divided into a physiological response to surgical trauma (i.e., the surgical stress response), a decline in nutritional status, and a reduction in physical fitness after surgery (20). For these reasons fatigue seems to be difficult to prevent and treat. Even in a fast track program such as that used in the present study, fatigue occurred frequently.

Randomized studies concerning abdominal hysterectomy have shown that PONV can be reduced with combination therapies (21,22). In the present study the use of pre-emptive antiemetics with acupressure wristbands and the need for rescue antiemetics did not differ significantly between women in the SA and the GA group, nor did the prevalence of perceived PONV. On the other hand, self-reported vomiting occurred significantly more often and more frequently in the SA group during the day of surgery, despite significantly less requirement for opioid analgesics. This could be explained by the fact that only the women who had general anesthesia received an orogastric tube and gastric emptying during the hysterectomy. It is a clinical observation that vomiting is not always preceded or accompanied by nausea. Thus vomiting may probably be triggered by the gastric paralysis after intraabdominal surgery or may be an effect of the intrathecally applied morphine.

The prevalence of itching reported in this study is in accordance with other studies (23). Itching seemed to be a troublesome symptom for the SA group women in the immediate postoperative period but disappeared within 48 hours.

The influence of surgical pathophysiology on perceived postoperative symptoms has not been investigated. Pain and PONV are the most common and disturbing postoperative symptoms following abdominal hysterectomy (24-26). We found that fatigue should be added to the list of common postoperative symptoms. Optimal management to prevent these symptoms is still warranted to achieve a faster postoperative recovery (1,2). Different fast track programs include multimodal strategies to reduce postoperative symptoms and have been successful, especially in gastrointestinal surgery (10,11).

Despite the importance of the patient's experience of symptoms in the postoperative course, this issue is often not described in textbooks covering gynecological surgery (27,28). The duration of the symptoms, and how recovery proceeds, is also sparsely studied. Randomized studies concerning abdominal hysterectomy do not contain detailed information about how women experienced postoperative symptoms and mainly described pain solely during hospital stay (29-31). In this study the postoperative symptoms were in general most prevalent and intense during the first week following surgery and decreased rapidly.

Using spinal anesthesia with intrathecal morphine in a fast track concept provides progress in pain management and less discomfort postoperatively, but is not sufficient to make abdominal hysterectomy a day surgery procedure. SA has disadvantages in the early postoperative period by giving rise to itching and vomiting although only during the first couple of days. Further efforts have to be made to prevent and treat these commonplace and annoying symptoms in order to improve early postoperative recovery.

Acknowledgements

The study was supported financially by grants from the Medical Research Council of South East Sweden; Linköping University and the County Council of Östergötland. The physicians and research nurses in the multicentre study group are thanked for invaluable work and support in the study.

Disclosure of Interests

None.

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		Fa	ctor analysis no	Factor analysis no. 2		
		Factor I	Factor II	Factor III	One predetermined factor	
Item no.	Symptom	Loadings	Loadings	Loadings	Loadings	
1	Pain in the area of surgery	0.112	0.043	0.873	0.575	
2	Nausea	0.068	0.874	0.175	0.601	
3	Retching	0.083	0.909	-0.030	0.516	
4	Headache	0.544	0.372	0.013	0.556	
5	Abdominal pain	0.108	0.074	0.903	0.605	
6	Tiredness	0.620	0.171	0.357	0.689	
7	Drowsiness	0.722	0.250	0.270	0.748	
8	Blurred vision	0.815	-0.077	0.024	0.501	
	Communality, after rotation	1.90	1.83	1.80	2.92	
	Explained variance, cumulative	0.24	0.47	0.69	0.37	
	Cronbach's alpha	0.65	0.75	0.78	0.73	

Table 1. Factor analyses (principal component factoring with orthogonal/varimax rotation) of the sum score in the SPSQ, n=155

Factor loadings ≥ 0.4 are defined as significant (marked with bold).

Table 2. Consumption of analgesics postoperatively after general anesthesia (GA) (n = 80) and spinal anesthesia with intrathecal morphine (SA) (n = 82). Information concerning equivalent morphine is shown only for day 0-4 and for day 0-8 for the non-opioids since the doses after these days were very low in both groups.

		SA		GA	Repea	ated measures AN	OVA*
		-	-	-	Main effect	Main effect	Interaction
	Median	Range	Median	Range	between groups	over time	effect
Equivalent i.v. morphine							
dose (mg)							
Day 0	0.4	0.0–35.8	18.5	5.0–49.5			
Day 1	0.0	0.0–40.8	0.4	0.0–42.7			
Day 2	0.0	0.0–27.6	0.0	0.0–15.0	<i>ρ</i> < 0.0001	p < 0.0001	<i>р</i> < 0.0001
Day 3	0.0	0.0–16.6	0.0	0.0–13.3			
Day 4	0.0	0.0–15.2	0.0	0.0–12.5			
Non-opioids (RDD)							
Day 0	1.8	1.2–2.8	2.1	1.0–2.8			
Day 1	2.0	0.0–2.7	2.0	0.0–2.7			
Day 2	1.7	0.0–3.3	1.7	0.0–2.7			
Day 3	1.8	0.0–2.7	2.0	0.0–2.7			
Day 4	1.4	0.0–2.4	2.0	0.0–2.7	p = 0.2590	<i>ρ</i> < 0.0001	p = 0.9061
Day 5	1.3	0.0–2.0	1.5	0.0–2.0			
Day 6	1.0	0.0–2.0	1.3	0.0–2.2			
Day 7	1.0	0.0–2.0	1.0	0.0–2.0			
Day 8	0.9	0.0–2.0	1.0	0.0–2.0			

RDD sum of recommended daily dosage.

* The repeated measure ANOVA includes measurement from day 0 to day 16 concerning equivalent morphine and from day 0 to day 35 regarding non-opioids. After day 4 the equivalent morphine dose remained very low. For the non-opioids the RDD was below 1 after day 8.

Table 3. Self reported occurrence and frequency of vomiting after abdominal hysterectomy in relation to mode of anesthesia. Only the first three days are shown.

	Day 0				Day 1				Day 2				
Frequency	SA		G	GA		SA		GA		SA		GA	
	n	%	n	%	n	%	n	%	n	%	n	%	
No vomiting episodes	43	53	59	77	72	89	67	84	80	99	75	95	
Once	11	13	11	14	5	6	4	5	0	0	2	2.5	
More times	28	34	7	9	4	5	9	11	1	1	2	2.5	
<i>p</i> -value*	0.0006			0.3316			0.2908						

 \overline{GA} = general anesthesia. SA = spinal anesthesia with intrathecal morphine * Yates' corrected χ^2 test (df = 2)