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The Effects of Intrathecal Morphine on Patient-controlled Analgesia, Morphine Consumption, Postoperative Pain and Satisfaction Scores in Patients Undergoing Gynaecological Oncological Surgery

I Kara[1], S Apiliogullari[1], B Oc[1], JB Celik[1], A Duman[1], C Celik[2] and NU Dogan[2]

[1]Department of Anaesthesia and Intensive Care, and [2]Department of Obstetrics and Gynaecology, Selcuklu Medical Faculty, Selcuk University, Konya, Turkey

OBJECTIVE: Gynaecological oncological surgery (GOS) includes a wide variety of surgical procedures and postoperative pain is a major concern. This study compared the impact of intrathecal morphine (ITM) plus patient-controlled analgesia (PCA) with PCA alone on morphine consumption, pain relief and patient satisfaction after GOS. METHODS: Sixty women undergoing GOS under general anaesthesia were randomized to receive either 0.3 mg ITM or placebo. On arrival at the postanaesthesia care unit each patient received a morphine PCA pump. The three primary outcome measures were pain, patient satisfaction scores evaluated using a 100-mm visual analogue scale and cumulative PCA morphine consumption. RESULTS: No significant differences were observed in the demographic data. Cumulative PCA morphine consumption was significantly lower in the ITM group compared with the control group. Fatigue scores were lower in the ITM group compared with the control group but did not reach statistical significance. Pain, sedation and patient satisfaction scores, and the rate of side-effects were similar for the two groups. CONCLUSIONS: Administering ITM in GOS could improve postoperative analgesia and reduce morphine consumption without serious side-effects.

KEY WORDS: Intrathecal morphine; Analgesics; Gynaecological oncological surgery (GOS); Morphine consumption; Pain; Patient satisfaction; Sedation; Fatigue

Introduction

Good pain control after major abdominal surgery is one of the most important factors for reducing hospital stay and increasing patient comfort and satisfaction.[1] Compared with benign gynaecological procedures, gynaecological oncological surgery (GOS) is associated with larger abdominal incisions, more extensive dissections and a more pronounced inflammatory response with a potentially more challenging pain profile.[2] Postoperative pain resulting from GOS, including cytoreductive surgery, is often underestimated and is usually managed in

the same way as it is for benign abdominal procedures.[1,2]

Patient-controlled analgesia (PCA) is an effective method of postoperative pain management and offers more advantages than conventional techniques.[3] Nevertheless, despite being on PCA, some patients still experience postoperative pain and PCA-related side-effects.[4] The introduction of intrathecal opioids has been one of the most important breakthroughs in pain management in the last two decades.[5] In a study by Karaman *et al.*,[6] intrathecal morphine (ITM) without local anaesthetic was very effective in reducing postoperative pain and also decreased systemic morphine consumption in patients undergoing simple abdominal hysterectomy for benign conditions with general anaesthesia.

Evaluation of the effectiveness of ITM on PCA morphine consumption, and on postoperative pain and satisfaction scores, in patients undergoing GOS has to our knowledge not previously been undertaken in a randomized trial. The present study compared the effects of ITM and PCA with PCA alone on pain relief, patient satisfaction and morphine consumption in women undergoing GOS under general anaesthesia.

Patients and methods

STUDY POPULATION

Consecutive patients aged 18 – 65 years (American Society of Anesthesiologists physical status I – II; http://www.asahq.org/clinical/physicalstatus.htm) who were scheduled for elective GOS at the Department of Obstetrics and Gynaecology, Selcuklu Medical Faculty, Selcuk University (Konya, Turkey) between January and September 2011 were enrolled in this prospective, randomized, double-blind study. The exclusion criteria were contraindication to spinal analgesia or ITM, insufficient comprehension to use a PCA pump, body mass index > 35 kg/m^2 and a history of analgesic drug abuse.

The study had institutional review board approval from the Ethics Committee of Selcuklu Medical Faculty Hospital (Ref. No. 2011-43) and written informed consent was obtained from each participant.

STUDY PROCEDURES

Patients were randomized by sealed envelope assignment to receive either 0.3 mg ITM (ITM group) or placebo (control group). In the ITM group, the same anaesthesiologist (I.K.) performed lumbar punctures in the sitting position at the L_3 – L_4 or L_4 – L_5 lumbar vertebral level with a 27G pencil point spinal needle. For the control group, the skin was punctured with a 27G dental needle without any medication, but the needle was not advanced beyond the subcutaneous tissue. This was performed by the same anaesthesiologist (I.K.) who was not involved in the study evaluation. Monitoring and anaesthesia were standardized. Anaesthesia was induced with 2 mg/kg propofol, 2 µg/kg fentanyl and 0.6 mg/kg rocuronium, all administered intravenously. After tracheal intubation, anaesthesia was maintained with a mixture of air (0.5 l/min) and oxygen (0.5 l/min) plus desflurane (4 – 6%). On arrival at the postanaesthesia care unit (PACU), each patient received a PCA pump programmed to deliver an initial morphine bolus of 0.05 mg/kg if their pain score was > 60 on a 100-mm visual analogue scale (VAS; 0 mm, no pain; 100 mm worst pain imaginable). On discharge from the PACU, the pump was reprogrammed to deliver a morphine bolus of 1.5 mg with a 7-min lockout without base flow.[7] PCA was maintained during the first 48-h postoperative period.

PRIMARY AND SECONDARY OUTCOME MEASURES

The three primary outcome measures were pain scores (0 – 100 mm VAS; defined as above), patient satisfaction scores (0 – 100 mm VAS; 0 mm very unsatisfied; 100 mm very satisfied), and cumulative PCA morphine consumption (mg). Secondary outcomes were side-effects including nausea, vomiting, pruritus, sedation, fatigue, and respiratory depression. Data were recorded postoperatively by the same trained nursing staff at 30 min and at 1, 3, 6, 12, 24 and 48 h. Patients were directly asked if they had experienced any nausea, vomiting or pruritus during the study. Intravenous antiemetics were administered (4 mg ondansetron and 20 mg diphenhydramine hydrochloride) as rescue drugs at the patient's request. The numbers of patients with nausea, vomiting or pruritus and the number of patients requiring rescue medication were recorded. Sedation was assessed using a five-point scoring scale: 0, fully awake; 1, drowsy, closed eyes; 2, asleep but easily aroused with light tactile stimulation or simple verbal command; 3, asleep and aroused only by strong physical stimulation; and 4, could not be aroused. Fatigue was assessed on a four-point categorical scale: 0, none; 1, mild; 2, moderate; and 3, severe. Respiratory depression was defined as a respiratory rate < 10 breaths/min and was reversed by administering 0.1 mg naloxone intravenously, repeated every 5 min until adequate respiration was restored.

STATISTICAL ANALYSES

In a pilot study, 20 patients scheduled for elective GOS under general anaesthesia consumed a mean ± SD of 57 ± 21 mg of morphine in the first 48 h with a PCA pump. To achieve a one-third reduction of opioid consumption with α error of 0.005 and power of 90%, the study needed 26 patients in each group.

The SPSS® statistical package, version 16.0 for Windows® (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were expressed as mean ± SD and number (%) of patients and were tested for normality using the Kolmogorov–Smirnov normality test. For categorical variables, the data were analysed using the χ^2-test. For continuous variables, the Student's *t*-test was used for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. A *P*-value < 0.05 was considered to be statistically significant.

Results

This study included 60 patients, aged 18 – 65 years, scheduled for GOS under general anaesthesia and randomized into two groups of 30 patients. Two patients from the ITM group and two from the control group were excluded because of technical problems with the PCA machine and missing data, respectively. The groups were comparable with respect to age, weight, height, duration of surgery and type of malignancy (Table 1).

Patients in the ITM group had significantly lower cumulative morphine consumption than the control group during the 48-h postoperative period ($P < 0.001$ at all time points; Table 1). Table 2 shows the results for the other primary outcomes and for the secondary outcomes. Pain scores, patient satisfaction scores and sedation scores were comparable in both groups at all times. Overall mean patient satisfaction scores were 59.3 ± 4.3 and 57.5 ± 3.1 for the ITM and control groups, respectively; there was no difference between the ITM and control group. More patients had lower fatigue scores in the ITM group than in the

TABLE 1:
Demographic and clinical characteristics of the patients (*n* = 56) who underwent gynaecological oncological surgery with general anaesthesia with intrathecal morphine (ITM group) or without ITM (control group)

Characteristic	ITM group (*n* = 28)	Control group (*n* = 28)	Statistical significance[a]
Age, years	49.3 ± 8.8	47.7 ± 5.7	NS
Weight, kg	73.4 ± 9.7	74.6 ± 14.4	NS
Height, cm	161.5 ± 5.1	160.0 ± 5.2	NS
Duration of surgery, min	175.0 ± 28.9	166.9 ± 41.8	NS
Malignancy type, uterine/ovary/cervix/other	7/15/1/5	6/16/2/4	NS
Cumulative morphine consumption, mg			
30 min	1.2 ± 1.0	2.8 ± 0.9	$P < 0.001$
1 h	2.6 ± 2.3	5.0 ± 1.8	$P < 0.001$
3 h	4.8 ± 3.5	10.8 ± 6.9	$P < 0.001$
6 h	7.3 ± 4.8	18.1 ± 10.8	$P < 0.001$
12 h	9.5 ± 6.2	27.7 ± 15.3	$P < 0.001$
24 h	12.6 ± 8.0	39.1 ± 18.8	$P < 0.001$
48 h	19.2 ± 12.0	54.4 ± 22.3	$P < 0.001$

Data presented as mean ± SD or number of patients
[a]For categorical variables, the data were analysed using the χ^2-test. For continuous variables, the Student's *t*-test was used for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. NS, No statistically significant between-group differences ($P \geq 0.05$).

control group, but the difference was not statistically significant. There were no statistically significant differences between the two groups in rates of nausea and pruritis at any time postoperatively. Nausea was observed in 13/28 patients in the ITM group and 10/28 patients in the control group (not statistically significant). Pruritis was observed in 4/28 patients in the ITM group and 0/28 patients in the control group (not statistically significant).

Discussion

The present study showed that ITM significantly reduced cumulative PCA morphine consumption without causing a significant difference in pain and satisfaction scores or the rate of side-effects in patients undergoing GOS with general anaesthesia.

A wide variety of surgical procedures are involved in GOS including radical hysterectomy, pelvic para-aortic lymphadenectomy, upper abdominal procedures and bowel resection.[2] Severe postoperative pain is a major concern in these patients. Pain has significant effects on multiple systems and induces physiological, immunological and psychological changes.[8,9] Nausea and fatigue are two important factors affecting patient satisfaction in those undergoing abdominal hysterectomy. PCA with intravenous opioids, such as morphine, has been considered the gold standard method for pain management following major abdominal surgery as it provides superior pain control compared with conventional opioid analgesia.[4,5,10] PCA allows for better titration to optimize postoperative pain management, minimize adverse effects and reduce postoperative complications and recovery time.[5,6] Systemic opioids may, however, cause respiratory depression, intestinal dysfunction, sedation,

TABLE 2:
Postoperative pain scores, patient satisfaction scores and side-effects for the patients who underwent gynaecological oncological surgery with general anaesthesia with intrathecal morphine (ITM group; $n = 28$) or without ITM (control [C] group; $n = 28$)

Time postoperatively	Group	Pain score[a]	Satisfaction score[b]	Sedation[c] (0/1/2/3/4)	Fatigue[d] (0/1/2/3)	Nausea	Pruritus
30 min	ITM	20 ± 11	48.8 ± 5.3	16/10/2/0/0	12/12/4/0	5 (17.9)	2 (7.1)
	C	29 ± 28	45.8 ± 3.6	15/7/6/0/0	8/10/8/2	1 (3.6)	0 (0)
1 h	ITM	21 ± 12	50.1 ± 6.2	15/10/3/0/0	15/9/4/0	1 (3.6)	2 (7.1)
	C	23 ± 17	49.6 ± 7.2	13/10/5/0/0	11/8/8/1	0 (0)	0 (0)
3 h	ITM	16 ± 11	52.2 ± 7.1	23/4/1/0/0	24/3/1/0	5 (17.9)	3 (10.7)
	C	18 ± 11	51.4 ± 8.4	22/5/1/0/0	15/6/6/1	0 (0)	0 (0)
6 h	ITM	12 ± 8	52.8 ± 5.4	25/3/0/0/0	25/3/0/0	4 (14.3)	4 (14.3)
	C	18 ± 7	50.3 ± 9.1	22/6/0/0/0	17/7/3/1	1 (3.6)	0 (0)
12 h	ITM	12 ± 8	54.5 ± 6.8	26/2/0/0/0	26/2/0/0	1 (3.6)	3 (10.7)
	C	15 ± 7	52.8 ± 4.2	23/5/0/0/0	23/3/2/0	0 (0)	0 (0)
24 h	ITM	13 ± 6	56.4 ± 2.4	27/1/0/0/0	27/1/0/0	2 (7.1)	3 (10.7)
	C	12 ± 5	53.8 ± 3.7	24/4/0/0/0	23/4/1/0	1 (3.6)	0 (0)
48 h	ITM	9 ± 4	59.3 ± 4.3	28/0/0/0/0	27/1/0/0	2 (7.1)	3 (10.7)
	C	10 ± 2	57.5 ± 3.1	26/2/0/0/0	25/2/1/0	0 (0)	0 (0)

Data presented as mean ± SD, number of patients, or number (%) of patients.
For categorical variables, data were analysed using the χ^2-test. For continuous variables, the Student's *t*-test was used for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. There were no statistical significant between-group differences ($P \geq 0.05$).
[a]Pain score: 100-mm visual analogue scale (0 mm, no pain; 100 mm worst pain imaginable).
[b]Patient satisfaction score: 100-mm visual analogue scale (0 – 100 mm VAS; 0 mm very unsatisfied; 100 mm very satisfied).
[c]Sedation score: 0, fully awake; 1, drowsy, closed eyes; 2, asleep, but easily aroused with light tactile stimulation or simple verbal command; 3, asleep and aroused only by strong physical stimulation; and 4, could not be aroused.
[d]Fatigue score: 0, none; 1, mild; 2, moderate; and 3, severe.

nausea and vomiting.[5,11] New ways to decrease systemic morphine-related side-effects are being sought.[11,12]

Use of ITM is a simple and quick procedure that is expected to decrease postoperative pain intensity and opioid requirements and accelerate recovery.[13] The ITM dose for major abdominal surgery varies widely. For gynaecological surgery, the results of Rodanant *et al.*[14] showed that 0.2 mg ITM produced adequate analgesia and fewer side-effects in women undergoing abdominal hysterectomy under spinal anaesthesia. These authors also reported that there was no advantage in increasing the dose in terms of efficacy but that higher doses led to an increase in the number of pruritic patients who required treatment.[14] A dose of 0.2 mg ITM may not, however, provide sufficient postoperative analgesia for patients undergoing GOS under general anaesthesia. Sarma and Boström[15] recommended 0.3 mg ITM for the pain associated with abdominal hysterectomy as an optimal dose compared with doses of 0.1 and 0.5 mg. Karaman *et al.*[6] showed that 0.5 mg ITM reduced PCA morphine consumption and enhanced the quality of postoperative analgesia in women undergoing abdominal hysterectomy. Also, nausea and pruritus were less frequently observed in the ITM group.[6] The lower dose of 0.3 mg ITM was selected over higher doses in the present study and combined with postoperative PCA morphine.

In the present study, morphine consumption was reduced by approximately three-fold in the ITM group compared with the control group. Compared with the study reported by Karaman *et al.*,[6] fewer patients in the ITM group in the present study experienced nausea, although this still amounted to nearly half of the patients (13/28 patients). This may be related to the lower dose of ITM administered in the current study (0.3 versus 0.5 mg, respectively) and indicates a need for prophylactic antiemetics.

More patients in the ITM group in the present study had lower postoperative fatigue scores compared with the control group (although the difference was not statistically significant). Reduced fatigue probably has multifactorial reasons, resulting from interactions between biological, psychological and, possibly, social factors, which makes it difficult to prevent and treat.[16] The physiological response to surgical trauma (i.e. the surgical stress response) can be controlled with neuraxial opioids.[17,18] Further research is needed to clarify the risk–benefit ratio of ITM compared with PCA morphine.

One of the major concerns regarding both ITM and PCA morphine is its safety with respect to respiratory depression and other side-effects. Some authors have used neuraxial morphine with parenteral narcotic in the postoperative period.[7,19] One study used 0.5 mg morphine combined with PCA after a liver resection without adverse outcomes.[7] Respiratory depression may be increased when intravenous morphine and ITM are combined. Thus, the PCA pump in the present study was programmed for a morphine bolus of 1.5 mg without base flow. It is not possible to predict, however, when respiratory depression will occur.[20]

In conclusion, the addition of ITM to PCA morphine significantly reduced cumulative PCA morphine consumption over a 48-h postoperative period in GOS patients, with no obvious increase in pain, reduction in patient satisfaction or increase in the rate of adverse effects compared with PCA morphine alone. Nevertheless, patient satisfaction scores were < 60 for the majority of patients, indicating that overall patient satisfaction was not high and there is, therefore, a need for further research in order

to provide a convenient multimodal postoperative pain treatment regimen for women undergoing GOS.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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Author's address for correspondence
Assistant Professor Inci Kara
Department of Anaesthesia and Intensive Care, Selcuklu Medical Faculty, Selcuk University, 42075 Selcuklu, Konya, Turkey.
E-mail: drincikara@yahoo.com