DOI: https://doi.org/10.2298/SARH190312116T
UDC: 615.212:618.14-089.85

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Efficiency and safety of intrathecal morphine for analgesia after hysterectomy

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SUMMARY

Introduction/Objective This prospective, randomized study was done to determine the efficiency and safety of the administration of intrathecal morphine chloride combined with the local anesthetic levobupivacaine given to female patients subjected to hysterectomy to ensure postoperative analgesia.

Methods The study sample consisted of 50 patients who were to undergo hysterectomy with adnexectomy and they were divided into two groups of 25 each. The patients in group A were given the combination of 0.3 mg of morphine chloride with 1.7 ml of 0.5% levobupivacaine immediately before the surgery, whereas the patients in group B were intravenously administered 5 mg of morphine chloride before the end of surgery, and after the surgery at certain time intervals. The postoperative pain was assessed at the first, sixth, 12th, and 24th hour by Numeric Rating Scale (NRS). Side effects, such as nausea, vomiting, itching and respiratory depressions were followed as well.

Results The postoperative pain was less expressed at any time interval both at rest and on exertion in group A ($p < 0.001$) and therefore the need for additional analgesia was less in group A ($p < 0.001$). The subjective feeling of satisfaction with postoperative analgesia was statistically significant in group A ($p < 0.001$).

Conclusion Intrathecal administration of morphine chloride combined with levobupivacaine ensures better postoperative analgesia after hysterectomy than intravenous morphine chloride, their side effects being equally frequent.

Keywords: hysterectomy; intrathecal morphine; postoperative analgesia

INTRODUCTION

Acute pain is the body's mechanism to signal tissue injury and danger [1]. The intensity of postoperative pain after hysterectomy ranges from moderate to severe. The efficient pain control leads to the earlier mobilization of patients and their faster recovery, thus leading to shorter hospitalization and lower treatment expenses [2–5]. Controlling acute pain after surgery is important not only in the immediate postoperative phase but also to prevent chronic postsurgical pain, which can develop in as many as 10% of patients [6].

The aim is to achieve good analgesia with minimum side effects. Currently, it cannot be said that there is an ideal mode of analgesia. Intravenous opioids and other analgesics are most frequently used drugs to alleviate the postoperative pain during the first 24 hours. The use of opioids for patients who have surgery presents a particularly challenging problem requiring clinicians to balance managing acute pain in the postoperative period and minimizing the risks of persistent opioid use after surgery [7].

Another good technique is epidural analgesia. A systemic review has shown that the continuous epidural analgesia is superior to the patient controlled analgesia (PCA) in the patients having had a major intra-abdominal surgery [8]. However, this procedure is a bit more invasive because a catheter must be inserted, which has to remain in the epidural space for at least 24 to 48 hours.

Intrathecal administration of local anesthetics with small doses of opioids is an attractive analgesic technique because the drugs are given directly into the liquor, close to the structures of the central nervous system through which these drugs act [9].This procedure is simple, easy to be performed, with a relatively low risk of failure. It is expected to decrease the postoperative pain as well as the necessity for additional analgesia. It has been shown to be effective in the alleviation of postoperative pain after prostatectomy, transurethral resection of the prostate and hepatectomy [10, 11, 12]. The most frequently used opioid is morphine. Analgesic effect of morphine administered intrathecally may persist for up to 48 hours [13]. A disadvantage of this technique is the occurrence of side effects such as nausea, vomiting, itching, urine retention, and respiratory depression, being the most severe complication [14–17].

This study was aimed at determining the efficiency and safety of administration of intrathecal

Received • Примљено: March 12, 2019
Revised • Ревизија: October 8, 2019
Accepted • Прихваћено: October 25, 2019
Online first: November 1, 2019

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morphine combined with a local anesthetic given to ensure analgesia in the patients to undergo hysterectomy.

METHODS

This prospective, randomized study included 50 patients from the elective surgical program performed at the Department of Surgical Oncology, Institute of Oncology of Vojvodina in Sremska Kamenica. The patients underwent hysterectomy with bilateral adnexectomy and lymphadenectomy. The study, which had been approved by the Ethics Committee of the Institute of Oncology of Vojvodina, was conducted from September 1, 2017 to February 15, 2018. The patients were divided into two groups according to the applied technique of postoperative analgesia:

Group A (25 subjects) – the patients having been given morphine chloride intrathecally in the combination with levobupivacaine before the surgery;

Group B (25 subjects) – the patients given morphine chloride intravenously before the end of surgery (when suturing began) and after the surgery.

The inclusion criteria were:

- Age ≥ 18 years
- American Society of Anesthesiologists (ASA) classification I or II
- Diagnosed neoplasm of the uterine body or cervix

The exclusion criteria were:

- Allergic reaction to morphine, local anesthetic, and metamizole
- Age < 18 years.

The patients meeting criteria were given both verbal and written details about the study method and aims as well as about the technique of premedication and anesthesia for the planned surgical intervention. The ones who had given their written consent to participate were included in the study sample.

The group A patients were given 0.3 mg of morphine chloride intrathecally with 1.7 ml of 0.5% levobupivacaine (L3–L4 space, 26G needle) 15 minutes before anesthesia, and the group B patients were intravenously given 5 mg of morphine chloride before the end of surgery when suturing began. Anesthesia in both groups of patients was general and balanced. All patients were premedicated with midazolam (0.05 mg/kg intravenously), and propofol (1.5 mg/kg) was used to introduce anesthesia along with opioid analgesic fentanyl (1.5 μg/kg). Rocuronium (1 mg/kg) was administered for muscle relaxation for intubation as well as during the surgery at a dose adequate to maintain the relaxation. Anesthesia was maintained with sevoflurane (1 minimum alveolar concentration). The lung ventilation was ensured with the gas mixture O_2:N_2O 40:60 so that $EtCO_2$ < 38 mmHg. Electrocardiogram, blood pressure, heart frequency, SpO_2, $EtCO_2$ and body temperature were monitored during the surgery. Boluses of fentanyl (50 μg) and of rocuronium (10 mg) were given when necessary. Anesthetics were administered in such a way so to provide satisfactory anesthesia, blood pressure values and heart frequency in the values ± 30% as compared with the values prior to anesthesia. Drugs for reversal of neuromuscular blockade (neostigmine 0.02 mg/kg and atropine 0.01 mg/kg) were given at the end of surgery. In addition, metoclopramide 10 mg intravenous was administered at the end of surgery, immediately before the patients woke up, to prevent nausea and vomiting. The group B patients were given metoclopramide at eight-hour intervals during the first 24 hours after the surgery.

The group A patients were given intravenous 2.5 g (maximum 5 g/24 h) of metamizole when necessary for postoperative analgesia in case of pain exceeding grade 4 according to the numeric rating scale (NRS), whereas morphine chloride (5 mg intravenously/6–8 hours) and metamizole 2.5 g (maximum 5 g/24 h) were administered alternatively after the surgery to the group B patients and 2–5 mg of intravenous morphine chloride was given when pain exceeded grade 4 according to NRS. The dose of additional morphine chloride in group B was dependent on the age and body weight of the patients, according to the protocol of our clinic.

Numeric values of postoperative pain intensity assessed according to NRS at rest, while coughing and active moving were recorded at intervals of one, six, 12, and 24 hours. These values ranged from 0 to 10 (0 – no pain, 10 – the most severe possible pain). In addition, the patients were asked to keep records of their subjective feeling of satisfaction (SFS) with analgesia, assessing it as: 1 – poor, 2 – medium, 3 – good, and 4 – excellent. Complications such as nausea, vomiting, itching, and respiratory depression were also recorded. All patients had urinary catheter so we could not follow urinary retention.

The data were analyzed and processed by IBM SPSS statistics 10.0 software (SPSS Inc., Chicago, IL, USA) and given in tables and figures created in Word and Excel Microsoft Office 2003 packs. The results were presented using standard statistical methods: frequency (f), arithmetic means (x), standard deviation (SD), value intervals (maximum and minimum), and percentages (%). The patients' characteristics were compared with Student's t-test and χ^2 test, $p < 0.05$ being the statistically significant value.

RESULTS

The study sample consisted of 50 female patients divided into two groups of 25 each. There were no statistically significant differences in age, body weight, ASA classification and the length of surgery between the group A and B (Table 1).

Table 1. Patient characteristics

Parameters	Group A	Group B	p
Age (years ± SD)	56.6 ± 11.1	57.7 ± 9.8	0.707
Weight (kg ± SD)	73.6 ± 13.2	75.5 ± 13.8	0.624
ASA I n (%)	2 (8)	3 (12)	1.000
ASA II n (%)	23 (92)	22 (88)	
Duration of the operation (min ± SD)	174.2 ± 38.8	150 ± 49.7	0.061

ASA – American Society of Anesthesiologists classification I or II

Table 2. Mean NRS (at rest) one, six, 12, and 24 hours after surgery

Parameters	Group A				Group B					
	Mean	Min	Max	Standard deviation	Mean	Min	Max	Standard deviation	t-test	p
NRS 1 h	1.04	0	5	1.485	4.32	0	9	1.97	-6.640	< 0.001
NRS 6 h	0.08	0	1	0.277	2.44	0	5	1.356	-8.523	< 0.001
NRS 12 h	0.04	0	1	0.2	1.44	0	3	1	-6.842	< 0.001
NRS 24 h	0	0	0	0	1.2	0	4	1	-6.000	< 0.001

NRS – Numeric Rating Scale

Table 3. Mean NRS on exertion, one, six, 12, and 24 hours after surgery

Parameters	Group A				Group B					
	Mean	Min	Max	Standard deviation	Mean	Min	Max	Standard deviation	t-test	p
NRS 1 h	1.48	0	6	2.044	6	2	10	1.848	-8.201	< 0.001
NRS 6 h	0.20	0	3	0.707	3.88	2	6	1.301	-12.424	< 0.001
NRS 12 h	0.08	0	2	0.400	2.76	1	5	0.879	-13.87	< 0.001
NRS 24 h	0.00	0	0	0.000	2.24	1	5	0.969	-11.552	< 0.001

NRS – Numeric Rating Scale

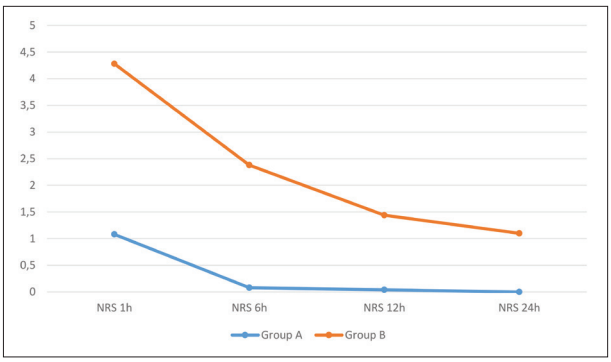

Figure 1. Mean NRS at rest, one, six, 12, and 24 hours after surgery

NRS – Numeric Rating Scale

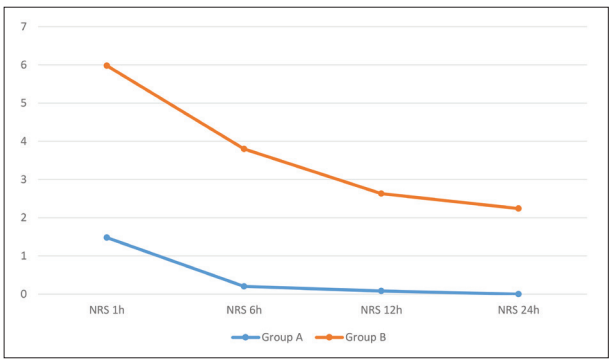

Figure 2. Mean NRS on exertion, one, six, 12, and 24 hours after surgery

NRS – Numeric Rating Scale

Table 2 and Figure 1 show the mean values of pain at rest assessed according to NRS during 24 hours after the surgery. A statistically significant difference was recorded. Patients in group A, who had received morphine chloride intrathecally, had the values lower than the numeric values found in the group B patients, and the difference was even more expressed after the first and sixth hour than after the 12th and 24th hour.

Table 3 and Figure 2 show the mean values of pain on exertion assessed according to NRS during the period of 24 hours after the surgery, with a statistically significant difference to the benefit of the group A patients.

The results of cross comparison of the need for additional analgesia an hour after the end of surgery are shown in Table 4. As it can be seen, only two patients, who had received morphine chloride intrathecally, needed additional analgesia, whereas the majority the group B patients needed additional analgesia. This difference was statistically highly significant ($\chi^2 = 12.834$; $p < 0.001$).

Tables 5, 6, 7 and 8 show the development of nausea as a side effect of analgesic. No statistically significant difference was found between the groups in various time intervals during the first 24 hours after the surgery.

There was no statistically significant difference in vomiting as a side effect of analgesic during the period of 12 hours after the surgery, as shown in Tables 9, 10, and 11. None of the patients had this problem 24 hours after surgery.

Table 4. Need for additional analgesia one hour after surgery

Additional analgesia after 1h	Total	Group A	Group B	χ^2	p
No n (%)	33 (66)	23 (92)	10 (40)	12.834	< 0.001
Yes n (%)	17 (34)	2 (8)	15 (60)		
Total n (%)	50 (100)	25 (100)	25 (100)		

Possible side effects of opioid analgesia are itching and respiratory depression. However, none of our patients developed any of them.

Table 12 shows the SFS with analgesia. Our patients assessed analgesia as: 1 – poor, 2 – medium, 3 – good, and 4 – excellent.

DISCUSSION

There were not statistically significant differences between the two groups regarding age, body weight, ASA classification and the length of surgery. We opted for the dose of 0.3 mg of morphine chloride based on a meta-analysis and a literature review [18, 19].

The results of pain assessment show that pain, both at rest and on exertion, was statistically significantly less expressed in patients having received morphine chloride intrathecally (Group A). The difference was even more

Table 5. Nausea one hour after surgery

Parameter			Group A	Group B	χ^2	p
Nausea 1h	No	n	23	20	1.495	0.417
		%	92	80		
	Yes	n	2	5		
		%	8	20		
Total		n	25	25		
		%	100	100		

Table 6. Nausea six hours after surgery

Parameters			Group A	Group B	χ^2	p
Nausea 6 h	No	n	23	21	0.758	0.667
		%	92	84		
	Yes	n	2	4		
		%	8	16		
Total		n	25	25		
		%	100	100		

Table 7. Nausea 12 hours after surgery

Parameters			Group A	Group B	χ^2	p
Nausea 12 h	No	n	23	20	1.495	0.417
		%	92	80		
	Yes	n	2	5		
		%	8	20		
Total		n	25	25		
		%	100	100		

Table 8. Nausea 24 hours after surgery

Parameters			Group A	Group B	χ^2	p
Nausea 24 h	No	n	25	22	3.191	0.235
		%	100	88		
	Yes	n	0	3		
		%	0	12		
Total		n	25	25		
		%	100	100		

Table 9. Vomiting one hour after surgery

Parameters			Group A	Group B	χ^2	p
Vomiting 1 h	No	n	24	24	0.000	1.000
		%	96	96		
	Yes	n	1	1		
		%	4	4		
Total		n	25	25		
		%	100	100		

Table 10. Vomiting six hours after surgery

Parameters			Group A	Group B	χ^2	p
Vomiting 6 h	No	n	24	24	0.000	1.000
		%	96	96		
	Yes	n	1	1		
		%	4	4		
Total		n	25	25		
		%	100	100		

Table 11. Vomiting 12 hours after surgery

Parameters			Group A	Group B	χ^2	p
Vomiting 12 h	No	n	23	23	0.000	1.000
		%	92	92		
	Yes	n	2	2		
		%	8	8		
Total		n	25	25		
		%	100	100		

Table 12. The subjective feeling of satisfaction (SFS) with analgesia

Parameters			Group A	Group B	χ^2	p
SFS	2 (medium)	n	0	4	29.684	0.001
		%	0	16		
	3 (good)	n	1	16		
		%	4	64		
	4 (excellent)	n	24	5		
		%	96	20		
Total		n	25	25		
		%	100	100		

prominent immediately after the surgery. Only two patients from group A asked for additional analgesia after the first postoperative hour and they received 2.5 gr of intravenous metamizole. The patients from this group required additional analgesia only 27 hours after the moment of intrathecal administration of morphine chloride. However, as many as 15 patients from group B asked for additional analgesia after the first hour and they received 2–5 mg of morphine chloride intravenously. The average consumption of morphine chloride after 24 hours was 21.7 mg in group B, which confirms the statement made by El Sherif et al. [20] who claimed that intrathecal morphine has about 100 times more potency than intravenous morphine. Jacobson et al. [21] believed that intrathecally administered morphine yields effective long-lasting analgesia (over 20 hours) and that the dose from 0.3 mg to 1 mg should ensure good analgesia without the major complication – respiratory depression. A team of Danish researchers has found in their study that it took 27 hours on average from the administration of 0.1 mg and 0.2 mg of intrathecal morphine given for Cesarean section until the first postoperative analgesic [22]. They recommend 0.1 mg as a dose of choice. Slappendel et al. [23] have compared various doses of intrathecal morphine in the patients having had hip replacement and their conclusion was that the dose of 0.1 mg ensures good analgesia with minimum side effects. An Egyptian team of researchers performed a study on safety and analgesic efficiency of intrathecal morphine (0.2, 0.5, and 1 mg) in patients undergoing a major abdominal surgery for cancer. They concluded that 1 mg of morphine resulted in superior analgesia 48 hours after surgery in comparison with 0.2 and 0.5 mg, without a significant difference in the frequency of side effects [24]. Urban et al. [25] have found that the dose of 20 μg/kg of intrathecal morphine considerably decreases the need for additional postoperative analgesia after lumbar fusion

surgery. It can be concluded that the dose of morphine, which is necessary for good postoperative analgesia, depends on the type of surgical procedure.

The following side effects were monitored: nausea, vomiting, itching, and respiratory depression. Since all patients had the urinary catheter, urinary retention, as a side effect, was not followed.

Nausea was less expressed in the patients who had received morphine chloride intrathecally; however, the difference was not statistically significant. Vomiting was equally frequent in both groups. It should be emphasized that the group A patients were given metoclopramide at the end of surgery as well as in the postoperative period if necessary because of nausea and vomiting, whereas the group B patients were given metoclopramide at the end of surgery and eight hours after the surgery. Similar results have been reported in other studies as well [26, 27].

None of our patients reported itching nor was respiratory depression observed as a side effect of morphine. Itching is often mentioned in literature as a frequent side effect of intrathecal morphine, particularly in obstetrics, where gestation hormones may lead to certain changes on opioid receptors [28]. Some researchers from the Netherlands have shown that intrathecal administration of morphine for laparoscopic colon resection is followed with itching more often [29].

Based on their study Jacobson et al. [21] have concluded that nausea, vomiting, and itching develop irrespectively of the dose given, whereas respiratory depression occurs after a dose exceeding 1 mg. In 2009, Gehling and Tryba [18] performed a meta-analysis of randomized controlled studies, which had dealt with the application of intrathecal morphine combined with spinal anesthesia. Their analysis included the following surgical procedures: Cesarean section, orthopedic surgery, gynecologic surgery, arthroscopy, transurethral prostatectomy, and hemorrhoidectomy. Morphine was administered in the doses ranging 0.025–2.5 mg. It has been found that the doses ≥ 0.3 mg increase the incidence of itching. The incidence of respiratory depression in the patients given a dose < 0.3 mg was 1%, whereas it was 9% in case of a dose ≥ 0.3 mg. The authors believe that intrathecal morphine requires prophylaxis and treatment of side effects. In addition, the respiratory function must be continuously followed for 24 hours. The same must be done in the patients who received systemic opioids. There is no evidence to corroborate the extended monitoring of patients receiving low doses of morphine.

The SFS with analgesia may be the most important factor when opting for postoperative analgesia. As many as 96% of the group A patients assessed analgesia as excellent, whereas only 20% of those from group B were of that opinion, which is in discrepancy with a similar study which showed almost equal satisfaction of patients with analgesia [29].

Finally, we should also mention a study performed by an American team of researchers on pregnant women who underwent Cesarean section delivery [30]. The study sample was divided according to the wish of the pregnant women when asked whether they wanted 0.1 mg or 0.2 mg of morphine after having been adequately informed about the advantages and shortcomings of such analgesia. The need for additional analgesia was found to be bigger in the patients who had received 0.2 mg of morphine. Therefore, it can be concluded that postoperative analgesia is a multifactorial problem, where the subjective feeling of the patients themselves and their fear of surgery, postoperative pain, and side effects are of uppermost importance.

Potential limitations to our study are a small sample and a subjective assessment of pain intensity according to NRS. It is difficult to observe a rare side effect in a small study sample. A similar study including a higher number of subjects would contribute to the strength of our conclusions. Urinary retention could not be followed as a side effect in this study because of routine placement of urinary catheter.

CONCLUSION

According to our study, it can be concluded that the combination of 0.3 mg of morphine chloride and 1.7 ml of 0.5% levobupivacaine provides very good analgesia after hysterectomy with adnexectomy and lymphadenectomy lasting for 24 hours after the surgery. Side effects do not differ from those associated with intravenous administration of opioids. Nausea and vomiting can be treated with antiemetics. Although respiratory depression was not observed in our study sample, intrathecal morphine must be administered with great caution and respiratory function must be monitored during the first 24 hours. Finally, our study has shown that the patients who received morphine chloride intrathecally were more satisfied than those who were given morphine intravenously.

Conflict of interest: None declared.

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Ефикасност и сигурност примене интратекалног морфина за аналгезију после хистеректомије

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САЖЕТАК

Увод/Циљ Циљ ове проспективне, рандомизоване студије је да одреди ефикасност и сигурност примене интратекалног морфин-хлорида у комбинацији са локалним анестетиком левобупивакаином за обезбеђивање постоперативне аналгезије код болесница које се подвргавају хистеректомији.

Методе Педесет болесница којима је индикована хистеректомија са аднексектомијом и лимфаденектомијом је подељено у две групе од по 25 испитаница. Испитаницама из групе А је непосредно пре операције интратекално апликована комбинација 0,3 *mg* морфин-хлорида и 1,7 *ml* 0,5% левобупивакаина, док су оне из групе Б интравенски добијале 5 *mg* морфин-хлорида пре завршетка операције и постоперативно у одређеним временским интервалима. Постоперативни бол је оцењен првог, шестог, 12. и 24. сата, уз помоћ нумеричке скале бола. Праћена су и нежељена дејства у виду мучнине, повраћања, свраба и респираторне депресије.

Резултати Постоперативни бол је у свим интервалима праћења, како у миру тако и приликом напора, био мање изражен у групи А ($p < 0,001$); због тога је и потреба за додатном аналгезијом била мања у групи А ($p < 0,001$). Субјективни осећај задовољства постоперативном аналгезијом је статистички значајан у групи А ($p = 0,001$).

Закључак Инратекално давање морфин-хлорида у комбинацији са левобупивакаином обезбеђује бољу постоперативну аналгезију после хистеректомије, у односу на интавенски морфин-хлорид, уз подједнаку учесталост нежељених дејстава.

Кључне речи: хистеректомија; интратекални морфин; постоперативна аналгезија